

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/012733 A3

- (51) International Patent Classification⁷: **A61K 31/41**, (74) Common Representative: **NEUROSEARCH A/S**; 93 Pederstrupvej, DK-2750 Ballerup (DK).
A61P 35/00, 43/00
- (21) International Application Number: PCT/DK2003/000518
- (22) International Filing Date: 31 July 2003 (31.07.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
PA 2002 01165 1 August 2002 (01.08.2002) DK
PA 2002 01839 28 November 2002 (28.11.2002) DK
PA 2003 00371 11 March 2003 (11.03.2003) DK
- (71) Applicant (*for all designated States except US*): **NEUROSEARCH A/S** [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **LICHTENBERG, Jens** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **CHRISTOPHERSEN, Palle** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK). **DAHL, Bjarne, H.** [DK/DK]; c/o NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup (DK).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (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: 18 March 2004
- 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: COMPOUNDS USEFUL FOR THE TREATMENT OF DISEASES RESPONSIVE TO ANTIANGIOGENETIC THERAPY

(57) Abstract: This invention relates to the use of certain compounds for the treatment of diseases that are responsive to antiangiogenic therapy. Excessive angiogenesis occurs in diseases such as cancer, diabetic blindness, age-related macular degeneration, rheumatoid arthritis and psoriasis. The compounds are particularly useful for anti-metastatic treatment or for the treatment of age-related macular degeneration.



WO 2004/012733 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00518

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/41 A61P35/00 A61P43/00		
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 C07C C07D		
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) BIOSIS, EPO-Internal, CHEM ABS Data, PAJ, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; December 2000 (2000-12) SHEN MENG-RU ET AL: "Differential expression of volume-regulated anion channels during cell cycle progression of human cervical cancer cells" Database accession no. PREV200100069159 XP002262442 abstract & JOURNAL OF PHYSIOLOGY (CAMBRIDGE), vol. 529, no. 2, December 2000 (2000-12), pages 385-394, ISSN: 0022-3751	7
Y	--- -/--	1-11
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		
<input checked="" type="checkbox"/> 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	"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	
"E" earlier document but published on or after the international filing date	"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	
"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)	"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.	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search <p style="text-align: center;">24 November 2003</p>	Date of mailing of the international search report <p style="text-align: center;">15. 12. 2003</p>	
Name and mailing address of the ISA 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	Authorized officer <p style="text-align: center;">INGRID EKLUND</p>	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00518

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VANGELIS G. MANOLOPOULOS ET AL: "Inhibition of angiogenesis by blockers of volume-regulated anion channels" GENERAL PHARMACOLOGY, vol. 34, 2000, pages 107-116, XP002262438 abstract, introduction	7
Y	---	1-11
X	A.J. NICHOLL ET AL: "The role of bicarbonate in regulatory volume decrease (RVD) in the epithelial-derived human breast cancer cell line ZR-75-1" PFLÜGERS ARCH - EUR J PHYSIOL, vol. 443, 2002, pages 875-881, XP002262439 abstract, introduction, page 880, column 2, lines 25-27	7
Y	---	1-11
Y	POUL BENNEKOU ET AL : "Treatment with NS3623, a novel CI-conductance blocker, ameliorates erythrocyte dehydration in transgenic SAD mice: a possible new therapeutic approach for sickle cell disease." BLOOD, vol. 97, no. 5, 1 March 2001 (2001-03-01), pages 1451-1457, XP002262440 abstract; figure 1	1-11
Y	ANTONIO R.T. ET AL: "Antiangiogenic and antiproliferative activity of suramin analogues" CANCER CHEMOTHER PHARMACOL, vol. 41, 1998, pages 117-124, XP002262441 figures 1,4 abstract	1-11
Y	WO 00 24707 A (DAHL BJARNE H ;NEUROSEARCH AS (DK); CHRISTOPHERSEN PALLE (DK)) 4 May 2000 (2000-05-04) abstract; claims	1-11
Y	WO 98 47879 A (NEUROSEARCH AS ;PEDERSEN OVE (DK); CHRISTOPHERSEN PALLE (DK)) 29 October 1998 (1998-10-29) abstract; claims	1-11
A	WO 00 76495 A (BENSON GREGORY MARTIN ;SMITHKLINE BEECHAM CORP (US); WIDDOWSON KAT) 21 December 2000 (2000-12-21) abstract; claims	1-11

