

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/US2023/083468

International filing date (day/month/year)
12.12.2023

Priority date (day/month/year)
14.12.2022

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/68 A61P35/00

Applicant
MERCK SHARP & DOHME LLC

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:



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

Fernandez Rodriguez

Telephone No. -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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.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:

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>3, 4, 19-21</u>
	No: Claims	<u>1, 2, 5-18, 22-25</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-25</u>
Industrial applicability (IA)	Yes: Claims	<u>1-25</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 V

Reference is made to the following documents:

- D1 WO 2017/214456 A1 (ABBVIE INC [US]) 14 December 2017
- D2 YANMING WANG ET AL: "Development and Properties of Valine-Alanine based Antibody-Drug Conjugates with Monomethyl Auristatin E as the Potent Payload",
INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES,
vol. 18, no. 9, 25 August 2017, page 1860, XP055694898,
DOI: 10.3390/ijms18091860
- D3 WO 2019/197602 A1 (MEDIMMUNE LTD [GB]) 17 October 2019
- D4 ZAMBALDO CLAUDIO ET AL: "2-Sulfonylpyridines as Tunable, Cysteine-Reactive Electrophiles",
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,
vol. 142, no. 19, 17 April 2020, pages 8972-8979, XP093146492,
ISSN: 0002-7863, DOI: 10.1021/jacs.0c02721

V.1 Remark

For the assessment of present claims 23-25 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. 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.

The examination of the patentability of present claims 23-25 has been made assuming that said claims would be reformulated according to EPO practice when entering into the regional phase.

V.2 Novelty (Article 33(2) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2, 5-18 and 22-25 is not new in the sense of Article 33(2) PCT.

V.2.1 D1 discloses anti-CD98 antibody drug conjugates (ADCs), wherein an anti-CD98 antibody is conjugated to a Bcl-xL inhibitor (a cytotoxic drug) (see page 2, lines 25-27, and page 66, lines 3-5). Among several synthons useful for making said ADCs, D1 discloses synthon BI (see page 155, table A, example 2.12). The chemical structure of synthon BI is encompassed by formula I of present claim 1 with R¹ being a maleimide group, n being 2, R³ and R⁴ being both a methyl group (C₁ alkyl or alanine side chain) and R² being a Bcl-xL inhibitor. D1 further explains that linkers comprising the alanine-alanine dipeptide are enzymatically cleavable (see page 106, lines 6-14). D1 also discloses the preparation of anti-CD98 ADCs by reduction of interchain disulfide bonds of the antibody to form reactive cysteines that are then conjugated to the maleimide group of the synthon (see page 386, example 5). The chemical structure of synthon BI and its anti-CD98 ADC are thus encompassed within the scope of present claims 1, 2, 11-14 and 16.

D1 also discloses anti-CD98 ADCs, wherein an anti-CD98 antibody is conjugated to monomethylauristatin E (MMAE) (see page 18, lines 35-36). Among several linkers used for the preparation of anti-CD98 ADCs, D1 discloses linker IVb.6 (see page 108). Therefore, D1 implicitly discloses a compound wherein the linker IVb.6 is conjugated to MMAE. The chemical structure of said compound is encompassed by formula I of present claim 1 with R¹ being a maleimide group, n being 2, R³ and R⁴ being both a methyl group (C₁ alkyl) and R² being MMAE. Its corresponding anti-CD98 ADCs will then be prepared following the same procedure as disclosed above. Therefore, the chemical structure of this compound and its corresponding anti-CD98 ADC are encompassed within the scope of present claims 1, 2, 5-9 and 11-18.

D1 discloses a pharmaceutical composition comprising the ADC disclosed herein and a pharmaceutically acceptable carrier (see page 19, lines 8-9, and claim 91), as referred to in present claim 22.

D1 discloses said ADCs and pharmaceutical composition for use in a method for treating a subject having cancer, including breast, lung and ovarian cancers among others (see page 14, line 16 - page 15, line 4, page 38, line 29 - page 39, line 4, and claims 95-102). D1 also discloses said ADCs and pharmaceutical composition for use in a method for inhibiting or decreasing solid tumour growth in a subject having a solid tumour (see page 15, lines 8-13, page 39, lines 5-9, and claim 103). Said methods are encompassed within the scope of present claims 23-25.

The subject-matter of claims 1, 2, 5-9, 11-18 and 22-25 is therefore not new in view of D1.

