

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/EP2018/081257

International filing date (day/month/year)
14.11.2018

Priority date (day/month/year)
16.11.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07C209/26 C07C211/40 C07C45/44 C07C45/35 C07C45/54 C07C49/467 C07D213/803

Applicant
SYNGENTA PARTICIPATIONS AG

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:



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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. 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>1-15</u> |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | <u>1-13, 15</u> |
| | No: Claims | <u>14</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-15</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

Reference is made to the following documents:

D1: US 2016/0157485 A1 (A.C. O'Sullivan, *et al.*) 9 June 2016

D2: M. Truong, *et al.*, Tetrahedron: Asymmetry, 2003, 14(8), 1063-1072

D3: M. Yamashita, *et al.*, Tetrahedron Letters, 1983, 24(1), 79-82

D4: WO 2015/178846 A1 (SP Process Development) 26 November 2015

Re Item IV

Lack of unity of invention

2. This Authority considers that there are four inventions covered by the claims indicated as follows:

I: Claims 1-10 directed to a process for the preparation of enantiomerically and diastereomerically enriched *N*-(1-substituted cyclobutyl) amides in three steps from 1-substituted cyclopropanenitriles.

II: Claims 11-13 directed to a process for the preparation of 2-substituted cyclobutanones from 1-substituted cyclopropanecarbaldehydes.

III: Claim 14 directed to a process for the preparation of enantiomerically and diastereomerically enriched 2-substituted cyclobutylamines from 2-substituted cyclobutanones.

IV: Claim 15 directed to a process for the preparation of 2-substituted *N*-cyclobutenyl amides from 1-substituted cyclopropanecarbaldehydes.

The reasons for this finding are as follows:

2.1 According to Rule 13.1 PCT, the International application "shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept".

This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".

2.2 *A priori*, the only feature of the present application which appears capable of being the special technical feature common to all the inventions is the involvement of the 2-substituted cyclobutanone derivatives of formula (III).

To decide whether this technical feature is the special technical feature, we must apply the teaching of Rules 13.1 and 13.2 PCT, which stipulate that the technical feature must define a contribution over the prior art to be recognised as the special technical feature (which gives rise to unity).

2.3 For the purposes of unity, a single general inventive concept is required. This means that the broadest possible problem to be solved has to be drawn up (*i.e.* to cover all claimed possibilities).

It is considered that the problem to be solved by the present application is the provision of further processes involving 2-substituted cyclobutanone derivatives. The applicant solves this problem by means of the various processes of present claims 1-15.

2.4 Each of the documents D1 and D2 discloses at least one process involving a 2-substituted cyclobutanone derivative according to formula (III) of the present invention:

D1: Examples P2-P5, P17 and P24

D2: Paragraphs 4.1, 4.2 and 4.3

Thus, the compounds of D1 and D2 solve the problem in an identical manner to the present application. In the light of the documents D1 and D2, the solution proposed in the present application to the problem mentioned above, namely the provision of further processes involving 2-substituted cyclobutanone derivatives, is known from the prior art. The 2-substituted cyclobutanone derivatives cannot be regarded as the special technical feature which links together all of the separate inventions disclosed in the present application.

Since there are no apparent features which may be regarded as the special technical feature, which could link the different inventions of the application, then there is a lack of unity.

In the light of the above, the examiner has identified, *a posteriori*, four different subjects (see list above).

2.5 The examiner has found that all of the inventions could be searched together without significant additional effort, so no further search fees are requested and the International Search Report and the attached opinion cover the subject-matter of all of the claims.

Re Item V

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

1. Subject-matter

The present application concerns

- (1) a process for the preparation of certain enantiomerically and diastereomerically enriched *N*-(1-substituted cyclobutyl) amides in three steps from 1-substituted cyclopropanenitriles by conversion to 1-substituted cyclopropanecarbaldehydes, rearrangement to 2-substituted cyclobutanones and reductive amination followed by acylation (claims 1-10);
- (2) a process for the preparation of 2-substituted cyclobutanones from 1-substituted cyclopropanecarbaldehydes by reaction with AlCl_3 or GaCl_3 (claims 11-13);
- (3) a process for the preparation of enantiomerically and diastereomerically enriched 2-substituted cyclobutylamines from 2-substituted cyclobutanones by reaction with an ammonium salt and H_2 in the presence of a chiral transition metal catalyst (claim 14); and
- (4) a process for the preparation of 2-substituted *N*-cyclobutenyl amides from 1-substituted cyclopropanecarbaldehydes by reaction with AlCl_3 or GaCl_3 and then reacting the 2-substituted cyclobutanones formed with acetonitrile and an additive (claim 15).

