

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

Moore, Michael
Keltie LLP
No. 1 London Bridge
London SE 18 7JA
ROYAUME UNI

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing (day/month/year) 20 September 2022 (20-09-2022)
Applicant's or agent's file reference P53636WOA/MRM	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/GB2022/051167	International filing date (day/month/year) 6 May 2022 (06-05-2022)
Applicant EXSCIENTIA AI LIMITED	

- ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.
How? Directly to the International Bureau preferably through ePCT, or on paper to:
 The International Bureau of WIPO, 34 chemin des Colombettes, 1211 Geneva 20, Switzerland
For more detailed instructions, see the *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.
- ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
- ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
 - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
 - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
- Reminders**
 The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.
 Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).
 Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.
 Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer BENITEZ SIERRA, Olga Maria Tel: +49 (0)89 2399-5715
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PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P53636WOA/MRM	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/GB2022/051167	International filing date (<i>day/month/year</i>) 6 May 2022 (06-05-2022)	(Earliest) Priority Date (<i>day/month/year</i>) 6 May 2021 (06-05-2021)
Applicant EXSCIENTIA AI LIMITED		

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 3 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 43.6bis(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/GB2022/051167

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 A61K31/437 A61P31/18 A61P35/00 A61P37/00 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) A61P C07D A61K		
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, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/240586 A1 (MANKIND PHARMA LTD [IN]) 3 December 2020 (2020-12-03) structurally close examples e.g. compounds 1051, 1147, 1177; claims 1, 13 -----	1-16
A	WO 2009/073300 A1 (VERTEX PHARMA [US]; JIMENEZ JUAN-MIGUEL [GB] ET AL.) 11 June 2009 (2009-06-11) claims 1, 70; compounds 2-3 -----	1-16
A	WO 2011/139273 A1 (VERTEX PHARMA [US]; JIMENEZ JUAN-MIGUEL [GB]; MILLER ANDREW [GB]) 10 November 2011 (2011-11-10) cited in the application claims 1, 43; compounds 1-8 -----	1-16
☐ 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 "E" earlier application or patent but published on or after the international filing date "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) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "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 "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 "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 "&" document member of the same patent family		
Date of the actual completion of the international search 10 September 2022		Date of mailing of the international search report 20/09/2022
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 Grégoire, Ariane

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2022/051167

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2020240586 A1	03-12-2020	AU 2020284742 A1	03-02-2022
		BR 112021023635 A2	01-02-2022
		CA 3141571 A1	03-12-2020
		CN 114174294 A	11-03-2022
		EP 3976612 A1	06-04-2022
		JP 2022534510 A	01-08-2022
		TW 202110838 A	16-03-2021
		US 2022235046 A1	28-07-2022
		WO 2020240586 A1	03-12-2020
		ZA 202109183 B	31-08-2022
WO 2009073300 A1	11-06-2009	AR 069174 A1	06-01-2010
		AU 2008331733 A1	11-06-2009
		CA 2704266 A1	11-06-2009
		CL 2008003280 A1	04-01-2010
		CN 101903384 A	01-12-2010
		EP 2215089 A1	11-08-2010
		ES 2389992 T3	05-11-2012
		JP 5444239 B2	19-03-2014
		JP 2011502994 A	27-01-2011
		KR 20100093552 A	25-08-2010
		NZ 585063 A	25-05-2012
		TW 200924762 A	16-06-2009
		US 2009291937 A1	26-11-2009
		US 2012149680 A1	14-06-2012
		WO 2009073300 A1	11-06-2009
		ZA 201003050 B	27-07-2011
WO 2011139273 A1	10-11-2011	AU 2010352577 A1	19-01-2012
		CA 2761074 A1	10-11-2011
		CN 102471342 A	23-05-2012
		EP 2566866 A1	13-03-2013
		JP 2013525481 A	20-06-2013
		WO 2011139273 A1	10-11-2011

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/GB2022/051167	International filing date (day/month/year) 06.05.2022	Priority date (day/month/year) 06.05.2021
International Patent Classification (IPC) or both national classification and IPC INV. C07D471/04 A61K31/437 A61P31/18 A61P35/00 A61P37/00		
Applicant EXSCIENTIA AI LIMITED		

