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(71) Applicant: **REVOLUTION MEDICINES, INC.**
[US/US]; 700 Saginaw Drive, Redwood City, CA 94063 (US).

(72) Inventors: **KNOX, John E.**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **KOLTUN, Elena S.**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **LIU, Jinyu**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **LIU, Yang**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **MADEJ, Benjamin D.**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **PARSONS, Dylan E.**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **TOMLINSON, Aidan**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **YIN, Jingwei**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **ALACHOUZOS, Georgios**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **BURNETT, G. Leslie**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **CHAN, Neil**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **CREGG, James**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **EDWARDS, Anne V.**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US). **GILL, Adrian L.**; Revolution Medicines, Inc., 700 Saginaw Drive, Redwood City, CA 94063 (US).

(74) Agent: **BELLIVEAU, Michael J.** et al.; Clark & Elbing LLP, 101 Federal Street, 15th Floor, Boston, MA 02110 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

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(88) Date of publication of the international search report:

22 May 2025 (22.05.2025)

(54) Title: MACROCYCLIC RAS INHIBITORS

(57) Abstract: The disclosure features macrocyclic compounds, and pharmaceutical compositions and protein complexes thereof, capable of inhibiting Ras proteins, and their uses in the treatment of cancers.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/050922

A. CLASSIFICATION OF SUBJECT MATTER		
INV. C07D498/22 C07D515/22 C07D519/00 A61P35/00 A61K31/504 C07K5/062		
ADD. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/060836 A1 (REVOLUTION MEDICINES INC [US]) 24 March 2022 (2022-03-24) cited in the application various compounds of tables 1a and 1b: e.g. ex A1-A164, A166-A197 etc., A354-608 (several of those feature a non-H substituent corresponding to present R10 such as A328, A334, A335, A339, A340 etc.); page 49ff.; claims; tables 1a, 1b; compounds A1-A164, A166-A197, A199353, A354-608 ----- - / - -	1, 2, 4 - 9, 11, 12, 14, 18, 19, 26 - 30, 49 - 80
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 30 January 2025		Date of mailing of the international search report 09/04/2025
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/050922

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
11, 12 (completely); 1, 2, 4-9, 14, 18, 19, 26-30, 49-80 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2024/050922

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/091956 A1 (REVOLUTION MEDICINES INC [US]) 14 May 2021 (2021-05-14) cited in the application table 1 (page 42ff.): compounds A1, A3-5, A13, A18, A25, A54, ...A176, A180-3, A207, A208, A261, A264-7 etc.; table 2 (page 174ff.): compounds B1, B44, B47, B57-B61, B66, B67 etc.; claims -----	1,2,4-9, 11,12, 14,18, 19, 26-30, 49-80
X	WO 2023/086341 A1 (BIOMEA FUSION INC [US]) 19 May 2023 (2023-05-19) cited in the application compounds of paragraph 332; claims 1-173; examples 1, 2 (pages 110-116); compounds 1, 2 -----	1,2,4-9, 11,12, 14,18, 19, 26-30, 49-80
X	WO 2022/212894 A1 (MASSACHUSETTS GEN HOSPITAL [US]; REVOLUTION MEDICINES INC [US]) 6 October 2022 (2022-10-06) claims 32-45; table D1a; compound DA228 (page 775) -----	1,2,4-9, 11,12, 14,18, 19, 26-30, 49-80

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2024/050922

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022060836 A1	24-03-2022	AU 2021345111 A1 CA 3194067 A1 CL 2023000730 A1 CL 2023003819 A1 CN 116457358 A CN 117683049 A CO 2023004548 A2 CR 20230165 A EP 4214209 A1 IL 301298 A JP 2023541916 A KR 20230067635 A PE 20231207 A1 TW 202227460 A US 2022105185 A1 US 2023226186 A1 WO 2022060836 A1	06-04-2023 24-03-2022 29-09-2023 12-07-2024 18-07-2023 12-03-2024 08-05-2023 02-06-2023 26-07-2023 01-05-2023 04-10-2023 16-05-2023 17-08-2023 16-07-2022 07-04-2022 20-07-2023 24-03-2022
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WO 2023086341 A1	19-05-2023	US 2025066386 A1 WO 2023086341 A1	27-02-2025 19-05-2023
WO 2022212894 A1	06-10-2022	AU 2022249177 A1 BR 112023020182 A2 CA 3214155 A1 CR 20230500 A EP 4320143 A1 IL 307396 A JP 2024512767 A KR 20240004436 A TW 202308632 A US 2024108630 A1 WO 2022212894 A1	19-10-2023 12-12-2023 06-10-2022 13-02-2024 14-02-2024 01-12-2023 19-03-2024 11-01-2024 01-03-2023 04-04-2024 06-10-2022

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 11, 12(completely); 1, 2, 4-9, 14, 18, 19, 26-30, 49-80(partially)

claimed subject matter directed to a compound of formula (I') wherein $X_4 = CH_2$

2. claims: 1-10, 13-64, 67-80(all partially)

claimed subject matter directed to a compound of formula (I') wherein $X_4 = NH$ and $R_{10} = H$

3. claims: 1-5, 8-10, 13-65, 67-80(all partially)

claimed subject matter directed to a compound of formula (I') wherein $X_4 = NH$ and $R_{10} = OR_{11}$

4. claims: 1-5, 8-10, 13-64, 66-80(all partially)

claimed subject matter directed to a compound of formula (I') wherein $X_4 = NH$ and $R_{10} = NR_{12}R_{13}$

5. claims: 81-90

a compound of formula (V)

6. claims: 91-97

a compound of formula (VI)

7. claims: 98-104

a compound of formula (VII)

8. claims: 105-112

a compound of formula (VIII)

9. claims: 113-118

a compound of formula (IX)

10. claims: 119-126

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

a compound of formula (X)

11. claims: 127-134

a compound of formula (XI)
