

(19) World Intellectual Property
Organization
International Bureau(43) International Publication Date
25 June 2020 (25.06.2020)(10) International Publication Number
WO 2020/132597 A8

(51) International Patent Classification:

A61K 31/504 (2006.01) C07K 5/02 (2006.01)
A61K 38/12 (2006.01)

(21) International Application Number:

PCT/US2019/068100

(22) International Filing Date:

20 December 2019 (20.12.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/783,816 21 December 2018 (21.12.2018) US
62/894,493 30 August 2019 (30.08.2019) US
62/930,489 04 November 2019 (04.11.2019) US(71) Applicant: **REVOLUTION MEDICINES, INC.**
[US/US]; 700 Saginaw Drive, Redwood City, CA 94063 (US).(72) Inventors: **JIN, Meizhong**; 34 Priscilla Circle, Wellesley, MA 02481 (US). **PERL, Nicholas**; 7 Gibbens Street, Somerville, MA 02143 (US). **KOHLMANN, Anna**; 58 Thornberry Road, Winchester, MA 01890 (US). **YIN, Ning**;240 Grove Street, Lexington, MA 02420 (US). **LOWE, Jason T.**; 30 Pine Wood Path, East Bridgewater, MA 02333 (US). **AHN, Jae Young**; 12 Bay State Avenue #2, Somerville, MA 02144 (US). **MULVIHILL, Mark Joseph**; 4 Webster Circle, Sudbury, MA 01776 (US). **KOLTUN, Elena S.**; 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.**; 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, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(54) Title: COMPOUNDS THAT PARTICIPATE IN COOPERATIVE BINDING AND USES THEREOF

FIG. 1

	Structure	Method	Analytic Data
1		Ex. 2	ESI-MS m/z: 714.3; ¹ H NMR (400 MHz, MeOD): d 8.64 (s, 1H), 7.79 (s, 1H), 7.70 (dd, J = 17.1, 10.5 Hz, 1H), 7.52 - 7.54 (m, 2H), 7.17 (s, 1H), 6.99 (s, 1H), 5.80 (s, 1H), 5.42 (dd, J = 17.1, 2.1 Hz, 1H), 5.82 (dd, J = 10.5, 2.1 Hz, 1H), 5.89 (t, J = 6.2 Hz, 1H), 4.44 (d, J = 15.2 Hz, 2H), 4.18 (s, J = 11.1 Hz, 1H), 4.12 (d, J = 15.5 Hz, 1H), 3.95 - 3.80 (m, 3H), 3.66 (c, J = 8.7 Hz, 1H), 3.57 (d, J = 6.3 Hz, 1H), 3.50 - 3.48 (m, 1H), 2.8* (d, J = 6.3 Hz, 2H), 2.80 - 2.73 (m, 1H), 2.67 (s, 3H), 2.26 - 2.15 (m, 2H), 1.94 (d, J = 9.9 Hz, 1H), 1.75 - 1.54 (m, 3H), 1.20 (s, 3H), 1.05 (s, 3H), 0.97 (dd, J = 17.6, 5.6 Hz, 6H).
2		Ex. 3	ESI-MS m/z: 685.3 [M+H] ⁺ ; ¹ H NMR (300 MHz, DMSO-d ₆): d 8.46 (s, 1H), 8.75 (d, J = 5.3 Hz, 1H), 8.38 (s, 2H), 8.03 - 7.98 (m, 2H), 7.62 (dd, J = 17.2, 10.4 Hz, 1H), 7.21 (s, 1H), 7.18 - 7.01 (m, 2H), 6.71 (s, 1H), 6.50 (dd, J = 17.1, 2.3 Hz, 1H), 5.90 - 5.77 (m, 1H), 5.84 (t, J = 6.5 Hz, 1H), 5.27 - 5.09 (m, 2H), 4.74 (d, J = 11.2 Hz, 1H), 4.49 - 4.31 (m, 1H), 4.17 - 4.03 (m, 3H), 3.52 (m, 1H), 3.74 (t, J = 7.9 Hz, 2H), 3.15 - 3.03 (m, 3H), 2.93 (d, J = 13.7 Hz, 1H), 2.73 - 2.70 (m, 1H), 2.10 - 2.02 (m, 2H), 1.75 - 1.68 (m, 3H), 0.92 (d, 3H), 0.79 (d, 3H).
3		Ex. 4	ESI-MS m/z: 773.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD): d 8.02 (d, 1H), 7.89-7.92 (m, 1H), 7.72-7.6* (m, 2H), 7.30 (d, 1H), 7.05 (d, 1H), 6.59-6.53 (m, 1H), 5.78 (d, 1H), 4.85 (s, 1H), 4.64 (m, 1H), 4.51-4.45 (m, 2H), 4.41-4.36 (m, 1H), 4.21 (m, 2H), 4.15-4.02 (m, 3H), 3.83-3.78 (m, 2H), 3.17 (m, 1H), 3.01 (m, 2H), 2.88-2.65 (m, 3H), 2.53 (d, 2H), 2.18-2.02 (m, 2H), 1.96 (d, 1H), 1.70 (d, 2H), 1.04-0.72 (m, 12H).
4		Ex. 5	ESI-MS m/z: 655.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, MeOD-d ₄): d 8.77 (d, J = 4.00 Hz, 1H), 8.3* (d, J = 4.00 Hz, 1H), 8.11 (s, 1H), 7.71 (s, 1H), 7.69-7.62 (m, 3H), 6.43-6.39 (m, 1H), 5.84-5.82 (m, 1H), 5.64-5.62 (m, 1H), 4.55-4.49 (m, 1H), 4.39-4.35 (m, 2H), 4.15-4.12 (m, 1H), 3.92-3.89 (m, 1H), 4.11-3.89 (m, 1H), 3.86-3.74 (m, 2H), 3.09-2.93 (m, 4H), 2.93-2.74 (m, 1H), 2.15-2.09 (m, 4H), 2.08-1.92 (m, 1H), 1.92-1.57 (m, 2H), 1.57-1.45 (m, 3H), 1.01-0.31 (m, 6H).

(57) Abstract: The disclosure features macrocyclic compounds, alone and in combination with other therapeutic agents, as well as pharmaceutical compositions and protein complexes thereof, capable of modulating biological processes including RAS and RAS-RAF inhibition, and their uses in the treatment of cancers.

[Continued on next page]

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

Published:

— *with international search report (Art. 21(3))*

(48) Date of publication of this corrected version:

16 July 2020 (16.07.2020)

(15) Information about Correction:

see Notice of 16 July 2020 (16.07.2020)