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 Grégoire, Ariane 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>1-16</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-16</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-16</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

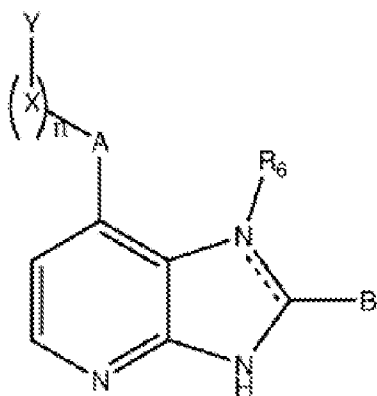
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

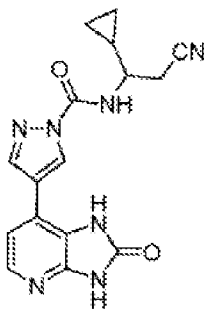
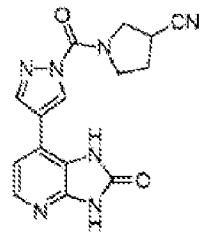
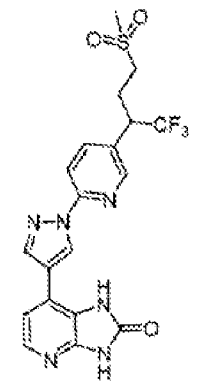
- D1 WO 2020/240586 A1 (MANKIND PHARMA LTD [IN]) 3 December 2020 (2020-12-03)
- D2 WO 2009/073300 A1 (VERTEX PHARMA [US]; JIMENEZ JUAN-MIGUEL [GB] ET AL.) 11 June 2009 (2009-06-11)
- D3 WO 2011/139273 A1 (VERTEX PHARMA [US]; JIMENEZ JUAN-MIGUEL [GB]; MILLER ANDREW [GB]) 10 November 2011 (2011-11-10) cited in the application

1) Novelty (Art. 33 (1) and (2) PCT) :

Document D1 discloses Janus Kinase 1 inhibitors of formula I which differ from those presently claimed

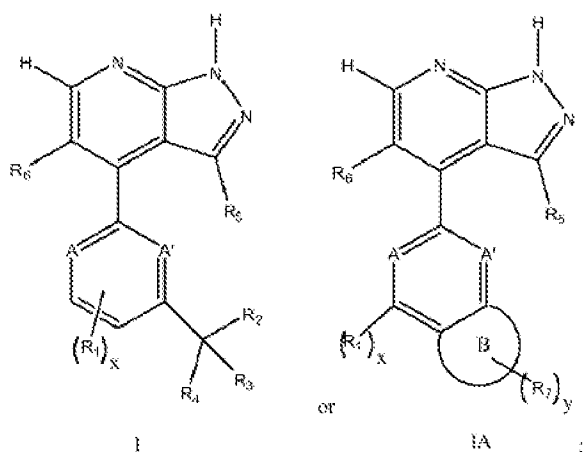


The structurally closest compounds differ from those presently claimed in the nature of the substituent attached to the pyrazole. Either an amido linker is present (see for instance compounds 1051 or 1177) or a pyridinyl ring instead of the ring CR₅R₆ is present (see for instance compound 1147).

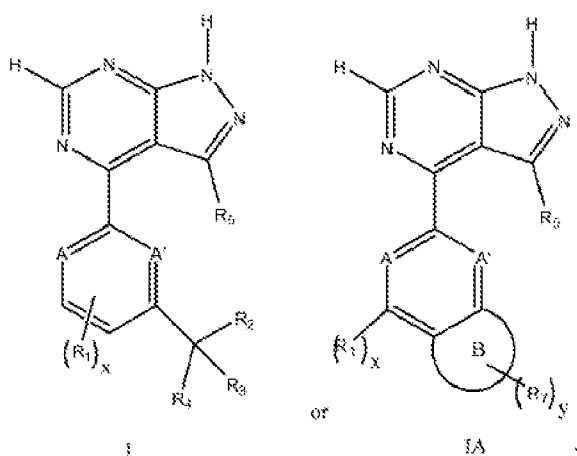
1051.		N-(2-cyano-1-cyclopropylethyl)-4-(2,3-dihydro-2-oxo-1H-imidazo[4,5-b]pyridin-7-yl)-1H-pyrazole-1-carboxamide
1177.		1-(4-(3H-imidazo[4,5-b]pyridin-7-yl)-1H-pyrazole-1-carbonyl)pyrrolidine-3-carbonitrile
1147.		7-(1-(5-(1,1,1-trifluoro-4-(methylsulfonyl)butan-2-yl)pyridin-2-yl)-1H-pyrazol-4-yl)-1H-imidazo[4,5-b]pyridin-2(3H)-one

