PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/4453, 31/40, 31/445, 31/138

A3

(11) International Publication Number: **WO 00/06254**

(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/EP99/05744

(22) International Filing Date: 29 July 1999 (29.07.99)

(30) Priority Data:

98401944.8	29 July 1998 (29.07.98)	EP
98403351.4	31 December 1998 (31.12.98)	EP

(71) Applicant *(for all designated States except US)*: SOCIETE CIVILE BIOPROJET [FR/FR]; 30, rue des Francs Bourgeois, F–75003 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SCHWARTZ, Jean–Charles [DE/FR]; 9, villa Seurat, F–75014 Paris (FR). ARRANG, Jean–Michel [FR/FR]; 3, avenue des Acacias, F–91410 Dourdan (FR). GARBARG, Monique [FR/FR]; 26, boulevard Gouvion Saint Cyr, F–75017 Paris (FR). LECOMTE, Jeanne–Marie [FR/FR]; 30, rue des Francs Bourgeois, F–75003 Paris (FR). LIGNEAU, Xavier [FR/FR]; 10, rue des Tanneries, F–75013 Paris (FR). SCHUNACK, Walter, G. [DE/DE]; Spanische Allee 95, D–14129 Berlin (DE). STARK, Holger [DE/DE]; Heiligendammer Strasse 11, D–14199 Berlin (DE). GANELLIN, Charon, Robin [GB/GB]; Kinwood Briary Wood End, Welwyn, Hert AL6 0TD (GB). LEURQUIN, Fabien [FR/GB]; 49 Chilton Street, London E2 6DZ (GB). SIGURD, Elz [DE/DE]; Albulaweg 7a, D–12107 Berlin (DE).

(74) Agent: OBOLENSKY, Michel; Cabinet Lavoix, 2, place d'Estienne d'Orves, F–75441 Paris Cedex 09 (FR).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

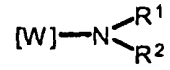
Published
With international search report.

(88) Date of publication of the international search report: 4 May 2000 (04.05.00)

(54) Title: NON–IMIDAZOLE ALKYLAMINES AS HISTAMINE H_3–RECEPTOR LIGANDS AND THEIR THERAPEUTIC APPLICATIONS

(57) Abstract

Use of a compound of formula (A), wherein:



(A)

W is a residue which imparts antagonistic and/or agonistic activity at histamine H_3–receptors when attached to an imidazole ring in 4(5) position; R^1 and R^2 may be identical or different and represent each independently a lower alkyl or cycloalkyl, or taken together with the nitrogen atom to which they are attached, a saturated nitrogen–containing ring (i) as defined, a non–aromatic unsaturated nitrogen–containing ring (ii) as defined, a morpholino group, or a N–substituted piperazino group as defined for preparing medicaments acting as antagonists and/or agonists at the H_3–receptors of histamine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 99/05744

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4453 A61K31/40 A61K31/445 A61K31/138

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BRANDES L J ET AL: "New evidence that the antiestrogen binding site may be a novel growth-promoting histamine receptor (?H3) which mediates the antiestrogenic and antiproliferative effects of tamoxifen" BIOCHEM. BIOPHYS. RES. COMMUN. (BBRCA9,0006291X);1986; VOL.134 (2); PP.601-8, XP002123595 Univ. Manitoba;Manitoba Inst. Cell Biol.; Winnipeg; R3E 0V9; MB; Can. (CA) the whole document --- -/--	16-28

