

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

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| To:                  |
| see form PCT/ISA/220 |

## 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<br>see form PCT/ISA/220                                                                        |                                                          | <b>FOR FURTHER ACTION</b><br>See paragraph 2 below |
| International application No.<br>PCT/EP2018/078567                                                                                   | International filing date (day/month/year)<br>18.10.2018 | Priority date (day/month/year)<br>27.10.2017       |
| International Patent Classification (IPC) or both national classification and IPC<br>INV. C07D487/04 A61P15/00 A61P13/00 A61K31/4985 |                                                          |                                                    |
| Applicant<br>BAYER AKTIENGESELLSCHAFT                                                                                                |                                                          |                                                    |

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:<br><br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0<br>Fax: +49 89 2399 - 4465 | Date of completion of<br>this opinion<br><br>see form<br>PCT/ISA/210 | Authorized Officer<br><br>Grégoire, Ariane<br><br>Telephone No. +49 89 2399-0 |  |
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**Box No. I Basis of the opinion**

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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:

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**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**

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1. Statement

|                               |             |             |
|-------------------------------|-------------|-------------|
| Novelty (N)                   | Yes: Claims | <u>1-12</u> |
|                               | No: Claims  |             |
| Inventive step (IS)           | Yes: Claims | <u>1-12</u> |
|                               | No: Claims  |             |
| Industrial applicability (IA) | Yes: Claims | <u>1-12</u> |
|                               | No: Claims  |             |

2. Citations and explanations

see separate sheet

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**Box No. VIII Certain observations on the international application**

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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**

Claim 8 relates to a subject-matter considered by this Authority to be covered by the provision 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 in a first or further medical treatment.

**1) Reference is made to the following documents :**

- D1 WO 2008/136756 A1 (ASTRAZENECA AB [SE]; BAYRAKDARIAN MALKEN [CA]; BUON CHRISTOPHE [CA]; C) 13 November 2008 (2008-11-13)
- D2 RAYID ABDULQAWI ET AL: "P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study",  
LANCET,  
vol. 385, no. 9974, 28 March 2015 (2015-03-28), pages 1198-1205,  
XP055537425,  
AMSTERDAM, NL  
ISSN: 0140-6736, DOI: 10.1016/S0140-6736(14)61255-1
- D3 COUMAR M S ET AL: "Aurora kinase A inhibitors: Identification, SAR exploration and molecular modeling of 6,7-dihydro-4H-pyrazolo-[1,5-a]pyrrolo[3,4-d]pyrimidine-5,8-dione scaffold",  
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON,  
AMSTERDAM, NL,  
vol. 18, no. 5, 1 March 2008 (2008-03-01), pages 1623-1627,

XP022683107,  
ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2008.01.068  
[retrieved on 2008-01-19]

**2) Novelty (Art. 33 (1) and (2) PCT) :**

The presently claimed compounds possess a specific tricyclic core structure substituted by an alkylamido chain which has not been disclosed in the art.

The compounds of Documents D1 and D2 do not have a tricyclic central structure as those presently claimed. The compounds of Document D3 do not have an alkylamido chain attached to the nitrogen atom of the central ring.

The compounds of formula (I) being novel, their use in pharmaceutical compositions as well as in the treatment of the diseases mentioned in claims 9-12 are novel as well.

The present application complies with the requirements of Art. 33(2) PCT.

**3) Inventive Step (Art. 33 (1) and (3) PCT) :**

Document D1 is considered as the closest prior art since it discloses pyrrolopyrimidinone derivatives as P2X3 receptors ligands useful for the treatment of pain.

The presently claimed compounds differ from those of Document D1 in their chemical structure which possess a specific tricyclic core structure substituted by an alkylamido chain as defined in claim 1.

The technical problem raised is considered as the provision of further compounds useful as P2X3 receptors ligands in the treatment of diseases such as pain, urinary tract diseases or gynecological diseases.

The biological data provided on pages 432-438 show that a representative set of compounds as claimed solve the problem raised.

Starting from Document D1 and wishing to solve the problem raised, the skilled person had no reason to modify the bicyclic structure of the compounds of D1 so as to arrive at the presently claimed compounds. The P2X3 antagonist disclosed in

Document D2 is structurally further remote from the compounds claimed (monocyclic) and the compounds of Document D3 possess a different biological activity (Aurora kinase inhibitors) and no substituent on the nitrogen atom of the central heteroring.

The presently claimed compounds can therefore not be considered as obvious solutions to the problem raised.

The present application complies with the requirements of Art. 33(3) PCT.

### **Re Item VIII**

#### **Certain observations**

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

According to page 24 line 6 and page 25 lines 1-4, prodrugs of the compounds claimed are also part of the present invention. The term "prodrug" is not allowable. The term is indeed to be seen as a functional feature. Functional features are, however, allowable, only if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to a person skilled in the art and which do not require undue experimentation. This is not achieved by the generic disclosure given p. 25 l.1-4. The description is completely silent as to what kind of prodrugs are contemplated with the claimed invention, e. g. which inactive functional derivatives are able or at least believed to be able to convert into a final drug. Furthermore "in vivo" tests to determine which compounds are inactive prodrugs represent per se an undue experimentation (Guidelines III-6.5, Art. 5 and 6 PCT).