

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

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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<br>see form PCT/ISA/220                                                                       |                                                          | <b>FOR FURTHER ACTION</b><br>See paragraph 2 below |
| International application No.<br>PCT/EP2018/078586                                                                                  | International filing date (day/month/year)<br>18.10.2018 | Priority date (day/month/year)<br>25.10.2017       |
| International Patent Classification (IPC) or both national classification and IPC<br>INV. C07D333/64 C07D333/68 C07D487/04 C07F5/02 |                                                          |                                                    |
| Applicant<br>BAYER PHARMA 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>P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk - Pays Bas<br>Tel. +31 70 340 - 2040<br>Fax: +31 70 340 - 3016 | Date of completion of<br>this opinion<br><br>see form<br>PCT/ISA/210 | Authorized Officer<br><br>Eberhard, Michael<br><br>Telephone No. +31 70 340-0 |
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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>1-6, 8, 9</u> |
|                               | No: Claims  | <u>7</u>         |
| Inventive step (IS)           | Yes: Claims | <u>1-6, 8, 9</u> |
|                               | No: Claims  | <u>7</u>         |
| Industrial applicability (IA) | Yes: Claims | <u>1-9</u>       |
|                               | No: Claims  |                  |

2. Citations and explanations

see separate sheet

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**Box No. VII Certain defects in the international application**

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

see separate sheet

**Re Item V**

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

**V.1 Subject matter**

The present application relates to a method of preparing a compound of formula (VI); a compound of formula (VIII), (XVI), (X); use of a compound of formula (VIII), (XVI), (X) for preparing a compound of formula (VI); use of a compound of formula (VIII), (XVI), (X) for preparing Rogaratinib of formula (I).

**V.2 Documents**

Reference is made to the following documents:

- D1        ELLANOVA LABORATORIES LC: "Benzo[b]thiophene, 5-(chloromethyl)-7-methoxy-",  
             CHEMICAL CATALOG, 8 August 2012 (2012-08-08), pages 1-1, XP055523647,
- D2        WO 2013/087578 A1 (BAYER PHARMA AG [DE]; BAYER IP GMBH [DE]) 20 Jun  
             2013 (2013-06-20)cited in the application

**V.3 Novelty**

**V.3.1** Document D1 discloses a compound with CAS RN 1388033-33-7, which falls within the scope of claim 7 of the present application. Thus, claim 7 of the present application cannot be considered novel with regard to D1 (Article 33(2) PCT).

**V.3.2** Document D2 discloses a process for preparing intermediate 5A using intermediate 4A, which is prepared from intermediates 3A, 2A and 1A respectively (p. 58-61; D2) and the use of intermediate 5 and 1A-4A respectively for preparing Rogaratinib (example 1; D2). The difference to the present application lies in the structure and substitution of the intermediate benzothiophene i.e. 7-methoxy and 5-methyl in intermediate 5A of D2 vs 7-methoxy and 5-chloromethyl in compound (VIII), 7-hydroxy and 5-hydroxymethyl in compound (XVI), and 7-methoxy and 5-methoxycarbonyl in compound (X) in the present application. Thus, claims 1-9 of the present application can be considered novel with regard to D2 (Article 33(2) PCT).

**V.4 Inventive step**

D2 is considered to be the closest prior art with regard to claims 1-6, 8, 9. D2 discloses a method for preparing intermediate 5A using intermediate 4A, which is prepared from intermediates 3A, 2A and 1A respectively (p. 58-61; D2) and the use of intermediate 5 and 1A-4A respectively for preparing Rogaratinib (example 1; D2).

The difference to the present application lies in the structure and substitution of the intermediate benzothiophene i.e. 7-methoxy and 5-methyl in intermediate 5A of D2 vs 7-methoxy and 5-chloromethyl in compound (VIII), 7-hydroxy and 5-hydroxymethyl in compound (XVI), and 7-methoxy and 5-methoxycarbonyl in compound (X) in the present application.

An improved technical effect is not discernible with regard to difference to the closest prior art.

The problem to be solved is considered to be the provision of an alternative method for preparing a 7-methoxy-5-methyl-1-benzothiophen-yl)boronic acid useful in the preparation of Rogaratinib and the use of alternative benzothiophene intermediates for preparing Rogaratinib.

The inventive solution are the method and use according to claims 1-6, 8, 9.

Starting from D2 the solution of the present application would not be obvious to the skilled person. D2 neither suggests nor hints at preparing the 7-methoxy-5-methyl-1-benzothiophene from other benzothiophene intermediates (VIII), (XVI), (X) as defined in the claims but uses aniline and benzenethiol derivatives 1A, 2A, 3A for its preparation. The structural and electronic differences between these intermediates are too great for this to be an obvious modification. The applicant has demonstrated the claimed method and use on p. 20-31. Thus, claims 1-6, 8, 9 of the present application can be considered inventive with regard to D2 (Article 33(3) PCT).

## **V.5 Industrial applicability**

Claims 1-9 fulfill the requirements of Art. 33(4) PCT.

## **Re Item VII**

### **Certain defects in the international application**

**VII.1** Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

**VII.2** Formatting errors with regard to all structures and schemes in the claims and description.

**VII.3** Label for compound (VIII) missing in claim 7.