

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/US2024/017497

International filing date (day/month/year)
27.02.2024

Priority date (day/month/year)
28.02.2023

International Patent Classification (IPC) or both national classification and IPC
INV. C07D211/96 A61K31/445 A61P35/00 A61P37/00 A61P17/02

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

Cortés Suárez, José

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 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.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. 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>66-69</u>
	No: Claims	<u>1-65</u>
Inventive step (IS)	Yes: Claims	<u>66-69</u>
	No: Claims	<u>1-65</u>
Industrial applicability (IA)	Yes: Claims	<u>1-69</u>
	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

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are cited in the present International Search Report:

- D1 CAULFIELD THOMAS J. ET AL: "Parallel Solid-Phase Synthesis of Peptidyl Michael Acceptors", JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 2, no. 6, 21 October 2000 (2000-10-21), pages 600-603, XP93179237, US, ISSN: 1520-4766, DOI: 10.1021/cc0000444;
- & CAULFIELD THOMAS J. ET AL: "Parallel Solid-Phase Synthesis of Peptidyl Michael Acceptors: Supplementary Information (1)", JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 6, no. S1, 21 October 2000 (2000-10-21), pages 1-40, XP93179326, US, ISSN: 1520-4766, DOI: 10.1021/cc0000444
- & CAULFIELD THOMAS J. ET AL: "Parallel Solid-Phase Synthesis of Peptidyl Michael Acceptors: Supplementary Information (2)", JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 6, no. S2, 21 October 2000 (2000-10-21), pages 41-56, XP93179334, US, ISSN: 1520-4766, DOI: 10.1021/cc0000444
- D2 WO 2009/098282 A1 (NOVASAID AB [SE]; WANNBERG JOHAN [SE] ET AL.) 13 August 2009 (2009-08-13)
- D3 KUMAR SANDEEP ET AL: "Piperlongumine, a piper alkaloid targets Ras/PI3K/Akt/mTOR signaling axis to inhibit tumor cell growth and proliferation in DMH/DSS induced experimental colon cancer", BIOMEDICINE & PHARMACOTHERAPY, vol. 109, pages 1462-1477, January 2019 (2019-01-00), XP085552009, ISSN: 0753-3322, DOI: 10.1016/J.BIOPHA.2018.10.182

The present claims 61 to 69 relate to methods of medical treatment, which are subject matter considered by this authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO does not recognise as patentable, claims directed to methods of medical treatment or medical uses, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

With entry into the regional phase before the EPO the present claims 61 to 69 must be deleted or rephrased into an allowable form (e.g. "*The compound of claim 1 for use in a method of treatment of ...*").

Novelty (Article 33(2) PCT)

D1 already discloses compounds within the scope of the present claims.

The claimed matter lacks novelty in view of D1.

The present compounds differ from the compounds in D2 at least in RA.

The present compounds differ from the compounds in D2 at least in -C(O)-N(RA)(R5a), R3, Z and the Y containing ring.

Inventive Step (Article 33(3) PCT)

D1 discloses pharmaceutically active compounds.

D2 discloses compounds for the treatment of cancer and immunological diseases.

D3 discloses the compound piperlongumine as a RAS-P13K modulator for the treatment of colon cancer.

D3 could be regarded as the closest prior art.

The problem of the invention was the provision of new RAS-PI3K modulators for the treatment of cancer, immunological disorders and wound healing.

The present description discloses the synthesis and characterisation of exemplary compounds as well as pharmacological data thereof (e.g. page 48 to page 101, table 1; page 116 to page 294; examples 1 to 4; compounds 1 to 314; tables 1 to 6).

Since D1 already discloses compounds of the present invention the claimed matter lacks an inventive step.

None of D2 or D3 discloses or suggests the present compounds.

With entry into the regional phase before the EPO the claimed matter must be delimited from D1.

Re Item VII

Certain defects in the international application

Description

Some parts of the description refer to the ambiguous term "*heteroalkyl*" (e.g. paragraphs [005], [007], [009], [0011], [0014], [0016], [0030], [0033], [0037], [0038], [0042], [0044], [0050], [0051], [0092] and [00165]). An ambiguous definition of the term is found in paragraph [00165].

Some parts of the description refer to methods of medical treatment (e.g. paragraphs [002], [003], [0022], [0023], [0139], [0140], [0145], [0148] and [0151]).

Some parts of the description contain irrelevant expressions:

- "*incorporated by reference*" (e.g. paragraphs [001], [0025], [00118] and [00762])
- the whole paragraph [00762]

The relevant prior art D1 to D3 has not been cited.

Some of the exemplary compounds are not encompassed by claim 1 (e.g. compound 230).

With entry into the regional phase before the EPO references to ambiguous terms must be deleted, references to methods of medical treatment must be rephrased or deleted, irrelevant expressions must be deleted, the relevant prior art D1 to D3 must be cited, and exemplary compounds not encompassed by the claims must be deleted or identified as reference compounds.

Re Item VIII

Certain observations on the international application

Lack of Clarity (Article 6 PCT)

The scope of the present claims 1, 7, 9, 15, 23 and 26 is unclear because of the use of the ambiguous term "*heteroalkyl*". The term "*heteroalkyl*" has no commonly recognised meaning in the art, and the claims lack a clear definition of this term.

The scope of the present claims 1, 7, 9, 15, 17, 23, 26, 31, 32, 36, 49 and 54 is unclear because the "*optional substituents*" are not defined.

The scope of the present claims 61 to 63 and 65 is unclear because they define a medical use by a mechanism of action (RAS-P13K modulation), instead of specifying actual diseases or disorders to be treated (see e.g. claims 66 to 69).

Some of the specific compounds of the dependent claims 56 to 59 are not encompassed by the present claim 1 (e.g. compound 230).

With entry into the regional phase before the EPO the ambiguous term "*heteroalkyl*" must be deleted in the claims and in the description (the ambiguous definition of paragraph [00165] is not suitable, because it includes all non-cyclic organic groups comprising a heteroatom O, N or S), the "*optional substituents*" must be defined (see e.g. paragraph [00177]), the technical features of e.g. the present claims 66 to 69 must be included into the present claims 61 to 63 and 65, and the specific compounds of the dependent claims 56 to 59 that are not encompassed by the present claim 1 should be deleted and optionally claimed in an additional independent claim.

Lack of Conciseness (Article 6 PCT)

The present claim set contains an unnecessary large number of claims.

With entry into the regional phase before the EPO the present claim set should be limited to 15 claims or less.