

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization

International Bureau

(43) International Publication Date
09 June 2022 (09.06.2022)



(10) International Publication Number
WO 2022/117782 A1

(51) International Patent Classification:

C07D 495/04 (2006.01) A61P 35/00 (2006.01)
C07D 495/14 (2006.01) A61K 31/4365 (2006.01)

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).

(21) International Application Number:

PCT/EP2021/084089

(22) International Filing Date:

03 December 2021 (03.12.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

20211730.5 03 December 2020 (03.12.2020) EP

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(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, IT, 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, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(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,

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))



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(54) Title: ALC1 INHIBITORS AND SYNERGY WITH PARPI

(57) Abstract: The present invention relates to small molecule compounds that allosterically inhibit ALC1 (CHD1L) and which induce the trapping of PARP1, PARP2 and/or PARP3 on chromatin or at DNA damage sites. Disruption of the chromatin remodeling forces of ALC1 through these agents enables a highly selective therapy for targeting the DNA damage functions of PARP enzymes in several proliferative diseases, notably BRCA-deficient cancers. Via inhibition of the enzymatic activity, the compounds engage the synthetic lethality between BRCA1/2 and ALC1. By trapping PARP enzymes, inhibitors of ALC1 potentiate the cancer cell killing properties of PARP inhibitors, enable therapeutic approaches where ALC1 is amplified as an oncogene, therapeutically make it possible to overcome PARP inhibitor resistance mechanisms and enable an alternative approach to the treatment of germline or acquired BRCA1/BRCA2 deficiency, including tumors defined by "BRCAness" or other changes in DNA repair networks.