

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/SA/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/EP2018/060313

International filing date (day/month/year)
23.04.2018

Priority date (day/month/year)
27.04.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07D513/00 A61P31/00 A61K31/429

Applicant
BAYER ANIMAL HEALTH 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 43 <i>bis</i> .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

Papathoma, Sofia

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. 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>1-10, 12-18</u>
	No: Claims	<u>11</u>
Inventive step (IS)	Yes: Claims	<u>8, 9</u>
	No: Claims	<u>1-7, 12-18</u>
Industrial applicability (IA)	Yes: Claims	<u>1-18</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. 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

This **Written Opinion** is based on the following application documents:

Description, Pages

1-128 as originally filed

Claims, Numbers

1-18 as originally filed

The present application relates to compounds of the formulae (I) and (II) useful for the treatment of infections with helminths.

Re Item V

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

Reference is made to the following documents:

- D2 ALPER PHIL ET AL: "Discovery of structurally novel, potent and orally efficacious GPR119 agonists",
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,
vol. 24, no. 10 , pages 2383-2387, XP028646705,
ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2014.03.023
- D3 LINDY HOLDEN-DYE ET AL: "Anthelmintic drugs and nematicides:
studies in *Caenorhabditis elegans*",
WORMBOOK, 16 December 2014 (2014-12-16), pages 1-29,
XP055478099,
DOI: 10.1895/wormbook.1.143.2
- D4 AGRAWAL V K ET AL: "COMBINATION THERAPY IN THE
TREATMENT OF HELMINTH DISEASES",
MEDICINAL RESEARCH REVIEWS, NEW YORK, NY, US,
vol. 5, no. 3, 1 January 1985 (1985-01-01), pages 333-369,
XP001056154,
ISSN: 0198-6325

- D5 BINDI S ET AL: "Thieno[3,2-c]pyrazoles: A novel class of Aurora inhibitors with favorable antitumor activity",
BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB,
vol. 18, no. 19, 1 October 2010 (2010-10-01), pages 7113-7120,
XP027286069,
ISSN: 0968-0896
[retrieved on 2010-07-25]
- D6 US 2011/086882 A1 (SHIN KOGYOKU [GB] ET AL) 14 April 2011
(2011-04-14)
- D7 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 20 April
2017 (2017-04-20),
Database accession no. 2092685-77-1

Claims 15, 17 and 18 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.

1) Article 33(2) PCT

Document D2 discloses the compound 45 in Table 2 characterised by a pyrazolo[5,1-b][1,3]thiazolyl core structure. However, said compound is characterised by a different substitution pattern and therefore the disclosure of D2 is not prejudicial to the novelty of the claimed subject-matter.

Documents D3 and D4 relate to compounds useful for the treatment of helminth diseases. In particular, they disclose the compound levamisole of the structural similar imidazothiazolyl core structure, which is, however, characterised by a different substitution pattern. The disclosure of documents D3 and D4 is therefore not prejudicial to the novelty of the claimed subject-matter.

Document D5 discloses the structurally similar compounds 31 and 32 in Table 1. However, said compounds are characterised by a thieno[3,2-c]pyrazolyl core structure and therefore the disclosure of D5 is not prejudicial to the novelty of the claimed subject-matter.

Document D6 discloses compounds of a pyrazolo[5,1-b][1,3]thiazolyl core structure. However, said compounds are characterised by a different substitution pattern and therefore the disclosure of D6 is not prejudicial to the novelty of the claimed subject-matter.

Document D7 discloses the compound with the Registry Number 2092685-77-1, which is prejudicial to the novelty of claim 11.

Summarizing the above, claim 11 does not fulfil the requirements of Article 33(2) PCT and only claims 1-10 and 12-18 can be acknowledged as novel.

2) Article 33(3) PCT

Documents D3 and D4 disclose compounds useful for the treatment of infections with helminths. Said documents may be equally considered to be the closest prior art.

In view of the closest prior art the technical problem underlying the present application is seen in the provision of further compounds useful for the treatment of infections with helminths.

As solution are claimed compounds of the formulae (I)/(II).

Pages 123-128 of the present application contain data of *in vitro* and *in vivo* assays, showing that the 15 exemplified entities have the claimed activity.

