

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2024/011615

International filing date (day/month/year)
16.01.2024

Priority date (day/month/year)
17.01.2023

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/68

Applicant
ELI LILLY AND COMPANY

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.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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.
 - b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
 - ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:
- see separate sheet**

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	<u>2, 5-7, 10, 13-26</u>
	No: Claims	<u>1, 3, 4, 8, 9, 11, 12</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-26</u>
Industrial applicability (IA)	Yes: Claims	<u>1-26</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

Re Item I

Basis of the report

Remark on the sequence listing:

The sequence listing on the date of filing was not WIPO Standard ST.26 compliant, therefore not used for search purposes.

Re Item V

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

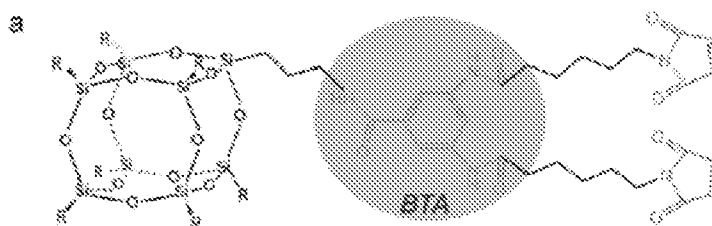
Reference is made to the following documents:

- D1 HAITAO WEI: "Transparent, robust, water-resistant and high-barrier self-healing elastomers reinforced with dynamic supramolecular nanosheets with switchable interfacial connections", JOURNAL OF MATERIALS CHEMISTRY A, vol. 8, no. 18, 16 April 2020 (2020-04-16), pages 9013-9020, XP093162200, GB ISSN: 2050-7488, DOI: 10.1039/D0TA01352H
- D2 ALEXANDRA J CLIPSON ET AL: "Bivalent Enzyme Inhibitors Discovered Using Dynamic Covalent Chemistry", CHEMISTRY - A EUROPEAN JOURNAL, JOHN WILEY & SONS, INC, DE, vol. 18, no. 34, 10 July 2012 (2012-07-10), pages 10562-10570, XP071835199, ISSN: 0947-6539, DOI: 10.1002/CHEM.201201507
- D3 US 2016/015832 A1 (AN DEQIANG [CN] ET AL) 21 January 2016 (2016-01-21)
- D4 US 2021/388082 A1 (HAN NIANHE [CN] ET AL) 16 December 2021 (2021-12-16)
- D5 WO 2012/173422 A1 (HANMI SCIENCE CO LTD [KR]; JUNG SUNG YOUNG [KR] ET AL.) 20 December 2012 (2012-12-20)

1 **Novelty**

1.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of present claims 1, 3, 4, 8, 9, 11, 12 is not new in the sense of Article 33(2) PCT.

1.2 D1 discloses the compound



(see Fig. 1).

Said compound is encompassed under the subject-matter of claim 1, wherein

R_1 and R_2 are each a C_5 linear alkyl;

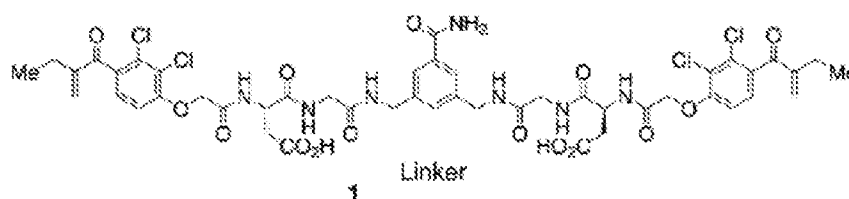
R_3 and R_4 are absent;

U is 1,3,5-substituted phenyl and

Z comprises NH and a C_3 alkyl.

Consequently the subject-matter of present claims 1, 3, 8, 9, 11 is not new in the sense of Article 33(2) PCT over D1.

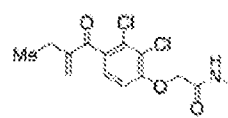
1.3 D2 discloses the compound



(see Figure 2).

Said compound is encompassed under the subject-matter of claim 4, wherein

Y_1 and Y_2 are each:



, i.e. comprise an amide;

R_1 , R_2 , R_3 and R_4 are each a C_1 alkyl;

U is 1,3,5-substituted phenyl and

Z is NH₂.

