

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/EP2019/069772	International filing date (day/month/year) 23.07.2019	Priority date (day/month/year) 24.07.2018
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International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/04 C07C45/46 C07C49/233 C07C57/58 C07C51/09 C07C67/00

Applicant
FAES FARMA, S.A.

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 Brandstetter, T 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>1-15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-15</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-15</u>
	No: Claims	

2. Citations and explanations

see separate sheet

1 Reference is made to the following documents:

- D1 WO 2009/102155 A2 (2009-08-20), cited in the application
- D2 CN 104 151 160 A (2014-11-19), cited in the application
- D3 S. J. Collier et al., Synthetic Communications, 41 (9), 2011, 1394-1402, cited in the application
- D4 CN 102 675 101 B (2014-01-29), cited in the application
- D5 WO 2014/188453 A2 (2014-11-27)
- D6 Sheng, Journal of Chemical Research, 2004, 392-393

2 **Re Item V**

The application refers to a process for the preparation of compounds of formula III (claim 1) and to synthesis precursors of formula II' (claim 15) which are used in said process.

3 Novelty (Article 33(2) PCT)

Compounds of formula II' have not been disclosed in the prior art and the subject-matter of claim 15 is therefore new.

D1 (examples 1-8), D2 (claim 1, paragraphs [0014] and [0053]), D3 (scheme 4 on page 1397), D4 (paragraph [0032]) and D5 (example 14, p. 27-28) disclose processes for the preparation of compounds of formula III. They have been described in detail on pages 1-3 of the application.

None of the documents discloses an oxidative rearrangement of compounds of formula II to give compounds of formula III. Novelty can therefore also be acknowledged for claim 1.

4 Inventive step (Article 33(3) PCT)

- 4.1 D1 to D5 represent the closest prior art in view of which the problem to be solved can be seen in the provision of alternative, maybe improved, process for the synthesis of compounds of formula III (which are key intermediates in the synthesis of Bilastine) and the corresponding synthesis precursors of formula II'.
- 4.2 As a solution, the application provides oxidative rearrangement of compounds of formula II.

- 4.3 Neither oxidative rearrangement nor precursors of formula II have been proposed anywhere in D1-D5. Oxidative rearrangement is of course known for the synthesis of 2-arylalkanoates (cf. e.g. scheme 1 of D6) and might have been envisaged by a skilled person in order to come up with an alternative. It is however not considered to be obvious to use exactly this reaction (out of many possibilities) as an alternative to solve the above problem. In addition, the applicant has described some advantages of the claimed process over the processes of the prior art such as avoidance of expensive and instable or toxic reagents (cf. page 1, lines 22-23; page 2, lines 5-6 and 11-15; page 3, 9-12) or avoidance of large amounts of waste (page 3, lines 5-7). Furthermore, the claimed process seems to have a higher productivity ($\text{kg}_{\text{output}}/\text{kg}_{\text{input}}$) than in the processes of the prior art (cf. table on page 20-21). Inventive step can therefore be acknowledged for the process of claim 1.

The compounds of formula II' (claim 15) can be considered to be inventive as they are suitable (tailor-made) starting materials in the inventive process of claim 1.

Claims 2-14 are dependent on claim 1 and their subject-matter is inventive by consequence.

5 Industrial Applicability

Claims 1-15 are considered to be industrially applicable, they fulfil the requirements of Article 33(4) PCT.