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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 2003/016351 A3

(51) International Patent Classification[7]: C07K 14/705, A61K 38/17, A61P 21/00, 25/00, 17/02, 35/00, C07K 7/00, A61K 38/04

(21) International Application Number:
PCT/DK2002/000541

(22) International Filing Date: 19 August 2002 (19.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PA 2001 01228	17 August 2001 (17.08.2001)	DK
PA 2002 00667	2 May 2002 (02.05.2002)	DK

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(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, 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, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, 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, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

(88) Date of publication of the international search report:
25 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: N - CAM RELATED COMPOUNDS MODULATING CELL GROTH

(57) Abstract: The present invention relates to a compound comprising the third Immunoglobulin (Ig3) module, and/or the fourth Immunoglobulin (Ig4) module, and/or the fifth Immunoglobulin (Ig5) module, and/or the first Fibronectin III (Fn3, 1) module, and/or the second Fibronectin III (Fn3, 2) module of neural cell adhesion molecule (NCAM), or a fragment, or a variant thereof, capable of interacting with a Fibroblast Growth Factor (FGF) receptor and/or Adenosine-Tri-Phosphate (ATP) and/or L1, and thereby the compounds are capable of inducing differentiation, modulating proliferation, stimulate regeneration, neuronal plasticity and/or survival of cells. Further, the present invention relates to a pharmaceutical composition comprising said compound, a process of producing a pharmaceutical composition and the use of said compound.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/705 A61K38/17 A61P21/00 A61P25/00 A61P17/02
A61P35/00 C07K7/00 A61K38/04

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 C07K A61K A61P

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)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	V.V. KISELYOV ET AL: "Structure of the second fibronectin type III module of NCAM. identification of a neuritogenic site" EUROPEAN JOURNAL OF NEUROSCIENCE, vol. 12, no. 11, 2000, page 274 XP002253822 the whole document ---	7,8,12, 15-18, 22-54
X	GALINA SKLADCHIKOVA ET AL: "Extracellular adenosine triphosphate affects neural cell adhesion molecule (NCAM)-Mediated cell adhesion and neurite outgrowth." JOURNAL OF NEUROSCIENCE RESEARCH, vol. 57, 1999, pages 207-218, XP002902868 Wiley-liss inc. see specially page 215, column 2, line 17. (AENQQGKS) --- -/--	7,15-18

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

[X] 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
10 September 2003	30. 09. 2003

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	MICAEL OWALD /EÖ

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 02/00541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHRISTINA KASPER ET AL: "Functional Characterization of NCAM Fibronectin Type III Domains: Demonstration of Modulatory Effects of the Proline-Rich Sequence Encoded by Alternatively Spliced Exons a and AAG " JOURNAL OF NEUROSCIENCE RESEARCH, vol. 46, 1996, pages 173-186, XP002253823 the whole document and see specially page 183, column 2, line 28 - page 184, column 1, line 4	7,8,12, 15-18, 22-54
X	US 6 576 607 B1 (SCHACHNER MELITTA) 10 June 2003 (2003-06-10) see specially claims	7,8,12, 15-18, 22-47, 53,54
X	MING YI ET AL: "A fibronectin fragment inhibits tumor growth, angiogenesis, and metastasis." PNAS, vol. 98, no. 2, 16 January 2001 (2001-01-16), pages 620-624, XP002902853 the whole document	7,8,12, 15-18, 22-45, 49,51, 52,54
X	US 5 837 813 A (RUOSLAHTI ERKKI I ET AL) 17 November 1998 (1998-11-17) the whole document	7,8,12, 15-18, 22-47, 50,53,54
A	FREI T ET AL: "Different extracellular domains of the neural cell adhesion molecule (N-CAM) are involved in different functions" JOURNAL OF CELL BIOLOGY, ROCKEFELLER UNIVERSITY PRESS, NEW YORK, US, US, vol. 118, no. 1, July 1992 (1992-07), pages 177-194, XP002104607 ISSN: 0021-9525 the whole document	7,8,12, 15-18, 22-54
P,X	WO 01 96364 A (IMP COLLEGE INNOVATIONS ;KING S COLLEGE LONDON (GB); SAFFELL JANE) 20 December 2001 (2001-12-20) the whole document	7,8,12, 15-18, 22-54
P,X	US 6 313 265 B1 (PHILLIPS G ET AL) 6 November 2001 (2001-11-06) see figure 3, Seq ID No 72, claim 3	8,12,17, 22-33, 35-47, 53,54

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00541

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. [X] Claims Nos.: 1-6,9-11,13-14,19-21 completely and 22-33, 35-54 partially
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

As a result of the prior review under R. 40.2(e) PCT, all additional fees are to be refunded.

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. [X] 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.:

The search has been directed to subject 1-3 which covers claims 7-8, 12, 15-16, 17 (parts related to SEQ ID No 1-6, 8-11 and 26-31), 18, 22-33 (partially), 34 and 35-54 (partially).

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

[X] 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.: 1-6,9-11,13-14,19-21 completely and 22-33, 35-54 partially

Claims 1-6, 9-11, 13-14, 19-21 completely and 22-33, 35-54 parts that are not subordinated to claim 7, 8 or 34.

Present claims 1-6, 9-11, 13-14, 19-33, and 35-54 relate to an extremely large number of possible compounds and related processes and uses. Support within the meaning of Article 6 PCT and or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. 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. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds comprising the first or second Fibronectin 3 (Fn 3,2 or Fn 3,1) module of NCAM or fragments thereof in general.

The wording "a variant thereof", in e.g. claims 7 and 34, is defined as any peptide or non-peptide substance having similar properties as a the related NCAM amino acid sequence, the application provides no support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds 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 impossible. No variants have been searched.

