PATENT COOPERATION TREATY **TRANSLATION**

From the INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	**11 February 2023**
Applicant's or agent's file reference **AI22CN09631P**	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CN2022/132627	**17 November 2022**	**17 November 2021**

International Patent Classification (IPC) or both national classification and IPC
A61K47/68(2017.01)i;A61K39/395(2006.01)i;A61P35/00(2006.01)i

Applicant
CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.

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 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/	Date of completion of this opinion	Authorized officer

Form PCT/ISA/237 (cover sheet) (July 2022)

TRANSLATION

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International application No.
PCT/CN2022/132627

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(b)).

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:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CN2022/132627

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**

1. Statement

Novelty (N)	Claims	1-16	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims	None	NO

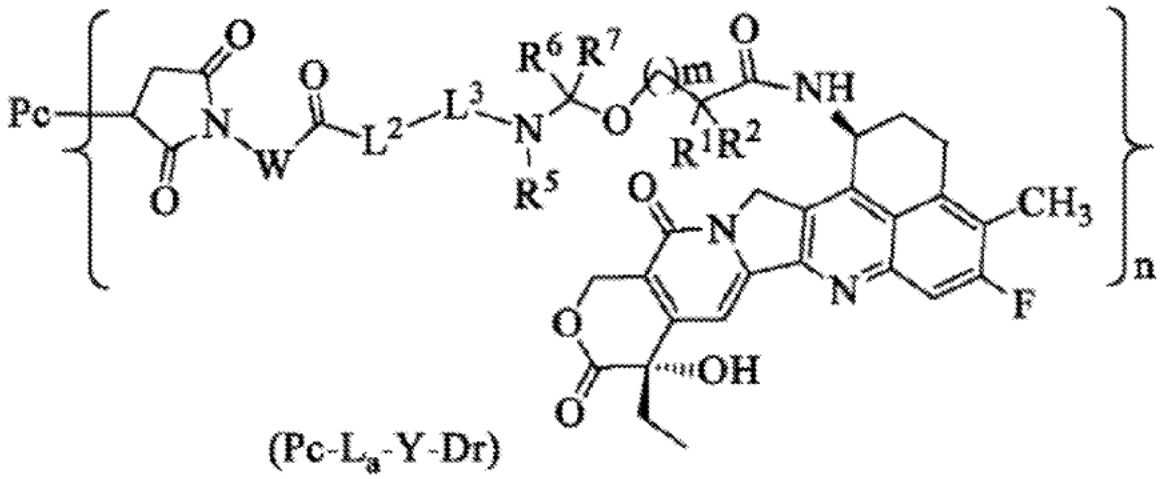
2. Citations and explanations:

Reference is made to the following documents:

1. WO 2020063676 A1
2. CN 112566942 A
3. WO 2016131409 A1

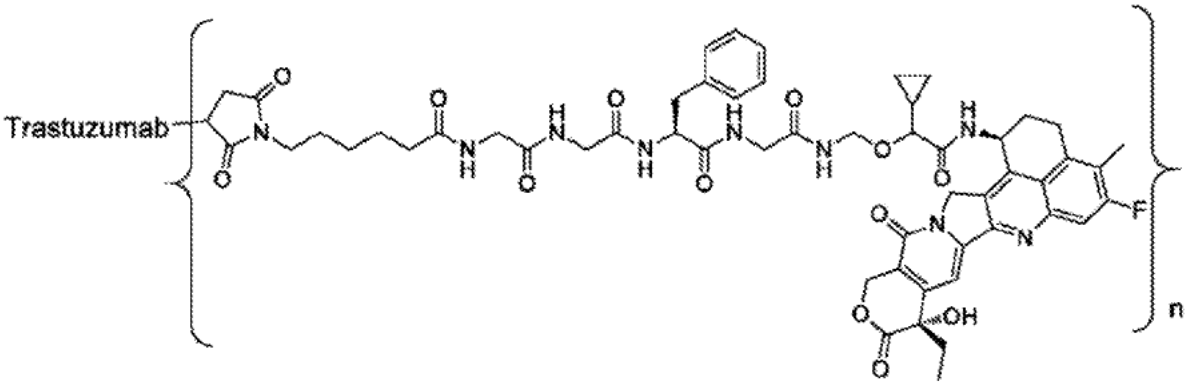
I. Novelty

D1 discloses a ligand-drug conjugate of an exatecan analogue, which ligand-drug conjugate has a structure of the following general formula:



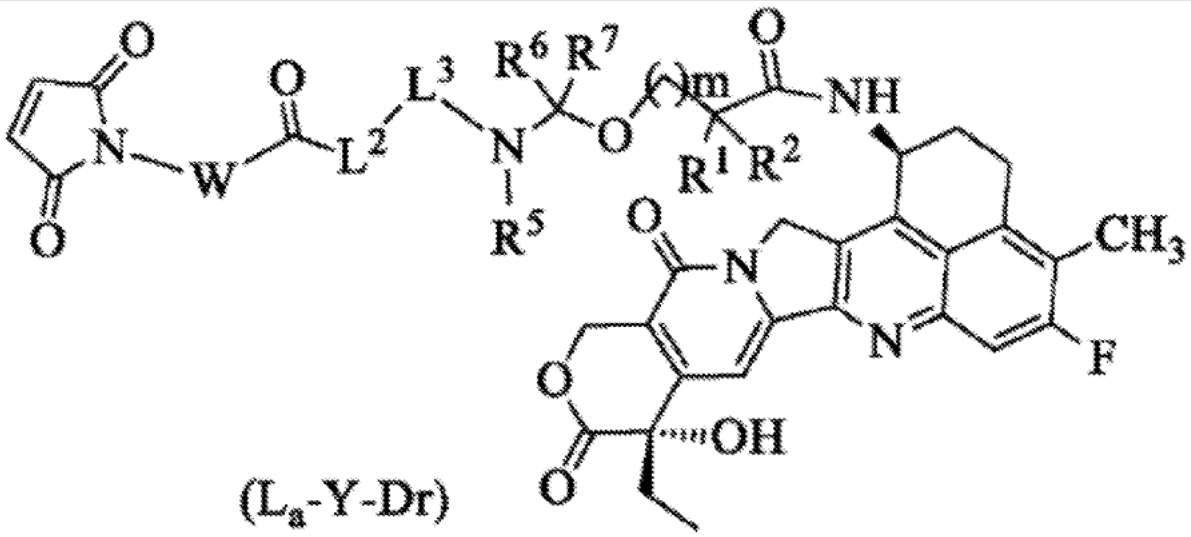
(Pc-L_a-Y-Dr)