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 1999	04.02.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	GANELLIN C R ET AL: "Synthesis of potent non-imidazole histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1998; VOL.331 (12); PP.395-404, XP002123596 Univ. London;Dep. Chemistry, College London, Christopher Ingold Lab.; London; WC1H OAJ; UK (GB)	16-28
P,Y	the whole document ---	16-28
A	KIEC-KONONOWICZ K ET AL: "Azines and diazines as potential histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1995; VOL.328 (5); PP.445-50, XP002123597 Jagiellonian Univ.;Dep. Chemical Technology of Drugs; Krakow; 30-688; Pol. (PL) the whole document ---	16-28
A	KIEC-KONONOWICZ K ET AL: "Pyrazoles as potential histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1995; VOL.328 (5); PP.469-72, XP002123598 Jagiellonian Univ.;Dep. Chemical Technology of Drugs; Krakow; 30-688; Pol. (PL) the whole document ---	16-28
Y	ARRANG J M ET AL: "Actions of betahistine at histamine receptors in the brain" EUR. J. PHARMACOL. (EJPHAZ,00142999);1985; VOL.111 (1); PP.73-84, XP002123599 Cent. Paul Broca;Unite Neurobiol.; Paris; 75014; Fr. (FR) the whole document ---	16-28
Y	CHEMICAL ABSTRACTS, vol. 124, no. 23, 3 June 1996 (1996-06-03) Columbus, Ohio, US; abstract no. 308211, IMAIZUMI M ET AL: "Effects of betahistine, a histamine H1 agonist and H3 antagonist, in a light/dark test in mice" XP002123600 abstract & METHODS FIND. EXP. CLIN. PHARMACOL. (MFEPDX,03790355);1996; VOL.18 (1); PP.19-24, Yamasa Corporation;Biology Laboratory; Choshi; Japan (JP) ---	16-28
	-/--	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 123, no. 1, 3 July 1995 (1995-07-03) Columbus, Ohio, US; abstract no. 000292, STARK H ET AL: "New potent histamine H3-receptor antagonists of the amide type" XP002123601 abstract & EUR. J. PHARM. SCI. (EPSCED,09280987);1995; VOL.3 (2); PP.95-104, Institut fuer Pharmazie, Freie Universitaet Berlin, Koenigin-Luise-Strasse 2+4;Berlin; 14195; Germany (DE) ---	16-28
Y	CHENEY L C ET AL: "Alkylaminoalkyl Ethers of the Benzylphenols" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,US,AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 71, page 60-64 XP002086293 ISSN: 0002-7863 see page 60, compound III and last paragraph of page 60 -----	16-28

INTERNATIONAL SEARCH REPORT

Inte. ational application No.
PCT/EP 99/05744

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See further information sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

16 - 28, 78 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-15,29-38,46-50,54,70,72,73,79-88

1) Present claims 1-15 relate to a use of a compound defined by reference to a desirable characteristic or property, namely that W is a residue that imparts antagonistic and/or agonistic activtiy at histamine H3-receptors when attached to an imidazole ring in 4(5) position. The claims cover the use of all such compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound to be used by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

2) Present claims 29-38,46-50,54,70,72 and 79-88 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Specifically, for claim 54, AViii may be absent, Xviii may be ,Y may be absent and R4viii may be H, such that none of the groups has any recognisable common definition.

3) Present claim 73 relates to the use of a compound of the formula XVI, wherein Zxvi may optionally comprise other substituents selected such that the activtiy of the derivative is not negatively affected. The claims cover the use of all compounds of formula XVI having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, this claim so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, this claim also lacks clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear,supported and disclosed, namely those parts relating to the claims 16-28.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 16-28,78(partially)

   Use of compounds of the formula I for the preparation of a medicament acting as a ligand of the histamine H3-receptors

2. Claims: 39-45,78(partially)

   Use of compounds of formulae III or IV for the preparation of a medicament acting as a ligand of the histamine H3-receptors

3. Claims: 51-53,78(partially)

   Use of the compounds of formula VII for the preparation of a medicament acting as a ligand on the hiatamine H3-receptors.

4. Claims: 55-56,78(partially)

   Use of a compound of the formulae VIIIa or VIIIb for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

5. Claims: 57-60,78(partially)

   Use of compounds of formulae IX or X for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

6. Claims: 61-67,78(partially)

   Use of a compound of formula XI or XIIfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

7. Claims: 68-69, 78(partially)

   Use of a compound of the formula XIIIfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

8. Claims: 71,78(partially)

   use of a compound of the formulae XIVa,XIVb or XIVcfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

9. Claims: 74,78(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of a compound of the formula XVII for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

10. Claims: 75-77,78(partially)

Use of a compound of the formula V for the preparation of a medicament acting as a ligand of the histamine H3-receptors.