

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/EP2022/052170

International filing date (day/month/year)
31.01.2022

Priority date (day/month/year)
01.02.2021

International Patent Classification (IPC) or both national classification and IPC
INV. A61K51/10 C07D413/14

Applicant
BAYER 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 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

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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 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>1-22</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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 MEMBRENO ROSEMERY ET AL: "Toward the Optimization of Click-Mediated Pretargeted Radioimmunotherapy",
MOLECULAR PHARMACEUTICS, vol. 16, no. 5, 26 March 2019
(2019-03-26), pages 2259-2263, XP055784093, ISSN: 1543-8384, DOI:
10.1021/acs.molpharmaceut.9b00062
- D2 LIKO FLONJA ET AL: "Dendrimers as Innovative Radiopharmaceuticals in Cancer Radionanotherapy",
BIOMACROMOLECULES, vol. 17, no. 10, 20 September 2016
(2016-09-20), pages 3103-3114, XP055928735, ISSN: 1525-7797, DOI:
10.1021/acs.biomac.6b00929
Retrieved from the Internet:
URL:<https://pubs.acs.org/doi/pdf/10.1021/acs.biomac.6b00929>
- D3 C. WÄNGLER ET AL: "Antibody-Dendrimer Conjugates: The Number, Not the Size of the Dendrimers, Determines the Immunoreactivity",
BIOCONJUGATE CHEMISTRY, vol. 19, no. 4, April 2008 (2008-04), pages
813-820, XP055020206, ISSN: 1043-1802, DOI: 10.1021/bc700308q
- D4 WU C ET AL: "Metal-chelate-dendrimer-antibody constructs for use in radioimmunotherapy and imaging",
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 4, no. 3, 10
February 1994 (1994-02-10), pages 449-454, XP026646436, ISSN:
0960-894X, DOI: 10.1016/0960-894X(94)80014-6 [retrieved on 1994-02-10]
- D5 MYNERICH JENASEE ET AL: "Evaluation of Specific Activity and Stable Impurities in ²²⁵Ac Derived from ISAC and ²²⁹Th Decay",
JOURNAL OF MEDICAL IMAGING AND RADIATION SCIENCES, vol. 50,
no. 4, December 2019 (2019-12), XP085964033, ISSN: 1939-8654, DOI:
10.1016/J.JMIR.2019.11.115 [retrieved on 2019-12-17]
- D6 KHAN BEHLOL ED - MCCUAIG CARLY: "Biparatopic Targeting of Epidermal Growth Factor Receptor Positive Breast Cancer Cells using Domain I/II and Domain III Specific Antibody Conjugates",

JOURNAL OF MEDICAL IMAGING AND RADIATION SCIENCES, vol. 50, no. 4, December 2019 (2019-12), XP085963976, ISSN: 1939-8654, DOI: 10.1016/J.JMIR.2019.11.092 [retrieved on 2019-12-17]

- D7 WO 2019/090242 A1 (ADVANCED PROTEOME THERAPEUTICS INC [US]; KRANTZ ALEXANDER [US] ET AL.) 9 May 2019 (2019-05-09)
- D8 WO 2018/183906 A1 (UNIV CORNELL [US]) 4 October 2018 (2018-10-04)
- D9 WO 2020/106886 A1 (UNIV CORNELL [US]) 28 May 2020 (2020-05-28)
- D10 NIKKI A THIELE ET AL: "An Eighteen-Membered Macrocyclic Ligand for Actinium-225 Targeted Alpha Therapy", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 56, no. 46, 13 November 2017 (2017-11-13), pages 14712-14717, XP055543785, ISSN: 1433-7851, DOI: 10.1002/anie.201709532

The presently claimed multimeric macropa chelator-based radiopharmaceuticals have not been found in the available prior art. The presently claimed subject-matter therefore meets the requirements of Article 33.2 PCT for novelty.

