

**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P114435PC00	<b>FOR FURTHER ACTION</b> see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/NL2018/050137	International filing date ( <i>day/month/year</i> ) 6 March 2018 (06-03-2018)	(Earliest) Priority Date ( <i>day/month/year</i> ) 6 March 2017 (06-03-2017)
Applicant  ACADEMISCH ZIEKENHUIS LEIDEN H O D N LUMC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out 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))

b.  This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c.  With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2.  **Certain claims were found unsearchable** (See Box No. II)

3.  **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- the text is approved as submitted by the applicant  
 the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant  
 the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_  
 as suggested by the applicant  
 as selected by this Authority, because the applicant failed to suggest a figure  
 as selected by this Authority, because this figure better characterizes the invention
- b.  none of the figures is to be published with the abstract

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/NL2018/050137

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out 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).
2.  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.
3. Additional comments:

# INTERNATIONAL SEARCH REPORT

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## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No  
PCT/NL2018/050137

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61K38/55 A61P31/14  
ADD.  
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED  
Minimum documentation searched (classification system followed by classification symbols)  
A61K A61P  
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, Sequence Search, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/020289 A2 (UNIV TORONTO [CA]; SIDHU SACHDEV [CA]; BEATTY LINDA [CA]; ERNST ANDREA) 16 February 2012 (2012-02-16) cited in the application claims 1-2; figures 6,13,21; sequences 27,28,95,96,139	1-15
A	----- Mark Kemp ET AL: "Recent Advances in the Discovery of Deubiquitinating Enzyme Inhibitors" In: "PROGRESS IN MEDICINAL CHEMISTRY.", 1 January 2016 (2016-01-01), ELSEVIER, AMSTERDAM., NL, XP055333853, ISSN: 0079-6468 vol. 55, pages 149-192, DOI: 10.1016/bs.pmch.2015.10.002, -----	1-15

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search <b>20 August 2018</b>	Date of mailing of the international search report <b>28/08/2018</b>
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer <b>Vandenbogaerde, Ann</b>
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2018/050137

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012020289 A2	16-02-2012	CA 2807774 A1	16-02-2012
		EP 2603519 A2	19-06-2013
		EP 2719707 A2	16-04-2014
		EP 3366697 A1	29-08-2018
		US 2013225436 A1	29-08-2013
		WO 2012020289 A2	16-02-2012
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**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2, 7, 13(completely); 5, 6, 9-12, 15(partially)

An inhibitor comprising a beta-grasp fold, wherein said fold comprises region 1 (amino acids 2-14), region 2 (amino acids 42-49), and region 3 (amino acids 62-76) of the amino acid sequence set forth in SEQ ID NO:1, wherein the inhibitor comprises one or more amino acid substitutions in said regions as compared to the amino acid sequence set forth in SEQ ID NO:1, and wherein said substitutions include an amino acid substitution of A to F at the amino acid position corresponding to 46 of SEQ ID NO: 1 and/or an amino acid substitution of E to Y at the amino acid position corresponding to 64 of SEQ ID NO: 1; the nucleic acid encoding said inhibitor, a vector expressing said nucleic acid, an in vitro cell line/non-human cell/non-human organism expressing said vector, a pharmaceutical composition comprising the inhibitor; its the use for inhibiting the biological activity of a viral protein, and its use in therapy; a method for identifying the inhibitor  
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2. claims: 3, 4, 8, 14(completely); 5, 6, 9-12, 15(partially)

An inhibitor comprising a beta-grasp fold, wherein said fold comprises region 1 (amino acids 2-14), region 2 (amino acids 42-49), and region 3 (amino acids 62-76) of the amino acid sequence set forth in SEQ ID NO:1, wherein the inhibitor comprises one or more amino acid substitutions in said regions as compared to the amino acid sequence set forth in SEQ ID NO:1, and wherein said substitution include an amino acid substitution of R to G at the amino acid position corresponding to 74 of SEQ ID NO: 1; the nucleic acid encoding said inhibitor, a vector expressing said nucleic acid, an in vitro cell line/non-human cell/non-human organism expressing said vector, a pharmaceutical composition comprising the inhibitor; its the use for inhibiting the biological activity of a viral protein, and its use in therapy; a method for identifying the inhibitor  
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