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 8, 12, 17

   Compounds comprising the sequence NGKGL or NGRGL e.g. SEQ ID NO 8-11,26-31 In particular claims 8, 12, 17.

2. Claims: 7,15-18, 34

   AENQXXK as defined in claim 15 e.g. SEQ ID NO 3-6, in particular claims 7, 15-18, 34.

3. Claims: 7, 17-18, 34

   Compounds comprising the sequence AENQ-L4-K as defined in claim 18 e.g. SEQ ID NO 1-2, in particular claims 7, 17-18, 34.

4. Claims: -

   Compounds comprising SEQ ID NO 7,176-188, 191-195 and 204.

5. Claims: -

   Compounds comprising SEQ ID NO 12.

6. Claims: -

   Compounds comprising SEQ ID NO 13 and 14.

7. Claims: -

   Compounds comprising SEQ ID NO 15-17.

8. Claims: -

   Compounds comprising SEQ ID NO 18-22.

9. Claims: -

   Compounds comprising SEQ ID NO 23 and 25.

10. Claims: -

    Compounds comprising SEQ ID NO 24.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

11. Claims: -

Compounds comprising SEQ ID NO 32-34 and 37-42.

12. Claims: -

Compounds comprising SEQ ID NO 35-36.

13. Claims: -

Compounds comprising SEQ ID NO 43-48, 93, 99, 107 and 110-111.

14. Claims: -

Compounds comprising SEQ ID NO 49 and 101-106.

15. Claims: -

Compounds comprising SEQ ID NO 50 and 94

16. Claims: -

Compounds comprising SEQ ID NO 51-54.

17. Claims: -

Compounds comprising SEQ ID NO 55-56, 86 and 109.

18. Claims: -

Compounds comprising SEQ ID NO 57 and 119-120.

19. Claims: -

Compounds comprising SEQ ID NO 58-61.

20. Claims: -

Compounds comprising SEQ ID NO 62-68 and 121-127.

21. Claims: -

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Compounds comprising SEQ ID NO 69-78, 128-130 and 132-133, 144-147.

22. Claims: -

Compounds comprising SEQ ID NO 79-81, 83, 134-137 and 139-140.

23. Claims: -

Compounds comprising SEQ ID NO 82 and 131.

24. Claims: -

Compounds comprising SEQ ID NO 84 and 142.

25. Claims: -

Compounds comprising SEQ ID NO 85, 138 and 143.

26. Claims: -

Compounds comprising SEQ ID NO 87.

27. Claims: -

Compounds comprising SEQ ID NO 88.

28. Claims: -

Compounds comprising SEQ ID NO 89-92.

29. Claims: -

Compounds comprising SEQ ID NO 95-97.

30. Claims: -

Compounds comprising SEQ ID NO 98 and 108.

31. Claims: -

Compounds comprising SEQ ID NO 100.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

32. Claims: -

Compounds comprising SEQ ID NO 112-113.

33. Claims: -

Compounds comprising SEQ ID NO 114-116 and 118.

34. Claims: -

Compounds comprising SEQ ID NO 141.

35. Claims: -

Compounds comprising SEQ ID NO 145-146.

36. Claims: -

Compounds comprising SEQ ID NO 148-149.

37. Claims: -

Compounds comprising SEQ ID NO 150 and 171.

38. Claims: -

Compounds comprising SEQ ID NO 151 and 170.

39. Claims: -

Compounds comprising SEQ ID NO 152.

40. Claims: -

Compounds comprising SEQ ID NO 153-155.

41. Claims: -

Compounds comprising SEQ ID NO 156-159, 161-162, 169 and 173.

42. Claims: -

Compounds comprising SEQ ID NO 160.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

43. Claims: -

Compounds comprising SEQ ID NO 163-168.

44. Claims: -

Compounds comprising SEQ ID NO 174-175.

45. Claims: -

Compounds comprising SEQ ID NO 189-190, 197-199 and 201.

46. Claims: -

Compounds comprising SEQ ID NO 196 and 200.

47. Claims: -

Compounds comprising SEQ ID NO 202-203.

48. Claims: -

Compounds comprising SEQ ID NO 205-206.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 02/00541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6576607 B1	10-06-2003	AU 718508 B2	13-04-2000
		AU 5557296 A	07-11-1996
		CA 2218599 A1	24-10-1996
		CZ 9703301 A3	15-04-1998
		EA 970323 A1	30-04-1998
		EP 0821591 A1	04-02-1998
		HU 9900060 A2	28-04-1999
		JP 11504211 T	20-04-1999
		NO 974811 A	19-12-1997
		PL 322947 A1	02-03-1998
		SK 142497 A3	06-08-1999
		TR 9701203 T1	21-03-1998
		TR 9801650 T2	22-03-1999
		WO 9632959 A1	24-10-1996
		US 5792743 A	11-08-1998
US 5837813 A	17-11-1998	US 5629291 A	13-05-1997
		US 5453489 A	26-09-1995
		US 5747452 A	05-05-1998
		AT 152173 T	15-05-1997
		AU 3656893 A	01-09-1993
		CA 2129115 A1	05-08-1993
		DE 69310145 D1	28-05-1997
		DK 624196 T3	03-11-1997
		EP 0624196 A1	17-11-1994
		FI 943568 A	29-07-1994
		JP 7506342 T	13-07-1995
		NO 942825 A	29-09-1994
		WO 9315203 A2	05-08-1993
WO 0196364 A	20-12-2001	EP 1294744 A2	26-03-2003
		WO 0196364 A2	20-12-2001
US 6313265 B1	06-11-2001	NONE	