Consequently the subject-matter of present claims 4, 8, 9, 11, 12 is not new in the sense of Article 33(2) PCT over D2.

2 Inventive step

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-26 does not involve an inventive step in the sense of Article 33(3) PCT.

2.2 Being not new the subject-matter of present claims 1, 3, 4, 8, 9, 11, 12 cannot involve an inventive step in the sense of Art. 33(3) PCT.

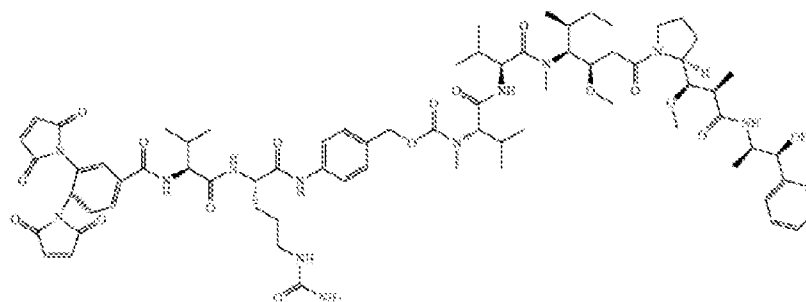
Independent claim 1

2.3 Should the applicant have overcome the objections of lack of novelty raised above, an inventive step could not be acknowledged over the teaching of any of D3 or D4, as the subject-matter of present claim 1 as far as novel, appears to be obvious starting from any of said documents as closest prior art, for the following reasons.

2.4 D3 discloses tridentate, bis-maleimide linkers comprising two maleimide groups for preparing antibody drug conjugates (see paragraphs [0017]-[0023], [0044], [0045], [00109], see also claims 1-13). The drug may also be a protein or polypeptide (paragraph [0088]) or a cytotoxic drug such as maytansines or auristatins (paragraphs [0089], [0091]).

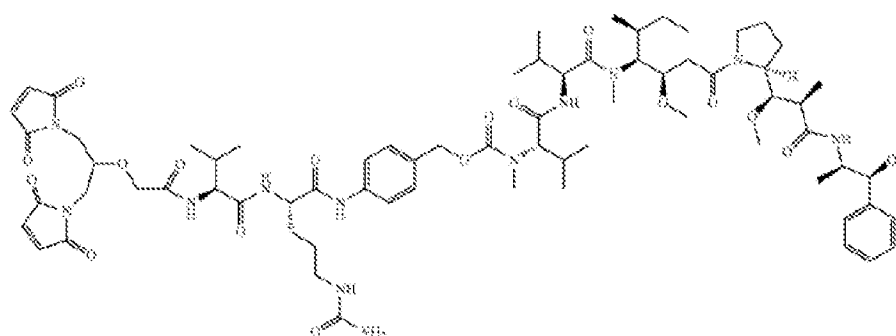
D3 discloses in claim 4 the general formulas of the antibody-drug conjugates. Q in Formulas VII and VIII of claim 4 may be a tertiary amine (Q is N or CR¹⁷ in claim 4 of D3).

For example, D3 discloses the linker-drug compounds:



(see example 6)

and



(see

example 25).

2.5 Similar to D3, D4 also discloses tridentate, bis-maleimide linkers comprising two maleimide groups for preparing antibody drug conjugates (see paragraph [0116], see also example 7, and in particular paragraphs [0217], [0219], [0221], [0227], [0230], [0233], [0236], [0241], [0246]). D4 also discloses that the antibody may be an Fc antibody fragment (paragraphs [0052], [0053]). D4 teaches that the drug may be a protein or polypeptide (see paragraph [0112]).

2.6 The subject-matter of claim 1 differs from any of D3 or D4 in the spacer between the two maleimide groups and the drug.

There is no technical effect which can be seen to derive from said difference over the whole scope of claim 1.

The objective technical problem can therefore merely be defined as the provision of alternative bis-maleimide-drug compounds comprising alternative spacers between the two maleimide groups and the drug.