	-/--	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00518

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 25157 A (HERTZBERG ROBERT PHILIP ;JUREWICZ ANTHONY JOSEPH (US); RUTLEDGE ME) 22 August 1996 (1996-08-22) abstract; claims <div style="text-align: center;">---</div>	1-11
A	WO 99 32436 A (BAYER AG) 1 July 1999 (1999-07-01) abstract; claims <div style="text-align: center;">-----</div>	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00518

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.: 10-11
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: 7
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:

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.:

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.1

Claims Nos.: 10-11

Claims relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

Continuation of Box I.2

Claims Nos.: 7

Present claim 7 relates to compounds defined by reference to a desirable characteristic or property, namely the ability to block volume-regulated anion channels. The claim covers all 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. Additionally, previously known compounds may be included in the scope of the present claims. In the present case, the claim so lacks 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 claim also lack 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 compounds defined in claim 1.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00518

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0024707	A	04-05-2000	AU 759275 B2 10-04-2003
			AU 6325999 A 15-05-2000
			BR 9914638 A 03-07-2001
			CA 2342626 A1 04-05-2000
			CN 1322194 T 14-11-2001
			WO 0024707 A1 04-05-2000
			EE 200100185 A 15-08-2002
			EP 1123274 A1 16-08-2001
			HU 0103673 A2 28-02-2002
			JP 2002528432 T 03-09-2002
			JP 2003246773 A 02-09-2003
			NO 20011956 A 20-04-2001
			NZ 510098 A 26-09-2003
			PL 347371 A1 08-04-2002
			SK 5222001 A3 09-05-2002
			TR 200101126 T2 21-09-2001
			US 2002032210 A1 14-03-2002
			US 2002037905 A1 28-03-2002
			ZA 200101824 A 05-03-2002

WO 9847879	A	29-10-1998	AT 226189 T 15-11-2002
			AT 248824 T 15-09-2003
			AU 735545 B2 12-07-2001
			AU 2962197 A 05-01-1998
			AU 728520 B2 11-01-2001
			AU 6919698 A 13-11-1998
			BR 9808938 A 01-08-2000
			CA 2255858 A1 04-12-1997
			CN 1118462 B 20-08-2003
			DE 69716424 D1 21-11-2002
			DE 69716424 T2 20-02-2003
			DE 69817802 D1 09-10-2003
			WO 9847879 A1 29-10-1998
			WO 9745400 A1 04-12-1997
			EP 0906273 A1 07-04-1999
			EP 0977741 A1 09-02-2000
			JP 2000511167 T 29-08-2000
			JP 2001521532 T 06-11-2001
			NZ 332789 A 26-05-2000
			NZ 337976 A 25-05-2001
			RU 2197482 C2 27-01-2003
			SK 144799 A3 16-05-2000
			TR 9902593 T2 21-03-2000
			US 6417393 B1 09-07-2002
			US 6297261 B1 02-10-2001
			US 2002037905 A1 28-03-2002

WO 0076495	A	21-12-2000	AU 766083 B2 09-10-2003
			AU 5741300 A 02-01-2001
			BR 0010802 A 19-02-2002
			CA 2377341 A1 21-12-2000
			CN 1355697 T 26-06-2002
			CZ 20014471 A3 14-08-2002
			EP 1185261 A1 13-03-2002
			HU 0201571 A2 28-08-2002
			JP 2003501459 T 14-01-2003
			NO 20016053 A 11-12-2001
			TR 200103680 T2 22-07-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00518

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0076495	A		WO 0076495 A1 ZA 200109479 A	21-12-2000 18-11-2002

WO 9625157	A	22-08-1996	EP 0809492 A1 JP 11503110 T NO 983737 A WO 9625157 A1 US 6180675 B1 US 5886044 A US 5780483 A	03-12-1997 23-03-1999 14-10-1998 22-08-1996 30-01-2001 23-03-1999 14-07-1998

WO 9932436	A	01-07-1999	AU 763024 B2 AU 1905499 A BG 104599 A BR 9814375 A CA 2315646 A1 CN 1283180 T DE 1049664 T1 EP 1049664 A1 ES 2153809 T1 GR 2001300006 T1 HU 0004437 A2 JP 2001526258 T NO 20003230 A NZ 505843 A PL 342078 A1 SK 9612000 A3 TR 200002616 T2 TR 200100874 T2 WO 9932436 A1	10-07-2003 12-07-1999 30-03-2001 21-05-2002 01-07-1999 07-02-2001 03-05-2001 08-11-2000 16-03-2001 28-02-2001 28-06-2001 18-12-2001 21-08-2000 30-06-2003 21-05-2001 12-03-2001 21-11-2000 21-06-2001 01-07-1999
