

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 April 2006 (27.04.2006)

PCT

(10) International Publication Number
WO 2006/042441 A3

(51) International Patent Classification:
A61K 31/37 (2006.01)

(21) International Application Number:
PCT/CH2005/000621

(22) International Filing Date: 21 October 2005 (21.10.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04025165.4 22 October 2004 (22.10.2004) EP

(71) Applicant (for all designated States except US): **DSM IP ASSETS B.V.** [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DE SAIZIEU, Antoine** [FR/FR]; 60, rue Bellevue, F-68350 Brunstatt (FR). **FOWLER, Ann** [GB/CH]; Marktgasse 13, CH-4310 Rheinfelden (CH). **GORALCZYK, Regina** [DE/DE]; Allmendweg 7, 79639 Grenzach-Wyhlen (DE). **MUS-SLER, Bernd** [DE/DE]; Alte Bahnhofstrasse 14, 77933 Lahr (DE). **SCHUELER, Goede** [DE/DE]; Märkter Strasse 9, 79591 Eimeldingen (DE).

(74) Agent: **STECK, Melanie et al**; c/o DSM Nutritional Products Ltd, Wurmisweg 576, CH-4303 Kaiseraugst (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, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
13 July 2006

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: NOVEL AGENTS FOR PREVENTING AND TREATING DISORDERS CONNECTED TO IMPAIRED NEUROTRANSMISSION

(57) Abstract: The present invention refers to coumarin ethers of the formula (I), wherein R¹ is H, OH or (E)-3-methyl-but-2-enyl, R² is selected from the group consisting of methyl, 3-(4,5-dihydro-5,5-dimethyl-4-furanon-2-yl)-2-(E/Z)-butenyl, (E/Z)-3,7-dimethylocta-2,6-dienyl, 7-hydroxy-3,7-dimethyl-2-octen-6-on-yl and (E/Z,E/Z)-11-acetyl-oxy-3,7,11,11-tetramethyl-undeca-2,7-dien-10-on-yl, R³ is H, R¹ and R²O together for the group -O-C(C(=CH₂))CH₃-H-CH₂-O- or the group -C(H)=C(H)-C(CH₃)₂-O- or R²O and R³ together form the group -O-C(H)(C(CH₃)₂(H))-O-C(O)CH₃-CH₂-, preferably to obliquin, for use as medicaments, especially for the treatment and/or prevention of disorders connected to impaired neurotransmission, as well as to dietary and pharmaceutical compositions and plant extracts containing such coumarin ethers and their uses.

WO 2006/042441 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/CH2005/000621

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/37

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)
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)

EPO-Internal, BIOSIS, FSTA, WPI Data, EMBASE, PAJ

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; May 2000 (2000-05), OGAWA KAZUNORI ET AL: "Evaluation of auraptene content in citrus fruits and their products" XP002377866 Database accession no. PREV200000297950 abstract & JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, vol. 48, no. 5, May 2000 (2000-05), pages 1763-1769, ISSN: 0021-8561 ----- -/--	1-12

☒ Further documents are listed in the continuation of Box C.

☒ See patent family 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

21 April 2006

Date of mailing of the international search report

17/05/2006

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

Bendl, E

INTERNATIONAL SEARCH REPORT

International application No

PCT/CH2005/000621

C(Continuation). 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; 1992, MASUDA TOSHIYA ET AL: "Coumarin constituents of the juice oil from Citrus hassaku and their spasmolytic activity" XP002377867 Database accession no. PREV199395019941 abstract & BIOSCIENCE BIOTECHNOLOGY AND BIOCHEMISTRY, vol. 56, no. 8, 1992, pages 1257-1260, ISSN: 0916-8451	1-12
X	----- DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 28 September 2001 (2001-09-28), BOCCA CLAUDIA ET AL: "Cytoskeleton-interacting activity of geiparvarin, diethylstilbestrol and conjugates" XP002377868 Database accession no. PREV200100535079 abstract & CHEMICO-BIOLOGICAL INTERACTIONS, vol. 137, no. 3, 28 September 2001 (2001-09-28), pages 285-305, ISSN: 0009-2797	1-12
X	----- DATABASE FSTA [Online] INTERNATIONAL FOOD INFORMATION SERVICE (IFIS), FRANKFURT-MAIN, DE; 2002, TAKAHASHI Y ET AL: "Rapid and convenient method for preparing aurapten-enriched product from hassaku peel oil: implications for cancer-preventive food additives." XP002377869 Database accession no. 2002-00-t0665 abstract & JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, vol. 50, no. 11, 2002, pages 3193-3196, ----- -/--	1-12

