

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/US2021/012333

International filing date (day/month/year)
06.01.2021

Priority date (day/month/year)
07.01.2020

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

INV. C07D401/04 C07D401/14 C07D405/04 C07D409/14 C07D413/14 C07D417/04 C07D471/04 C07D491/04
A61P25/00 A61K31/4439

Applicant
DISARM THERAPEUTICS, 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 21, 22, 24-26(completely); 1-20, 23, 27-32(partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 21, 22, 24-26(completely); 1-20, 23, 27-32(partially)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).
- ☒ See Supplemental Box for further details

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>31, 32(partially)</u>
	No: Claims	<u>1-20, 23, 27-30(all partially)</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-20, 23, 27-32(all partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>1-20, 23, 27-32(all partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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 III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The current claims do not comply with Article 6 PCT to such an extent (cf. item V.2.1 below) that the search was focused to subject-matter relating to a combination of the features of the current claims 1, 8, 13, and 28. Including the initial phase of the search, this corresponds with a partial search for the current claims 1-20, 23, and 27-32 and no search for the current claims 21-22 and 24-26.

For such partially searched and unsearched claims, respectively, it is not possible to determine whether, and if so to what extent, the matter to which said claims relate is novel and might involve an inventive step. No International preliminary examination will thus be carried out with regard to novelty and inventive step for subject-matter which is not covered by the search report (cf. Rule 66.1(e) PCT).

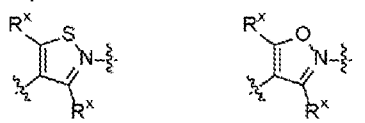
Re Item V

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

- 1 Claims 30-31 relate to a 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 a first or further medical treatment.
- 2 The application does not comply with Articles 5 and 6 PCT for the following reasons.
 - 2.1 The present claims 1-32 relates to an extremely large number of possible compounds (I). They contain a plethora of options, variables, open-ended values possible permutations, an nearly no fixed structural element. Moreover, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty of claim 1 and dependent claims thereof (for an incomplete

selection cf. D1-D9). Even a limited search on a combination of the features of the current claims 1, 8, 13, and 28 resulted in a large number documents relevant to the issue of novelty (for an incomplete selection cf. D10-D15). So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

- 2.2 Claim 4 lacks clarity (Article 6 PCT) and disclosure (Article 5 PCT) due to the impossible valence of the ring N-atom in the following entries



- 3 Reference is made to the following documents.

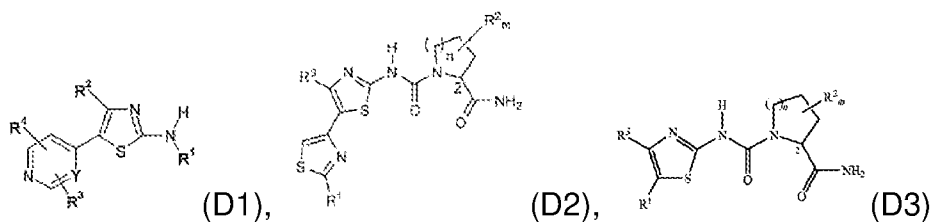
- D1 WO 2004/096797 A1, 11 November 2004; & DATABASE Reaxys, Database accession no. WO2004/96797, XP055778791 (D1a).
- D2 WO 2009/080705 A2, 2 July 2009.
- D3 US 2009/163469 A1, 25 June 2009; & DATABASE Reaxys, Database accession no. US2009/163469, XP055778810 (D3a).
- D4 US 2004/157861 A1, 12 August 2004; & DATABASE Reaxys, Database accession no. US2004/157861, XP055778823 (D4a).
- D5 WO 2010/093849 A2, 19 August 2010.
- D6 WO 02/088113 A1, 7 November 2002.
- D7 WO 2008/034600 A1, 27 March 2008.
- D8 US 2004/122016 A1, 24 June 2004; & DATABASE Reaxys, Database accession no. US2004/122016, XP055778905 (D8a).
- D9 US 2005/272779 A1, 8 December 2005; & DATABASE Reaxys, Database accession no. US2005/272779, XP055778978 (D9a).
- D10 WO 2018/107056 A1, 14 June 2018.

- D11 GREEN ET AL. J. MED. CHEM. 2015, 58, 5028-5037, XP055613567.
- D12 EP 2 036 905 A1, 18 March 2009.
- D13 US 2006/019956 A1, 26 January 2006; & DATABASE Reaxys, Database accession no. US2006/19956, XP055779340 (D13a).
- D14 DATABASE CAPLUS Database accession no. 2015:2051338, XP055779402; & RU 2 570 907 C2, 20 December 2015.
- D15 WO 2006/065946 A1, 22 June 2006.
- D16 WO 2019/236890 A1, 12 December 2019.

