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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2018/050085	02.01.2018	27.12.2016

International Patent Classification (IPC) or both national classification and IPC
INV. C07K5/11 C07D241/04 C07K5/113 C07K7/06 C07K5/103 C07K5/117 C07K5/078 C07K5/02 C07K5/093 A61P7/02 A61P1/00

Applicant
ZEDIRA GMBH

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 notifed 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:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Schleifenbaum, A Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2018/050085

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. 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	2-14
	No:	Claims	1, 15
Inventive step (IS)	Yes:	Claims	2-14
	No:	Claims	1, 15
Industrial applicability (IA)	Yes:	Claims	1-15
	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

1 Reference is made to the following documents:

D1 WO 2008/055488 A1 (ZEDIRA GMBH [DE]; OERTEL KAI [DE]) 15 May 2008 (2008-05-15)

D2 PÖHNER CLAUDIA ET AL: "Chemoselective coupling of sugar oximes and [alpha]-ketoacids to glycosyl amides and N-glycopept", TETRAHEDRON LETTERS, vol. 55, no. 14, 26 February 2014 (2014-02-26), pages 2197-2200, XP028835475, ISSN: 0040-4039, DOI: 10.1016/J.TETLET.2014.02.056

D3 MARKUS OBKIRCHER ET AL: "Photochemical Synthesis of N-Substituted 3-Hydroxy-2-pyrrolidinones", SYNLETT, no. 7, 1 January 2005 (2005-01-01), pages 1182-1184, XP055403250, DE
ISSN: 0936-5214, DOI: 10.1055/s-2005-865229

D4 WOLFGANG SEUFERT ET AL: "Cyclizations of [alpha]-Keto Ester Modified Aspartic Acids in Peptides", SYNLETT, vol. 2006, no. 11, 1 July 2006 (2006-07-01), pages 1774-1776, XP055403247, DE
ISSN: 0936-5214, DOI: 10.1055/s-2006-944203

D5 RUSSELL J. COX ET AL: "Synthesis and in vitro enzyme activity of peptide derivatives of bacterial cell wall biosynthesis inhibitors", ROYAL CHEMICAL SOCIETY. JOURNAL. PERKIN TRANSACTIONS 1, vol. 1, no. 13, 1 January 2000 (2000-01-01), pages 2023-2036, XP055403254, GB
ISSN: 1470-4358, DOI: 10.1039/b002701o

D6 LASZLO OTVOS JR. ET AL: "The flexible termini of conantokin G define its interactions with NMDA receptors", LETTERS IN PEPTIDE SCIENCE, vol. 4, no. 2, 1 April 1997 (1997-04-01), pages 85-93, XP055403259, NL
ISSN: 0929-5666, DOI: 10.1007/BF02443519

D7 DOYLE P M ET AL: "Peptides incorporating electrophilic glutamine analogues as potential transglutaminase inhibitors", BIOCHEMICAL SOCIETY TRANSACT, PORTLAND PRESS LTD, GB, vol. 18, no. 6, 1 December 1990 (1990-12-01), pages 1318-1320, XP008090045, ISSN: 0300-5127

Article 33(2) PCT - Novelty

2 The subject-matter of claims 1 and 15 is not novel in the sense of Article 33(2) PCT:

2.1 D1 (page 27, lines 1-10) discloses that peptide of D1 can be prepared by first synthesising the peptide sequence and then transforming the intermediate into an intermediate diketo amino acid. Compounds of the present application are therefore anticipated in D1. Further, D2 (compound 23), D3 (compounds 5b, 5c), D4 (compounds 6-9 with R1=H), D5 (compounds 19, 20, 22a, 25a, 26, 29, 30), D6 (table 1) disclose diketo-compounds as claimed. The compounds also disclose the synthesis of these compounds using a diketo group precursor.

3 Claims 2-10 define compounds which are not disclosed in the cited documents; the claims therefore comply with Article 33(2) PCT.

4 The subject-matter of claims 11 and 12 is novel since the novelty destroying compounds of the prior art are intermediates and not used in medicine.

5 The subject-matter of claims 13 and 14 is novel since in the prior art compounds, the diketo group is introduced after peptide synthesis.

Article 33(3) PCT - Inventive Step

6 Even if rendered novel, the subject-matter of claims 1 and 11-15 would not be inventive in the sense of Article 33(3) PCT:

7 The example compounds do not represent the claimed compounds over the whole scope (eg peptide length and sequence). The examples are therefore not suitable to show a technical effect (transglutaminase binding) over the whole scope of the claim. Therefore, it is not credible that essentially all claimed compounds have the desired technical effect. Consequently, the problem to be solved can only be regarded as the provision of novel compounds. However, the provision of novel compounds as such does not require any inventive skills.

8 The subject-matter of claims 2-10 is regarded to be inventive in the sense of Article 33(3) PCT:

9 D1 may be regarded to represent the closest prior art and discloses Michael-system carrying glutamate derivatives as transglutaminase inhibitors. The subject-matter of the claims differs therefrom in at least that the compounds comprise a diketo group in place of the Michael-system. A technical effect is that claimed compounds are reversible and not irreversible inhibitors. The problem to be solved is therefore seen in the provision of reversible transglutaminase inhibitors. The problem is solved by compounds as set forth in the claims.

10 This solution is regarded to be inventive since the prior art does neither disclose nor suggest compounds as claimed carrying a diketo group.

Article 33(4) PCT - Industrial Applicability

11 The application meets the requirements of Article 33(4) PCT since its subject-matter can be used in industry.

Re Item VIII

12 The subject-matter of claims 13 and 14 is not sufficiently disclosed in the sense of Article 5 PCT: the application as filed does not disclose the synthesis of claimed compounds using a non-protected warhead. Also the prior art does not disclose peptide synthesis using a diketo amino acid. Exploring suitable chemical methods to put the method of claims 13 and 14 into practice is therefore see as an undue burden for the skilled person.