V.2.2 D2 discloses anti-HER2 ADCs, wherein MMAE is conjugated to an anti-HER2 antibody via a linker comprising a dipeptide unit (see abstract). In particular, D2 discloses the dipeptide-based drug linker compound 12a (see figure 2) and its anti-HER2 ADC mil40-12a (see section: "2.2. Evaluation of Antibody-Drug Conjugates (ADC) Preparation"). The chemical structure of compound 12a is encompassed by formula I of present claim 1 with R^1 being a maleimide group, n being 2, R^3 being an isopropyl group (C_3 alkyl or valine side chain), R^4 being a methyl group (C_1 alkyl or alanine side chain) and R^2 being MMAE. D2 further explains that linkers comprising the valine-alanine dipeptide are enzymatically cleavable by cathepsin B (see abstract and section: "2.4. Cathepsin B Reactivity"). D2 also discloses the preparation of the anti-HER2 ADC mil40-12a (DAR = 3.91) by reduction of interchain disulfide bonds of the antibody to form reactive cysteines that are then conjugated to the maleimide group of compound 12a (see section: "2.2. Evaluation of Antibody-Drug Conjugates (ADC) Preparation"). The chemical structure of compound 12a and its anti-HER2 ADC mil40-12a are thus encompassed within the scope of present claims 1, 2, 5-9, 11, 13, 16 and 18.

D2 discloses in vitro efficacy studies (see section: "2.5. In Vitro Evaluation of Cytotoxic Agents and ADCs") and in vivo efficacy studies wherein the disclosed ADCs were administered to mice bearing breast tumour xenografts (see section: "2.6. In Vivo Evaluation"). Therefore, D2 teaches a composition comprising the disclosed ADCs (as referred to in present claim 22) and said ADCs for use in a method for treating cancer or a tumour, encompassed by present claims 23-25.

The subject-matter of claims 1, 2, 5-9, 11, 13, 16, 18 and 22-25 is therefore not new in view of D2.

V.2.3 D3 discloses ADCs, wherein a pyrrolobenzodiazepine (PBD) dimer is conjugated to an antibody via a linker comprising a dipeptide unit (see claims 15, 18 and 19). In particular, D3 discloses the dipeptide-based drug linker compounds 19, 27, 33, 34, 44 and 45 (see examples 1-4). The chemical structure of compounds 19, 27, 33, 34, 44 and 45 is encompassed by formula I of present claim 1 with R^1 being a maleimide group, n being 2, R^3 being an isopropyl group (C_3 alkyl or valine side chain), R^4 being a methyl group (C_1 alkyl or alanine side chain) and R^2 being a PBD dimer. D3 further explains that linkers comprising the valine-alanine dipeptide are enzymatically cleavable by cathepsin B (see page 66, lines 5-22). D3 also discloses the preparation of corresponding ADCs (ConjA-F) by reduction of interchain disulfide bonds of the antibody to form reactive cysteines that are then conjugated to the maleimide group of the peptide-based drug linker compounds (see example 5). The chemical structure of compounds 9, 27, 33, 34, 44 and 45 and their ADCs (ConjA-F) are thus encompassed within the scope of present claims 1, 2, 5, 10, 11, 13 and 16.

D3 discloses in vitro efficacy studies (see example 6) and in vivo efficacy studies wherein the disclosed ADCs were administered to mice bearing NCI-N87 human gastric carcinoma xenografts (see example 7). Therefore, D3 teaches a composition comprising the disclosed ADCs (as referred to in present claim 22) and said ADCs for use in a method for treating cancer or a tumour, encompassed by present claims 23-25.

The subject-matter of claims 1, 2, 5, 10, 11, 13, 16, 18 and 22-25 is therefore not new in view of D3.

V.3 Inventive step (Article 33(3) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-2 and 5-25 does not involve an inventive step in the sense of Article 33(3) PCT.

V.3.1 The subject matter of claims 1, 2, 5-18 and 22-25 is not new in the sense of Article 33(2) PCT and therefore not inventive.

V.3.2 D1-D3 can independently be considered to represent the prior art closest to the subject-matter of claims 3 and 4.

The subject-matter of claims 3 and 4 differs from the linker-payload compounds of D1-D3 in that R¹ is 5-cyano-6-(methylsulfonyl)picolinamide (claim 3) or 5-cyano-6-(methylsulfonyl)nicotinamide (claim 4), as the group for antibody conjugation.