4 Novelty

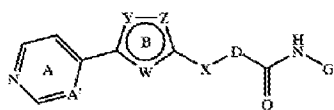
The claims 1-20, 23, and 27-30 lack novelty as explained in this section.

D1-D3 discloses phosphatidylinositol 3-kinase inhibitors and corresponding medicaments (D1: claims 1, 11; D2: claims 1, 7, 8; D3: claims 1, 6, 15). The compounds of these documents have the following structures



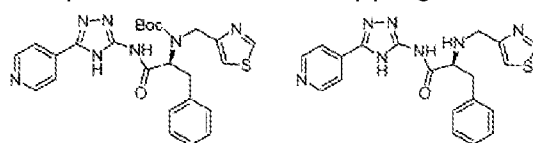
and overlap with the present compounds (I). Furthermore, D1-D3 discloses specific examples in the overlapping area (cf. D1: claims 7-8, and D1a: XRN numbers; D2: examples; D3: examples, and D3a: XRN numbers). Hence, the claims 1-2, 7-12, 14, 18-20, 23, 27, and 29 lack novelty for the overlapping area with D1. The claims 1-2, 9, 11-12, 14, and 29 lack novelty for the overlapping area with D2. The claims 1, 2, 9, 11, 12, 14, 18, 19, and 29 lack novelty for the overlapping area with D3.

D4 relates to inhibitors of TGF-beta and corresponding medicaments (cf. claims 1, 17, 21). The compounds of D4 have the structure



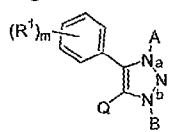
and overlap with the present compounds (I). In addition, D4 discloses specific examples in the overlapping area (cf. D4: tables 1-2, and D4a: XRN numbers). The present claims 1, 2, 6-8, 10-12, 14, 17, 27, and 29 lack thus novelty for the overlapping area with D4.

D5 relates to phenylalanine derivatives against insulin-related diseases and corresponding medicaments (cf. claims 1, 13-15, 19). The compounds of D5 overlap with the present compounds (I) and D5 shows on page 36 the following compounds in the overlapping area



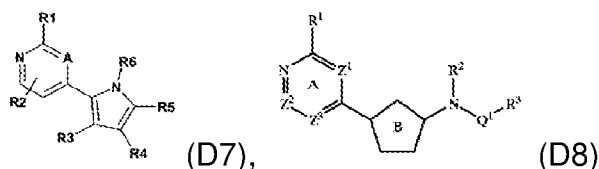
. The claims 1, 2, 6-8, 10, 11, 14, 17, and 27-29 lack thus novelty for the overlapping area with D5.

D6 concerns inhibitors of the release of inflammatory cytokines and corresponding medicaments (claims 1, 8, 9). The compounds of D6 have the structure



and overlap with the present compounds (I). In addition, D6 discloses specific embodiments in the overlapping area (without being limitative cf. e.g. pages 32-33: examples 42-50, pages 36-37: examples 54-64, page 40: examples 66-70). The claims 1-3, 9, 14, 17, 27-29 lack thus novelty for the overlapping area with D6.

D7-D8 relates to kinase inhibitors and corresponding medicaments (D7: claims 1, 5, 10; D8: claims 1, 45, 46). The compounds of have the following structures

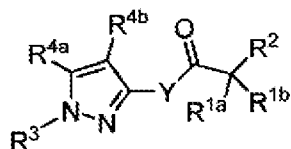


and overlap with the present compounds (I). In addition, D7-D8 disclose specific embodiments in the overlapping area (D7: e.g. pages 35-36: examples 5-7, page 98: example 98, pages 125-126: examples 138-140; D8: claim 45, and D8a: XRN numbers). The claims 1, 2, 4, 5, 10, 14, 16, 29 lack thus novelty for the overlapping area with D7. Furthermore, the claims 1, 2, 7-14, 17, and 27-29

lack novelty for the overlapping area with D8.

D9 discloses mGluR antagonists of current formula (I), corresponding medicaments, and their use e.g. in the treatment of Alzheimer's disease (D9: claim 1: e.g. compounds 969, 971, 975, 978-981, 984, 987, 988; claims 2, 10; and D9a: XRN numbers). The claims 1, 3, 7-9, 15, 18, 19, 29, and 30 lack thus novelty over D9.

