

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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/US2024/013911

International filing date (day/month/year)
01.02.2024

Priority date (day/month/year)
03.02.2023

International Patent Classification (IPC) or both national classification and IPC
INV. C07K7/08 C07K7/54 A61P19/02 A61P37/00

Applicant
MERCK SHARP & DOHME LLC

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
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Cervigni, S

Telephone No. -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 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.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>1-22</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>12, 13</u>
	No: Claims	<u>1-11, 14-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</u>
	No: Claims	

2. Citations and explanations

see separate sheet

- 1 Amended claims and description filed on 15.05.2024 are regarded to meet the requirements of Article 34(2)(b) PCT since they appear to consist of a mere recasting of the original text to overcome objections raised by the receiving Office under Rules 11 and 26 PCT.

SECTION V

- 2 The present application claims a macrocycle compound of Formula (I), comprising a 13-mer peptide cyclised through an "X-linker" moiety, comprising either a cyclic γ - or δ -amino acid or a thioether-comprising linker having an optional exocyclic tether. Furthermore, the claimed macrocycle has an optionally α -substituted Ser at position 9 and comprises a variety of cyclic/bicyclic/aromatic groups on the side chains of a least residues located at positions 2, 4, 7, 8, 10, 11 and 13, as further characterised in claim 1. Substituents R^1 to R^{14b} are additionally defined throughout claims 2-11, claims 12 and 13 listing a number of particular compounds. Pharmaceutical compositions comprising them, their use in therapy, especially in methods of treating IBD and other TNF α -driven inflammatory diseases, are claimed as well.
- 2.1 Reference is made to the following documents:
- D1 TSUKAMOTO KEITA ET AL: "In vitro display evolution of the PURE system-expressed TNF[alpha]-binding unnatural cyclic peptide containing an N-methyl-d-amino acid", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 534, 2 December 2020, pages 519-525;
- D2 WO 2017/176608 A1 (BRISTOL MYERS SQUIBB CO [US]) 12 October 2017;
- D3 Goto Yuki ET AL: "The RaPID Platform for the Discovery of Pseudo-Natural Macrocyclic Peptides", Accounts of Chemical Research, vol. 54, no. 18, 21 September 2021, pages 3604-3617;
- D4 Katoh Takayuki ET AL: "Ribosomal Elongation of Cyclic [gamma]-Amino Acids using a Reprogrammed Genetic Code", Journal of the American Chemical Society, vol. 142, no. 11, 4 March 2020, pages 4965-4969.
- D5 Ji-Ae Park ET AL: "Cyclic RGD Peptides Incorporating Cycloalkanes: Synthesis and Evaluation as PET Radiotracers for Tumor Imaging", ACS MEDICINAL CHEMISTRY LETTERS, vol. 5, no. 9, 14 July 2014, pages 979-982;

D6 ZHANG NAN ET AL: "Selective inhibition of Tumor necrosis factor receptor-1 (TNFR1) for the treatment of autoimmune diseases", CYTOKINE & GROWTH FACTOR REVIEWS, vol. 55, 12 April 2020, pages 80-85;

D7 CN 102 321 155 A (UNIV HUAZHONG SCIENCE TECH) 18 January 2012.

2.2 D1 to D4 are cited as examples of prior art documents teaching the preparation and selection of macrocyclic peptide scaffolds comprising non-natural amino acids selected from semisynthetic libraries obtained after genetic code reprogramming and ribosomal elongation followed by cyclisation. In detail, D1 describes the preparation of TNF α -binding thioether-cyclised peptides comprising unnatural residues (see D1, Figure 4). D2 is one among several patents covering thioether-closed macrocyclic inhibitors having the same backbone as those claimed at present (see D2, claim 1). D3 and D4 additionally teach macrocycles incorporating cyclic γ -amino acids as structurally constrained bicyclic analogues (D3, Figure 7; D4, Figures 1,3) that in combination with the RaPID system may be useful for generating potent and specific binders against a target protein of interest (see D4, page 4968). Cyclic peptides comprising cycloalkanes are known as well (see D5, abstract). D6 is also introduced in the procedure as a review summarising the current approaches for treatment of autoimmune diseases and pathological inflammation by selective inhibition of TNFR1. A "TNFR1 blocking peptide" for the treatment of ulcerative colitis is disclosed in D7.

2.3 Since the presently claimed compounds of Formula (I) do not appear to be disclosed in the cited documents, novelty is acknowledged.