The application discloses two compounds whose chemical structure is encompassed by present claims 3 and 4 with R¹ being 5-cyano-6-(methylsulfonyl)picolinamide (for linker-payload 2) or 5-cyano-6-(methylsulfonyl)nicotinamide (for linker-payload 3), n being 2, R³ and R⁴ being both a methyl group and R² being MMAE (see examples 2 and 3, linker-payloads 2 and 3). The application further discloses the conjugations of said linker-payloads to an antibody via engineered cysteine residues (see example 4, ADCs 5 and 6). The application shows experimental data regarding in vitro cytotoxicity assay of said ADCs and demonstrates that the specific ADCs 5 and 6 (which comprise the linker-payloads 2 and 3, respectively) are cytotoxic. From these results, it can thus be inferred that the specific alanine-alanine peptide linker is cleaved and the cytotoxic MMAE drug is released. However, this technical effect does not derive from the above-mentioned only technical difference, which is the moiety to conjugate the antibody and the linker-payload.

The objective technical problem to be solved in claims 3 and 4 in view of the linker-payloads of D1-D3 may therefore be regarded as the provision of a linker-payload compound comprising an alternative group (R¹) for selective conjugation to cysteine residues of a targeting moiety, such as an antibody or a protein.

As solution to this problem, claims 3 and 4 propose a linker-payload of formula I as referred to in present claim 1 with R¹ being 5-cyano-6-(methylsulfonyl)picolinamide (claim 3) or 5-cyano-6-(methylsulfonyl)nicotinamide (claim 4), as the group for conjugation to cysteine residues.

D4 discloses a series of 2-sulfonylpyridines that selectively react with cysteine residues via nucleophilic aromatic substitution (S_NAr) and, in particular, D4 discloses 2-methylsulfonyl-3-cyano-substituted pyridines (see abstract, and figures 1B and 1D). Additionally, D4 discloses the use of said 2-methylsulfonyl-3-cyano-substituted pyridines in a selective covalent modifier of adenosine deaminase (ADA), demonstrating the utility of this electrophilic group for targeting reactive cysteines (see abstract and figure 5). Since D4 already teaches the selectivity of said 2-sulfonylpyridines for cysteine residues, the 2-sulfonylpyridines specified in claims 3 and 4 are obvious alternatives to the cysteine-reactive maleimide and their transposition to an antibody is also obvious. In view of any of D1-D3 taken in combination with D4, the skilled person facing the above mentioned objective technical problem will consider, without the exercise of any inventive skill, to exchange the cysteine-reactive maleimide group of the linker-payloads of D1-D3 for a 2-sulfonylpyridine group, such as 2-methylsulfonyl-3-cyano-substituted pyridine.

Therefore, the subject-matter of claims 3 and 4 is obvious over any of D1-D3 taken in combination with D4 (Article 33(3) PCT).

V.3.3 D2 is considered to be the closest prior art to the subject-matter of claims 19-21.

V.3.3.1 Concerning claims 19-21 directed to the linker-payload 1 and the ADC 4 (as referred in the application, see pages 47 and 54, respectively), with R¹ being a maleimide group.

V.3.3.1.1 The subject-matter of claims 19 and 20 differs from the compound 12a and its anti-HER2 ADC mil40-12a of D2 in that R³ is a methyl group, and it thus comprises the alanine-alanine dipeptide linker.

Both the anti-HER2 ADC mil40-12a of D2 and the ADC 4 of the application are cytotoxic, and comprise a dipeptide linker that is enzymatically cleaved.

The objective technical problem to be solved in claims 19 and 20 in view of compound 12a and its anti-HER2 ADC mil40-12a of D2 may therefore be regarded as the provision of a linker-payload and an ADC comprising an alternative cleavable dipeptide linker.

As solution to this problem, claims 19 and 20 propose the specific linker-payload 1 and the specific ADC 4 (as referred to in the application), comprising an alanine-alanine dipeptide linker.

D1 already discloses the dipeptide alanine-alanine as an enzymatically cleavable linker (see page 106, lines 6-14). Additionally, D1 already discloses a maleimide-dipeptide linker and a linker-payload comprising said alanine-alanine dipeptide (see linker IVb.6 in page 108, and synthon BI in page 155, table A, example 2.12).

In view of D2 taken in combination with D1, the skilled person facing the above mentioned objective technical problem will consider, without the exercise of any inventive skill, to exchange the valine amino acid (R^3 group) of the valine-alanine linker of compound 12a and its anti-HER2 ADC mil40-12a of D2 for an alanine amino acid, in order to introduce the cleavable alanine-alanine dipeptide linker.

