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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 July 2007 (05.07.2007)

PCT

(10) International Publication Number
WO 2007/074078 A3

(51) International Patent Classification:
C07D 413/04 (2006.01) *A61K 31/4178* (2006.01)
A61K 31/42 (2006.01)

(21) International Application Number:
PCT/EP2006/069722

(22) International Filing Date:
14 December 2006 (14.12.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
05113011.0 27 December 2005 (27.12.2005) 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)*: **BUETTELMANN, Bernd** [DE/DE]; Amselweg 10, 79650 Schopfheim (DE). **HAN, Bo** [CN/CN]; 801 Ying Hua Road, Building 11-1202, Pudong Shanghai 201204 (CN). **KNUST, Henner** [DE/DE]; Untere Dorfstrasse 20, 79618 Rheinfelden (DE). **THOMAS, Andrew** [GB/CH]; Weinbergstrasse 29, CH-4102 Binningen (CH).

(74) Agent: **WASNER, Marita**; 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, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, 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, LV, LY, MA, MD, 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.

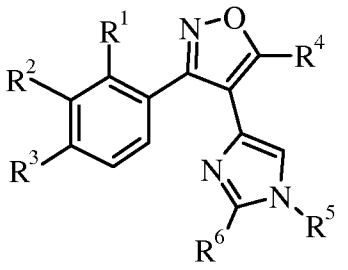
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, 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:
— *with international search report*

(88) Date of publication of the international search report:
17 January 2008

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ARYL-ISOXAZOL-4-YL-IMIDAZOLE DERIVATIVES



I

(57) Abstract: The present invention is concerned with aryl-isoxazol-4-yl-imidazole derivatives of formula (I), wherein R^1 to R^3 are each independently hydrogen or halogen; R^4 is hydrogen, lower alkyl, cycloalkyl, $-(CH_2)_n$-O-lower alkyl or lower alkyl substituted by hydroxy; R^5 is $-(CH_2)_m$-aryl or $-(CH_2)_m$-heteroaryl which are optionally substituted by one or more substituents selected from the group consisting of halogen, cyano, nitro, lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkyl substituted by halogen, -C(O)-lower alkyl, -C(O)-O-lower alkyl, -NH-C(O)-O-lower alkyl or -C(O)-NH-R', wherein R' is lower alkynyl or lower alkyl substituted by halogen, or is $-(CH_2)_n$-cycloalkyl, $-(CH_2)_n$-heterocyclyl, $-(CH_2)_n$-heteroaryl or $-(CH_2)_n$-aryl, optionally substituted by halogen; R^6 is hydrogen, -C(O)H, $-(CH_2)_n$-O-lower alkyl, -C(O)O-lower alkyl, lower alkyl substituted by hydroxy or halogen, or is cycloalkyl, aryl, or is $-(CH_2)_n$-O-CH_2-aryl, optionally substituted by halogen or lower alkyl, or is $-(CH_2)_n$-O-CH_2-heteroaryl, optionally substituted by halogen, lower alkyl or lower alkyl substituted by halogen, or is $-(CH_2)_n$-NH-$(CH_2)_o$-heterocyclyl; n is 0, 1, 2 or 3 m is 0 or 1; o is 1, 2 or 3; as well as with pharmaceutically acceptable acid addition salts thereof. It has been found that this class of compounds show high affinity and selectivity for GABA A α5 receptor binding sites and might be useful as cognitive enhancer or for the treatment of cognitive disorders like Alzheimer's disease.

WO 2007/074078 A3