

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/EP2020/078248

International filing date (day/month/year)
08.10.2020

Priority date (day/month/year)
09.10.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61P33/14 A61K31/506 C07D401/04 C07D401/14 C07C317/22 C07C321/18

Applicant
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.

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Date of completion of
this opinion

see form
PCT/ISA/210

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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. 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:

see separate sheet

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

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>2-5, 7-21</u> |
| | No: Claims | <u>1, 6, 22</u> |
| Inventive step (IS) | Yes: Claims | <u>11</u> |
| | No: Claims | <u>1-10, 12-22</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-22</u> |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43*bis*.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 II

Priority

The present application is claiming the priority of 19202293.7, 19215749.3 and 20177852.9. However the previously first two mentioned applications do not disclose part of the present definitions for R4 (with substituents S1 to S39 and R41 to R45) and R5 of formula T1 in claims 1-4. The present claims 7-9 and 11 represent novel combinations of structural parameters which were not provided in these earlier applications.

Claim 1 of the present application is supported by claim 1 of 20177852.9. However claims 2-5 are only partly supported in this earlier application, since no basis could be detected in this given priority document as a whole (claims/description) for R51, R52 as -CO₂alkyl or last paragraph on page 355 in claim 2 and in claim 3 for the specific definitions of R51/R52 and in claims 4-5 for specific definitions for instance R2 = 4-chlorophenyl-sulfonyl, R41/R42 = pyrrolidine-1-yl or 2,6-dimethylmorpholin-4-yl, R5 = pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl. Present claim 8 is supported by pages 43-44 of this earlier application, to the exception of the list of possible substituents for the selected group A (for instance at least -COOH or -NH₂ are not present in the earlier document). Present claims 9 and 11 are new and have no support in this earlier application. Hence, the priority of the present application is only partially valid in view of all cited prior applications and in particular based on 20177852.9 for the subject-matters of claims 2-5, 8-9, 11 and dependent thereof.

Re Item IV

Lack of unity of invention

This Authority considers that the application does not meet the requirements of unity a priori of invention for the reasons as indicated below.

The present application pertains to:

- 1) compound (I) and their use
- 2) compound (a)
- 3) compound (b1).

All three compounds have altogether no common structural moiety and furthermore they are not so kinked to form a single general inventive concept as required by Rule 13.1 PCT since: group 1) is concerned with the provision of further triazole derivatives useful for controlling ectoparasites on animals and groups 2) and 3) are faced with alternative production processes for a triazole derivative. Consequently, the requirements of unity are accordingly not fulfilled a priori and the present application consists of the following two inventions:

invention 1: compound (I) and intermediate (a) (claims 1-10, 12-22)

invention 2: compound (b-1) (claim 11).

Re Item V

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

1 Prior art documents

D1: ChemBridge Corporation, 1452979-00-8 (22-09-2013)

D2: ChemBridge Corporation, 1609831-36-8 (06-06-2014)

D3: Aurora Fine Chemicals, 2192638-31-4 (16-03-2018)

D4: ChemBridge Corporation, 1453044-62-6 (22-09-2013)

D5: ChemBridge Corporation, 1269046-03-8 (21-03-2011)

D6: ChemBridge Corporation, 1269003-64-6 (21-03-2011)

D7: WO 2017 192 385 cited in the application

D8: WO 2012 080 376

D9: WO 2020 094 363

D10: WO 2020 079 198

D11: EP 1 544 202

2 **INVENTION 1**

2.1 Novelty (Article 33(2) PCT)

Compounds of present formula (I) are known from the prior art, as follows:

D1 (R5 = 3-Cl-benzyl, R2 = Me, R4 = 1-Me-piperidinyI); D2 (R5 = 3-Cl-benzyl, R2 = Me, R4 = 6-Me-pyridinyI); D3 (R5 = 4-OMe-phenyl, R = pyridine); D4 (R5 = phenylethyl, R2 = Me, R4 = 1,3-benzodioxolyl) ; D5 (R5 = phenylethyl, R2 = Me, R4 = pyridine) and D6 (R5 = phenylethyl, R2 = phenyl, R4 = pyridine).

Examples 73 and 74 of D7 are characterized by R2 = 2,5-bis(trifluoromethyl)benzamide, X = O, R1 = H, R3a = H, R3b = Me, R4 = pyrimidine according to present formula (I), however with R5 = diethoxymethyl or methylcarboxylate. For their preparation analogs to the one of preparation 20 on page 30 of D7 are needed. These precursors are according to present formula (a) differing also only by the R5 parameter.

Novelty is accordingly not recognized for the subject-matter of claims 1 and 6 in view of D1-D6.

Claim 22 refers to a seed in general. The method of protection according to claim 21 is not seen as making any difference in technical features *versus* any known seed, for instance D8 (page 35, lines 8-17).

The subject-matter of present claim 22 is accordingly not novel.

2.2 Inventive step (Article 33(3) PCT)

D7 is directed to triazole derivatives useful for controlling ectoparasites on animals, same purpose as in the present application. The closest structurally related compounds of D7 are those of examples 73 and 74 characterized by R2 = 2,5-bis(trifluoromethyl)benzamide, X = O, R1 = H, R3a = H, R3b = Me, R4 = pyrimidine, R5 = diethoxymethyl or methylcarboxylate. They have been shown to be active in vitro against *Rhipicephalus sanguineus* (Assay B on page 72 of D7). These compounds do not fall under present formula (I) because of the sole structural parameter R5: for example 74 of D7 R5 = COOMe instead of COOH as in the present application and for example 73 of D7 R5 = (EtO)₂-CH instead of CH₂-NH-C(O)-Alkoxy.

