

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/US2018/058315	International filing date (day/month/year) 31.10.2018	Priority date (day/month/year) 01.11.2017
International Patent Classification (IPC) or both national classification and IPC INV. C07D413/14 C07D413/04 A61K31/422 A61K31/4245 A61K31/428 A61K31/429 C07D417/12 C07D417/14 C07D471/04 C07D261/08		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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 Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Rufet, Jacques Telephone No. +49 30 25901-0	
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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

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 V

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

1 Reference is made to the following documents:

- D1 EP 3 034 501 A1 (GILEAD SCIENCES INC [US]) 22 June 2016
- D2 WO 2012/087519 A1 (IRM LLC [US]) 28 June 2012 cited in the application
- D3 WO 2017/118294 A1 (GUANGZHOU HENOVCOM BIOSCIENCE CO LTD [CN]) 13 July 2017

2 Novelty

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 15 is considered to be new over the prior art D1 to D3 in the sense of Article 33(2) PCT for the following reasons:

D1 discloses similar bridged bicyclic compounds as farnesoid X receptor modulators.

The structural distinguishing feature of the present compounds of formula (I) should be seen in that present substituent R17 if present cannot be a hydroxyl group (-OH).

D2 and D3 refer also to bridged bicyclic compounds as farnesoid X receptor modulators. The structural distinguishing feature should be seen in that the compounds of D2 and D3 have a nitrogen atom instead of a carbon atom as attachment atom of cycle B to L1 or Z.

It is stressed that compounds with an hetero-atom (e.g. nitrogen atom) as attachment atom of cycle B to L1 or Z are excluded in present claim 1; see definition of ring B.

3 Inventive step

3.1 The present application addresses the problem of providing farnesoid X receptor modulators useful for treating diseases for which an FXR modulator is indicated, like pathological fibrosis, cancer, inflammatory disorders, metabolic or cholestatic disorders.

3.1 D1 is considered to represent the closest prior art, since it discloses structurally similar compounds having also a bridged bicyclic moiety as farnesoid X receptor modulators.

The structural distinguishing feature of the present compounds according to formula (I) should be seen in the nature of substituent R17, which when present, cannot be an hydroxyl group (-OH).

3.2 There is no comparative data in the present application showing that this distinguishing feature as mentioned above is responsible for an unexpected effect, thus the objective technical problem solved by the subject-matter of claim 1 should be seen in the provision of further bridged bicyclic farnesoid X receptor modulators.

In view of the examples and the biological data (EC50) given in for these examples in table 1 it is credible that the distinguishing feature solves the above-mentioned problem.

3.3 There is no technical link in D2 nor in D3 which would have incited the skilled worker to remove the mandatory hydroxyl group of the compounds of D1 (see D1, formula (I), if he was looking for alternative farnesoid X receptor modulators. Thus claims 1 to 15 meet the requirements of Art. 33(3) PCT.

3.4 However, the breadth of the claims should be such that it could be expected that all the compounds comprised by the subject-matter of these claims would actually solve the problem underlying the invention.

It is realized that the Applicant is entitled to claim all obvious modifications of what he has described and that alternative variations have to be supported by a certain number of examples. However, it is noted that the definition of ring B, especially the term "cycloheteroalkyl" as well as the definition of the linker atoms E1, E2 and E3 with their substituents, and combinations thereof, are considered to be speculative in the sense of Article 33(3) PCT, embracing a great variety of several thousands of structural possibilities not yet explored by the Applicant, the effect of which cannot be foreseen having regard to the problem to be solved.

It is stressed that all exemplified compounds with a cycloheteroalkyl group for ring B show always only one oxygen atom.

Furthermore it belongs to the common general knowledge of the skilled worker in the field of chemistry that small changes in the molecule can lead to large change in its properties.

Consequently, in the absence of further evidence, and in view of the examples, the subject-matter of claims 1 to 4, 7 and 10 to 15 does not represent a fair and reasonable scope of protection.

Re Item VIII

Certain observations on the international application

According to Rule 6.2(a) PCT, claims having a reference to the description are not allowed, claim 9 is therefore not acceptable.