

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 127553-01420	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2019/021076	International filing date (<i>day/month/year</i>) 7 March 2019 (07-03-2019)	(Earliest) Priority Date (<i>day/month/year</i>) 7 March 2018 (07-03-2018)
Applicant IRONWOOD PHARMACEUTICALS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out 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))

b. ☐

This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐

With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐

Certain claims were found unsearchable (See Box No. II)

3. ☐

Unity of invention is lacking (see Box No III)

4. With regard to the **title**,

☒

the text is approved as submitted by the applicant

☐

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒

the text is approved as submitted by the applicant

☐

the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐

as suggested by the applicant

☐

as selected by this Authority, because the applicant failed to suggest a figure

☐

as selected by this Authority, because this figure better characterizes the invention

b. ☐

none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/021076

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YULING WU ET AL: "Synthesis and photoelectric properties of asolution-processable yellow-emitting iridium(III)complex", NEW JOURNAL OF CHEMISTRY, vol. 39, no. 11, 1 January 2015 (2015-01-01), pages 8908-8914, XP55583200, GB ISSN: 1144-0546, DOI: 10.1039/C5NJ01514F scheme 1, compound 4	1
A,P	----- WO 2018/045276 A1 (IRONWOOD PHARMACEUTICALS INC [US]) 8 March 2018 (2018-03-08) page 97, general procedure A ----- -/-	1-57



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 April 2019

Date of mailing of the international search report

08/05/2019

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Gutke, Hans-Jürgen

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/021076

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/044446 A2 (IRONWOOD PHARMACEUTICALS INC [US]; RENNIE GLEN ROBERT [US] ET AL.) 24 March 2016 (2016-03-24)	2-35, 44-57
A	page 247 claim 1 -----	36-43

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/021076

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018045276 A1	08-03-2018	AU 2017321810 A1 CA 3035210 A1 SG 11201901729Y A TW 201811798 A US 2018065971 A1 WO 2018045276 A1	07-03-2019 08-03-2018 28-03-2019 01-04-2018 08-03-2018 08-03-2018
WO 2016044446 A2	24-03-2016	AU 2015317823 A1 CA 2961489 A1 CN 107406421 A EP 3194386 A2 JP 2017527604 A US 2018155345 A1 WO 2016044446 A2	23-03-2017 24-03-2016 28-11-2017 26-07-2017 21-09-2017 07-06-2018 24-03-2016

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.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/US2019/021076

International filing date (day/month/year)
07.03.2019

Priority date (day/month/year)
07.03.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04

Applicant
IRONWOOD PHARMACEUTICALS, INC.

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 43*bis*.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 66.1*bis*(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
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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Gutke, Hans-Jürgen

Telephone No. +49 89 2399-0



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>2-58</u>
	No: Claims	<u>1</u>
Inventive step (IS)	Yes: Claims	<u>36-43, 58</u>
	No: Claims	<u>1-35, 44-57</u>
Industrial applicability (IA)	Yes: Claims	<u>1-58</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.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

Item V

1 Reference is made to the following documents:

- D1 YULING WU ET AL: "Synthesis and photoelectric properties of asolution-processable yellow-emitting iridium(III)complex", NEW JOURNAL OF CHEMISTRY, vol. 39, no. 11, 1 January 2015 (2015-01-01), pages 8908-8914, XP55583200, GB
ISSN: 1144-0546, DOI: 10.1039/C5NJ01514F
- D2 WO 2018/045276 A1 (IRONWOOD PHARMACEUTICALS INC [US]) 8 March 2018 (2018-03-08)
- D3 WO 2016/044446 A2 (IRONWOOD PHARMACEUTICALS INC [US]; RENNIE GLEN ROBERT [US] ET AL.) 24 March 2016 (2016-03-24)

2 **Novelty**

- 2.1 D1 discloses the formation of a triazole from an amidrazone and a carboxylic acid chloride. Present claim 1 lacks novelty over D1.
- 2.2 D2 does not constitute prior art under Rule 33.1(a) and (b), but falls under the provisions of Rule 33.1(c) PCT. Cf. item VI.
- 2.3 D3 does not disclose the formation of triazoles from amidrazones but instead discloses processes which start from triazoles in order to build up the bicyclic ring (cf. D3, page 247). D3 can therefore not be relevant for novelty of claims 2-57.

3 **Inventive Step**

- 3.1 D3 is regarded as closest prior art since D3 discloses compounds which overlap with the final compounds of the present processes. The objective problem is seen in the provision of an alternative process to prepare compounds generically described by D3 which are stimulators of the soluble guanylate cyclase.
- 3.2 The present process relies on using an amidrazone derivative for constructing the triazole at the bicyclic ring. D3 instead rather starts from triazoles in order to build up the bicyclic ring. Moreover, the amidrazone derivative in the present processes and intermediates are protected at the nitrogen. It is noted that at least this last feature is not suggested by D3 and also not generally the prior art, for instance D1. However, it is considered that the scope of this distinguishing feature is completely unclear since the definition is purely functional (cf. also item VIII). It is also noted that there is no evidence that the whole scope of the claimed processes and intermediates leads to compounds which are active as stimulators of the soluble guanylate cyclase. The problem can therefore only be seen in the provision of any processes or any compounds/intermediates. The solution of a such problem is regarded to be obvious over any prior art disclosing compounds and processes to prepare them.
- 3.3 At present the requirements of inventive step are fulfilled only for claims 36-43.

Item VI

- 4 D2 does not constitute prior art under Rule 33.1(a) and (b), but falls under the provisions of Rule 33.1(c) PCT. Following considerations would apply: D2 cannot be relevant for novelty of claims 2-57, since the intermediates employed are protected whereas the amidrazone intermediates in the processes of D2 are unprotected. For inventive step, in case that the present priority would be found to be not valid, D2 would also not become relevant.

Item VIII

- 5 The expression "protective group" is regarded as unclear in the meaning of Art. 6 PCT and leaves the scope of the claims unclear. Moreover, the description demonstrates only for G1 = boc the feasibility of the reaction and support in the meaning of Art. 6 PCT is found only for a small appt of the claimed protective groups. In this context it is noted that claim 56 is also completely unclear. In especially it is not clear if the features listed therein refer to the substrate to be protected, or describe the chemical structure of the protective group.