

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/US2024/048567

International filing date (day/month/year)
26.09.2024

Priority date (day/month/year)
27.09.2023

International Patent Classification (IPC) or both national classification and IPC
INV. C07D207/06 C07D207/08 C07D207/10 C07D207/12 C07D207/26 C07D209/44 C07D209/46 C07D209/52
C07D211/14 C07D211/18 C07D211/38 C07D211/74 C07D223/04 C07D241/08 C07D241/28 C07D265/30

Applicant
VIVIDION THERAPEUTICS, INC.

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

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Kiernan, Andrea

Telephone No. -0



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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>1-73</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>39, 62</u>
	No: Claims	<u>1-38, 40-61, 63-73</u>
Industrial applicability (IA)	Yes: Claims	<u>1-73</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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

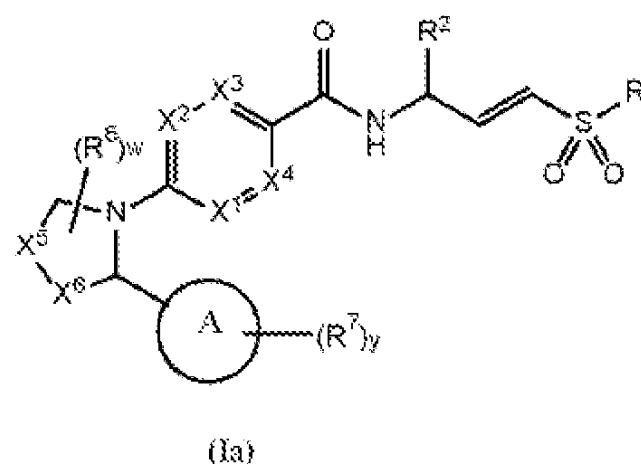
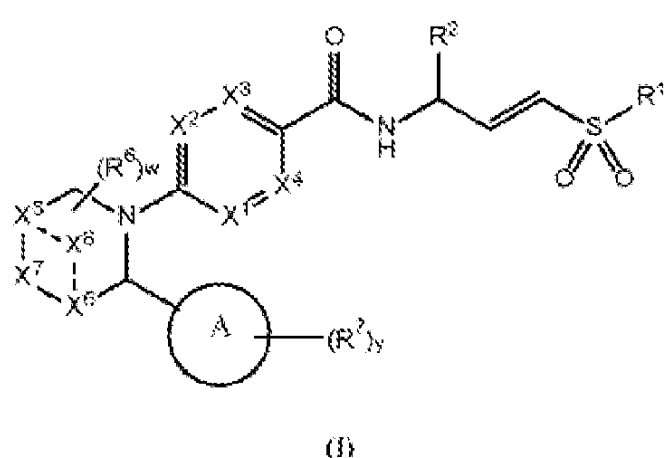
Re Item V

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

D1 XP085552009 (Kumar, S. et al., Biomedicine & Pharmacotherapy, vol. 109 (2019), p. 1462-1477)

D2 WO 2021/204159 A1

The application relates to inhibitors of RAS-PI3K of formula (I) or (Ia) useful for the treatment of cancer and immunological diseases.



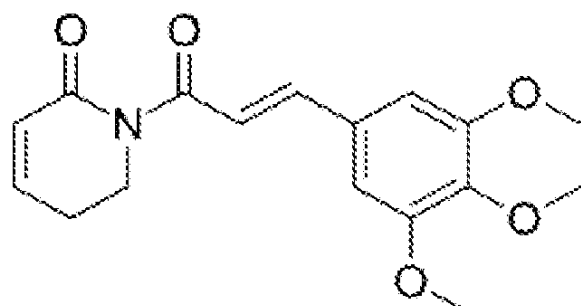
Methods of Treatment

Claims 64-73 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.

For the assessment of the present claims 64-73 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to compounds or compositions for use in a first or further medical treatment.

