



(51) International Patent Classification:

C07D 213/57 (2006.01) C07D 309/08 (2006.01)
C07D 213/70 (2006.01) C07D 309/14 (2006.01)
C07D 215/36 (2006.01) C07D 333/24 (2006.01)
C07D 223/10 (2006.01) C07D 271/07 (2006.01)
C07D 231/12 (2006.01) C07C 317/44 (2006.01)
C07D 235/16 (2006.01) A61P 35/00 (2006.01)
C07D 263/32 (2006.01) A61P 35/04 (2006.01)
C07D 263/56 (2006.01)

(21) International Application Number:

PCT/US2012/026274

(22) International Filing Date:

23 February 2012 (23.02.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/446,246 24 February 2011 (24.02.2011) US

(71) Applicants (for all designated States except US): **CEPHALON, INC.** [US/US]; 41 Moores Road, P.O. Box 4011, Frazer, Pennsylvania 19355 (US). **UNIVERSITY OF HAWAII** [US/US]; 2800 Woodlawn Drive, Suite 280, Honolulu, Hawaii 96822 (US). **UNIVERSITY OF UTAH RESEARCH FOUNDATION** [US/US]; 615 Arapeen Drive, Suite 310, Salt Lake City, Utah 84108 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DORSEY, Bruce** [US/US]; 1213 Meetinghouse Road, Ambler, Pennsylvania 19002 (US). **KUWADA, Scott K.** [US/US]; 7018 Hawaii Kai Drive, Honolulu, Hawaii 96813 (US). **THEROFF, Jay P.** [US/US]; 9 Patrick Avenue, West Chester, Pennsylvania 19380 (US). **ZIFICSAK, Craig A.** [US/US]; 7 Maple Street, Downingtown, Pennsylvania 19335 (US).

(74) Agent: **DARKES, Paul R.**; Cephalon, Inc., 41 Moores Road, Frazer, Pennsylvania 19355 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, 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, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

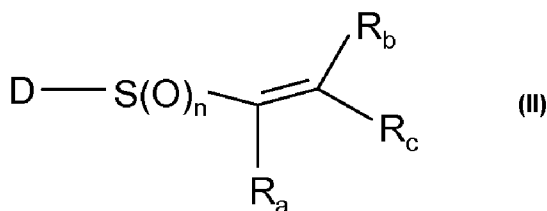
Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(88) Date of publication of the international search report:

3 January 2013

(54) Title: VINYL -ARYL - SULFONES FOR USE IN PERITONEAL CARCINOMATOSIS



(57) Abstract: Compounds of formula II are described, wherein D, n, R_a, R_b, and R_c are as herein defined, along with pharmaceutical compositions and methods of using compounds of formula II for treating or reducing the risk of peritoneal carcinomatosis in a patient.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/026274

A. CLASSIFICATION OF SUBJECT MATTER					
INV.	C07D213/57	C07D213/70	C07D215/36	C07D223/10	C07D231/12
	C07D235/16	C07D263/32	C07D263/56	C07D309/08	C07D309/14
	C07D333/24	C07D271/07	C07C317/44	A61P35/00	A61P35/04
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) C07D C07C A61P 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 practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 03/072038 A2 (UNIV UTAH RES FOUND [US]; KUWADA SCOTT K [US]) 4 September 2003 (2003-09-04) (2E)-3-[4-(tertiary butylphenyl)sulfonyl]-2-propenenitrile is BAY-11-7085 ;; page 21 BAY 11-7085 is NF-kappaB inhibitor that prevents intraabdominal metastasis in vivo ;; page 68; claim 42; table 1 use of BAY 11-7085 in a method of preventing cancer cell proliferation and metastasis ;; claims 1, 4, 42</p> <p align="center">----- -/--</p>	<p>1-3, 6-50, 52-60</p>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>
---	---