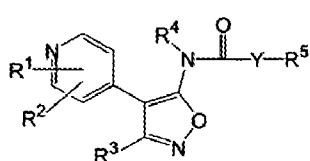
D10 shows pyrazole derivatives for the reduction of long chain fatty acid levels and corresponding medicaments (cf. claims 1, 25). The compounds have the following structure



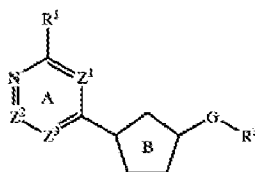
and overlap with the present compounds (I). In addition, D10 discloses specific embodiments in the overlapping area (cf. pages 176-338: examples). The claims 1, 2, 7-14, 17-20, and 27-29 lack thus novelty for the overlapping area with D10.

D11 discloses kinase inhibitors of the present formula (I), thereby resulting in a lack of novelty of the claims 1, 2, 6-9, 11-14, 17, 27, and 28 (cf. D11: compounds 4-18 and 20-41).

D12-D13 concern kinase inhibitors, corresponding medicaments and their use e.g. in the treatment of Alzheimer's disease (D12: claims 1, 13, 15; D13: claims 1, 19, 20, 26). The compounds have the following structures



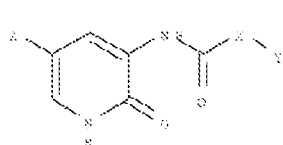
(D12),



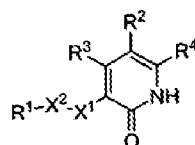
(D13).

They overlap with the present compounds (I), and the documents disclose specific embodiments in the overlapping area (cf. D12: page 6, paragraph 33, lines 49-52; D13: claim 19, and D13a: XRN numbers). The claims 1-2, 7-9, 11-14, 17, and 27-30 lack thus novelty for the overlapping area with D12. Furthermore, the claims 1, 2, 6-9, 11-14, 17, 27-30 lack novelty for the overlapping area with D13.

D14-D15 disclose further kinase inhibitors and medicaments (D14, whole document; D15: claims 1, 47, 49). The compounds have the structures



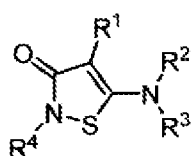
(D14),



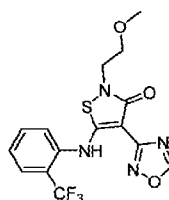
(D15)

and overlap with the present compounds (I). In addition, D14-d15 disclose specific embodiments in the overlapping area (cf. D14: RN 893434-37-2; D15: claim 47). The claims 1, 2, 6-9, 11-14, 17, 27-29 lack thus novelty for the overlapping area with D14 and D15.

D16 relates to inhibitors of SARM1. The compounds of D16 have the structure



, wherein R3 = $-(CH_2)_0-2Cy$ and R1 = e.g. 5-membered heteroaryl (cf. D16, claim 1). The compounds of D16 overlap with the present compounds (I), but the document does not disclose specific embodiments in the overlapping area wherein according to the prior art document R3 = $-(CH_2)_1-2Cy$ and R1 = 5-membered heteroaryl. The present claims may thus be considered as a novel selection of D16 with the combination of the present values L and R1 as novel technical feature. The most similar example of D16 has the structure



(cf. page 129, example 152).

5 Inventive step and unity

5.1 As the claims 1-20, 23, and 27-30 lack novelty, they also lack inventive step.

5.2 In as far as the claims may relate to novel subject-matter the following observations would apply to the requirement of inventive step and unity.

5.2.1 Certain subject-matter of claim 1 and dependent claims thereof is a novel selection of D16. Merely as a solution of the problem of selecting SARM1 inhibitors from D16, the selected compounds are obvious to the skilled artisan, because the activity and utility of these compounds is already taught in D16. In the ab-

sence of any common novel feature of the compounds (I) which is shown to contribute to any substantiated unexpected effect over the most similar example 152 of D16, no inventive step would be acknowledged for the novel subject-matter of the current claims.

- 5.2.2 Furthermore, the present tested examples with an activity designated as "D" do not appear to exhibit the desired SARM1 inhibiting activity. No inventive step will be acknowledged for these examples and generic claims comprising such inactive compounds.
- 5.2.3 Furthermore, for the requirement of unity to be met the subject-matter should be characterized by a common distinguishing feature over D16. Such a common distinguishing feature is at present however not evident. Consequently, the claims lack of unity in the sense of Rule 13 PCT.

Re Item VII

Certain defects in the international application

D1-D16 are not cited in the description (Rule 5.1(a)(ii) PCT). Furthermore, the significance of statements referring to "incorporated by reference" is not evident.

Re Item VIII

Certain observations on the international application

See item V.2 above.