



(51) International Patent Classification:

A61K 31/4402 (2006.01) A61K 31/44 (2006.01)
A61K 31/4425 (2006.01) A61K 31/4406 (2006.01)
A61P 35/00 (2006.01) A61K 31/4409 (2006.01)
A61K 31/05 (2006.01)

(21) International Application Number:

PCT/IB2012/052861

(22) International Filing Date:

6 June 2012 (06.06.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1154910 6 June 2011 (06.06.2011) FR
61/614,680 23 March 2012 (23.03.2012) US

(71) Applicants (for all designated States except US): **UNIVERSITÉ DE STRASBOURG** [FR/FR]; 4 rue Blaise Pascal, F-67000 Strasbourg (FR). **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE - CNRS -** [FR/FR]; 3 rue Michel-Ange, F-75794 Paris Cedex 16 (FR).

(72) Inventors; and

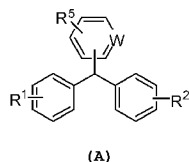
(75) Inventors/Applicants (for US only): **FEVE, Marie** [FR/FR]; 14 Domaine de l' Ile, F-67400 Illkirch-Graffenstaden (FR). **ZENYOU-MEYER, Maria** [CY/FR]; 8 quai des Joncs, F-67000 Strasbourg (FR). **HAIECH, Jacques** [FR/FR]; 2 rue du Dôme, F-67000 Strasbourg (FR). **CHNEIWEISS, Hervé** [FR/FR]; 20 rue des Quatre Fils, F-75003 Paris (FR). **KILHOFFER, Marie-Claude** [FR/FR]; 2 rue du Dôme, F-67000 Strasbourg (FR). **MAMERI, Samir** [FR/FR]; 7 rue des Gravières, F-67700 Saverne (FR). **HIBERT, Marcel** [FR/FR]; 21 rue Alfred Kastler, F-67114 Eschau (FR).

(74) Agent: **NOVAGRAAF TECHNOLOGIES**; 122 rue Édouard Vaillant, F-92593 Levallois-perret Cedex (FR).

(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,

[Continued on next page]

(54) Title: BISACODYL AND ITS ANALOGUES AS DRUGS FOR USE IN THE TREATMENT OF CANCER



(57) Abstract: The present invention provides compounds having the formula A: (A) or pharmaceutically acceptable salt thereof, wherein W, R1, R2 and R5 are as defined in classes and subclasses herein, and pharmaceutical compositions thereof, as described generally and in subclasses herein, which compounds are useful as cytotoxic agents towards proliferating and/or quiescent cancer stem cells, and thus are useful, for example, for the treatment of cancer.

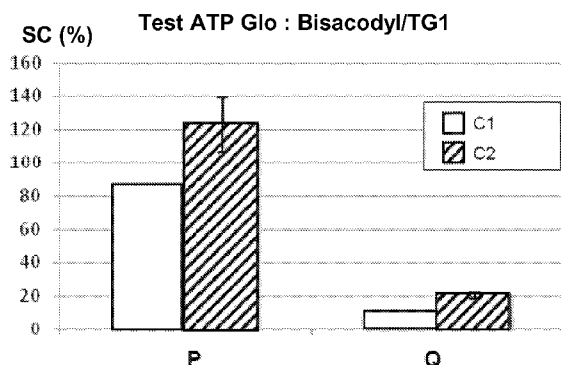


FIGURE 2



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, 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:

31 January 2013

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/052861

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K31/4402 A61K31/4425 A61P35/00 A61K31/05 A61K31/44
 A61K31/4406 A61K31/4409
 ADD.
 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 practicable, search terms used)
 EPO-Internal, CHEM ABS Data, 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	WO 02/056880 A1 (CYTOKINETICS INC [US]; FINER JEFFREY T [US]; CHABALA JOHN C [US]; LEWI) 25 July 2002 (2002-07-25)	1-9, 11-16
Y	claims 1,9-10	9,10
X	WO 96/08240 A1 (HARVARD COLLEGE [US]; CHILDRENS MEDICAL CENTER [US]) 21 March 1996 (1996-03-21) claims 2, 5-7 page 7, lines 5-23 cancer treatments; pages 6-7	1-16
X	US 2010/189762 A1 (ARBISER JACK L [US]) 29 July 2010 (2010-07-29) claims 1-8 first triarylmethane compound; page 8, paragraph 96	1-16
	----- -/--	

