

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/EP2020/062040

International filing date (day/month/year)
30.04.2020

Priority date (day/month/year)
07.05.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07K7/08

Applicant
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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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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	
	No: Claims	<u>1-15</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-15</u>
Industrial applicability (IA)	Yes: Claims	<u>1-15</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

ITEM V

- 1 The present application claims cyclised oligopeptides as characterised in claims 1-7, as well as any derivative, prodrug and analogue thereof. Process for preparing them, pharmaceutical compositions comprising them and their medical uses are claimed as well.
- 1.1 Reference is made to the following documents:
 - D1 WO 2010/136831 A1 (EOTVOS LORAND TUDOMANYEGYETEM [HU] ET AL.) 2 December 2010;
 - D2 ANDREA KOCSIS ET AL: "Selective Inhibition of the Lectin Pathway of Complement with Phage Display Selected Peptides against Mannose-Binding Lectin-Associated Serine Protease (MASP)-1 and -2: Significant Contribution of MASP-1 to Lectin Pathway Activation", THE JOURNAL OF IMMUNOLOGY, vol. 185, 2010, pages 4169-4178;
 - D3 D. Heja ET AL: "Monospecific Inhibitors Show That Both Mannan-binding Lectin-associated Serine Protease-1 (MASP-1) and -2 Are Essential for Lectin Pathway Activation and Reveal Structural Plasticity of MASP-2", Journal of Biological Chemistry, vol. 287, no. 24, 8 June 2012, pages 20290-20300;
 - D4 Tunjung Mahatmanto: "Review seed biopharmaceutical cyclic peptides: From discovery to applications : Seed Biopharmaceutical Cyclic Peptides", Biopolymers, vol. 104, no. 6, 19 September 2015, pages 804-814;
 - D5 WO 2013/192240 A2 (OMEROS CORP [US]; UNIV LEICESTER [GB]) 27 December 2013.
- 1.2 D1 to D5 are cited to exemplify the available prior art for the claimed subject-matter, said documents teaching SFMI-1 (*i.e.*: GICSRSLPPICIPD, where the two Cys side chains form a disulfide bond) and various analogues thereof as MAPS inhibitors for the same uses. Such peptides were obtained after phage display from the sunflower trypsin inhibitor SFTI-1, a well-known inhibitor of a range of serine proteases (see D4).
- 1.3 Since the present formulation of the claims encompasses each imaginable "derivative, prodrug and analogue" of the peptides of Formula (II), any peptide, such as those of D1-D5, effectively anticipates the present set of claims. As a consequence, claims 1-15 are not novel.

- 2 Concerning inventive step, the problem to be solved by the present application can *prima facie* be defined in the light of any of D1 to D3 - which may be regarded as the closest prior art - as the provision of further cyclised peptide MASP inhibitors. The proposed solution is the provision of the actual compounds represented by the Markush Formula (II), the only difference being a conservative substitution of Cys at position X¹¹. Also Pro at X⁹ might be replaced by its known analogue Oic. A number of additional substitutions are also allowed at X³, X⁵, X⁷ and X¹⁴, the N- and C-terminal ends being optionally substituted.
- 2.1 Since the mere provision of new compounds not showing an advantageous property compared with those known in the art cannot be regarded as involving an inventive step, the applicant explained in the description that the claimed compounds have an "improved inhibitory effect on human and/or rat MASP-1 and or MASP-2 enzymes" (see page 3) over that of known peptides. Therefore, the objective technical problem shall be defined as the provision of improved MASP inhibitor peptides, the suggested solution being the peptides of claim 1.
- 2.2 It has been clearly shown by the very extensive experimental data provided in the application as originally filed (see Tables 18-19) that - as it is usually the case with oligopeptide compounds - even very minor modifications may have a profound impact on the half maximal inhibitory concentration of the resulting analogues. Merely as a few examples, the two Hyp and Oic SFMI-1 analogues at position X⁹ (*i.e.*: compound Nr. 410 and 323) unexpectedly have a very different inhibitory activity (see page 162). Similarly, only specific N-terminal modifications appear not to be detrimental to the activity, for instance ODD surprisingly increasing IC₅₀ towards both MASP enzymes (see Nr 434 and 512). As a result, it is agreed that while the prior art may provide general guidance as to certain modifications to make in order to improve activity, the effect of any particular change in this particular cyclic peptide SFMI-1 is not always obvious to predict *a priori*.
- 2.3 Therefore, it is acknowledged that the available prior art does not disclose nor renders obvious the provision of specific MASP inhibitory peptides, provided that such peptides have been actually shown to have an enhanced inhibitory activity compared to SFMI-1 and its known analogues.

- 2.4 The applicant has successfully demonstrated that a large number of compounds falling in the scope of the claims have indeed a better inhibitory activity in at least one of the assays carried out. The disulfide-cyclised peptides corresponding to Compounds Nr 4-100 are examples of such inventive compounds, showing an improved activity in all assays (see Table 19). As a consequence, an inventive step may be acknowledged for particular peptides consisting of the sequences identified above, or to a reasonable generalisation thereof.
- 2.5 On the other hand, when a technical effect solving a technical problem is the sole ground for an alleged inventive step, this effect must be achieved by substantially all embodiments falling within the scope of a claim. As this is not the case for a number of compounds falling in the scope of the claims, an inventive step cannot be acknowledged.
- 2.6 The above argument also applies to any claimed peptide for which no biological effect has been shown in the application as filed. This subject-matter cannot be regarded to solve the technical problem underlying the present invention, since it cannot be reasonably expected that substantially all cyclised peptides comprising the motif of formula (I) will invariably possess the desired improved activity, no matter their sequence length and how they are cyclised at positions X^3 and X^{11} (only disulfide bonds were shown in the application as originally filed), independently from the presence of exocyclic residues X^1 - X^2 and X^{13} - X^{14} and also from the actual structure of their N-terminal modifications. In the absence of such an experimental evidence, the subject-matter of claims 1-7 must be considered an arbitrary selection of compounds, which does not involve an inventive step.
- 2.7 As the recognition of an inventive step for dependent claims further characterising the claimed compounds by functional features or being related to methods and uses in therapy or their methods of preparation, are entirely dependent on that for the compound claims, the subject-matter of claims 8-15 lacks an inventive step as well.
- 2.8 In view of all the above, the present application does not satisfy the criteria set forth in Article 33(2) and 33(3) PCT because the subject matter of claims 1-15 is not new in respect of prior art as defined in the regulations (Rule 64 PCT) and does not involve an inventive step (Rule 65 PCT).

- 3 The EPO does not recognise as patentable claims to a medical or a diagnostic method practised on the human/animal body but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. Therefore, patentability - in particular novelty and inventive step - of claim 15 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the substance or composition.
- 4 **ITEM VIII**
- 5 The scope of claim 3 appears to be identical to the one of claim 2.