There is no comparative data in the present application to sustain a surprising effect due to this structural difference. Accordingly the objective technical problem is the provision of further alternative compounds with the same activity.

The proposed solution are the compounds of formula (I).

This solution was exemplified for compounds of formula (I') according to present claim 6, wherein X = O, Y = bond with R1 = H, R3a = H, R3b = Me, R2 = substituted phenyl or pyridine, R4 = pyridine or pyrimidine or thiazole and R5 = amino group (compounds 1-27, 88, 108, 112, 165, 167-286), sulfur group (compounds 28-30, 58-70, 166), benzyl (compounds 82-87, 109-111), CN (compounds 71, 80-81), amide (compounds 74-79), COOH (compounds 72-73) and heterocyclyl (compounds 31-57) (see table 1). Some of them were tested for their activity (pages 312 onward). The alleged effect was shown for a very narrow scope of what is actually claimed.

If the applicant sustained that the structural modification in R5 = COOMe from example 74 of D7 to COOH in the present application cannot be anticipated by the skilled person to keep the sought activity of pesticide, then for the same reasons no generalization can be made of the present examples, since it encompasses structural modifications which are far remote from the deprotection of a carboxylate (see R1 being hydroxyl, alkyl, ring system; R2 being heteroaryl, heterocyclyl, condensed aryl, alkyl; R4 further heteroaryl system; R3a, R3b possibly forming a ring or independently being a ring). Accordingly either further experimental data should be submitted to support the presently claimed scope or the scope should be restricted to a fair generalization of the examples.

Hence, the requirements of Article 33(3) PCT are not considered met for the claimed subject-matters.

3 **INVENTION 2**

3.1 Novelty (Art. 33(2) PCT)

Example 4 in D7 discloses as starting material a benzoic acid derivative missing a substituent in position 5.

Reference example 1 in D11 discloses a benzoic acid analog missing a substituent in position 5 (see page 50).

None of the cited prior art documents disclose a compound (1b). Novelty prevails for present claim 11.

3.2 Inventive step (Art. 33(3) PCT)

D7 is directed to the process of triazoles using benzoic acid derivatives as starting materials. Hence, D7 is considered as the closest prior art document. The closest related process in D7 concerns the production of example 4, wherein the starting benzoic acid bears a 3-trifluoromethoxy substituent, but is missing any substituent in position 5. In view of the absence of any comparison between example 4 of D7 and the technical problem posed is to provide an alternative starting material.

The proposed solution is the use of compound (b1).

Such process was exemplified for $R_{41} = -SO_2-CHF_2$ in the productions of compounds I-280 and I-279. The sulfenyl and sulfinyl compounds are precursors for the sulfonyl starting material used in these productions. The technical problem was accordingly shown solved.

D7 already suggests a benzoic derivative having a 3-trifluoromethyl substituent. However phenyl group as parameter R2 in the compound of D7 is not substituted by a sulfenyl, sulfinyl or sulfonyl moiety (see claim 1 in D7). A 3-(difluorosulfenyl)-benzoic acid is already used in D11 for the production of heteraryl herbicides (see reference example 1, compound 1-1 for formula (XXXVI), compound (3-10) for formula (IX)). There is however neither a triazole core in the proposed compounds (I) in D4, nor the hint towards a sulfur substituent in position 5 of the benzoic starting materials. The only disclosed triazoles in paragraph 197 of D4 are commercially available herbicides structurally far remote: -C(O)N moiety connected directly to the triazole. The proposed solution is therefore not obvious in view of D7 and D11.

Hence, the requirements of Article 33(3) PCT are met by present claim 11.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/ year)	Filing date (day/month/ year)	Priority date (<i>valid claim</i>) (day/month/year)
WO2020094363	14.05.2020	17.10.2019	05.11.2018 12.02.2019

WO2020079198	23.04.2020	17.10.2019	19.10.2018
			27.02.2019

At least compounds according to P21, P26, P30 and P37 of WO 2020 093 363 are highly relevant since falling under present Formula (I) (R5 = OH, CONH2, SO2Me, oxadiazol), and having the same use as in the present application. Those of WO 2020 079 198 of claim 1 with R5 = CN are also considered relevant.

Re Item VIII

Certain observations on the international application

Dependencies of some claims seem erroneous for the following reasons: the possible substitution with CO2alkyl for the parameters R51 and R52 in present claim 2; the parameters R46 and R47 in present claim 8 cannot both having the same definition in view of the definition of R42 for the substituents S1 to S39. This needs to be clarified (Article 6 PCT).

The present application is not considered to fulfill the requirements of unity a posteriori in view of the prior art, for instance D7 for the following reasons: The present application pertains to compounds of formula (I), wherein compounds (I) is characterized by a 1,2,4-trisubstituted triazole, which is already known from D7 (see examples 73 and 74 with Assay B having also R5 not being a hydrogen atom and formula (a) in scheme 1 on page 17). There exists accordingly in view of D7 no common structural moiety in formula (I) making a contribution over the prior art D7 (formula (I) with all parameters Y, X, R2, R1, R3, R4). The objective technical problem is the provision of further alternative pesticides to the ones already suggested in D7. The proposed solution are the compounds of formula (I) with the different R5 definitions. There is no special technical feature among the different definitions in R5 supporting a common inventive concept. The requirements of Rule 13 PCT are therefore not met a posteriori.