wherein Pc is an antibody or a fragment that can be selected from HER2, HER3, or EGFR. The structure can specifically be



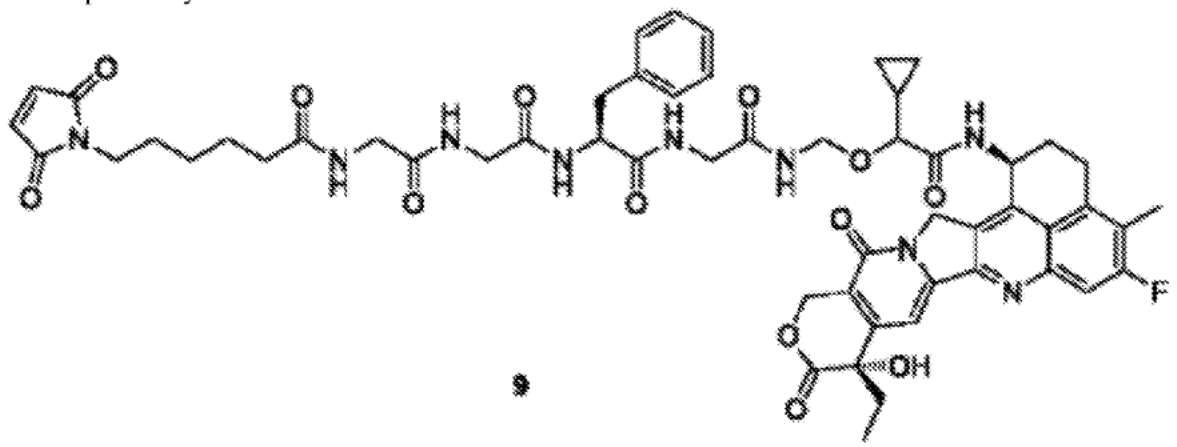
Moreover, D1 further discloses an intermediate structure thereof, which has a general formula as follows:

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**



$(L_a\text{-}Y\text{-}Dr)$

and can specifically be



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Moreover, D1 discloses a method for preparing the conjugate thereof and the use thereof in the preparation of an anti-tumor drug (see claims 22-28, 32-34 and 38-46).

However, the configuration of the conjugate disclosed in D1 is different from that of the conjugates of formulas I, Ia and Ib, and the compounds of formulas III, IIIa and IIIb involved in the present application, and formulas II, I-1, Ia-1 and Ib-1 and the structures of specific compounds are not disclosed. Therefore, claims 1-16 are novel (PCT Article 33(2)).

II. Inventive Step

D1 is used as the closest prior art. The configuration of the conjugate of formula I involved in claim 1 is different from that of the conjugate disclosed in D1, and the linking arm in the conjugate of formula II is different. The configuration of the conjugate thereof would have been determined by a person skilled in the art only according to the common configuration of exatecan in the art. The structure of the linking arm in the conjugate of formula II would have been determined by means of extension by a person skilled in the art only according to the selectable linking arm structures disclosed in D1. Moreover, using the corresponding pharmaceutical salt, hydrate, solvate, stereoisomer or isotopically labeled substance as a drug is a conventional technique. Therefore, claim 1 does not involve an inventive step (PCT Article 33(3)). On the basis of similar reasoning, claims 2, 3 and 7-9 also do not involve an inventive step (PCT Article 33(3)).

Claim 4 further defines the antibody structure thereof. D2 discloses that the HC/LC structures of HER2 and HER3 that can be conjugated to exatecan are respectively SEQ ID NOs: 1/2 and 3/4 (totally identical to SEQ ID NOs: 9, 10, 19 and 20 of the present application) (see description, paragraphs 597-613). D3 discloses the HV/LV and HCDR1-3/LCDR1-3 of EGFR that can be conjugated to a drug and SEQ ID NOs: 1/2 and 5-7/12-14 (totally identical to SEQ ID NOs: 27/28 and 21-23/24-26 of the present application) (equivalent to SEQ ID NOs: 9, 10, 19, and 20 of the present application) (see description, page 19). Therefore, a person skilled in the

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**

art would have been able to determine the specific antibody structure of the conjugate thereof according to the antibody structures disclosed in D2 and D3. Therefore, claim 4 also does not involve an inventive step (PCT Article 33(3)).

The antibody types involved in claims 5-6, the pharmaceutical composition involved in claim 10, the use involved in claims 11-15, and the preparation method involved in claim 16 are merely conventional techniques in the art. Therefore, claims 5-6, 10 and 11-16 also do not involve an inventive step (PCT Article 33(3)).

III. Industrial Applicability

Claims 1-16 can be used in the field of tumor therapy, and are industrially applicable (PCT Article 33(4)).