INTERNATIONAL SEARCH REPORT

International application No

PCT/CH2005/000621

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMADA Y ET AL: "SPASMOLYTIC ACTIVITY OF AURAPTEN ANALOGS" BIOSCIENCE BIOTECHNOLOGY BIOCHEMISTRY, JAPAN SOC. FOR BIOSCIENCE, BIOTECHNOLOGY AND AGROCHEM, TOKYO, JP, vol. 61, no. 4, 1997, pages 740-742, XP001000834 ISSN: 0916-8451 abstract; figure 1 page 740, right-hand column -----	1-12
E	WO 2005/102316 A (INTE:LIGAND; LEOPOLD-FRANZENS UNIVERSITAET INNSBRUCK; STUPPNER, HERMAN) 3 November 2005 (2005-11-03) page 3, paragraph 2 - paragraph 3 claims 1-3 -----	1-12
E	WO 2006/024545 A (STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN; HAGEMAN, GERRIGJE, JOHANNA) 9 March 2006 (2006-03-09) page 12, line 4 - line 5; figure IV page 15, line 3 - line 33 -----	1-12
Y	US 3 707 474 A (RAJ K. RAZDAN ET AL) 26 December 1972 (1972-12-26) column 2, line 8 - line 10; figures I-III -----	1-12
Y	US 4 079 066 A (GARDNER ET AL) 14 March 1978 (1978-03-14) column 1, line 51; figure I column 2, line 40 - line 42 column 3, line 19 - line 22 -----	1-12
Y	DATABASE WPI Section Ch, Week 199224 Derwent Publications Ltd., London, GB; Class B02, AN 1992-190098 XP002377874 & JP 04 128224 A (SANKYO CO LTD) 28 April 1992 (1992-04-28) abstract -----	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CH2005/000621

Box II Observations where certain claims were found unsearchable (Continuation of item 2 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:

Although claims 4,11-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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:
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 III Observations where unity of invention is lacking (Continuation of item 3 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/CH2005/000621

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005102316 A	03-11-2005	EP 1588705 A1	26-10-2005
WO 2006024545 A	09-03-2006	NONE	
US 3707474 A	26-12-1972	AT 305281 B	26-02-1973
		BE 766890 A1	08-11-1971
		BE 713490 A	10-10-1968
		CH 499541 A	30-11-1970
		CH 554365 A	30-09-1974
		CH 556355 A	29-11-1974
		CY 665 A	09-12-1972
		DE 1770171 A1	23-09-1971
		DE 2122643 A1	25-11-1971
		FR 2100643 A5	24-03-1972
		FR 1559520 A	07-03-1969
		GB 1314428 A	26-04-1973
		GB 1162784 A	27-08-1969
		NL 6805288 A	15-10-1968
		NL 7106410 A	15-11-1971
		US 3847928 A	12-11-1974
		US 3726883 A	10-04-1973
US 4079066 A	14-03-1978	AT 61876 A	15-01-1978
		AU 497409 B2	14-12-1978
		AU 1066476 A	04-08-1977
		BE 837950 A1	27-07-1976
		CA 1072554 A1	26-02-1980
		CH 619208 A5	15-09-1980
		DE 2603178 A1	03-02-1977
		DK 34276 A	20-01-1977
		ES 444765 A1	01-12-1977
		FR 2318628 A1	18-02-1977
		FR 2318624 A1	18-02-1977
		GB 1497161 A	05-01-1978
		IE 42403 B1	30-07-1980
		JP 52012150 A	29-01-1977
		NL 7600846 A	21-01-1977
		SE 422794 B	29-03-1982
		SE 7600673 A	20-01-1977
		ZA 7601954 A	27-04-1977
JP 4128224 A	28-04-1992	NONE	