

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

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| <p>To:</p><br><br><br><br><br><br><br><br><br><br><br><p>see form PCT/ISA/220</p> |
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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<br>see form PCT/ISA/220                                                |                                                          | <b>FOR FURTHER ACTION</b><br>See paragraph 2 below |
| International application No.<br>PCT/EP2019/066819                                                           | International filing date (day/month/year)<br>25.06.2019 | Priority date (day/month/year)<br>25.06.2018       |
| International Patent Classification (IPC) or both national classification and IPC<br>INV. C07K7/62 A61K38/12 |                                                          |                                                    |
| Applicant<br>NEW PHARMA LICENCE HOLDINGS LIMITED                                                             |                                                          |                                                    |

### 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.

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| <p>Name and mailing address of the ISA:</p><br> <p>European Patent Office<br/>D-80298 Munich<br/>Tel. +49 89 2399 - 0<br/>Fax: +49 89 2399 - 4465</p> | <p>Date of completion of<br/>this opinion</p><br><p>see form<br/>PCT/ISA/210</p> | <p>Authorized Officer</p><br><p>R. von Eggelkraut-G.<br/>Telephone No. +49 89 2399-0</p> |
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**Box No. I Basis of the opinion**

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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:

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**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**

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1. Statement

|                               |             |                  |
|-------------------------------|-------------|------------------|
| Novelty (N)                   | Yes: Claims | <u>1-20</u>      |
|                               | No: Claims  |                  |
| Inventive step (IS)           | Yes: Claims | <u>7</u>         |
|                               | No: Claims  | <u>1-6, 8-20</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-20</u>      |
|                               | No: Claims  |                  |

2. Citations and explanations

see separate sheet

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**Box No. VIII Certain observations on the international application**

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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

Reference is made to the following documents:

- D1 WO 2016/083531 A1 (NEW PHARMA LICENCE HOLDINGS LTD [MT]) 2 June 2016 (2016-06-02)cited in the application
- D2 WO 2015/135976 A1 (NEW PHARMA LICENCE HOLDINGS LTD [MT]) 17 September 2015 (2015-09-17)cited in the application
- D3 WO 2017/054047 A1 (UNIV MONASH [AU]) 6 April 2017 (2017-04-06)
- D4 US 2012/316105 A1 (MAGEE THOMAS VICTOR [US] ET AL) 13 December 2012 (2012-12-13)
- D5 WO 2016/166103 A1 (XELLIA PHARMACEUTICALS APS [DK]) 20 October 2016 (2016-10-20)
- D6 KOH JUN-JIE ET AL: "Recent advances in synthetic lipopeptides as anti-microbial agents: designs and synthetic approaches", AMINO ACIDS, SPRINGER VERLAG, AU, vol. 49, no. 10, 19 August 2017 (2017-08-19), pages 1653-1677, XP036320623, ISSN: 0939-4451, DOI: 10.1007/S00726-017-2476-4 [retrieved on 2017-08-19]

**Re Item V.**

- 1 NOVELTY
- 1.1 The subject-matter of claims 1-20 is regarded to be novel according to Article 33 (2) PCT, because Polymyxin B or Colistin derivatives having a deacylated nonapeptide polymyxin core, with the amino acid residue at position 3 substituted with Dap, and having at its N terminal a gamma-aminopropyl group which is substituted at the beta position with an optionally substituted aryl group, have not been disclosed in the prior art (D1: Ex. 39, 50, 51, p. 60, line 35 - p. 62, line 27, claims 1-56; D2: D5-D9, D68-D77, claims 1-79; D3: Claims 1-16; D4: Claims 1-22; D5: Claims 1-16, 23-30; D6: pp. 1656 - 1657, "Polymyxin analogs").

2 INVENTIVE STEP

- 2.1 D1 (Ex. 39, 50, 51, p. 60, line 35 - p. 62, line 27, claims 1-56) is regarded as being the closest prior art to the subject-matter of claims 1-20 and discloses Polymyxin B-derivatives containing a Dap-residue in position 3, the hydrophobic cyclohexylalanine replacing phenylalanine at position 6 and N-terminal groups including beta-aryl or beta-aralkyl groups falling under the definition of R<sup>15</sup> according to claim 1 of the present application. The compounds find use in a method of treatment or prophylaxis, optionally in combination with a second active agent, of a microbial infection, such as a Gram-negative bacterial infection.

The subject-matter of claims 1-20 differs from D1 in that the residue at position 6 is selected from other hydrophobic residues, i.e. phenylalanine, leucine, norleucine, valine or norvaline. The alleged technical effect of this difference is the provision of Polymyxin B-derivatives having a lower cytotoxicity and lower kidney drug levels.

The technical problem to be solved by the present invention therefore is: How to provide Polymyxin B-derivatives containing a Dap-residue in position 3, a hydrophobic residue at position 6 and aromatic N-terminal groups falling under the definition of R<sup>15</sup> according to claim 1 of the present application, having a lower cytotoxicity and lower kidney drug levels? It should however be noted that if the inventive step of a claimed invention is based on a given technical effect (namely lower cytotoxicity and lower kidney drug levels), the latter should, in principle, be achievable over the whole area claimed. As this is not the case here since the patent application does not demonstrate the achievement of the desired technical effect in cases different than relating to the use of a specific isomeric form corresponding to the isomer according to present claim 7 (see description of the present application, Tables A, B and C, p. 12, lines 25-29), inventive step must be denied for the subject-matter of claims 1-6 and 8-20.

Moreover, the combination of an aromatic, amino-group containing N-terminus replacing the fatty acid moiety of Polymyxin B, a Dap-residue in position 3 and a phenylalanine, leucine, norleucine, valine or norvaline residue at position 6, is already known from the prior art to provide Polymyxin B-derivatives having a lower cytotoxicity and/or lower kidney drug levels (see D2-D6).

Thus, the subject-matter of claim 7 involves an inventive step according to Article 33 (3) PCT, whereas the subject-matter of claims 1-6 and 20 does not involve an inventive step according to Article 33 (3) PCT.

3 INDUSTRIAL APPLICABILITY

- 3.1 The subject-matter of claims 1-20 is considered industrially applicable (Article 33 (4) PCT).

**Re Item VIII.**

4 ARTICLE 6 PCT

- 4.1 According to claims 3 and 4, -R<sup>2</sup> comprises aminobutyrate which however does not fall under the definition of -R<sup>2</sup> according to claim 1, thereby rendering the definition of the subject-matter of said claims unclear (Art. 6 PCT).