

AS. 161090

Señora directora
DIRECCIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESPUESTA A OFICIO No. 21138 DEL 26 DE NOVIEMBRE DE 2025

REF: Expediente No. NC2025/0015477 - Solicitud de Patente Fase Nacional
A favor de **REVOLUTION MEDICINES, INC.**
Titulada: INHIBIDORES MACROCÍCLICOS DE RAS

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492, obrando como apoderado de la sociedad **REVOLUTION MEDICINES, INC.**, según lo acredita el documento de poder presentado en esa Dirección, para dar cumplimiento al requerimiento notificado de manera automática el 27 de noviembre de 2025, de acuerdo con los Artículos 38 y 39 de la Decisión 486 de la comisión de la Comunidad Andina, me permito:

1. Aclarar que si bien se solicitó el estudio de la invención bajo el Capítulo II del tratado PCT, no se presentó ninguna modificación a la descripción o reivindicaciones, únicamente se modificó el título y, por lo tanto, la Oficina Internacional no va a expedir el Reporte del Examen Preliminar Internacional Capítulo II según se aclara en comunicación adjunta emitida por la Oficina Internacional. No obstante, y para su mejor referencia, adjuntamos copia del Examen Preliminar Internacional Capítulo I.

De la señora directora atentamente,



JUAN PABLO CADENA SARMIENTO
C.C. No. 80.410.337 de Usaquén
T. P. 57.492 del Consejo Superior de la Judicatura

Bogotá, 26 de enero de 2026
JPC/jpg

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
CLARK & ELBING LLP
Attn. Belliveau, Michael J.
101 Federal Street
15th Floor
Boston, MA 02110
ETATS-UNIS D'AMERIQUE

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

	Date of mailing (day/month/year) 03/01/2025
Applicant's or agent's file reference 51432-042WO2	REPLY DUE See paragraph 1 below
International application No. PCT/US2024/023208	International filing date (day/month/year) 05/04/2024
Applicant REVOLUTION MEDICINES, INC.	

1. ☒ **REPLY DUE** within 14 ~~xxxx~~ days from the above date of mailing

☐ **NO REPLY DUE**

2. **COMMUNICATION:**

We acknowledge receipt of your PCT Chapter II demand filed on 16.12.2024. While performing the formal check it draws our attention the fact that it seems to be a request to change the title of the invention rather than a PCT Chapter II demand. If you wish to amend the title and a republication of the international application, please file a request to the International Searching Authority. It will be brought to the attention of the search examiner and if your request is granted the title will be amended. You are invited the clarify within the above time limit if you only want the title to be amended or a PCT Chapter II demand.

A copy of this communication is sent to the International Bureau.

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	Authorized officer Angela López Navarro
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 51432-042WO2	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2024/023208	International filing date (<i>day/month/year</i>) 05 April 2024 (05.04.2024)	Priority date (<i>day/month/year</i>) 07 April 2023 (07.04.2023)	
International Patent Classification (IPC) or national classification and IPC See relevant information in Form PCT/ISA/237			
Applicant REVOLUTION MEDICINES, INC.			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 7 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. 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 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
4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

	Date of issuance of this report 02 October 2025 (02.10.2025)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Xin Wang e-mail pct.team2@wipo.int

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/US2024/023208

International filing date (day/month/year)
05.04.2024

Priority date (day/month/year)
07.04.2023

International Patent Classification (IPC) or both national classification and IPC
INV. C07D498/22 A61P35/00

Applicant
REVOLUTION MEDICINES, 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
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Schuemacher, Anne

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. 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	<u>1-23</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>12, 13, 17-23</u>
	No: Claims	<u>1-11, 14-16</u>
Industrial applicability (IA)	Yes: Claims	<u>1-23</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

Re Item V

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

1. Claims 21-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/ 67.1(iv) PCT. For the assessment of the present claims 21-23 on the question whether it is patentable, no unified criteria exist in the PCT Contracting States. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a known compound for first or further medical treatment.

