

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
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International application No. PCT/EP2015/079587	International filing date (day/month/year) 14.12.2015	Priority date (day/month/year) 19.12.2014
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International Patent Classification (IPC) or both national classification and IPC INV. C07D495/04 A61K31/519

Applicant BAYER PHARMA AKTIENGESELLSCHAFT
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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 Traegler-Goeldel, M 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, 26</u>
	No: Claims	<u>25</u>
Inventive step (IS)	Yes: Claims	<u>1-24, 26</u>
	No: Claims	<u>25</u>
Industrial applicability (IA)	Yes: Claims	<u>1-26</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

re item V:

1. Prior art

The relevant prior art is to be seen in the documents as cited in the International Search Report:

- D1 SHESTOPALOV, ANATOLIY M. ET AL: "Microwave-assisted synthesis of substituted fluoroazines using KF.2H₂O",
TETRAHEDRON LETTERS,
vol. 50, no. 37, 16 September 2009 (2009-09-16), pages 5727-5259,
XP002741589,
ISSN: 0040-4039, DOI: 10.1016/J.TETLET.2009.07.015
- D2 AZAB, MOHAMMAD EMAD: "Utility of the enamionitrile moiety in the synthesis of some biologically active thienopyrimidine derivatives",
PHOSPHORUS, SULFUR AND SILICON AND THE RELATED ELEMENTS,
vol. 183, no. 7, 24 June 2008 (2008-06-24), pages 1766-1782,
XP002741590,
ISSN: 1042-6507, DOI: 10.1080/10426500701734802
- D3 MIYASHITA, AKIRA ET AL: "Aroylation of fused pyrimidines; synthesis of 4-aroylefuro[2,3-d]-, 4-aroylethieno[2,3-d]-, and 4-aroyleisoxazolo[5,4-d] pyrimidines",
HETEROCYCLES,
vol. 45, no. 11, 1997, pages 2159-2173, XP001525986,
DOI: 10.3987/COM-97-7914
- D4 PATIL, C. D. ET AL: "Synthesis of 7-methyl-4-substituted-5,6,7,8-tetrahydrobenzo[b]thieno[2,3- d]pyrimidines as antimicrobial agents",
JOURNAL OF THE INDIAN CHEMICAL SOCIETY,
vol. 68, no. 3, 1991, pages 169-171, XP008077314,
ISSN: 0019-4522
- D5 MERTENS, M. D. ET AL.: "Regioselective Sulfonylation and N- to IO-Sulfonyl Migration of Quinazolin-4(3H)-ones and Analogous Thienopyrimidin-4(3H)-ones",
THE JOURNAL OF ORGANIC CHEMISTRY,

vol. 78, no. 18, 24 August 2013 (2013-08-24), pages 8966-8979,
XP002741592,
DOI: 10.1021/jo4010876

- D6 WO 2005/010008 A1 (BAYER PHARMACEUTICALS CORPORATION, USA) 3 February 2005 (2005-02-03)
- D7 WO 2006/023843 A2 (BAYER PHARMACEUTICALS CORPORATION, USA) 2 March 2006 (2006-03-02)
- D8 WO 2012/097013 A1 (NIMBUS IRIS, INC., USA) 19 July 2012 (2012-07-19)
- D9 WO 2013/174735 A1 (BAYER PHARMA AKTIENGESELLSCHAFT, GERMANY) 28 November 2013 (2013-11-28)
- D10 WO 2013/174744 A1 (BAYER PHARMA AG, GERMANY) 28 November 2013 (2013-11-28)
- D11 WO 2014/118229 A1 (BAYER PHARMA AG [DE]) 7 August 2014 (2014-08-07)

Documents D1 to D11 are all relevant for the novelty of present claim 25 concerning intermediates, but only documents D9 to D11 are relevant for the consideration of novelty and inventive step for the compounds of claim 1 and the subject matter of claims 2 to 24 and 26.