In the absence of any apparent surprising or unexpected effect relating to the bis-maleimide compounds as presently claimed in claim 1, the spacer comprised in the compound, between the maleimide groups and the drug, appears to be arbitrarily designed and does not involve an inventive step. It is

considered that an arbitrary selection of a solution from a number of possibilities, even in the absence of a hint to do so, is not inventive if not justified by hitherto unknown technical effect that distinguishes the claimed solution from the other solutions.

In any case, a bis-maleimide linker comprising a 1,3,5-substituted phenyl as claimed in claim 1 is already known from D1 (see above). Moreover, that the branching point can be a tertiary amine is already known from D3 (as said above, see claim 4 of D3).

It should be noted that also D4 discloses that the linker may have a branching point being a tertiary amine (see for example paragraph [00249]).

The linker-drug conjugate of paragraph [00249] of D4 differs from claim 1 in the substitutions on the C₄ alkyls R₁ and R₂ which is a maleimide group in D4 while in present claim 1 (and present claim 2) the optional substitution may be one or more of -NH₂, -CH₂NH₂, -CH₂CH₂NH₂.

There is no technical effect which can be seen to derive from said difference over the whole scope of claim 1.

In this case the objective technical problem can therefore merely be defined as the provision of alternative bis-maleimide-drug compounds comprising alternative substitutions on the R₁, R₂ alkyls.

In the absence of any apparent surprising or unexpected effect relating to the particular substituents on the R₁, R₂ alkyls as presently claimed in claim 1, these substituents appear to be arbitrarily designed and do not involve an inventive step. It is considered that an arbitrary selection of a solution from a number of possibilities, even in the absence of a hint to do so, is not inventive if not justified by hitherto unknown technical effect that distinguishes the claimed solution from the other solutions.

Consequently, claim 1 does not appear to involve an inventive step also for this reason.

The same applies to the subject-matter of the dependent claims 2, 3, 7-26 which apparently does not contain any technical feature which could be regarded as inventive per se.

This is in particular due to the fact that no further technical effect can be acknowledged and/or have been demonstrated in the context of the subject-matter of said claims.

2.7 Independent claim 4

2.8 Should the applicant have overcome the objections of lack of novelty raised above, an inventive step could not be acknowledged over the teaching of D5, as the subject-matter of present claim 4 as far as novel, appears to be obvious over said document for the following reasons.

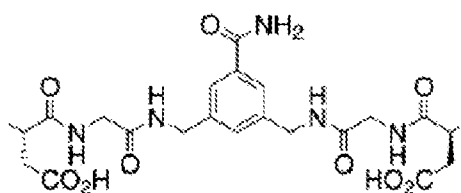
D5 discloses that conjugates of oxyntomodulin linked to immunoglobulin Fc have increased half-life (see claims 1-21, see also paragraphs [12], [14], [200]) .

The subject-matter of claim 4 therefore differs from D5 in the linker.

There is no technical effect which can be seen to derive from said difference over the whole scope of claim 4.

The objective technical problem can therefore merely be defined as the provision of alternative oxyntomodulin-immunoglobulin Fc conjugates comprising alternative linkers for linking oxyntomodulin to immunoglobulin Fc.

A linker such as



is already known from D2 (see above). The skilled person faced with the problem of providing mere alternative oxyntomodulin-immunoglobulin Fc conjugates would have found in D2 linkers such as depicted above thereby coming to the same solution as present claim 4 (as far as novel).

In any case, in the absence of any apparent surprising or unexpected effect relating to the linker as presently claimed in claim 4, the linker appears to be arbitrarily designed and does not involve an inventive step. It is considered that an arbitrary selection of a solution from a number of possibilities, even in the absence of a hint to do so, is not inventive if not justified by hitherto unknown technical effect that distinguishes the claimed solution from the other solutions.

The same applies to the subject-matter of the dependent claims 5-26 which apparently does not contain any technical feature which could be regarded as inventive per se.

This is in particular due to the fact that no further technical effect can be acknowledged and/or have been demonstrated in the context of the subject-matter of said claims.

Re Item VIII

Certain observations on the international application

3 Clarity (Art. 6 PCT)

- 3.1 The term "analogs thereof" used in claims 16 and 17 renders their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term. There is no clear definition to which extent the therapeutics according to claims 16 and 17 may be modified while still being regarded as analogues. This has the effect that the person skilled in the art cannot decide clearly which compounds are to be covered by the claims and which are not.