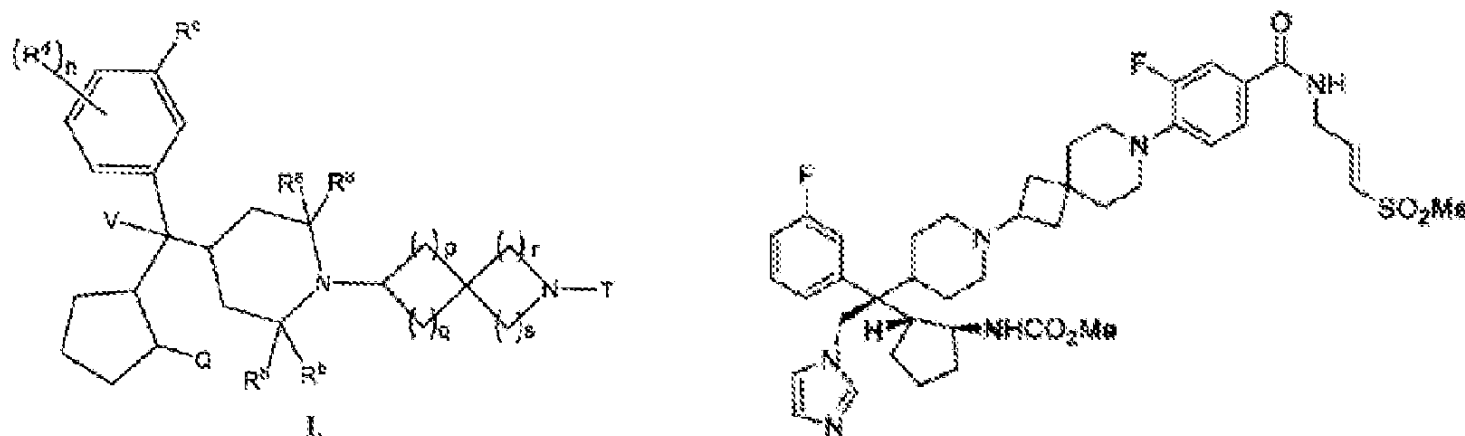
Novelty

D1 discloses the compound piperlongumine which is reported to target Ras/PI3K/Akt/mTOR signaling axis to inhibit tumor cell growth and proliferation (see abstract and page 1463, Figure 1):



The presently claimed compounds differ considerably from this compound for example in that they comprise 3 rings or ring systems which are located at one side of the double bond only, and in that the other side of the double bond is substituted by an alkyl- or cycloalkylsulfonyl group.

D2 discloses Menin inhibitors of the general Formula (I) (see claim 1) useful for the treatment of cancer. The structurally closest compound in D2 is Compound 326 on page 131 of D2:



Inventive Step

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-38, 40-61 and 63-73 does not involve an inventive step.

D1 can be considered the closest prior art since it also relates to inhibitors of RAS-PI3K useful for the treatment of cancer.

As discussed under Novelty above, the presently claimed compounds structurally differ considerably from the compound piperlongumine disclosed in D1.

The problem to be solved can be seen in the provision of further inhibitors of RAS-PI3K useful for the treatment of cancer.

The compounds of formula (I) or (Ia) as defined in the independent claims 1 and 40 are suggested as a solution.

The activity data in Tables 2 and 3 on pages 527-548 and 551-559 provided for all Examples 1-484 listed in Table 1 on pages 72-149 demonstrate that the specific compounds prepared and tested in the application solve the problem posed.

However, it is observed that the moiety defined under ring A including its substituents is always a phenyl, pyridyl or cyclohexyl ring substituted by a group R⁷ as defined in claims 19 and 53 only (namely by Cl, F, methyl, methoxy or trifluoromethoxy), whereas independent claims 1 and 40 cover compounds with a C₃-C₇ cycloalkyl group or an aryl or heteroaryl group of just any nature and size as ring A, unsubstituted or substituted by just any halogen or alkyl, haloalkyl, alkoxy or haloalkoxy groups having up to 6 carbon atoms.

In view of the great structural similarity of this moiety in all 484 examples in the application, it must be concluded that this part of the molecule is part of the pharmacophore responsible for the activity of the compounds.

The scope of the definition of ring A and its substituents is therefore considered far too broad in comparison with what has been demonstrated in the application, and the above-mentioned problem cannot be considered credibly solved over the entire claimed scope.

Consequently, an inventive step can at present be acknowledged for the specific compounds listed in claims 39 and 62 only (Article 33(3) PCT).

Industrial Applicability

Industrial applicability is acknowledged.

Re Item VI

Certain documents cited

- D3 WO 2024/182404 A1 (VIVIDION THERAPEUTICS, INC.) (2024-09-06)
- D4 WO 2024/010782 A1 (VIVIDION THERAPEUTICS, INC.) (2024-01-11)

Re Item VII

Certain defects in the international application

- 1 Statements such as "hereby incorporated by reference" on pages 1, 11, 62, 149 and 560 should be deleted.
- 2 To meet the requirements of Rule 5.1(a)(ii) PCT, the prior art documents D1 and D2 should be cited in the description, and the relevant background art disclosed therein should be briefly discussed.

Re Item VIII

Certain observations on the international application

- 3 Claim 64 is not acceptable under Article 6 PCT.

The therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

- 4 According to pages 68 and 69, the terms "cycloalkyl" and "heterocycloalkyl" may also be partially unsaturated or even fused with an aromatic ring; since this is not the normal understanding of the terms (an unsaturated version would normally be called cycloalkenyl or heterocycloalkenyl, and a ring fused with an aromatic ring would be considered an aryl or heteroaryl group rather than a cycloalkyl or heterocycloalkyl group), these passages in the description render the scope of the claims unclear (Article 6 PCT).

- 5 The vague and imprecise statement in the description on page 559, last paragraph implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, PCT/GL/3 III, 4.3a).