

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

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
18 June 2020 (18.06.2020)



(10) International Publication Number
WO 2020/120521 A1

(51) International Patent Classification:

C07D 487/04 (2006.01) A61K 31/46 (2006.01)
A61K 31/4196 (2006.01) A61P 25/28 (2006.01)
A61K 31/501 (2006.01) A61P 27/16 (2006.01)
A61K 31/506 (2006.01)

(21) International Application Number:

PCT/EP2019/084538

(22) International Filing Date:

11 December 2019 (11.12.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

18212199.6 13 December 2018 (13.12.2018) EP

(71) Applicant (for all designated States except US): **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(71) Applicant (for US only): **HOFFMANN-LA ROCHE INC.** [US/US]; Overlook at Great Notch, 150 Clove Road 8th Floor, Suite 8 - Legal Department, Little Falls, New Jersey 07424 (US).

(72) Inventors: **FREI, Beat**; c/o F. Hoffmann-La Roche AG, Grenzacherstrasse 124, 4070 Basel (CH). **RATNI, Hasane**; c/o F. Hoffmann-La Roche AG, Grenzacherstrasse 124, 4070 Basel (CH).

(74) Agent: **AYAD, Doria**; Grenzacherstrasse 124, 4070 Basel (CH).

(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.

(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).

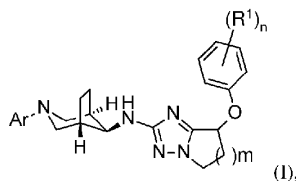
Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

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

(54) Title: 7-PHOXY-N-(3-AZABICYCLO[3.2.1]OCTAN-8-YL)-6,7-DIHYDRO-5H-PYRROLO[1,2-b][1,2,4]TRIAZOL-2-AMINE DERIVATIVES AND RELATED COMPOUNDS AS GAMMA-SECRETASE MODULATORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE



(I),

(57) Abstract: The invention provides 7-phenoxy-N-(3-azabicyclo[3.2.1]octan-8-yl)-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-2-amine derivatives and related compounds of the general formula (I) wherein R¹, Ar, n and m are as described herein, compositions including the compounds, processes of manufacturing the compounds and the compounds for use in methods of medical treatment. The present compounds are as gamma-secretase modulators for the treatment of diseases associated with the deposition of β -amyloid in the brain, such as Alzheimer's disease, cerebral amyloid angiopathy, cochlear synaptopathy, hearing loss, hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome. The present description discloses the preparation of exemplary compounds as well as pharmacological data thereof (e.g. pages 54 to 74; examples 1 to 64; table). An exemplary compound is e.g. (R)-7-(3,5-difluorophenoxy)-N-((1R,5S,8s)-3-(6-methoxypyridazin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl)-6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-2-amine (example 1).