

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.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/IB2015/056986	International filing date (day/month/year) 11.09.2015	Priority date (day/month/year) 12.09.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D403/12 C07D413/14 C07D213/74 C07D413/04 A61K31/5377 A61P35/00		
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 43*bis*.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 66.1*bis*(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 Goss, Ilaria 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:

see separate sheet

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

2. Citations and explanations

see separate sheet

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

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 I

Basis of the report

This report is based on compounds according to main independent claim 1. pharmaceutical composition comprising a compound (claims 7 and 8) and medical use related matter (claims 9 to 11).

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Re Item V

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

Rule 39 PCT

Claim 9 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39(1)(iv) and Rule 67(1)(iv) PCT.

For the assessment of the present claim 9 on the question whether it is patentable, 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 patentable 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 or further use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Consequently, and even if no opinion should be formulated with respect to the subject-matter of this claim 9 (Article 34(4)(a)(I) PCT), this authority has decided to carry out and base the search and present opinion on the alleged effects of the compounds and/or compositions.

Reference is made to the following documents:

- D1 US 2014/275003 A1 (AVERSA R; BARSANTI P A; BURGER M; DILLON M P; DIPESA A; HU C; LOU Y; N) 18 September 2014 (2014-09-18)
- D2 LYNE P D ET AL: "Identification of amidoheteroaryls as potent inhibitors of mutant (V600E) B-Raf kinase with in vivo activity", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 19, no. 3, 1 February 2009 (2009-02-01), pages 1026-1029, XP025925876,

- D3 N. BABCHIA ET AL: "The PI3K/Akt and mTOR/P70S6K Signaling Pathways in Human Uveal Melanoma Cells: Interaction with B-Raf/ERK", INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol. 51, no. 1, 1 January 2010 (2010-01-01), pages 421-429, XP055046622,

Novelty

D1, intermediate document, discloses certain biaryl amide kinase inhibitors (c.f.. D1, claim 1) and their use for the treatment of cancer. The compounds of D1 show a certain overlap with the present compounds when ring B = pyrimidine substituted with a specific group and ring C = phenyl substituted with a certain amide CY substituent. Since D1 does not disclose specific compounds wherein the pyridinyl rest is specifically substituted with a 2-(phosphonooxy)methyl or phosphonooxy. The proviso at the end of claim 1 makes the presence of this substituent mandatory and excludes compound 58 of D1 (the compound shows present X being N and Y being N). Therefore D1 is not relevant for novelty.

D2 describes bisamidophenyl Raf inhibitors which are structurally very distant from the compounds now claimed.

D3 is concerned with certain kinase signalling pathways leading to cell proliferation, but does not disclose compounds according to the present definitions. Therefore D2 as well as D3 are not relevant for novelty.

Inventive Step

D2 may be regarded as closest prior art since this document also discloses compounds for the treatment of cancer which . The objective problem may be seen in the provision of alternative compounds for the treatment of cancer characterized by their ability to inhibit certain raf kinases .

The problem underlying the present invention is seen in the provision of further i. a. anticancer compounds acting via a different kinase pathway.

The applicant provides the present compounds of formula I. For a number of specific representative compounds the applicant demonstrates their ability to inhibit certain raf kinases (c.f.. pages 40-43). The problem appears to have been solved. their potential usefulness for the treatment of cancer is not known from D2 as the compounds are structurally not closely related.

It is thus considered that the applicant describes for the present distinct compounds a mechanism of action which is specific, i.e. it involves an alternative signalling pathway (c.f.. D2). The inhibition of the signalling pathway demonstrated by the applicant may have therapeutic significance and it is considered that first the structural modification to arrive at the present compounds (not suggested by D2) as well as the very specific mechanism of action confer an inventive character to the subject-matter claimed.

It appears that the solution of the problem is not obvious in the light of D2 and the requirements of inventive step appear to be therefore met.

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Re Item VI

Certain documents cited

The content of the US application (its WO family member) may be considered by the EPO authority, when entering the regional phase before the EPO, as comprised in the state of the art relevant to the question of novelty. An opinion on that has been however already anticipated above.

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Re Item VIII

Certain observations on the international application

In main independent claim 1 the definition of X and Y being i. a. $-\text{OCH}_2\text{CHR}_3\text{R}_4$ should read **CH**- $\text{OCH}_2\text{CHR}_3\text{R}_4$.

Claim 6 comprises all the features of claim 1 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).