

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 036844-106335 (P37221) PC	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/US2022/050221	International filing date (<i>day/month/year</i>) 17.11.2022	Priority date (<i>day/month/year</i>) 19.11.2021
International Patent Classification (IPC) or national classification and IPC INV. C07D213/36		
Applicant ICAGEN, LLC		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>10</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ a total of <u>7</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ a separate electronic file containing a sequence listing (<i>sent to the International Bureau only</i>) 4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ 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 Article 35(2) with regard to novelty, inventive step or 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		
Date of submission of the demand 19.09.2023	Date of completion of this report 02.02.2024	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Authorized officer Sotoca Usina, E Telephone No. +49 89 2399-4863 	

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-648, 650-671, as originally filed
674-769, 771-1086,
1088-1092

649, 672, 673, 770, filed with telefax on 19-09-2023
1087

Claims, Numbers

1-78 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

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6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☐ A top-up search was carried out by this Authority on (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☒ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>28, 31-34, 51, 53, 54, 56</u>
	No: Claims	<u>1-27, 29, 30, 35-50, 52, 55, 57-78</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-78</u>
Industrial applicability (IA)	Yes: Claims	<u>1-78</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

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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

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 DATABASE Registry [Online]
 American Chemical Society; 17 July 2013 (2013-07-17),
 Chemcats: "Urea, N-(3-cyclopropylcyclohexyl)-N'-[[2-(1H-imidazol-1-yl)-4-pyridinyl]methyl]-(CA INDEX NAME)",
 XP093024665,
 Database accession no. 1445165-41-2
- D2 DATABASE Registry [Online]
 American Chemical Society; 16 December 2009 (2009-12-16),
 Chemcats: "Urea, N-cyclopentyl-N'-[[2-(1H-pyrazol-1-yl)-4-pyridinyl]methyl]-",
 XP093024674,
 Database accession no. 1197676-62-2
- D3 WO 2021/219594 A1 (IDORSIA PHARMACEUTICALS LTD [CH]) 4
 November 2021 (2021-11-04)
- D4 WO 2020/191227 A1 (UNIV CORNELL [US]) 24 September 2020
 (2020-09-24)
- D5 WO 2020/163268 A1 (LILLY CO ELI [US]) 13 August 2020 (2020-08-13)
- D6 US 2021/047301 A1 (KIM KYUNG-HEE [KR] ET AL) 18 February 2021
 (2021-02-18)

1 Amendments

Pages 649, 672, 673, 770 and 1087 have amended "Kv7.3_7.5/Kv7.2" to "Kv7.5_7.3/Kv7.2" and "Kv4/KV2" to "Kv7.4/Kv7.2" based on examples 295 and 298 on pages 1019 and 1020. Since the amended pages showed the activity of compounds against the receptors and examples 295 and 298 disclose which tests and which receptors are used, this is seen as allowable under Article 34 PCT.

2 Patentability

Claim 70 relates to a method of treatment which pertains to Rule 39.1(iv) PCT, a method for treatment of the human or animal body by surgery. 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. The same rationale is seen throughout the description.

3 Novelty

D1 discloses compound with RN 1445165-41-2 which is seen as novelty hindering for claims 11-14, 20-22, 25-27, 36, 37, 40, 42, 44, 46, 47, 78 under Article 33(2) PCT. This compound is one of those disclaimed in claim

D2 discloses compounds with RNs 1197676-62-2 and 1197507-69-9 which are seen as novelty hindering for claims 11-14, 20-22, 25-27, 35, 36, 40-44, 46-48, 52, 78 under Article 33(2) PCT. These compounds are two of those disclaimed in claim

A question arises on the fourth compound disclaimed.

D3 discloses compounds on page 111 lines 15, 16, 24, 26; on page 112 lines 11, 17, 19, 27, 30, 31; page 113 lines 3, 4, 6, 21, 23, 25; page 114 lines 11, 16, 25, 31; page 115 lines 1, 7, 8, 9, 21, 22, 23, 24, 30; page 62 Example 1 step 1; page 66 Example 189 lines 12-13;

which together with table 2 and claims 1-15 are seen as novelty hindering for claims 1-19, 22-27, 36-41, 46, 47, 57-78 and 71 (second 71) under Article 33(2) PCT.

D4 discloses compounds on page 144 4th compound and on page 146 2nd compound which are seen as novelty hindering for claims 1-5, 7, 8, 10-15, 22, 26, 27, 35, 37-43, 57, 71, 78 and 71 (second) under Article 33(2) PCT.

D5 discloses examples 1-3, claims 1-25 and tables 1-3 which are seen as novelty hindering for claims 1-19, 22, 25, 29, 30, 35, 36, 39-43, 46-50, 57-78 and 71 (second) under Article 33(2) PCT.