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	"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 application or patent 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	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search 18 September 2012	Date of mailing of the international search report 10/12/2012
--	--

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/IB2012/052861

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2011/091213 A2 (ACETYLON PHARMACEUTICALS [US]; VAN DUZER JOHN H [US]; MAZITSCHKEK RALPH) 28 July 2011 (2011-07-28)	1-9, 11-16
Y,P	page 35 claims 46-48 page 57 - page 58 page 67, line 17 - page 68, line 1	10
X	----- AL-QAWASMEH R A ET AL: "Triaryl methane derivatives as antiproliferative agents", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 14, 1 January 2004 (2004-01-01), pages 347-350, XP002508695, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2003.11.004	1-8, 11-16
Y	figure scheme 1; compound 6 table 1	9,10
X	----- YUAN-HSIAO SU ET AL: "Solution-phase parallel synthesis and screening of anti-tumor activities from fenbufen and ethacrynic acid libraries", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 21, no. 5, 17 January 2011 (2011-01-17), pages 1320-1324, XP028144472, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.01.068 [retrieved on 2011-01-22]	1-8, 11-16
Y	compound 6+B16 tables 1 - MTT assay	9,10
X	----- US 4 757 076 A (HIRSCH KENNETH S [US] ET AL) 12 July 1988 (1988-07-12)	1-8, 11-16
Y	claims 1, 7, 9, 11, 14 3-bis(4-chlorophenyl)-methylpyridine 2-bis(4-chlorophenyl)-methylpyridine 4-bis(4-chlorophenyl)methyl-pyridine hydrochloride; table 1 DMBA-Induced mammary tumor inhibition; column 6	9,10
X	----- NOBUKO MIBU ET AL: "Synthesis and antiviral activities of some heteroaryl-substituted triarylmethanes", JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 47, no. 6, 24 August 2010 (2010-08-24), pages 1434-1438, XP055013517, ISSN: 0022-152X, DOI: 10.1002/jhet.457	1-8, 11-16
Y	table 3; compounds 5a, 5b	9,10
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/052861

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHORKHUBER M ET AL: "Effect of anthraquinone-laxatives on the proliferation and urokinase secretion of normal, premalignant and malignant colonic epithelial cells", EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 34, no. 7, 1 June 1998 (1998-06-01), pages 1091-1098, XP004284991, ISSN: 0959-8049, DOI: 10.1016/S0959-8049(98)00037-9	1-16
Y	tables 1,2 page 1094, right-hand column, paragraph end of first one page 1095, left-hand column, paragraph third -----	9,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/052861

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 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.:

1-16

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: 1-16

Compounds of formula (A) for use in the treatment of cancer

2. claims: 17-19

Method of screening

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/052861

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02056880	A1	25-07-2002	EP 1351671 A1 15-10-2003
			US 2004132830 A1 08-07-2004
			WO 02056880 A1 25-07-2002

WO 9608240	A1	21-03-1996	AU 703863 B2 01-04-1999
			AU 3590895 A 29-03-1996
			CA 2200084 A1 21-03-1996
			DE 69528992 D1 09-01-2003
			DE 69528992 T2 18-09-2003
			EP 0783303 A1 16-07-1997
			ES 2190788 T3 16-08-2003
			JP 4099226 B2 11-06-2008
			JP H10511080 A 27-10-1998
			JP 2007277273 A 25-10-2007
			WO 9608240 A1 21-03-1996

US 2010189762	A1	29-07-2010	NONE

WO 2011091213	A2	28-07-2011	AU 2011207289 A1 16-08-2012
			CA 2787756 A1 28-07-2011
			EP 2526093 A2 28-11-2012
			SG 182646 A1 30-08-2012
			TW 201141480 A 01-12-2011
			US 8148526 B1 03-04-2012
			US 2011300134 A1 08-12-2011
			US 2012190693 A1 26-07-2012
			WO 2011091213 A2 28-07-2011

US 4757076	A	12-07-1988	NONE
