

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/US2015/028264	International filing date (day/month/year) 29.04.2015	Priority date (day/month/year) 01.05.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D487/04 A61K31/519 A61P29/00 A61P31/12 A61P37/00 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 Sáez Díaz, R 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>1-24</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-24</u>
Industrial applicability (IA)	Yes: Claims	<u>1-24</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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 The present application relates to pyrrolo[3,2-d]pyrimidine derivatives of formula (I) as toll-like receptor 7 (TLR7) agonists for use in therapy, e.g. in the treatment of cancer, respiratory and dermatological disorders.
- 2 Claims 18-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. 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.
- 3 Reference is made to the following document:
D1 WO 2014/056953 A1
- 4 Document D1 discloses pyrrolo[3,2-d]pyrimidine derivatives of formula (I) (claim 1). The presently claimed formula (I) shows a considerable overlap with formula (I) of D1. However, there are no specific examples in D1 falling under said overlap. The structurally closest compounds to the ones presently claimed are examples 97-102. These prior art compounds differ from the ones presently claimed through the substitution pattern of the phenyl ring (6-OCH₃ instead of at 4-R³ or 5-R⁴).

Therefore, compound claims 1-12 as well as the further claims 13-24 drawn to subject-matter related to said compounds, are novel and meet the requirements of Article 33(2) PCT.

- 5 Document D1 is considered to be the closest prior art to the subject-matter of claims 1-24 as it discloses pyrrolo[3,2-d]pyrimidine derivatives of formula (I) as toll-like receptor 7 (TLR7) agonists for use in therapy, e.g. in the treatment of cancer, respiratory and dermatological disorders (claims 1-7; examples 97-102; table 2). The claimed compounds falling in the above-mentioned overlap with D1 as solution to the problem of providing alternative pyrrolo[3,2-d]pyrimidine derivatives as toll-like receptor 7 (TLR7) agonists for use in therapy are obvious since they are already disclosed in D1 although not explicitly described therein. The mere choice of specific compounds within a group of compounds known for the same pharmacological activity cannot be considered inventive. The problem to be solved may actually be reformulated

as the provision of further pyrrolo[3,2-d]pyrimidine derivatives with unexpected properties, e.g. a improved TLR7 agonism over D1. No comparative tests including the structurally closest examples of D1 have been provided in order to support the involvement of an inventive step, so that it is at present not apparent whether the problem has been solved or not. Thus, at present the subject-matter of claims 1-24 does not meet the requirements of Article 33(3) PCT.

Furthermore, the compounds not falling in the overlap are structurally closely related to the ones falling within. Since no effect seems to be associated to the minor structural variations, no inventive step can be recognized on the basis of such modifications.

Re Item VII

Certain defects in the international application

- 6 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.

Re Item VIII

Certain observations on the international application

- 7 The subject-matter of the present claims 14 and 18 is not considered to be clear, since no instructions, in the form of any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise, which conditions fall within the functional definition, e.g. any condition susceptible of being improved or prevented by the modulation of the activity of TLR7, and accordingly within the scope of the claim (Article 6 PCT). The reason for the necessity of this clarification is, that a claim referring to a condition to be treated, which is functionally defined, would not be limited to the treatment of said specified condition (here for e.g. cancer), but by contrast embraces an undefined number of conditions all allegedly capable of being improved or prevented by the modulation of said kinases. Under these circumstances the independent claim can only be regarded as clear if means are available to the skilled person for assessing whether or not an additional condition not expressly filed in the application but nevertheless affected by the administration of the said compounds is comprised in the scope of the claim.

- 8 The vague and imprecise statement in the description on page 72 "...various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims" implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity when used to interpret them (Article 6 PCT).