2. Novelty

The claimed 4-amino-5,6,7,8-tetrahydrobenzothieno[2,3-d]-pyrimidine derivatives differ structurally from those as disclosed in documents D9 to D11 by the pyrazolo [1,5-a]pyridinyl residue connected to the amino nitrogen instead of a 2-oxo-2,3-dihydro-1,3-benzothiazolyl residue as in D9 or a 1H-indazolyl residue as in D10 and D11. Thus the subject matter of present claims 1 to 24 and 26 is considered to fulfil the requirement of novelty with regard to the cited prior art. Nevertheless, the novelty of claim 25, concerning the -5,6,7,8-tetrahydrobenzothieno[2,3-d]-pyrimidine intermediates with a leaving group, is destroyed by the disclosure of compounds 1f and 3f according to D1, compound 7 according to D2, compound 6 in scheme 4 according to D3, compound (3) in the first scheme according to D4, compound 14c according to D5, step 3 of example 14, step 6 of example 63 and step 3 of example 242 according to D6, compound (5) in reaction scheme 1 according to D7, compound

C on p. 130 according to D8, starting materials of examples 1, 16, 17, 30, and examples 31 and 85 to 93 according to D9, compound 2a, the starting materials of examples 60, 63, 80-169, 184-205, 238, 254 and 280 according to D10 and the starting materials for examples 1a, 2, 3, 17a, 24, 25-32, 35-37, 49b, 50b, 50c, 50d, 50g, 51b and c according to D11. Thus the present application does not fulfil the requirement of Art. 33 (2) PCT.

3. Inventive step

Documents D9 to D11 are concerned with 4-amino-5,6,7,8-tetrahydrobenzothieno[2,3-d]-pyrimidine derivatives which inhibit MAP kinase interacting kinase Mnk1 and/or Mnk2 as is the present application. The structural difference between these compounds and the claimed ones is significant: whereas the 5,6,7,8-tetrahydrobenzothieno[2,3-d]-pyrimidine derivatives according to D9, D10 and D11 bear a 2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl-amino residue (D9) or a 1H-indazol-5-yl-amino residue in position 4 (D10, D11) the present ones must have a pyrazolo[1,5-a]pyridin-5-yl-amino residue in this position, being the essential structural difference.

a, Therefore, if the problem underlying the present application were to be seen in the provision of further Mkn1 and/or Mkn2 inhibitors, this problem has obviously been solved as demonstrated by the Applicant by providing corresponding data of biological assays (see p. 131 to 146 of the description). This solution, at least as far as the exemplified compounds and the compounds according to claim 13 are concerned, could in principle be considered to involve an inventive step, since documents D9 to D11, neither taken alone nor in combination could have taught the skilled person to replace the 2-oxo-2,3-dihydro-1,3-benzothiazolyl residue or the 1H-indazol-5-yl residue at the amino nitrogen in position 4 by a pyrazolo[1,5-a]pyridin-5-yl residue.

b, Nevertheless, as far as the huge breadth of present claim 1 and unlimited definitions like "heterocycloalk(en)yl and aryl" without further specifications is concerned, the corresponding claims can obviously not be considered to fulfil the requirements of Art. 33(3) PCT, since the claimed area can clearly not be considered represent a reasonable generalization or obvious modifications or equivalents of the examples given in the description covered by the scope of present claim 1. Consequently, the question arises as to whether the scope of unlimited definitions like "heterocycloalk(en)yl and heteroaryl" without further specification is justified, since the skilled person is the same reading the present application and the prior art: if it was not obvious to arrive at the claimed compounds starting from the prior art, then consequently the present scope, i.e. generalisation of example 1 cannot be obvious

neither. Therefore, as yet, claim 1 does not fulfil the requirements of Art. 33 (3) PCT and these expressions should be specified according to the description as filed to be in accord with Art. 33 (3) PCT.

4. Industrial applicability

No problem arises, since the claimed compounds may be used for the production of pharmaceutical products.

re item VII:

a, Claim 20 is defined in functional terms (... is mediated by the MKNK1 pathway, the MKNK2 pathway or both pathways) that are not considered to be clear in the sense of Art. 6 PCT. The therapeutic application is defined by means of a mechanism of action which does not allow for a practical application in the treatment of a specific pathological condition (disease). The objection could be overcome by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition or merely by deleting the following term "more particularly" since then a list of specified pathological conditions (diseases) follows said terms.

b, Claim 21 seems to be incomplete, since no disease is following the unfinished sentence.