2. Reference is made to the following documents:

- D1 WO 2021/091967 A1 (REVOLUTION MEDICINES INC [US]) 14 May 2021
cited in the application
- D2 WO 2021/091982 A1 (REVOLUTION MEDICINES INC [US]) 14 May 2021
cited in the application

3. The presently claimed macrocycles of formula (Ia) and (Ib) as defined in claim 1 differ from those disclosed on D1 and D2 on account of the additional cycle formed by the linker -L- between the ring A and the -CO-NR⁴-CR³CONH- moiety.

Additionally the compounds of formula (Ib) differ on account of their -C(R^{L5})₂-NH-X⁹- moiety present instead of the hexahydropyridazinyl ring in the compounds of D1/D2.

Claims 2-23 comprising the novel compounds of claim 1, are therefore also considered to be novel over D1-D2.

The requirements of Art.33(2) PCT are therefore considered to be fulfilled.

4. The present application is directed to compounds of formula (Ia) and (Ib) as defined in claim 1 and their use for the treatment of cancer in the view of their biological activity as RAS inhibitors.

D1 or D2 could be equally be considered to represent the closest prior art document.

The macrocycles (Ia) and (Ib) as defined in claim 1 differ from those disclosed in D1/D2 on account of the additional cycle formed by the linker -L- between the ring A and the -CO-NR⁴-CR³CONH-moiety. The compounds of formula (Ib) further on account of the -C(R^{L5})₂-NH-X⁹- moiety present instead of the hexahydropyridaziny ring in the compounds of D1/D2.

It is stated on p.304 of the description that each of examples A1 to A450 exhibited an IC₅₀ of less than 2 µM in at least one of the following: K-Ras Q61H, G12C, G12D, G12R, G12S, G12V, G12A, G13C, G13D and wild-type; N-Ras Q61K, Q61R, Q61L, G12C and wild-type; and H-Ras G13R and WT.

Thus, the objective technical problem to be solved may be seen in the provision of novel macrocyclic compounds useful as anti-cancer agents in the view of their activity as RAS inhibitors.

Starting from D1 or D2 the skilled person gets no hint that would lead him to add a linker L between the ring A and the other end of the molecule -CO-NR⁴-CR³CONH- with a reasonable expectation that the RAS inhibitory activity would remain.

Furthermore, none of the prior art documents suggests that the hexahydropyridazine ring can be replaced by a -C(R^{L5})₂-NH-X⁹- moiety without loss of the RAS inhibitory activity.

Thus, the proposed compounds (Ia) and (Ib) of claim 1 are not obviously derivable from the prior art D1/D2.

However, it must be credible that the technical problem is solved over the whole breadth of claim 1:

There is no preparation and tests for compounds of formula (Ib); thus, It was not credibly shown that the compounds of formula (Ib) solve the above mentioned technical problem. The compounds of formula (Ib) of claims 1, 4 7, 11, 16 do therefore not involve an inventive step according to Article 33(3) PCT.

Furthermore, all the tested examples of the description are of formula (Ia), wherein the ring A is a phenyl or pyridine ring, R1 is a pyridine ring and the linker L is -O-CH₂-(heterocyclyl)- or -OCH₂CH₂CHR-.

Since this linker is the essential distinguishing feature of the invention it must be defined the most accurately possible, which is not the case in current claims 1-9.

Thus, an inventive step can only be acknowledged for the compounds for which it has been credibly shown that they solve the technical problem, namely the compounds of formula (Va) of claim 11, dependent claims 12-13, part of claim 14 as far as it refer to compounds of formula (Ia), dependent claims 15-18 and the specific examples A1-A450 as claimed in claim 19.

Re Item VII

Certain defects in the international application

Claim 19 contains a reference to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

The embodiments disclosed on p.305-323 are claim-like clauses and must be deleted since they otherwise may lead to unclarity as to the actual scope of protection.

Prior art documents were acknowledged throughout the description by the expression "incorporated herein by reference". It is vague and ambiguous which technical features are referred to. Furthermore, it should be noted that this kind of reference contravenes the basic requirement of each application that the invention must be comprehensible from the specification by itself.