2. Novelty

2.1 Claims 1-10

Document D1 discloses certain chiral compounds which are useful as nematocides including *N*-(2-phenylcyclobutyl) amide derivatives (claim 1). D1 further discloses various methods for the preparation of these compounds (paragraphs [0458] - [0583]). None of the processes disclosed in D1 starts from the corresponding cyclopropanenitriles of the process of present claim 1.

The subject-matter of present claims 1-10 is therefore new (Article 33(2) PCT).

2.2 Claims 11-13

Document D2 discloses a method for converting a cyclopropanecarbaldehyde derivative into 2-substituted cyclobutanones. In particular, 1-MEM-O-

cyclopropanecarbaldehyde is treated with phenyllithium followed by HCl hydrolysis to yield 2-phenylcyclobutanone (compound 3b; paragraph 4.1). Replacing the phenyllithium with isopropylmagnesium chloride yields 2-isopropylcyclobutanone (compound 3c; paragraph 4.2).

Document D3 discloses a process for the transformation of 1-(*p*-tolylthio)cyclobutylcarbaldehyde (compound 1a) into the corresponding cyclopentanone derivative (compounds 2a) using Lewis acids including AlCl₃ in solvents including toluene (page 80; table 3).

D2 and D3 do not disclose the use of AlCl₃ or GaCl₃ to convert 1-substituted cyclopropanecarbaldehydes into 2-substituted cyclobutanones.

The subject-matter of present claims 11-13 is therefore new (Article 33(2) PCT).

2.3 Claim 14

Document D1 discloses the preparation of *cis*- and *trans*-2-(4-chlorophenyl)cyclobutylamine from 2-(4-chlorophenyl)cyclobutanone via reduction of its oxime with sodium borohydride (example P2). D1 further discloses the preparation of 2-(2,4-dichlorophenyl)cyclobutylamine with an ee of 88% and 2-(2,4-dichlorophenyl)cyclobutylamine with an ee of 86% from 2-(2,4-dichlorophenyl)cyclobutanone and 2-(4-chlorophenyl)cyclobutanone, respectively, via hydrogenation of *N*-[2-(2,4-dichlorophenyl)-1-cyclobutenyl]acetamide and *N*-[2-(4-chlorophenyl)-1-cyclobutenyl]acetamide using a chiral ruthenium catalyst (examples P5 and P17). D1 does not disclose preparation of enantiomerically and diastereomerically enriched 2-substituted cyclobutylamines by reaction of 2-substituted cyclobutanones with an ammonium salt and hydrogen in the presence of a chiral transition metal catalyst.

Document D4 discloses a process for the preparation of chiral amines in which prochiral ketones are reacted with hydrogen gas in the presence of a mixture of an ammonium salt, ammonia in a solvent and a catalyst comprising a transition metal selected from ruthenium, rhodium, iridium and palladium and a chiral bidentate phosphorus ligand (claim 1). This process is used in the preparation of various benzyl amines including the conversion of 1,2-diphenyl-1-propanone into 1,2-diphenylpropylamine having an ee of 97% (example 25) using RuCl(Cymene)(S-Xyl-Binap)Cl as catalyst. D4 does not disclose the application of this process to the conversion of 2-substituted cyclobutanones to enantiomerically and diastereomerically enriched 2-substituted cyclobutylamines.

The subject-matter of present claim 14 is therefore new (Article 33(2) PCT).

2.4 Claim 15

Document D1 discloses a method for the preparation of *N*-[2-(4-chlorophenyl)cyclobuten-1-yl]acetamide by reaction of 2-(4-chlorophenyl)cyclobutanone with acetamine in toluene in the presence of toluene-4-sulfonic acid under reflux with a Dean-Stark trap (example P17.a). The 2-(4-chlorophenyl)cyclobutanone was prepared in two steps from 4-chlorobenzaldehyde (example P3). The process of D1 does not use a cyclopropanecarboxyaldehyde of formula (II) of present claim 15.

The subject-matter of present claim 15 is therefore new (Article 33(2) PCT).

3. **Inventive step**

3.1 Claims 1-10

Document D1 is considered to be the prior art closest to the subject-matter of present claims 1-10 and discloses methods for the preparation of chiral *N*-cyclobutyl amide derivatives starting from the corresponding 2-substituted cyclobutanone derivative, for example, via an *N*-cyclobutenylacetamide derivative (example P5). The process of present claim 1 differs from this prior art process in that the 2-substituted cyclobutanone derivative is prepared from a cyclopropanenitrile derivative and then converted directly to a cyclobutylamine derivative which is then *N*-acylated. No surprising technical effect is apparent which arises from these differences.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative process for the preparation of enantiomerically and diastereomerically enriched *N*-(1-substituted cyclobutyl) amides. The applicant provides the process of present claim 1 as a solution to this problem, supported by worked examples of each step.

