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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 August 2010 (26.08.2010)

PCT

(10) International Publication Number
WO 2010/094667 A1

(51) International Patent Classification:
C07D 207/08 (2006.01) *A61K 31/496* (2006.01)
C07D 401/12 (2006.01) *A61K 31/506* (2006.01)
C07D 401/14 (2006.01) *A61K 31/4439* (2006.01)
C07D 403/14 (2006.01) *A61K 31/4545* (2006.01)
A61P 25/00 (2006.01) *A61K 31/501* (2006.01)

(21) International Application Number:
PCT/EP2010/051887

(22) International Filing Date:
16 February 2010 (16.02.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09153097.2 18 February 2009 (18.02.2009) EP

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

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KNUST, Henner** [DE/DE]; Im Ortsetter 26a, 79618 Rheinfelden (DE). **LIMBERG, Anja** [DE/CH]; Wettsteinallee 105, CH-4058 Basel (CH). **NETTEKOVEN, Matthias** [DE/DE]; Ruetteweg 3, 79639 Grenzach-Wyhlen (DE). **RATNI, Hasane** [FR/FR]; Louis Pasteur 4, F-68440 Habsheim (FR). **RIEMER, Claus** [DE/DE]; Dreikoenigstrasse 31, 79102 Freiburg (DE).

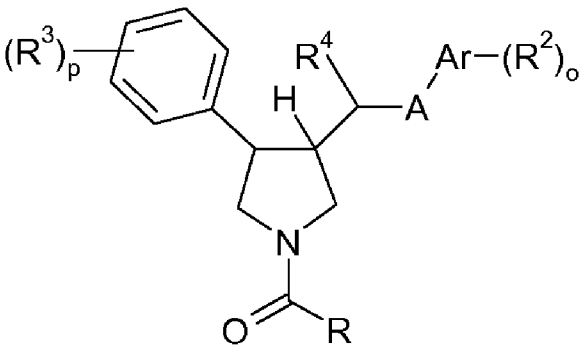
(74) Agent: **POPPE, Regina**; Grenzacherstrasse 124, CH-4070 Basel (CH).

(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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

(54) **Title**: PYRROLIDINE DERIVATIVES AS NK3 RECEPTOR ANTAGONISTS



I

(57) **Abstract**: The present invention relates to a compounds of formula I wherein A is -NR'-, -S-, -S(O)- or -$S(O)_2$-; R' is hydrogen or lower alkyl; Ar is aryl or is a five or six membered heteroaryl group, containing one or two N-atoms; R is a five or six membered heterocyclic group X^1 is N or CH; and X^2 is -$N(R^1)$-, -CH_2-, -O-, -S-, -S(O)-, or -$S(O)_2$-, R^1 is hydrogen, lower alkyl, $S(O)_2$-lower alkyl, C(O)-lower alkyl, C(O)-cycloalkyl optionally substituted by lower alkyl; with the proviso that at least one of X^1 or X^2 contains a heteroatom, or is a five or six membered heteroaryl group, containing one or two N-atoms, which groups are unsubstituted or may be substituted by one or two R^1; wherein R^1 is lower alkyl or cyano; R^2 is lower alkyl substituted by halogen, halogen, cyano or nitro; R^3 is halogen; R^4 is hydrogen or lower alkyl; o is 1 or 2; in case o is 2, R^2 may be the same or different; p is 1 or 2; in case p is 2, R^3 may be the same or different; or to a pharmaceutically active salt thereof. It has been found that the present compounds are high potential NK-3 receptor antagonists for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, bipolar disorders, anxiety and attention deficit hyperactivity disorder (ADHD).

WO 2010/094667 A1