The solution claimed i.e. the compounds of the formulae (I)/(II) differs from the solution disclosed in the closest prior art D3/D4, and from the compound levamisole in particular, not only in the core structure: imidazothiazolyl in levamisole vs pyrazolo[5,1-b][1,3]thiazolyl in the claimed entities but also in their substitution pattern.

In addition, the other prior art documents cited in the search report do not give any hint relevant for the structural design / substitution pattern of the claimed entities.

It is therefore considered that the structural design of the claimed entities is not obvious.

However, before a positive opinion is expressed with regard to the inventive merit of the claimed subject-matter it should be pointed out that the present application discloses only 15 compounds all having a 7-phenyl-6-methyl-3-(propan-2-

yl)pyrazolo[5,1-b] [1,3]thiazolyl-2-carboxamide core structure, in which the nitrogen atom of the amido moiety is substituted in 13 of the examples by a 3,4-dihydro-2H-chromen-4-yl ring system and in 2 of the examples by a 2,3-dihydro-1H-inden-1-yl ring system.

That means that the variations in the substitution pattern of the claimed compounds in the disclosed examples are limited and said limited variations do not justify the breadth of claims (Article 6 PCT: fully supported by the description).

The applicant is entitled to claim only obvious modifications of what was described (close related variations), since the claims should represent a reasonable generalisation of the examples given in the description: the technical features stated in the description/examples as being essential must be the same as those used to define the invention in the claims. The reason for that is that the problem to be solved should be solved by the whole scope of the claimed subject matter (every compound falling within its scope) and not just by individual compounds- especially since the problem may be seen in the provision of compounds acting on a biological system (i.e. on a system depending upon very different parameters). If this were not the case, an invention could arbitrarily be broadened to any limit without consideration, whether the compounds are actually solving the problem underlying the invention (Article 33(3) PCT).

On that basis, broader variations would be allowed only in the case that it is made credible that the claimed effect is retained. At the moment only claims 8 and 9 appear to be supported by the examples.

Since it has not been shown that the technical problem underlying the present application can be solved over the whole breadth claimed (i.e. by compounds of the broader defined formula (I)), it is at present considered that only claims 8, 9 and claims 10 and 12-18 relating to the subject-matter of claims 8 and 9 fulfil the requirements of Article 33(3) PCT.

Re Item VI

Certain documents cited

Document:

D1 WO 2017/178416 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 19
 October 2017 (2017-10-19)

can not be considered as prior art document under Article 33(2) PCT, because it is published after the priority and before the filing date of the application.

An intermediate document may be of relevance upon entry into the regional phase before the EPO.

However, in present case document D1 disclosing pyrazolopyrimidine compounds for use in the treatment, control and/or prevention of diseases, in particular of helminth infections i.e. disclosing compounds of a different core structure, is not prejudicial to the novelty of the claimed subject-matter.

In addition, document D1 is not prejudicial to the inventiveness of the claimed subject-matter, since in present case the priority of the present application is validly claimed and an intermediate document can only be relevant for the assessment of inventive step of subject-matter not entitled to the priority.

Re Item VII

Certain defects in the international application

Use-claim 17 erroneously refers back to claims 11, 13 and 14, as latter claims are not use-claims. The requirements of Rule 6.4 (a) PCT are thus not fulfilled.

Re Item VIII

Certain observations on the international application

As mentioned under Re Item V, 2) claims 1-7 and by consequence claims 10-17 referring back to said claims do not fulfil the support requirement under Article 6 PCT.

Furthermore, the terms "aryl", "heteroaryl", "heterocyclyl" used in the claims are considered to be non-limitative and embrace an infinite number of possibilities not yet explored by the Applicant. Therefore it is not clear whether all compounds implied fall

within the scope of the present claims and/or represent a solution of the problem underlying the present application. Consequently, for reasons of inventive step and clarity these terms should be limited to the specific meanings given in the description.

As mentioned under Re Item VII, use-claim 17 refers back to claims 11, 13 and 14, which, however, are not use-claims. Claim 17 therefore does not fulfil the requirements of clarity under Article 6 PCT.