Of the various steps of the process of present claim 1, only the final step of reacting the cyclobutylamine derivative with an acylating agent is disclosed in D1. None of the other steps of the process are disclosed in D1 or in the other available prior art. The skilled person would have to use inventive skill to arrive at the process of present claim 1.

The subject-matter of present claims 1-10 therefore involves an inventive step (Article 33(3) PCT).

3.2 Claims 11-13

Document D2 is considered to be the prior art closest to the subject-matter of present claims 11-13 and discloses a method for preparing 2-substituted cyclobutanones by reaction of cyclopropanecarbaldehyde derivatives with organolithium and

organomagnesium reagents which both enlarge the ring and adds the 2-substituent. The process of present claim 11 differs from this prior art process in that a cyclopropanecarbaldehyde derivative already comprising the substituent is reacted with a Lewis acid selected from AlCl_3 and GaCl_3 . No surprising technical effect is apparent which arises from these differences.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative process for the preparation of 2-substituted cyclobutanone derivatives. The applicant provides the process of present claim 11 as a solution to this problem, supported by worked examples.

As noted above (paragraph 2.2), D3 discloses a method for the conversion of a 1-substituted cyclobutanecarbaldehyde (i.e. 1-(*p*-tolylthio)cyclobutylcarbaldehyde) to the corresponding 2-substituted cyclopentanone using AlCl_3 . Even if the skilled person were aware of this document, the application of this process to the preparation of 2-substituted cyclobutanones would not be obvious to the skilled person because (i) he would not know that it could be used in the ring expansion of cyclopropane and (ii) that it would still work with the substituents A defined in present claim 11 (aryl, heteroaryl, alkyl, alkenyl, alkynyl or cycloalkyl) in place of the *p*-tolylthio substituent in the process of D3. The skilled person would have to use inventive skill to arrive at the process of present claim 11.

The subject-matter of present claims 11-13 therefore involves an inventive step (Article 33(3) PCT).

3.3 Claim 14

Document D1 is considered to be the prior art closest to the subject-matter of present claim 14 and discloses the preparation of chiral 2-arylcyclobutylamines by hydrogenation of oximes (prepared from the corresponding 2-arylcyclobutanones) using a chiral ruthenium catalyst. The process of present claim 14 differs from this prior art process in that the 2-substituted cyclobutanone derivatives are directly hydrogenated with an ammonium salt in the presence of a chiral transition metal catalyst. No surprising technical effect is apparent which arises from these differences.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative process for the preparation of enantiomerically and diastereomerically enriched 2-substituted cyclobutylamine derivatives. The applicant provides the process of present claim 14 as a solution to this problem, supported by worked examples.

As noted above (paragraph 2.3), D4 discloses a method for converting prochiral

ketones to enantiomerically enriched amines by reaction with an ammonium salt and hydrogen in the presence of a metal catalyst with a bidentate phosphorus ligand. The ketone of D4 may be cyclic and optionally substituted (i.e. R1 and R2 in D4 together form a ring structure) and the ammonium salt may be ammonium acetate (examples 23 and 24) and may be generated *in situ* from ammonia and the acid (claim 14). The skilled person would thus not have to use inventive skill to apply the method of D4 to the problem of preparing enantiomerically and diastereomerically enriched 2-substituted cyclobutylamine derivatives from 2-substituted cyclobutanone derivatives.

The subject-matter of present claim 14 does not therefore involve an inventive step (Article 33(3) PCT).

3.4 Claim 15

Document D1 is considered to be the prior art closest to the subject-matter of present claim 15 and discloses a process for the preparation of *N*-[2-(4-chlorophenyl)-cyclobuten-1-yl]acetamide in three steps starting from 4-chlorobenzaldehyde (see paragraph 2.4, above). The processes of both present claim 15 and D1 involve the conversion of the 2-substituted cyclobutanone into the acetamide product, but the process of present claim 15 differs from the prior art process of D1 in that the intermediate is prepared from the corresponding 1-substituted cyclopropanecarboxaldehydes of formula (II). No technical effect which arises from this difference can be identified.

There is no suggestion in D1 or elsewhere in the available prior art (e.g. D2 and D3: cf. paragraph 3.2, above) that the intermediate 2-substituted cyclobutanones can be prepared from the corresponding 1-substituted cyclopropanecarboxaldehydes. The skilled person would therefore have to use inventive skill to arrive at the process of present claim 15.

The subject-matter of present claim 15 therefore involves an inventive step (Article 33(3) PCT).

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D2-D4 is not mentioned in the description, nor are these documents identified therein.