PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2019/082969	28.11.2019	28.11.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/155 A61P35/00 A61P35/02 C07C335/32

Applicant
CENTRE LEON BERARD

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 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 notifed 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
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Uryga-Polowy, V Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2019/082969

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(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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13, 21
	No:	Claims	14-20
Inventive step (IS)	Yes:	Claims	1-13, 21
	No:	Claims	14-20
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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.

1 Cited documents

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure:

D1: WO 01/07029 A2 (KADMUS PHARMACEUTICALS INC [US]) 1 February 2001 (2001-02-01)

D2: WO 2012/047630 A2 (TEINTZE MARTIN [US]; WILKINSON ROYCE A [US]; LABIB MOHAMED [US]) 12 April 2012 (2012-04-12)

D3: DOMANSKA U M ET AL: "A review on CXCR4/CXCL12 axis in oncology: no place to hide", EUROPEAN JOURNAL OF CANCER, ELSEVIER, AMSTERDAM, NL, vol. 49, no. 1, 1 January 2013 (2013-01-01), pages 219-230, XP002724533, ISSN: 0959-8049, DOI: 10.1016/J.EJCA.2012.05.005 [retrieved on 2012-06-09]

D4: ABU KHALAF R ET AL: "Discovery of new cholesteryl ester transfer protein inhibitors via ligand-based pharmacophore modeling and QSAR analysis followed by synthetic exploration",EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 45, no. 4, 1 April 2010 (2010-04-01), pages 1598-1617, XP026932335,ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2009.12.070 [retrieved on 2010-01-14]

D5: CARMELA SATURNINO ET AL: "Antioxidant activity of thioureidic derivatives I",IL FARMACO, vol. 58, no. 9, 1 September 2003 (2003-09-01), pages 823-828, XP055588617,FR ISSN: 0014-827X, DOI: 10.1016/S0014-827X(03)00139-3

2 Novelty - Article 33(2) PCT

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 14-20 is not new within the meaning of Article 33(2) PCT.

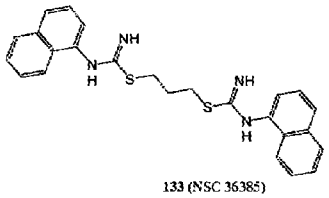
2.2 Claims 14-20 are directed to compounds per se of general formula (I). Many such compounds could be found in the STN database, and in particular the compounds with a CAPLUS publication, having the following Registry Numbers:

1613471-67-2, 1360588-38-0, 1360588-33-5, 857397-58-1,744948-04-7 , 732983-95-8 , 675881-89-7 , 675881-88-6 ,675881-87-5 ,675881-85-3 , 404888-64-8 ,201943-51-3 ,148720-05-2 ,109698-65-9 ,106936-74-7 , 106936-73-6 ,96370-20-6 ,96061-55-1 ,94675-92-0 ,63498-33-9 ,7478-44-6 , 6272-79-3 ,6270-93-5 ,908-20-3 ,900-43-6 ,856-52-0 ,854-41-1 ,852-54-0

Further compounds have been found corresponding to the definition of present claim 14 listed in particular in chemical libraries , which also result in a lack of novelty for the present claims 1-14.

2.3 Documents D4-D5 are cited as exemplary documents.

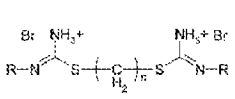
D4 discloses compound 133 (NSC 36385) as defined p.1606 fig.4 of D4:

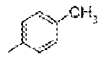
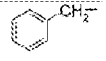
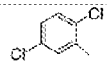
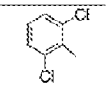
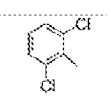


133 (NSC 36385)

The subject-matter of claims 14-20 is not novel over D4.

D5 discloses compounds 2-6 as defined in table 5 p.827 of D5:



N° Composto	n	R
2	8	
3	10	
4	8	
5	8	
6	9	

The subject-matter of claims 14-16, 19, 20 is not novel over D5.

2.4 No prior art document discloses the claimed compound for use in treating cancer as presently claimed, so that the subject-matter of claims 1-13 appears to be new within the meaning of Article 33(2) PCT.

The specific compounds of claim 21 are also not known, so that the subject-matter of claim 21 appears to be new within the meaning of Article 33(2) PCT.

3 Inventive step - Article 33(3) PCT

Document D3 or D6 can be considered to be the closest prior art.

D3 and D6 both disclose the use of CXCR4 inhibitors for treating cancer, such as e.g. lymphoma or myeloma in D3 or breast metastasis in lung in D6.

The subject-matter of claims 1-13 and 21 differs in the structure of the active compounds.

There is no special technical effect resulting from this difference.

The problem to be solved may therefore be regarded as the provision of an alternative CXCR4 inhibitor for treating cancer.

The solution is the use of compounds of formula (I) as defined in claim 1. Data in the application support the efficacy of the claimed compounds and the claims as presently formulated are considered as a reasonable generalization from the examples of the application.

There is no hint in the prior art to use compounds of general formula (I) which are known e.g. from D4 or D5 in other unrelated fields, or to modify the CXCR4 inhibitors known from D2 or the compounds of D1 (known to modify mitochondrial membrane permeability), for treating cancer

Therefore, the solution proposed in claims 1-13 and 21 appears to involve an inventive step within the meaning of Article 33(3) PCT.

4 **Re Item VII**

Form of the claims

4.1 Claims 12 and 13 relate to subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv) 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.

4.2 The attention of the Applicant is further drawn to the fact that the therapeutic application of the products should be clearly defined in the form of a real pathological condition (disease) and no functional definition defining the therapeutic application by a mechanism of action, such as "inhibiting mitochondrial complex I" can be accepted (see objection for lack of clarity hereafter).

5 **Re Item VIII**

Clarity - Article 6 PCT

5.1 The application does not meet the requirements of Article 6 PCT, because the subject matter of claims 5 and 13 is not clear.

5.2 The definition in claim 5 of Ar1 or Ar2 as being a phenyl or naphthyl substituted by [...] a group COOR**1** is drafted as dependent on claim 1 but COOR1 is broader than the COOR**3** group which is used in the definition of claim 1, resulting in an inconsistency within the set of claims. This inconsistency should be removed.

5.2.1 The therapeutic application of the products in claim 13 is functionally defined by a mechanism of action: "inhibiting mitochondrial complex I". It is not fully clear which diseases do exactly fall within the scope of this definition (Guidelines G-II, 4.2).