With regard to inventive step, the present application proposes to solve the general problem of providing an agent for targeted radioimmunotherapy, by using a conjugate of a targeting moiety, i.e., an antibody, with a dendrimeric compound to which the chelator macropa is attached.

The closest prior art is found in a document, that also proposes targeted multimeric chelators for use in radioimmunotherapy.

According to D1, pretargeting using an huA33 immunoconjugate bearing a trans-cyclooctene-decorated dendritic scaffold (SShuA33-DEN-TCO) produced significantly higher tumoral activity concentrations at 120 h post-injection (23.0 ± 2.2 %ID/g) than those achieved with an analogous, dendrimer-lacking immunoconjugate (12.7 ± 2.6 %ID/g).

D2 uses conjugation of radiolabelled dendrimers to monoclonal antibodies for a more efficient targeting.

According to D3, the potential of radioimmunotherapy could be further improved by increasing the specific activity of the labeled proteins, either by coupling a large number of chelators which leads to a decreased immunoreactivity or by conjugating a small number of multimeric chelators. The results show that the dendrimer size does not influence the immunoreactivity of the derivatised antibody significantly over a wide molecular weight range, whereas the number of derivatisation sites has a crucial effect.

In D4, polyamidoamine dendrimers were modified chemically by reaction with DOTA and DTPA type bifunctional metal chelators and were coupled to monoclonal antibody 2E4 without loss of protein immunoreactivity. Both the DTPA- and DOTA-dendrimer-antibody constructs were easily labeled with ^{90}Y , ^{111}In , ^{212}Bi or cold Gd(III) suggesting use of this dendrimer-macrocycle for mAb guided radiotherapy or imaging.

Each of these documents can be chosen as closest prior art.

The presently claimed radioimmunotoxins can be distinguished from this closest prior art by the choice of the chelator: in the present application, macropa is used.

The examples of the present application do demonstrate an improvement of the presently claimed multimeric macropa chelators when compared to monomeric macropa chelators. They do, however, not demonstrate an effect when compared to the closest prior art. Therefore, the objective problem to be solved by the distinguishing technical feature, i.e., by the choice of macropa as chelator, is the provision of an alternative targeted multimeric chelator for use in radioimmunotherapy.

The use of macropa in targeted radioimmunotherapy is, however, already known from the cited prior art.

D5 uses a targeted (single) diaza crown ether chelator.

D6 prepares an antibody conjugate of monomeric macropa, labelled with ^{225}Ac .

D7 also attaches a single macropa on an antibody.

According to D8, paragraph [0169], the long half-life of ^{225}Ac necessitates its stable complex retention in vivo to avoid off-target damage to normal tissues arising from the release of free $^{225}\text{Ac}^{3+}$. Paragraph [0173] explains that due to the inherent stability of the $[\text{}^{225}\text{Ac}(\text{macropa})]^+$ complexes, macropa was incorporated into tumor-targeting constructs (see pages 61-62).

D9 also attaches a single macropa on an antibody.

In D10, the 18-membered macrocycle H₂macropa was investigated for ²²⁵Ac chelation in targeted alpha therapy (TAT). Radiolabeling studies showed that macropa, at sub-micromolar concentration, complexed all ²²⁵Ac (26 kBq) in 5 min at RT. ²²⁵Ac(macropa)⁺ remained intact over 7 to 8 days when challenged with either excess La³⁺ ions or human serum, and did not accumulate in any organ after 5 h in healthy mice.

The skilled person, starting from any of D1-D4 as closest prior art, and wishing to solve the objective problem of providing an alternative targeted multimeric chelator for use in radioimmunotherapy, would find in any of D5-D10 the incentive to choose macropa as chelator. The teachings of D8 or D10, which disclose an improved chelating capability of macropa towards alpha-emitting ions like ²²⁵Ac, would certainly confirm this choice.

Therefore, the presently claimed subject-matter does not involve an inventive step in the sense of Article 33.3 PCT.

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.

Patentability, in particular novelty and inventive step, of claims 17-22 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.