

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/US2018/058326	International filing date (day/month/year) 31.10.2018	Priority date (day/month/year) 01.11.2017
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International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/14 A61K31/42 A61K31/428 A61K31/429 C07D413/08 C07D417/14 C07D471/04 C07D261/08 C07D487/04

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 43*bis*.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

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

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 compounds having also a spirobicyclic moiety. The structural distinguishing feature of the claimed compounds should be seen in the absence of the linking group -CH₂-O- between the 5-membered heteroaryl ring and the spirobicyclic moiety.

D2 and D3 refer to farnesoid X receptor modulators which do not have a spirobicyclic moiety as presently claimed.

3 Inventive step

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.

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

The structural distinguishing feature of the present compounds according to formula (I) should be seen in the absence of the linking group -CH₂-O- between the 5-membered heteroaryl ring and the spirobicyclic moiety.

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 farnesoid X receptor modulators.

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

Furthermore taking into account the structural diversity of the 224 examples, the scope of protection conferred by formula (I) of claim 1 is considered to be fair.

There is no technical link in D2 nor in D3 which would have incited the skilled worker to remove the linking group -CH₂-O- from the compounds of D1, if he was looking for alternative farnesoid X receptor modulators.

Thus claims 1 to 15 meet the requirements of Art. 33(3) PCT.