

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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 see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/EP2015/055228	International filing date (day/month/year) 12.03.2015	Priority date (day/month/year) 19.03.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D413/12 C07D417/12 C07D498/04 C07D513/04 A61K31/505 A61P11/06		
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

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 Telephone No. +49 89 2399-0	
--	--	---	---

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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-17</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-17</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 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:

- D2 WO 2013/014060 A1 (BOEHRINGER INGELHEIM INT [DE];
HOFFMANN MATTHIAS [DE]; BISCHOFF DANIEL) 31 January 2013
cited in the application
- D3 WO 2010/015520 A1 (BOEHRINGER INGELHEIM INT [DE];
BOUYSSOU THIERRY [DE]; DAHMANN GEORG [D] 11 February 2010
- D4 WO 2011/092128 A1 (BOEHRINGER INGELHEIM INT [DE];
HOFFMANN MATTHIAS [DE]; DAHMANN GEORG [D] 4 August 2011
cited in the application
- D5 WO 01/83485 A1 (BAYER AG [DE]; YURA TAKESHI [JP];
CONCEPCION ARNEL B [JP]; HAN GYOONHE) 8 November 2001

2. The claimed subject-matter appears to be novel and to involve an inventive (Art. 33 (2) and (3) PCT).

2.1 The products of D2-D4 do not have a bicycle containing a 5-membered heterocycle as in present ring 1. The products of D5 neither have the present -O-CH (R3)-lactam moiety nor exhibit a fused oxazole or thiazole ring. Also the claimed intermediates are not disclosed in the prior art. Consequently, the claims may be seen as novel.

2.2 D2, D3 and D4 are structurally closer to the present compounds. They share the ability with the present compounds to inhibit Syk kinases. Accordingly, the objective technical problem is seen in the provision of alternative compounds which are useful in treating diseases related to Syk kinase activity.

Representative products have been tested and described as effective Syk inhibitors. The problem is therefore considered to be solved.

A skilled person faced with the task of solving the technical problem would not have arrived at the claimed compounds without inventive ingenuity starting with the teachings of D2-D4, or a combination with D5. D2-D4 all have an invariable pyridine

ring at the place of the present 5-membered ring 1. The skilled person would believe that such a pyridine ring is essential for achieving the desired activity and would not have considered the modification of this structural element. The structural modification of the presently claimed compounds therefore appear to be major and thus non-obvious. The compounds as claimed, their pharmaceutical compositions and medical uses appear to involve an inventive step. Since the claimed intermediates are precursors of the final products, inventive step also seems to be acknowledgeable.

Re Item VI

Certain documents cited

1. Reference is made to the following document:

D1 WO 2015/017610 A1 (GILEAD SCIENCES INC [US]) 5 February 2015

The present end-products and intermediate compounds represent a selection from the Syk inhibitors disclosed in D1. Specific compounds of D1 fall within the ambit of the present claims, such as compound 4.30 disclosed on page 474. Given its publication date, however, D1 does not belong to the state of the art as defined in the PCT. D1 has been disregarded from further consideration in this report. In the regional phase before the EPO D1 will be considered relevant for the issue of novelty.

Re Item VIII

Certain observations on the international application

1. The expression "for use" should be introduced before "the treatment" in present claims 12-15 so that the category of this claim is rendered clear (Art. 84 EPC).
2. 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.