

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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.
PCT/EP2015/071941

International filing date (day/month/year)
24.09.2015

Priority date (day/month/year)
26.09.2014

International Patent Classification (IPC) or both national classification and IPC
INV. A61K38/22 C07K14/575

Applicant
BAYER PHARMA AKTIENGESELLSCHAFT

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 notified 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:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Hohwy, Morten

Telephone No. +49 89 2399-0



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 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	<u>1-15</u>
	No: Claims	
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

Reference is made to the following documents:

- D1 WO 2012/138867 A2 (UNIV LELAND STANFORD JUNIOR [US]; HSU SHEAU YU [US]; CHANG CHIA LIN [U] 11 October 2012 (2012-10-11)
- D2 A K Galande ET AL: "Thioether side chain cyclization for helical peptide formation: inhibitors of estrogen receptor-coactivator interactions Authors' affiliations: Correspondence to: Introduction", J. Peptide Res. Copyright Blackwell Munksgaard, vol. 63, 1 January 2004 (2004-01-01), pages 297-302, XP055234462,
- D3 LIMAL D ET AL: "SOLID-PHASE SYNTHESIS AND ON-RESIN CYCLIZATION OF A DISULFIDE BOND PEPTIDE AND LACTAM ANALOGUES CORRESPONDING TO THE MAJOR ANTIGENIC SITE OF HIV GP41 PROTEIN", JOURNAL OF PEPTIDE RESEARCH, BLACKWELL PUBLISHING LTD, OXFORD; GB, vol. 52, no. 2, 1 August 1998 (1998-08-01), pages 121-129, XP000768524, ISSN: 1397-002X
- D4 CUTHBERTSON A S: "Design of low molecular weight hematoregulatory agents from the Structure-Activity relationship of a dimeric pentapeptide", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 40, no. 18, 1 January 1997 (1997-01-01), pages 2876-2882, XP002110232, ISSN: 0022-2623, DOI: 10.1021/JM9702443

Re Item V

1 Method of treatment

- 1.1 The patentability of claim 15 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.

- 1.2 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 compound/composition.

2 Novelty

- 2.1 The present application describes adrenomedullin (ADM) variants for medical treatment, wherein the natural (wild type) intramolecular cysteine disulfide bridge has been replaced by redox stable moieties by replacing the two cysteins with residues capable of forming e.g. lactam, thioether, and alkane bridges. Further, variants with an N-terminal modification such as a lysine-palmitic acid residue are also claimed. The use of the disclosed compounds for treatment is also covered.

2.2 Prior art

- 2.3 Document D1 discloses (D1, abstract; par. 23; example 2; claim 6) adrenomedullin peptides for therapy, wherein the active peptide has the formula K(mod)GCRFGTCTVQKLAHQIYQ-FTDKDKDNVAPRSKISPQGY, wherein the peptide comprises an internal disulfide bridge between the two cysteins and wherein the N-terminal lysine is modified by attachment of a lipid such as palmitic acid.

Document D2 discloses (D2, abstract; table 1) a method of replacing an internal disulfide bridge with a thioether bridge in order to obtain redox stability without interfering with receptor binding.

Document D3 discloses (D3, abstract; schemes 1-2) a method of replacing an internal disulfide bridge with a lactam bridge by replacing the two cysteines with Asp and Dap residues, respectively.

Document D4 discloses (D4, abstract; fig. 1; table 2) a method of replacing a disulfide bond in a dipeptide by an alkane bridge and cyclizing it to a cyclic peptide.

- 2.4 It follows from the comments above, that the present subject-matter is new in the sense of Article 33(2) PCT.

3 Inventive step

- 3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-15 does not involve an inventive step in the sense of Article 33(3) PCT.

- 3.2 Claim 1 does not involve an inventive step for the following reasons: D1 is the closest prior art (CPA), the difference between the compound of present claim 1 and that of the CPA being that in the former, the cysteine disulfide bridge of the CPA has been replaced by a redox stable moiety. The effect of this difference is the redox stability, and the objective technical problem is therefore to provide improved adrenomedullin (ADM) derivatives. However, D2-D4 each discloses methods of replacing internal disulfide bridges in peptides in order to make them redox stable by replacement with a thioether, lactam, or alkane bridge, respectively. Hence, the person skilled in the art would be directly led to the solution of the problem and to the compounds of claim 1. Claim 1 does consequently not involve an inventive step.

It is noted that the person skilled in the art would not know precisely how to solve the problem while preserving activity of the compound since this would require extensive research. However, the scope of the compounds of present claim 1 includes compounds that are not active as documented by tables 1 and 2 in the description. For example, the variant with an alkane bridge (example 17) appears to completely lose activity as does the [K¹⁶, E²¹]-variant and several others. Hence, claim 1 does not solve the objective technical problem beyond the capability of the person skilled in the art.

Further, it is noted that the effect documented in table 3 of prolonged stability in human blood plasma appears to derive from the N-terminal modification (Lys-palmitic acid) and not from the redox stabilized cyclization. This effect was already demonstrated in the CPA (*cf.* D1, fig. 8) and does not confer inventiveness to the subject matter.

- 3.3 Claim 2 contains the alkane bridge option (option two) and is consequently not inventive for the same reasons as stated for claim 1.
- 3.4 Dependent claims 3-8 do not add any features which could be seen as conferring inventiveness to the subject matter and are consequently not inventive either.
- 3.5 Claim 9 covers the lactam option corresponding to the [K¹⁶, E²¹]-variant, which is not active (*supra*) and said claim consequently lacks inventiveness for the same reasons as stated for claim 1.
- 3.6 Claims 10-15 do not involve an inventive step for the same reasons as claims 1-9, *mutatis mutandis*.

4 Re Item VIII

- 4.1 Clarity and sufficiency of disclosure
- 4.2 The application does not meet the requirements of Article 6 and 5 PCT, because claim 1, 3, and 10-11 are not clear and/or not sufficiently disclosed.
- 4.3 Claim 1 is not clear because the term "heterologous moiety" is not clear.
- 4.4 Claim 3 is not clear because the term "a polymer" is not clear.
- 4.5 It appears that there is no disclosure for the use of the claimed compounds in all the indications listed in claims 10-11, contrary to Art. 5 PCT.