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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2008 (26.06.2008)

PCT

(10) International Publication Number
WO 2008/074679 A2

(51) International Patent Classification:
C07D 233/64 (2006.01) *A61P 25/00* (2006.01)
A61K 31/415 (2006.01) *A61P 9/00* (2006.01)

(21) International Application Number:
PCT/EP2007/063585

(22) International Filing Date:
10 December 2007 (10.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
06126307.5 18 December 2006 (18.12.2006) 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)*: **GALLEY, Guido** [DE/DE]; Katzenbuckelweg 14, 79618 Rheinfelden (DE). **GROEBKE ZBINDEN, Katrin** [CH/CH]; Laubibergstrasse 61, CH-4410 Liestal (CH). **NORCROSS, Roger** [GB/CH]; Rheinfelderstrasse 2, CH-4305 Olsberg (CH). **STALDER, Henri** [CH/CH]; Strassburgerallee 83, CH-4055 Basel (CH).

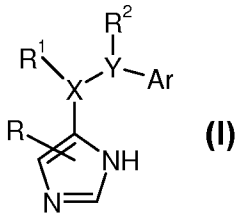
(74) Agent: **POPPE, Regina**; Grenzacherstrasse 124, CH-4070 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

(54) **Title:** 4-IMIDAZOLINES AS TAAR'S LIGANDS



(I)

(57) **Abstract:** The invention relates to compounds of formula (I) wherein R is hydrogen, lower alkyl or amino; X-R^1 is -CH_2 -, -CH(lower alkoxy)- or -CH(OH)- and Y-R^2 is -CH_2, -CH(lower alkyl)-, -CH(lower alkoxy)- -O-, -S-, -S(O)-, -$S(O)_2$ -, -CH(phenyl)- or -C(lower alkyl)$_2$ -; or X-R^1 is -NH- and Y-R^2 is -CH_2, -CH(lower alkyl)-, -CH(lower alkoxy)-, -CH(phenyl)- or -C(lower alkyl)$_2$ -; Ar is phenyl, napthyl or benzofuranyl, which rings are unsubstituted or substituted by one or more substituents, selected from the group consisting of lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy, lower alkoxy substituted by halogen, hydroxy, amino, di-alkylamino, morpholinyl, phenyl, benzyl or by O-benzyl; or to pharmaceutically suitable acid addition salts. It has been found that the compounds of formula (I) have a good affinity to the trace amine associated receptors (TAARs), especially for TAAR1. The compounds may be used for the treatment of depression, anxiety disorders, bipolar disorder, attention deficit hyperactivity disorder (ADHD), stress-related disorders, psychotic disorders such as schizophrenia, neurological diseases such as Parkinson's disease, neurodegenerative disorders such as Alzheimer's disease, epilepsy, migraine, hypertension, substance abuse and metabolic disorders such as eating disorders, diabetes, diabetic complications, obesity, dyslipidemia, disorders of energy consumption and assimilation, disorders and malfunction of body temperature homeostasis, disorders of sleep and circadian rhythm, and cardiovascular disorders.

WO 2008/074679 A2