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/CY2017/000002	05.07.2017	

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/54 C07D311/76

Applicant
E P O S IASIS RESEARCH AND DEVELOPMENT 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 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	Jetter, Sonya Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CY2017/000002

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	1-50
	No:	Claims	
Inventive step (IS)	Yes:	Claims	4, 6-43
	No:	Claims	1-3, 5, 44-50
Industrial applicability (IA)	Yes:	Claims	1-50
	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

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

1. Cited documents

Reference is made to the following documents:

D1 MASAYOSHI YAMAGUCHI ET AL: "Combination of alendronate and genistein synergistically suppresses osteoclastic differentiation of RAW267.4 cells in vitro",
EXPERIMENTAL AND THERAPEUTIC MEDICINE,
vol. 14, no. 2, 27 June 2017 (2017-06-27), pages 1769-1774,
XP055458539,
GR
ISSN: 1792-0981, DOI: 10.3892/etm.2017.4695

D2 US 2014/356423 A1 (ANGRES ISAAC A [US]) 4 December 2014 (2014-12-04)

D3 WO 2005/027921 A1 (PFIZER PROD INC [US]; LEE ANDREW GEORGE [US]) 31 March 2005 (2005-03-31)

D4 US 2009/227544 A1 (KARPEISKY ALEXANDER [US] ET AL) 10 September 2009 (2009-09-10)

2. Novelty (Art. 33(2) PCT)

2.1. Claim 1 relates to a compound of formula Q-T-L wherein Q is a bisphosphonate moiety, T is linker and L is an anti-osteolytic or osteoinductive phytochemical.

2.2. The document D1 (abstract; page 1770, column 2, line 36 - page 1771, column 1, line 10; page 1773, column 1, line 1 - line 6) discloses compositions comprising alendronate (a bisphosphonate) and genistein (an anti-osteolytic phenolic phytochemical) and their therapeutic use for the treatment of diseases involving bone resorption.

2.3. The difference between the subject-matter of claim 1, and the known compositions of D1, is that in D1 the two compounds are not conjugated together.

2.4. The document D2 discloses (paragraph [0003] - paragraph [0005]; claims 1-9) compositions comprising a bisphosphonate and lycopene (an anti-osteolytic phenolic phytochemical) and their therapeutic use for the treatment of diseases involving bone resorption.

2.5. The difference between the subject-matter of claim 1, and the known compositions of D2, is that in D2 the two compounds are not conjugated together.

2.6. The document D3 discloses (claims 1-6, 11) a composition comprising a vitamin D derivative and a bisphosphonate and their use in the treatment of diseases involving bone resorption. In particular, D3 mention the use in the treatment of cancers.

2.7. The difference between the subject-matter of claim 1, and the known compositions of D3, is that in D3 the two compounds are not conjugated together.

2.8. The document D4 discloses (claims 1, 2, 29-35, 39, 41) bisphosphonates conjugated to active agents (in particular, anti-angiogenesis agents) via a linker, and their use in the treatment of bone related diseases or disorders.

2.9. The difference between the subject-matter of claim 1, and the known conjugates of D4, is that in D4 the active agent attached to the bisphosphonate is an anti-angiogenic agent rather than an anti-osteolytic or osteoinductive phytochemical.

2.10. That is, the subject-matter of claim 1, and of claims 2-6 which are dependent thereon, and of claims 7-43 which all also relate to bisphosphonates conjugated to vitamin E derivatives, and of claims 44 and 50 which relate to compositions thereof, and of claims 45-46 which relate to compounds for use in therapy, and of claims 48 and 49 which relate to methods of treatment using the said conjugates, can be considered to be novel in the sense of Article 33(2) PCT.

3. Inventive Step (Art. 33(3) PCT)

3.1. The difference between the subject-matter of claim 1, and the known compositions of D1, D2 and D3 is discussed above. It is clear from the documents D1, D2 and D3 that the combination of bisphosphonates with anti-osteolytic or osteoinductive phytochemicals for the treatment of diseases involving bone resorption is known in the prior art. In particular in D3, the treatment of cancers is mentioned.

3.2. Based on the currently available data, it is not clear whether there is any advantage resulting from the difference (that is, conjugation of the two agents), over the whole claimed scope.

3.3. Therefore, the problem to be solved can be considered to be to adapt the compositions of D1, D2 or D3 so as to provide an alternative.

3.4. The concept of conjugation of drugs and targeting groups, or of conjugation of two active groups together, is well known in the art. It is also noted that D4 demonstrates, in particular, the conjugation of bisphosphonates with active agents for the treatment of bone diseases.

3.5. That is, it would appear to be obvious to the person skilled in the art that the bisphosphonates and anti-osteolytic or osteoinductive phytochemicals of D1, D2 or D3 could be conjugated together via a linker so as to provide an alternative to the known compositions comprising the two agents.

3.6. Therefore, **the subject-matter of claims 1, 2, 3, 5, and 44-49 cannot be considered to involve an inventive step in the sense of Article 33(3) PCT.** Furthermore, the addition of a further therapeutic agent to a composition is considered to fall within the usual working scope of the person skilled in the art. Therefore, **the subject-matter of claim 50 can also not be considered to involve an inventive step in the sense of Article 33(3) PCT.**

3.7. The remaining claims show further differences from the prior art documents (in particular, the presence of a vitamin E derivation as the phytochemical). This does not appear to be an obvious alternative to the known compositions and conjugates of the prior art. Therefore, **the subject-matter of claims 4 and 6-43 can be considered to involve an inventive step in the sense of Article 33(3) PCT.**

4. Industrial applicability (Art. 33(4) PCT)

Claims 1-50 relate to conjugates useful in the treatment of diseases, and to uses thereof. Therefore, the subject-matter of claims 1-50 can be considered to be industrially applicable.

5. Patentability

Claims 48 and 49 relate to methods of treating a proliferative disease. 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.

Re Item VIII

Certain observations on the international application

Throughout the description there are passages where spaces between words have been omitted or lost during text processing. This renders the description (in places) unclear to the reader. There are also chemical structure drawings (for example on

page 46, but also on subsequent pages) where the structure appears to be overlaid on the page on to a number or text. This renders some of the structure drawings unclear to the reader.