The presently claimed are considered to be a novel selection over those of Document D1 in view of the specific definition of the substituent $-(CH_2)_n-ER_5R_6$ in combination with the other cyclic elements.

Document D2 discloses PKC- θ inhibitors of formulae I and IA which differ from those presently claimed in the nature of the central bicyclic ring system and the heteroaryl rings attached to them which are not based on a five-membered heteroaryl.



Document D3 also discloses PKC- θ inhibitors of formulae I and IA which differ from those presently claimed in the nature of the central bicyclic ring system and the heteroaryl rings attached to them which are not based on a five-membered heteroaryl.



The requirements of Art. 33(2) PCT are complied with.

2) Inventive Step (Art. 33 (1) and (3) PCT) :

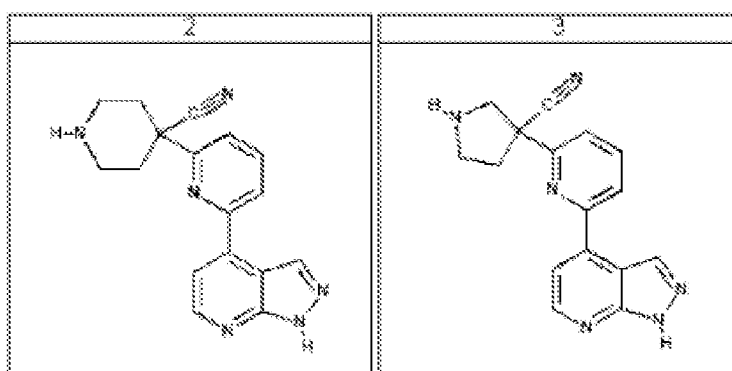
Document D1 might be considered as the closest prior art because it discloses structurally close kinase inhibitors having the same central core structure (bicyclic ring linked to an aryl/heteroaryl ring) and are useful for instance in the treatment of cancer, inflammatory diseases or autoimmune diseases (see page 88).

The compounds presently claimed differ from those of the art in the presence of a specific substituent E5R6 in position meta of the five-membered heteroaryl group comprising a nitrogen. They are moreover active as PKC inhibitors.

Starting from Document D1, the technical problem raised by the present application is the provision of further protein kinase inhibitors in particular PKC-thêta inhibitors useful in the treatment of autoimmune disease, inflammatory disease, cancer and/or HIV infection.

The biological data provided in the description, in particular example 2 table 2 on pages 148-151, show that a representative set of compounds as claimed are active as PKC inhibitors and solve the problem raised.

Starting from Document D1 and wishing to solve the problem raised the skilled person would not have obviously chosen the specific cyclic substituent ER5R6 on the 5-membered heteroaryl ring and expect them to be active as PKC inhibitors. Document D2 and D3 disclose compounds which are PKC inhibitors. Some compounds of Document D2 do possess a substituent equivalent to present ER5R6. However they differ in the nature of both rings (see bicyclic ring and no 5-membered ring as claimed) as illustrated by examples 2 and 3 copied below. The same applies for some compounds of Document D3.



Without hindsight knowledge of the present invention, a combination of the teaching of Document D1 with D2 or with D3 is not obvious for the skilled person and would not lead to the compounds presently claimed having the activity shown. The presence of an inventive step may therefore be recognised for the novel compounds claimed.

Re Item VIII

Certain observations

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in Documents D1 and D2 is not mentioned in the description, nor is this document identified therein.