Therefore, the subject-matter of claims 19 and 20, regarding the linker-payload 1 and the ADC 4 (as referred in the application), is obvious over D2 taken in combination with D1 and does not involve an inventive step within the meaning of Article 33(3) PCT.

V.3.3.1.2 Dependent claim 21 does not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT with respect to inventive step. In the absence of any indication as to a technical effect being obtained by these features, claim 21 lacks an inventive step.

V.3.3.2 Concerning claims 19-21 directed to the linker-payloads 2 and 3, and the ADCs 5 and 6 (as referred in the application, see pages 50, 53 and 54), with R^1 being 5-cyano-6-(methylsulfonyl)picolinamide or 5-cyano-6-(methylsulfonyl)nicotinamide.

V.3.3.2.1 The above-mentioned subject-matter of claims 19 and 20 differs from the compound 12a and its anti-HER2 ADC mil40-12a of D2 in that R^3 is a methyl group, and in that R^1 is 5-cyano-6-(methylsulfonyl)picolinamide or 5-cyano-6-(methylsulfonyl)nicotinamide.

The anti-HER2 ADC mil40-12a of D2 and the ADCs 5 and 6 of the application are cytotoxic, and comprise a dipeptide linker that is enzymatically cleaved.

The objective technical problem to be solved in claims 19 and 20 in view of compound 12a and its anti-HER2 ADC mil40-12a of D2 may therefore be regarded as the provision of a linker-payload and an ADC comprising an alternative cleavable dipeptide linker and an alternative group (R^1) for selective conjugation to an antibody via cysteine residues.

Following a similar reasoning as in point V.3.3.1.1, in view of D2 taken in combination with D1, the skilled person will consider to exchange the valine amino acid (R^3 group) of the valine-alanine linker of compound 12a and its anti-HER2 ADC mil40-12a of D2 for an alanine amino acid, in order to introduce the cleavable alanine-alanine dipeptide linker. Following a similar reasoning as in point V.3.2, in view of D2 taken in combination with D4, the skilled person will consider to exchange the cysteine-reactive maleimide

group (R¹ group) of compound 12a and its anti-HER2 ADC mil40-12a of D2 for a 2-methylsulfonyl-3-cyano-substituted pyridine as the group for conjugation to an antibody via cysteine residues. However, there is no hint in the prior art (D1, D2 and D4) for the combination of two modifications.

Thus, the subject-matter of claims 19 and 20, regarding the linker-payloads 2 and 3, and the ADCs 5 and 6 (as referred in the application) is considered inventive (Article 33(3) PCT) over D1, D2 and D4.

V.3.3.2.2 The above-mentioned subject-matter of claim 21 is dependent on claim 20 (see point VIII.4) and as such also meet the requirements of the PCT with respect to inventive step (Article 33(3) PCT), concerning ADCs 5 and 6 (as referred to in the application).

Re Item VIII

VIII.1 The term "5-benzoylvaleric acid-AE ester", "lipophilic monomethyl aurstatin F", "nicotinamide phosphoribosyltransferase inhibitor (NAMPTi)" and "CC-1065", employed in claim 6, 15 and/or 17 renders their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by these terms.

VIII.2 The terms "CC-1065 analogue", "analog of dolastatin 10", "baccatin derivatives" and "taxane analogs" in claim 6 render its scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by these terms. Terms like analogues and derivatives include an unlimited number of compounds obtainable from another compound by some undetermined chemical modification (including compounds which are structurally remote from the starting material), functional derivatives (such as compounds, wherein hetero atoms are exchanged by alternative atoms), compounds with numerous different types of side groups etc. There is, however, no clear definition to which extent the compounds according to claim 6 may be modified while still being regarded as "analogues" or "derivatives". 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.

Consequently, claim 6 does not fulfil the requirements of Article 6 PCT.

VIII.3 Claim 6, 8, 15 and 17 contain spelling mistakes, for instance "benzoyl-aurstatin E ester", "monomethyl aurstatin F", and "aurstatin E". Claim 8 is also missing commas between the names of the specific auristatins mentioned.

VIII.4 The dependency of claims 21 seems erroneous. Claim 21 cannot be dependent of claim 19 because claim 21 defines p but claim 19 does not comprise said feature. It seems that claim 21 should depend on claim 20.