

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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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/US2022/019759	International filing date (day/month/year) 10.03.2022	Priority date (day/month/year) 10.03.2021
International Patent Classification (IPC) or both national classification and IPC INV. A61P11/00 A61P13/12 A61P35/00 C07D471/04 C07D491/18 C07D495/04		
Applicant DICE MOLECULES SV, 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 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 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 Schuemacher, Anne 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 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>32-38, 64-80</u>
	No: Claims	<u>1-31, 39-63, 81-86</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-86</u>
Industrial applicability (IA)	Yes: Claims	<u>1-86</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. Claims 82-86 relate 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 recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a known compound for first or further medical treatment.

2. Reference is made to the following documents:

- | | |
|----|---|
| D1 | WO 2018/089355 A1 (SQUIBB BRISTOL MYERS CO [US]) 17 May 2018 |
| D2 | WO 00/09503 A1 (MERCK & CO INC [US]; HUTCHINSON JOHN H [US])
24 February 2000 (2000-02-24) |
| D3 | WO 2005/082889 A1 (JANSSEN PHARMACEUTICA NV [BE]; DE CORTE
BART [US] ET AL.) 9 September 2005 (2005-09-09) |
| D4 | WO 2018/160522 A1 (LAZULI INC [US]) 7 September 2018 (2018-09-07) |

3. The present application is directed to piperidine-propanoic acid derivatives of formulae (I) and (Ia) according to current claims 1 and 41 as alpha V beta 6 and alpha V beta 1 integrin inhibitors.

The compounds of claims 1 and 41 differ from those of D4 because of their linker between the piperidine ring and the carboxylic acid moiety (-X-Y-CR6(A)-CR7(B)-). The compounds of claims 1 and 41 differ from those of D2 because the compounds of D2 have always a carbonyl substituent on their central pyrrolidine ring.

The scope of claims 1 overlaps with that of formula (I) of D3 and the scope of claim 41 overlaps with formula (II) of claim 1 of D3. Furthermore, D3 discloses example 8 which falls in the overlapping area with claim 41. The compounds of D3 are also disclosed as integrin inhibitors so that there is no apparent new structural element which distinguishes the subject matter claimed from the prior art in the sense of a novel selection. An objection of lack of novelty under Article 33(2) PCT consequently arises for the subject-matter of claims 1,2,5,7-12,15-25,39-40,41-63.

The same objection is raised in the view of D1: The scope of claims 1 overlaps with that of formula (I) of D1. D1 discloses examples 14 and 40 which fall in the overlapping area. The compounds of D1 are also disclosed as integrin inhibitors so that there is no apparent new structural element which distinguishes the subject matter claimed from the prior art in the sense of a novel selection. An objection of lack of novelty under Article 33(2) PCT consequently arises for the compounds of claims 1-31.

The compounds of claim 41 are novel over D1 because q=1-3, whereas all the compounds of D1 have an azetidine ring.

4. The present opinion on inventive step is only to be considered once novelty over D1 and D3 is restored:

D3 is considered to represent the closest prior art document.

Since the formula (I) of the compounds of claim 1 and formula (Ia) of the compounds of claim 41 overlap with formulae (I) and (II) of claim 1 of D3, it is not surprising that the presently claimed compounds exhibit the same activity as the compounds of D3, i.e. the affinity for integrins. Thus, an inventive step under Art.33(3) PCT cannot be based on the modulator activity of an alpha V integrin of the claimed compounds. An inventive step can only be recognized once it is shown that the claimed compounds of formula (I) and (Ia) present unexpected effects or properties in relation to already known alpha V integrin modulators. Since no such effects or properties are indicated and supported in the application, the subject-matter of claims 1-86 does not involve an inventive step within the meaning of Article 33(3) PCT.

In addition, it should be credibly shown that such surprising technical effect occurs over the whole claimed range. The extent of a reasonable generalisation depends on the credibility that substantially all the alternatives claimed must be a solution to the technical problem. Extremely broad generalisations like e.g. the definition of -E-D- or X-Y- whereas an activity has not been shown for D being phenyl, cyclohexyl, cyclopentyl or X-Y being any other claimed groups in claims 1 and 41 except -CONR46 or -NR47CO- are in contradiction to the basis of qualitative structure-activity-relationships. The same objection applies to the definition of the central nitrogen containing heterocycle which is in all the tested examples of the description a piperidine ring. Taking into account the relevant state of the art and the common knowledge, it appears to be not predictable, that all claimed alternatives would achieve the technical effect. In the absence of evidence demonstrating an unexpected technical effect of a representative set of claimed compounds over the prior art compounds, Article 33(3) PCT taken in conjunction with Articles 5 and 6 PCT cannot be considered to be satisfied. If necessary, the claims have to be restricted to the scope of claims defining such

compounds which illustrate respectable patentable effects. In this respect, it appears that formula (VII) in claim 32, formula (VIII) in claim 35 and formula (IX) in claim 39 represent a reasonable generalisation of the examples of the present description.

Re Item VIII

Certain observations on the international application

The vague and imprecise statement in the description on [0336] implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them. Furthermore, in this paragraph prior art documents were acknowledged by the expression "incorporated herein by reference". This is vague and ambiguous which technical features are referred to. Furthermore, it should be noted that this kind of reference contravenes the basic requirement of each application that the invention must be comprehensible from the specification by itself.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 and D3 is not mentioned in the description, nor is this document identified therein.