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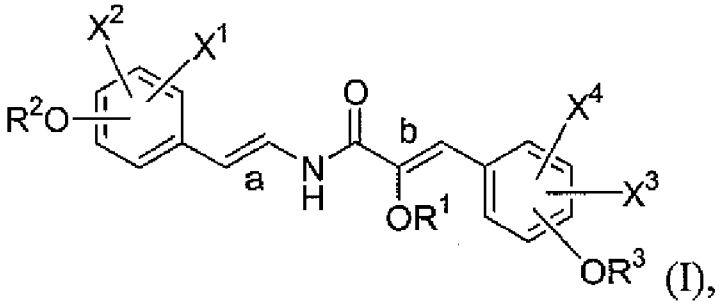
Published:

— *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 December 2009

(54) Title: METHOD OF INHIBITING ABCG2 AND OTHER TREATMENT METHODS



(57) Abstract: Disclosed are methods of enhancing the chemotherapeutic treatment of tumor cells, reducing resistance of a cancer cell to a chemotherapeutic agent, a method of inhibiting ABCG2, Pgp, or MRP1 in a mammal afflicted with cancer, and a method of increasing the bioavailability of an ABCG2 substrate drug in a mammal. The methods comprise administering effective amounts of certain compounds to the mammal, for example, a compound of the formula (I): Formula (I), wherein R^1, R^2, R^3, X^1, X^2, X^3, a, and b are as described herein. Uses of these compounds in the preparation of a medicament are also disclosed. Also disclosed are compounds of formula (II), pharmaceutical compositions comprising such compounds and uses thereof.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/088446

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/165 C07C233/29 A61P35/00

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)
A61K 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)
EPO-Internal, EMBASE, BIOSIS, BEILSTEIN Data, 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.
Y	AHMED-BELKACEM ABDELHAKIM ET AL: "Inhibitors of cancer cell multidrug resistance mediated by breast cancer resistance protein (BCRP/ABCG2)" ANTI-CANCER DRUGS, RAPID COMMUNICATIONS, OXFORD, vol. 17, no. 3, 1 March 2006 (2006-03-01), pages 239-243, XP009095752 ISSN: 0959-4973 the whole document	1-30,35, 38-61

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

[X] 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	Date of mailing of the international search report
3 March 2009	12/10/2009

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, Fax: (+31-70) 340-3016	Damiani, Federica

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MCDONALD L A ET AL: "Botryllamides A-D, new brominated tyrosine derivatives from styelid ascidians of the genus Botryllus" TETRAHEDRON 1995 GB, vol. 51, no. 18, 1995, pages 5237-5244, XP002517392 ISSN: 0040-4020 page 5237 - page 5240	1-30,35, 38-61
Y	RAO M RAMA ET AL: "Botryllamides E-H, four new tyrosine derivatives from the ascidian Botrylloides tyreum." JOURNAL OF NATURAL PRODUCTS JUN 2004, vol. 67, no. 6, June 2004 (2004-06), pages 1064-1066, XP002517393 ISSN: 0163-3864 the whole document	1-30,35, 38-61
X	HORENSTEIN B A ET AL: "SYNTHESIS OF UNPROTECTED RACEMIC TUNICHROME AN-1 A TUNICATE BLOOD PIGMENT" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 111, no. 16, 1989, pages 6242-6246, XP002517394 ISSN: 0002-7863 page 6243; compound 17	38,46-48
X	KIM D ET AL: "SYNTHESIS OF TUNICHROMES MM-1 AND MM-2, BLOOD PIGMENTS OF THE IRON-ASSIMILATING TUNICATE, MOLGULA MANHATTENSIS" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, vol. 31, no. 49, 1 January 1990 (1990-01-01), pages 7119-7122, XP009005640 ISSN: 0040-4039 page 7121; compounds 12A, 12B	38,46-48
X	OLTZ E M ET AL: "THE TUNICHROMES A CLASS OF REDUCING BLOOD PIGMENTS FROM SEA SQUIRTS ISOLATION STRUCTURES AND VANADIUM CHEMISTRY" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 110, no. 18, 1988, pages 6162-6172, XP002517395 ISSN: 0002-7863 page 6164	38,46-48

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STONARD R J ET AL: "LINEAR PEPTIDE ALKALOIDS FROM THE SPONGE CLIONA-CELATA CELENAMIDE C AND CELENAMIDE D" CANADIAN JOURNAL OF CHEMISTRY, vol. 58, no. 20, 1980, pages 2121-2126, XP002517396 ISSN: 0008-4042 page 2122; compound 13	38,46-48
X	MARCHAND J ET AL: "[Peptide alkaloids. VII. Lasiodines A and B, alkaloids of Lasiodiscus marmoratus C. H. Wright (Rhamnaceae)]" TETRAHEDRON MAR 1969, vol. 25, no. 5, March 1969 (1969-03), pages 937-954, XP002517398 ISSN: 0040-4020 page 943; compounds 6A, 6B, 6C	38-42, 46-50
X,P	PHUWAPRAISIRISAN PREECHA ET AL: "Phenylethyl cinnamides: A new series of alpha-glucosidase inhibitors from the leaves of Aegle marmelos" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 18, no. 18, September 2008 (2008-09), pages 4956-4958, XP002517397 ISSN: 0960-894X page 4956 - page 4958; compounds 1,2	38-42, 46-50,54
A	HENRICH CURTIS J ET AL: "New inhibitors of ABCG2 identified by high-throughput screening" MOLECULAR CANCER THERAPEUTICS,, vol. 6, no. 12, Part 1, 1 December 2007 (2007-12-01), pages 3271-3278, XP002513063 the whole document	1-30,35, 38-61
A	EP 1 864 972 A (YAKULT HONSHA KK [JP]) 12 December 2007 (2007-12-12) abstract page 8, paragraph 30 - page 10	1-30,35, 38-61
A	BOUMENDJEL AHCÈNE ET AL: "Anticancer multidrug resistance mediated by MRP1: recent advances in the discovery of reversal agents." MEDICINAL RESEARCH REVIEWS JUL 2005, vol. 25, no. 4, July 2005 (2005-07), pages 453-472, XP002517399 ISSN: 0198-6325 abstract page 475; figure 3	1-30,35, 38-61

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/088446

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SZAKÁCS GERGELY ET AL: "Targeting multidrug resistance in cancer" NATURE REVIEWS. DRUG DISCOVERY MAR 2006,, vol. 5, no. 3, 1 March 2006 (2006-03-01), pages 219-234, XP002513064 the whole document	1-30,35, 38-61

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/088446

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.:
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 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 allsearchable 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 reportcovers 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.:

see annex

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: 1-30, 35, 38-61

Compounds of formula (I), formula (II) and botryllamide J and combinations comprising them for the treatment of cancer.

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2. claims: 31-34, 36-37

Compounds 1-11 and combinations comprising them for the treatment of cancer.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/088446

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1864972 A	12-12-2007	AU 2006232435 A1	12-10-2006
		CA 2602467 A1	12-10-2006
		CN 101166719 A	23-04-2008
		EA 200702110 A1	28-02-2008
		WO 2006106778 A1	12-10-2006
		KR 20080006543 A	16-01-2008
		ZA 200708786 A	28-01-2009