

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/EP2015/079773	International filing date (day/month/year) 15.12.2015	Priority date (day/month/year) 17.12.2014
International Patent Classification (IPC) or both national classification and IPC INV. A61K51/10 A61P35/00		
Applicant BAYER AS		

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Bliem, Barbara Telephone No. +31 70 340-0
---	--	--



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:
 - ☒ 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>1-27</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-27</u>
Industrial applicability (IA)	Yes: Claims	<u>1-27</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

- 1 For the assessment of the present claims 24 and 25 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, 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 24 and 25 has been made assuming that claims 24 and 25 would be reformulated according to EPO practice when entering into the regional phase.
- 2 Patentability, in particular novelty and inventive step, of claim 26 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the substance or composition.
- 3 Reference is made to the following documents:
 - D1 WO 2011/098611 A2 (ALGETA AS [NO]; RAMDAHL THOMAS [NO]) 18 August 2011 (2011-08-18)
 - D2 WO 2013/167754 A1 (ALGETA ASA [NO]) 14 November 2013 (2013-11-14)
 - D3 WO 2013/167755 A1 (ALGETA ASA [NO]) 14 November 2013 (2013-11-14)
 - D4 WO 2013/167756 A1 (ALGETA ASA [NO]) 14 November 2013 (2013-11-14)
 - D5 Greg T Hermanson: "Bioconjugate Techniques (3rd Edition) - Chapter 3: The Reactions of Bioconjugation", ProQuest ebrary. Web, 1 November 2013 (2013-11-01), XP55258103, [retrieved on 2016-03-14]
 - D6 MICHELLE T. MA ET AL: "Tripodal tris(hydroxypyridinone) ligands for immunoconjugate PET imaging with $^{89}\text{Zr}^{4+}$: comparison with desferrioxamine-B",

DALTON TRANSACTIONS: THE INTERNATIONAL JOURNAL
FOR INORGANIC, ORGANOMETALLIC AND BIOINORGANIC
CHEMISTRY,
vol. 44, no. 11, 17 October 2014 (2014-10-17), pages 4884-4900,
XP55255269,
GB
ISSN: 1477-9226, DOI: 10.1039/C4DT02978J

- 3.1 D1 discloses a method for the formation of a tissue-targeting thorium complex, said method comprising: a) forming an octadentate chelator comprising four hydroxypyridinone (HOPO) moieties, substituted in the N-position with a methyl group, and a coupling moiety terminating in an amino group; b) coupling said octadentate chelator to at least one tissue-targeting peptide or protein via isothiocyanate coupling whereby to generate a tissue-targeting chelator; and c) contacting said tissue-targeting chelator with an aqueous solution comprising an ion of at least one alpha-emitting thorium isotope (examples 2-10).

The subject-matter of claim 1 differs from D1 in that the coupling group terminates in a carboxylic acid group and a tissue-targeting chelator is formed by reacting an amine group of the tissue-targeting peptide or protein and the chelator by means of at least one amide-coupling reagent.

D2-D4 disclose an octadentate chelator comprising four HOPO moieties, substituted in the N-position with a hydroxyalkyl group, and a coupling moiety terminating in a carboxylic acid group (D3: example 8; D4: example 11; D5: example 18).

The subject-matter of claim 1 differs from D2-D4 respectively in that the HOPO moieties are substituted in the N-position with a C₁-C₃ alkyl group. For the respective chelator no coupling reaction to a tissue targeting peptide or protein is disclosed in D2-D4.

D6 discloses a method for the formation of a tissue targeting zirconium complex, said method comprising: a) forming a chelator comprising three HOPO moieties, substituted in the N-position with a methyl group, and a coupling moiety terminating in a carboxylic acid group; b) coupling said chelator to trastuzumab via reduced cysteine side chains whereby to generate a tissue-targeting chelator; and c) contacting said tissue-targeting chelator with an aqueous solution comprising ⁸⁹Zr (abstract; chart 1; page 4896, section "Immunoconjugate preparation"; page 4897, left column, paragraph 2).

The subject-matter of claim 1 differs from D6 in that a tissue targeting thorium complex is formed. Moreover, the chelator of D6 comprises only three HOPO moieties and is coupled to the tissue-targeting peptide or protein via reduced cysteine side chains.

None of the prior art documents discloses the method of claim 1, a tissue-targeting thorium complex formed or formable by said method as referred to in claim 12, a pharmaceutical formulation comprising said tissue-targeting thorium complex as referred to in claim 19, the medical use of said tissue-targeting thorium complex as referred to in claims 22, 24 and 26, or a kit as referred to in claim 27.

The subject-matter of claims 1-27 is therefore new in view of the prior art (Article 33(2) PCT).

3.2 D1 is regarded as being the prior art closest to the subject-matter of claim 1.

The problem to be solved by the present invention may be the provision of a method for the formation of a (more stable) tissue-targeting thorium complex.

As solution to said problem, the invention proposes coupling an octadentate chelator comprising four HOPO moieties, such as the chelator disclosed in D1, and a coupling moiety terminating in a carboxylic acid group, to a tissue-targeting peptide or protein via an amine reaction.

Octadentate chelators comprising four HOPO moieties and a coupling moiety terminating in a carboxylic acid group are disclosed in the prior art (D2-D4) to enable alternative coupling chemistry via formation of an amide bond. Said coupling chemistry is generally known to the skilled person, as exemplified by textbook knowledge (e.g. D5: table 3.1; page 229 - page 240).

In view of D2-D4, the skilled person facing the above-mentioned problem would modify the method of D1 in order to provide a method comprising the steps of a) forming a chelator comprising HOPO moieties, substituted in the N-position with a methyl group, and a coupling moiety terminating in a carboxylic acid group; b) coupling said chelator to a tissue-targeting peptide or protein by means of at least one amide-coupling reagent whereby to generate a tissue-targeting chelator, and c) contacting said tissue-targeting chelator with an aqueous solution comprising an ion of at least one alpha-emitting thorium isotope.

Therefore the subject-matter of claim 1 is obvious over the prior art and does not involve an inventive step within the meaning of Article 33(3) PCT.

Claims 2-27 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.