3 Concerning inventive step, the problem to be solved can be defined in the light of D1 - which may be regarded as the closest prior art - to be the provision of "therapeutic approaches beyond the standard of care of current anti-TNF α biologics medications" (see page 2). The proposed solution is the provision of macrocycles falling in the scope of Formula (I) as defined in independent claim 1. The claimed subject-matter differs from the disclosure of D1 in its actual peptide sequence and/or the "X-linker" moiety.

3.1 Although RaPID/FIT/PURE platforms are versatile tools routinely used in drug discovery to select potent peptide ligands for a number of target proteins, and although D1 does teach cyclic peptides capable of interfering with TNF α /TNFR1 interaction (see D1, page 524) it is agreed that a person of skill in the art at the priority date of the present application would have not been motivated to develop and modify the teachings of D1 as done in the present application with

- the aim of solving the problem above. As a consequence, in view of the fact that the effect of any particular modification in a cyclic oligopeptide is not always obvious to predict *a priori*, it is acknowledged that the available prior art does not render obvious the provision of specific compounds, provided that they have been credibly shown in the application to possess the desired binding and/or inhibitory properties.
- 3.2 The applicant successfully demonstrated that several macrocyclic peptides falling in the scope of claim 1 and prepared in the application do solve the problem above. As a matter of fact, multiple specific peptides listed in Table 1 were clearly shown in Table 2 to be potent and selective TNFR1 ligands with a substantial inhibitory effect. As a consequence, an inventive step may be acknowledged for such compounds.
- 4 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. This however does not seem to be the case here because it cannot be reasonably expected *prima facie* that substantially all compounds of Formula (I), cyclised via any "X-linker" selected from a cyclic amino acid or an optionally substituted thioether as indicated in claim 1, and further having an optionally α -substituted Ser at a position 9 and somehow comprising cyclic/heterocyclic/aromatic/heteroaromatic side chains at positions 2, 4, 7, 8, 10, 11 and 13, will invariably remain effective TNFR1 ligands and/or inhibitors, independently from their actual sequence and N-substitution pattern at R^{3a}, R^{5a}, R^{6a} and R^{12a}, no matter what chemistry is used for cyclisation and how all further substituents are to be chosen among a plethora of possibilities allowed at present at most positions of the macrocycle of formula (I).
- 4.1 The objection above is especially valid in view of the fact that it was shown in the application that even apparently minor sequence modifications of the presently claimed macrocyclic compounds may have a profound impact on their binding and inhibitory activity. For instance, compounds 1 and 289 - that seem to be the only two compounds prepared in the application having Ser at position 9 - were shown in Table 2 to have a THP-IC₅₀ at least 100 times higher than similar compounds where R⁹ is CH₃. The same reasoning applies to compound 206, which has an even lower inhibitory activity than 1 and 289 although it appears to be structurally very similar to all other presently claimed compounds. A similar observation can also be made for example for Sar at position 12, since the only compound where it was replaced by dNMeA (*i.e.*: compound 276) was

- unfortunately not tested in the application ("NT" in table 2), while its replacement with Pro (*i.e.*: compound 278) resulted in a substantial reduction of inhibitory activity.
- 4.2 Therefore, it is not plausible at present that the desired bioactivity would be maintained over the whole range of claimed macrocyclic peptides, as demonstrated by the applicants themselves. Such arguments apply *a fortiori* to any compound covered by Formula (I) that was not prepared at all in the application as originally filed, let alone tested for any activity. The subject-matter of present claims 1-11 must therefore be considered to represent an arbitrary selection of compounds, which does not involve an inventive step.
- 4.3 Since the recognition of an inventive step for claims related to compositions, medical methods and use in therapy appears to be entirely dependent on that for the compound claims, the subject-matter of claims 14-22 lacks an inventive step as well.
- 5 In view of all the above, the present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of at least claims 1-11 and 14-22 does not involve an inventive step (Rule 65 PCT).
- 5.1 The applicant will be invited in a later regional stage to present additional arguments and experimental data substantiating that all claimed macrocyclic peptides embraced by claims 1-11 do solve the problem underlying the application. Alternatively, the subject-matter claimed should be restricted to be commensurate with the teachings of the invention, as suggested above, or to a reasonable generalisation thereof, provided that an adequate basis for such an amendment could be found in the description as originally filed.
- 5.2 Moreover, in view of the fact that even compounds, such as 206 and 237, having a substantially reduced inhibitory effect compared to all other macrocyclic peptides prepared in the application are explicitly included among the most preferred compounds of Formula (I) listed in claim 13, the applicant will be invited to explain the significance of the provision of such compounds in the light of the teachings of the prior art, such as D1, D6 and D7.
- 6 The EPO does not recognise as patentable claims to medical methods and uses 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 claims 15-22 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the substance or composition.