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2012	16/11/2012

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/026274

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHENG-HUI GUAN, WEI ZUO, LIAN-BIAO ZHAO, ZHI-HUI REN, YONG-MIN LIANG: SYNTHESIS, no. 10, 2 May 2007 (2007-05-02), pages 1465-1470, XP002678921, DOI: 10.1055/s-2007-966039 table 2; compounds 3aa, 3ac, 3ad, 3ag, 3ah, 3aja, 3al -----	1
X	RINO LEARDINI, DANIELE NANNI, AND GIUSEPPE ZANARDI: "Radical Addition to Isonitriles: A Route to Polyfunctionalized Alkenes through a Novel Three-Component Radical Cascade Reaction", JOURNAL OF ORGANIC CHEMISTRY, vol. 65, 8 April 2000 (2000-04-08), pages 2763-2772, XP002678922, DOI: 10.1021/jo991871 table 1; compound 15a -----	1
X	TOSHIYA OZAKI, AKIHIRO NOMOTO, IKUYO KAMIYA, JUN-ICHI KAWAKAMI, AND AKIYA OGAWA: "Transition-Metal-Catalyzed Cyanoalkylation of Alkynes with Chalcogenocyanates", BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 84, no. 2, 28 January 2011 (2011-01-28), pages 155-163, XP008153155, DOI: 10.1246/bcsj.20100187 comprising both E and Z isomer; compounds 3a,3b,3f, -----	1
X	WO 2006/024611 A2 (CIBA SC HOLDING AG [CH]; GERSTER MICHELE [CH]; MAEDER DIETMAR [DE]; RO) 9 March 2006 (2006-03-09) page 66; examples 21,22,43,44,51 -----	1
X	WILLIAM E. TRUCE, CHRISTIAN T. GORALSKI: "trans-1-(Arylsulfonyl)-2-arylcyclopropane s and derivatives of cyclopropanesulfonic acid", JOURNAL OF ORGANIC CHEMISTRY, vol. 34, no. 11, November 1969 (1969-11), pages 3324-3328, XP002678923, DOI: 10.1021/jo01263a022 1-t-Butyl-4-((E)-2-phenylethenesulfonyl)-benzene as starting material described for compound IV ;; page 3327, left-hand column, paragraph 6; table 1; compound IV -----	1,46

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/026274

Box No. 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:

2. Claims Nos.: 1-3, 6, 7(all 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 No. 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:

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 fees, this Authority did not invite payment of additional fees.

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.:
3, 8-50, 52, 55(completely); 1, 2, 6, 7, 53, 54, 56-60(partially)

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 3, 8-50, 52, 55(completely); 1, 2, 6, 7, 53, 54, 56-60(partially)

Compounds of Markush formula II where the variable "D" takes the value (A1,A2)-substituted phenyl; pharmaceutical compositions with these and their use in treating cancerous diseases or reducing the risk of carcinomatosis.

2. claims: 4(completely); 1, 2, 6, 7, 53, 54, 57-60(partially)

Compounds of Markush formula II where the variable "D" takes the value (A1,A2)-substituted pyridinyl; pharmaceutical compositions with these and their use in treating cancerous diseases or reducing the risk of carcinomatosis.

3. claims: 5, 51(completely); 1, 2, 6, 7, 53, 54, 57-60(partially)

Compounds of Markush formula II where the variable "D" takes the value (A1,A2)-substituted quinolin-6-yl; pharmaceutical compositions with these and their use in treating cancerous diseases or reducing the risk of carcinomatosis.

4. claims: 1, 2, 6, 7, 53, 54, 57-60(all partially)

Compounds of Markush formula II where the variable "D" takes the value (A1,A2)-substituted naphthen-2-yl; pharmaceutical compositions with these and their use in treating cancerous diseases or reducing the risk of carcinomatosis.

5. claims: 1, 2, 6, 7, 53, 54, 57-60(all partially)

Compounds of Markush formula II where the variable "D" takes the value 3-A1-2-A2-substituted thiophen-4-yl; pharmaceutical compositions with these and their use in treating cancerous diseases or reducing the risk of carcinomatosis.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-3, 6, 7(all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim 1-3, 6-7 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1, 2, 6, 7, 53, 54, 56-60 (in part) and 3, 8-50, 52, 55 (fully). The search of the claims therefore is only completed with respect to the subject-matter of compounds as described by formula (I) in claims 8-50, pharmaceutical compositions with these (claim 52) and their use therapy of cancerous diseases and peritoneal carcinomatosis as defined by claim 55.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/026274

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 03072038	A2	04-09-2003	AU 2003217649 A1	09-09-2003
			CA 2477172 A1	04-09-2003
			US 2005124590 A1	09-06-2005
			US 2011306675 A1	15-12-2011
			WO 03072038 A2	04-09-2003

WO 2006024611	A2	09-03-2006	CA 2576808 A1	09-03-2006
			CN 101023128 A	22-08-2007
			CN 101649203 A	17-02-2010
			EP 1791901 A2	06-06-2007
			JP 2008511576 A	17-04-2008
			US 2008269382 A1	30-10-2008
			WO 2006024611 A2	09-03-2006
