

PATENT COOPERATION TREATY

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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/EP2016/082835	International filing date (day/month/year) 29.12.2016	Priority date (day/month/year) 05.01.2016
International Patent Classification (IPC) or both national classification and IPC INV. B01D15/18 A61K51/06 B01D15/36 B01J39/05 B01J41/05 A61K51/12 G21G1/00		
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 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 Fourgeaud, Damien Telephone No. +49 89 2399-0	
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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>1-28</u>
	No: Claims	<u>29-31</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-31</u>
Industrial applicability (IA)	Yes: Claims	<u>1-31</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

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

1. The following documents are cited in the international search report:

- D1 ROY H LARSEN ET AL: "Preparation of TH 227-labeled radioimmunoconjugates, assessment of serum stability and antigen binding ability",
CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS, LIEBERT, US,
vol. 22, no. 3, 1 June 2007 (2007-06-01), pages 431-437, XP002639642,
DOI: 10.1089/CBR.2006.321
[retrieved on 2007-07-26]
- D2 BAGHERI REZA ET AL: "Production of ^{223}Ra from ^{226}Ra in Tehran Research Reactor for treatment of bone metastases",
JOURNAL OF RADIOANALYTICAL AND NUCLEAR CHEMISTRY, AKADEMIAI KIADO RT, HU,
vol. 304, no. 3, 14 January 2015 (2015-01-14), pages 1185-1191,
XP035496597,
ISSN: 0236-5731, DOI: 10.1007/S10967-015-3931-X
[retrieved on 2015-01-14]
- D3 EP 2 564 396 A1 (ALGETA ASA [NO]) 6 March 2013 (2013-03-06)
- D4 US 5 809 394 A (BRAY LANE A [US] ET AL) 15 September 1998 (1998-09-15)
- D5 HORWITZ E P ET AL: "Purification of radionuclides for nuclear medicine: The multicolumn selectivity inversion generator concept",
CZECHOSLOVAK JOURNAL OF PHYSICS, KLUWER ACADEMIC PUBLISHERS-CONSULTANTS BUREAU, NE,
vol. 53, no. 1, 1 January 2003 (2003-01-01), pages A713-A716,
XP019499324,
ISSN: 1572-9486, DOI: 10.1007/S10582-003-0091-Y

2.1. D1 discloses a method for the preparation of ^{227}Th (see dedicated paragraph on page 432) comprising the production of a solution comprising ^{227}Ac , ^{223}Ra and ^{227}Th , passage of this solution on an anion-exchange column comprising an AG-1x8 resin on which ^{227}Th adsorbs, whereby ^{227}Ac and ^{223}Ra do not bind, and ^{227}Th is extracted using a solution of 12M HCl.

2.2. Present claim 29 is directed to a product, namely ^{227}Th comprising less than a given threshold of ^{227}Ac . It is not possible to distinguish a product as called for in present claim 29 from the ^{227}Th product extracted from the column of D1. The quantity of ^{227}Ac only represents a kind of impurity whose content usually does not confer novelty to the claimed product.

In the absence of technical features related to a product and not to the quantity of other impurities, that would allow a distinction between ^{227}Th claimed and ^{227}Th of D1, novelty of claim 29 cannot be recognized (Article 33(2) PCT).

2.3. The same argumentation applies *mutatis mutandis* to dependent claim 30, and to claim 31 directed to a pharmaceutical composition comprising the ^{227}Th of claim 29. These claims are not novel too (Article 33(2) PCT).

2.4. It is also not possible to distinguish ^{227}Th produced in D2 (see detailed description below) and in particular retained on the cation-exchanger column, or ^{227}Th produced in D3 (see [0087]) from ^{227}Th as claimed in present claims 29 and 31. Thus for the same reasons as above, these claims lack novelty over each of D2 and D3 (Article 33(2) PCT).

3.1. As to claim 1, its subject-matter differs from D1's disclosure in that ^{227}Th extracted from the anion-exchange column is then sent to a cation-exchange column on which it remains bound, while ^{227}Ac and ^{223}Ra elute, then ^{227}Th is extracted using an aqueous buffer solution.

The technical effect linked to this difference is the obtention of ^{227}Th in a very pure form i.e. with substantial absence of the other radionuclides. Accordingly, the problem to be solved by the present application may be seen as to provide an improved method for the obtention of ^{227}Th .

3.2. The solution proposed is thus to carry out a further purification step of the ^{227}Th bound on the anion-exchange column, by eluting it and passing the eluate on a cation-exchange column.

This solution cannot be considered as inventive in view of D2: this document discloses a general method for the obtention of ^{223}Ra comprising a first anion-exchange step where ^{227}Th is bound, while ^{227}Ac and ^{223}Ra pass through the column, and these fractions are then treated on a cation-exchange column. While the process disclosed is different from the process of claim 1, it is the teaching of D2 that is very interesting: It is stated clearly that ^{227}Th is retained by the cation-exchanger (see § bridging p.1189-1190 and following paragraphs, as well as fig. 6 and 7; see also p. 1186, left-hand column, first full paragraph: "Thorium is adsorbed on the cation-exchanger in all HNO_3 concentrations") while ^{223}Ra and its daughters are eluted from the column. Accordingly, a skilled person wishing to solve the above-mentioned problem, namely wishing to further purify ^{227}Th , would obviously take this statement into account and then carry out a further cation-exchange step on the ^{227}Th -eluate of the anion-exchange step. Eluting with an aqueous buffer solution the ^{227}Th from the cation-exchanger is only a matter of optimization of the process, and belongs to the know-how of the skilled practitioner. Consequently, the subject-matter of present claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

3.3. Dependent claims 2-28 appear to relate to minor process adaptations which either belong to the general knowledge of the person skilled in the art, or are known for instance from D3, from the same applicant, see in particular the claims of this document.

Accordingly these claims do not appear to contain any additional features which, in combination with the features of claim 1, to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).

3.4. The industrial applicability is obvious since ^{227}Th finds application in the medical field.

Re Item VIII

Certain observations on the international application

4.1. Present claims 3, 4 and 6 do not comply with the requirements of clarity of Article 6 PCT for the following reasons: Claims 3 and 4 relate to a percentage of radionuclide eluted, but this is not a process feature, rather a *desiderata*. It is however not clear which specific measures related to the process claimed are necessary in order to reach this result.

As to claim 6, it is also not related with the process of producing ^{227}Th but rather with the intended use of the product obtained.

Accordingly it is unclear which limitations are intended to be given to the claimed process for said claims 3, 4 and 6 (Article 6 PCT).

4.2. In claim 21, two sentences are present. The second one is only seen as optional. Moreover it is in part in contradiction with the previous sentence since "does not comprise any significant amount of " clearly covers the fact that some alcohol may be present, while the second sentence is clearer and excludes the presence of methanol .

The manner of claiming first do not comply with Rules 6.3 and 6.4 PCT, and moreover the two embodiments claimed therein do not comply with Article 6 PCT.