D6 discloses example 37 - steps 4, 5, 6;

examples 38, 39, 40, 41, 42, 43, 46, 47, 48, 49, 50, 51, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 79, 80, 81, 83;

example 84 steps 4, 5, 6; example 85 steps 4, 5; example 86 steps 4, 5;

example 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99, 102, 103, 104, 105, 106, 107, 108, 109, 110;

example 111 step 1; example 132 step 4;

examples 133, 134, 136, 137 which together with claims 1-12 are seen as novelty hindering for claims 1-19, 22, 25, 27, 36, 40-48, 55, 57-78 under Article 33(2) PCT.

Claim 78 is directed to compounds of claims 11-58 when manufactured according to a process of claims 72-77. Claims directed to products which are defined in terms of a process for their manufacture are only allowable if there is no other information available in the application which could be used to define the product satisfactorily by reference to its composition, structure or some other testable parameter and if the products per se fulfil the requirements for patentability, i.e. if they are new and inventive. A product is not rendered novel merely by the fact that it is produced by means of a novel process. In this case, it does not appear that the product is novel over the previously cited documents.

4 Inventive Step

Should novelty objection be overcome, the following assessment would be given.

- 4.1 D3 and D5 are seen as the closest prior art because they disclose compounds having a (hetero)aryl-methylene-urea core. The compounds can be further substituted at the (hetero)aryl, methylene or urea. These compounds act against several illnesses, mainly neurological conditions, via inhibition of Kv7.2
- 4.2 The main differences between D3 and the application are seen in the particular combination of substituents, some of them not present in D3.

The main differences between D5 and the application are seen in the particular combination of substituents, some of them not present in D5.
- 4.3 The objective technical problem is seen in the provision of further compounds acting against several illnesses, mainly neurological conditions, via inhibition of Kv7.2
- 4.4 Table 1 on pages 547-637 show the compounds of the invention inhibiting Kv7.2. The proposed solution can be seen as a working one.
- 4.5 The person skilled in the art would combine D3 and D5 and arrive at the particular compounds of the application.

The proposed solution is seen as a working, yet obvious and non-inventive under Article 33(3) PCT.

Re Item VI

Certain documents cited

Reference is made to the following document:

D7 WO 2021/260090 A1 (IDORSIA PHARMACEUTICALS LTD [CH]) 30
December 2021 (2021-12-30)

D7 discloses compounds on page 45 example 29, page 46 example 30, 33, page 47 example 43m page 48 examples 44, 45, 46 and page 50 example 55 (stereoisomers 1 + 2) which together with claims 1-15 could become relevant for the assessment of the novelty of claims 1-19, 22, 25, 27, 36, 40-48, 55, 57-78 and 71 (second).

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1-D7 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

Certain observations on the international application

Claim 56 relates to compounds of Tables 1-9, since these tables are not present in the claims, this claim is seen as not complying with Article 6 PCT under clarity.

Claims 59, 69, 70, 71 do not meet the requirements of Article 6 PCT for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of modulating/regulating Kv7.2), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available (in the form of experimental tests or testable criteria, either disclosed in the patent application or known from the common general knowledge), which would allow the skilled person to recognise which additional conditions fall within the functional definition.

The same rationale is seen throughout the description.

There are two claims 71, one between claim 70 and claim 72 and another one after claim 78. This is seen as not complying with the criterion of clarity under Article 6 PCT.

Several discrepancies, resulting in a lack of clarity under Article 6 PCT when using the description to interpret the claims, are seen on:

- page 15 lines 6-17 seems to allow all exchanges of H for a substituent. This is not present in the claims.
- although the claims do not include prodrugs or metabolites of the compounds of the invention, the description does so on page 19 lines 18-25 and page 20 line 7. The very concept of a prodrug or metabolite is seen as not clear under Article 6 PCT.
- page 21 lines 14-16, page 21 lines 18-22 discloses particular definitions of saturated monocyclic cyclolalkyl which is not the standard one. Had these definitions been present in the claims, this objection would not have been raised.
- page 27 lines 7 to page 11 gives a particular definition of cycloalkyl which includes unsaturated rings into it. Had this definition been present in the claims, this objection would not have been raised.
- the description gives several overlapping Markush formulae for the compounds of the invention, including several compounds to be excluded from the scope of the application. Since not all of these Markush formulae and compounds to be excluded are present in the claims, this is seen as a lack of clarity under Article 6 PCT.

Page 1026 line 3 relates to the full scope of equivalents to which claims are entitled. This is seen as not complying with clarity under Article 6 PCT, since it casts a doubt on the scope of the claims (what are its equivalents?).

Page 1028 lines 5-7 relates to documents being incorporated by reference. This is seen as irrelevant subject matter to be deleted.

The claim-like clauses appended at the end of the description on pages 1028-1092 lead to doubts as to the actual scope of protection.