

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 51432-043WO4	FOR FURTHER ACTION See item 4 below	
International application No. PCT/US2024/023272	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 8 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 Fiona Doherty e-mail pct.team4@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/US2024/023272

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:



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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>1-6</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>2-6</u>
	No: Claims	<u>1</u>
Industrial applicability (IA)	Yes: Claims	<u>1-6</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 with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Claims 4-6 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 4-6 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 (2021-05-14) cited in the application
- D2 WO 2022/217053 A1 (REVOLUTION MEDICINES INC [US]) 13 October 2022 (2022-10-13)

3. The presently claimed macrocycles of formula (Ia) to formula (VIIb) and formula (XI) as defined in claim 1 differ from those disclosed on D1 and D2 on account of the additional cycle comprising the linker L.

Claims 2-6 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) to formula (VIIb) and formula (XI) 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 as defined in claim 1 differ from those disclosed in D1/D2 on account of the additional cycle comprising the linker L.

It is stated on p.316 of the description that each of examples A1 to A181 exhibited an IC_{50} 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 further condensed cycle with a reasonable expectation that the RAS inhibitory activity would remain.

Thus, the proposed compounds (Ia) to (VIIb) and (XI) 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:

All the tested examples of the description have

Q= indolyl,

-the ring A is a phenyl, pyridine or thiazole ring,

-there is always a $-COO-CH_2-C(Me)_2-CH_2-$ chain between the hexahydropyridazine ring and the indole ring,

-the hexahydropyridazine is always unsubstituted and;

it appears essential for the biological activity that the indolyl Q is substituted with a pyridine ring.

On contrary, in the different formulae of claim 1, Q can be any kind of cyclic group without precision on the kind of substituent, A can even be aliphatic groups and L is not structurally defined but only functionally, namely to be a linker.

Thus, an activity has only been demonstrated for the compounds of formula (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIIa) and (VIIb).

Nevertheless, since this linker -L- is the essential distinguishing feature of the invention it must be defined the most accurately possible, which is not the case in any of the formulae of current claim 1.

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 claim 2 and part of claims 3-6 as far as they refer to the compounds of claim 2.

Re Item VII

Certain defects in the international application

Claim 2 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. Additionally, claim 2 discloses preferred embodiments of claim 1 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

The embodiments disclosed on p.316-330 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.

Re Item VIII

Certain observations on the international application

Present claim 1 relates to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed, namely compounds of claim 1,

wherein the ring A is a phenyl, pyridine or thiazole ring,

Q is always a 2-(pyridin-3-yl)indolyl ring;

the hexahydropyridazine ring is always unsubstituted;

there is always an -COO-CH₂-C(Me)₂-CH₂- chain between the hexahydropyridazine ring and the indole ring.

Therefore, the compounds of formula (Ia), (Ib), (IIa), (IIb), (IIa-1), (IIIa) and (IIIb) in claim 1 are not considered to be clear in the sense of Art.6 PCT and nor supported by the description (Art.5 PCT).

Furthermore, it seems that formula (Ib) encompasses formula (Ia) when one of R^{L5} and R^{L6} (in X⁹) form together an optionally substituted 3- to 8-membered heterocyclyl.

Formula (IIb) seems to encompass formula (IIa) and (IIa-1), which appear all three to be preferred embodiment of formula (Ia) and (Ib). Therefore said formula (IIb), (IIa) and (IIa-1) cannot be in the same independent claim without rendering the scope for which protection is sought unclear. The preferred embodiments of the claimed compounds should be introduced into dependent claims.

Therefore, claim 1 is considered to lack clarity in the sense of Art.6 PCT.