PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 42.133062/01	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2018/080832	International filing date *(day/month/year)* 09 November 2018 (09.11.2018)	Priority date *(day/month/year)* 10 November 2017 (10.11.2017)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PCI BIOTECH AS		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	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 Article 35(2) with regard to novelty, inventive step or 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 12 May 2020 (12.05.2020)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pct.team5@wipo.int

Form PCT/IB/373 (January 2004)

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/EP2018/080832	09.11.2018	10.11.2017

International Patent Classification (IPC) or both national classification and IPC
INV. A61K45/06 A61K31/7036 A61P31/04 A61K41/00

Applicant
PCI BIOTECH AS

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	Gradassi, Giulia Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2018/080832

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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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	1-18
	No:	Claims	19-24
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	19-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Reference is made to the following documents:

D1 WO 00/23117 A1 (GEN HOSPITAL CORP [US]) 27 April 2000 (2000-04-27)

D2 US 2002/183808 A1 (BIEL MERRILL A [US]) 5 December 2002 (2002-12-05)

D3 US 2009/304803 A1 (HASAN TAYYABA [US]) 10 December 2009 (2009-12-10)

D4 WO 2011/018636 A2 (PCI BIOTECH AS [NO]; KLAVENESS JO [NO]; HOGSET ANDERS [NO]; GOLDING LO) 17 February 2011 (2011-02-17)

D5 WO 99/30686 A1 (INEX PHARMACEUTICALS CORP [CA]; WEBB MURRAY S [CA]; LUTWYCHE PETER [CA) 24 June 1999 (1999-06-24)

D6 XIAOLIN ZHANG ET AL: "Photochemical internalization enhances cytosolic release of antibiotic and increases its efficacy against staphylococcal infection",
JOURNAL OF CONTROLLED RELEASE,
vol. 283, 1 August 2018 (2018-08-01), pages 214-222, XP055553320, NL
ISSN: 0168-3659, DOI: 10.1016/j.jconrel.2018.06.004

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 21, 23 and 24 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Novelty (Article 33(2) PCT) and cited documents

Reference is made to the corresponding passages cited in the search report.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 19-24 is not new in the sense of Article 33(2) PCT.

D1 discloses the use of photosensitizers conjugated with a targeting moiety in combination with an antibacterial agent such as an antibiotic, for the photodynamic treatment of intracellular bacterial infections such as mycobacterium tuberculosis. However, D1 does not disclose the internalization of the antibiotic in the cytosol of the infected cell to kill intracellular bacteria. In fact, it is specified in D1 that the photosensitizers do not need to be internalized. Therefore, the subject-matter of claims 19-24 is not novel over D1.

D2 discloses the combined use of a photosensitizer in combination with a surfactant (i.e. an antibacterial agent) such as SDS or the surfactant/antibiotic substance polymixin B in the photodynamic treatment of bacterial infections, including intracellular bacterial infections. The surfactant allows the accumulation of the photosensitizer in the cytosol of the pathogen. However, D2 does not disclose the internalization of the antibiotic in the cytosol of the infected cell to kill intracellular bacteria. Therefore, the subject-matter of claims 19-24 is not novel over D2.

D3 discloses the combined use of photosensitizers and antibiotic agents, including vancomycin and gentamicin for the treatment of bacterial infections. Intracellular bacterial infections such as Rickettsia are mentioned in D3. However, in order to arrive at the subject-matter of claims 21-24 a double selection has to be carried out. In addition, D3 does not disclose the internalization of the antibiotic in the cytosol of the infected cell to kill intracellular bacteria. Therefore, the subject-matter of claims 19 and 20 is not novel in D3.

D4 discloses the use of photosensitizing agents in combination with antibacterial agents in a method of photochemical internalization (PCI) for the treatment of bacterial infections. It is mentioned in D4 that the photosensitizing agent is used to increase the delivery of the therapeutic agent (e.g. the antibacterial) in the cytosol of cell located in a cavity of patient. However, it is not mentioned in D4 that the bacterial infection is intracellular bacterial infection, and said feature is not implicit to D4, since the photosensitizing agent could be used to increase the delivery of the antibacterial in the cytosol of a bacteria cell and not necessarily in the cytosol of a human cell infected with bacteria. Therefore, the subject-matter of claims 19 and 20 is not novel over D4, whereas the subject-matter of claims 1-18 and 21-24 is not clearly and unambiguously anticipated in said document.

D5 discloses the use of gentamicin-filled nanoliposomes for treating intracellular bacterial infection by increasing the intracellular delivery of gentamicin, thus allowing the intracellular killing of the bacteria. However, D5 does not disclose the combined use of an antibacterial agent and a photosensitirzer. Therefore, the subject-matter of claims 1-24 is novel over D5.

Inventive step (Article 33(3) PCT)

Even if rendered novel by appropriate amendments, the subject-matter of claims 19-24 would lack an inventive step in view of D1-D4.

The subject-matter of claims 1-18 involves an inventive step for the following reasons;

D5 may be regarded as the closest prior art document to the subject-matter of present claims 1-18.

Present claims differ from D5 in that a different method is used to increase the intracellular delivery of gentamicin.

There is no technical effect brought about by this difference. However, it is shown in the examples of the present application that PCI is effective to enhance the antibacterial efficacy of gentamicin and vancomycin against Staphylococcal intracellular infection (examples 1 and 2).

Therefore, the objective technical problem may be regarded as how to provide an alternative effective method to enhance the intracellular delivery of antibacterials for treating intracellular bacterial infections.

D4 suggests the use of PCI for treating bacterial infections. However, the therapeutic effect of PCI against bacterial infections is not shown. Although it could be considered obvious to expect that PCI would lead to an increased internalization of the antibacterial agent, the skilled person could neither predict that said method would allow to retain and increase the antibacterial activity of the therapeutic agent nor that it would enable the killing of the intracellular bacteria.

In addition, D4 does not suggest the use of PCI for treating intracellular bacterial infections, therefore, the skilled person has no reasonable basis to combine D5 and D4.

It would not be obvious for the skilled person to combine the teachings of D4 and D5, and to arrive at the subject-matter of present claims with a reasonable expectation of success.

Therefore, the subject-matter of claims 1-18 involves an inventive step.

Re Item VI

Certain documents cited

The examination has been carried out assuming that the priority of the application is valid. However, attention is drawn to the fact that the document D6 may become relevant in the national/regional phase examination.

D6 discloses that photochemical internalization enhances the cytosolic release of gentamicin and increases its efficacy against intracellular staphylococcal infection (see whole document).