

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 127553-05220	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2019/021080	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/US2019/021080

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/4985 A61P25/00
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 A61P

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.
A	WO 2016/087342 A1 (BAYER PHARMA AG [DE]) 9 June 2016 (2016-06-09) example 19	1-43
A	----- LEE R ROBERTS ET AL: "Acidic triazoles as soluble guanylate cyclase stimulators", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 21, no. 21, 13 August 2011 (2011-08-13), pages 6515-6518, XP028308807, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.08.071 [retrieved on 2011-08-28] table 1 ----- -/-	1-43



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

10 April 2019

Date of mailing of the international search report

23/04/2019

Name and mailing address of the ISA/

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Lauro, Paola

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/021080

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2018/045276 A1 (IRONWOOD PHARMACEUTICALS INC [US]) 8 March 2018 (2018-03-08) examples I-1 -----	1-43

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/021080

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016087342 A1	09-06-2016	CA 2969265 A1	09-06-2016
		CN 107257796 A	17-10-2017
		EP 3227286 A1	11-10-2017
		JP 2017537922 A	21-12-2017
		US 2017313700 A1	02-11-2017
		WO 2016087342 A1	09-06-2016

WO 2018045276 A1	08-03-2018	AU 2017321810 A1	07-03-2019
		CA 3035210 A1	08-03-2018
		SG 11201901729Y A	28-03-2019
		TW 201811798 A	01-04-2018
		US 2018065971 A1	08-03-2018
		WO 2018045276 A1	08-03-2018

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/US2019/021080	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 A61K31/4985 A61P25/00		
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 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Lauro, Paola 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 43*bis*.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 13*ter*.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 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>1-43</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-43</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-43</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

1 **Re Item V**

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

1.1 Reference is made to the following documents:

D1 WO 2016/087342 A1 (BAYER PHARMA AG [DE]) 9 June 2016 (2016-06-09)

D2 LEE R ROBERTS ET AL: "Acidic triazoles as soluble guanylate cyclase stimulators",
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,
PERGAMON, AMSTERDAM, NL,
vol. 21, no. 21, 13 August 2011 (2011-08-13), pages 6515-6518,
XP028308807,
ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.08.071
[retrieved on 2011-08-28]

D3 WO 2018/045276 A1 (IRONWOOD PHARMACEUTICALS INC [US]) 8 March 2018 (2018-03-08)

1.2 Claim 43 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

1.3 **Novelty**

D1 discloses a compound with a imidazo-pyrazine nucleus (see example 19) which differs from the claimed 8-(2-fluorobenzyl)-6-(3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl)imidazo[1,2-a]pyrazine (hereinafter referred to as Compound A) in the type and position of the substituents. D2 discloses compounds characterized by a different core bicyclic ring. Novelty is thus acknowledged (Art. 33 (2) PCT).

1.4 **Inventive step**

D1 discloses imidazopyrazine derivatives as stimulators of the soluble guanylate cyclase (sGC).

The problem underlying the present application resides in the provision of further imidazopyrazine derivatives as sGCstimulators. The solution is

provided by compound A in two different crystalline forms, or in three different hydrate forms: however, it is noted that no activity data for the claimed forms have been given in the description. The structurally closest compound is disclosed in Example 19 of D1. The main structural differences re compound A is reside in the presence of an oxygen atom as linkage between the benzyl substituent and the bicyclic core and the presence of a pyrazole (instead of a triazole) attached to the fused imidazole ring (instead of the pyrazine ring). In view of the number and type of structural differences re the closest prior art, the provision of the current compound A in all different crystalline/hydrate forms for the claimed use would be considered to involve an inventive step in case data were to be provided to demonstrate that all of the claimed forms possess the alleged activity and are thus to be considered to represent an inventive solution to the underlying problem.

2 Re Item VI

Certain documents cited

D3 was published after the priority date of the current application and it is therefore not taken into account for the purpose of the present opinion.

3 Re Item VIII

Certain observations on the international application

The crystal forms as well as the hydrates claimed in claims 1 to 41 are only arbitrarily defined by means of the label A or B and 1, 2, 3, respectively.. However, no standard nomenclature for polymorphic crystal forms or hydrate forms exists. It is therefore unclear which product is covered by the said definitions (Art. 6 PCT). The crystal or hydrate forms should be defined by reproducible physicochemical parameters.