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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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
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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, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
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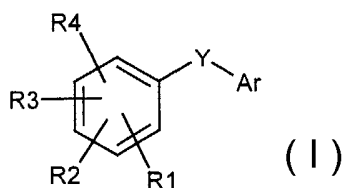
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see PCT Gazette No. 19/2005 of 12 May 2005, Section II

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: COMBRETASTATIN DERIVATIVES WITH CYTOTOXIC ACTION



(57) Abstract: The invention described herein relates to new combretastatin derivatives obtained by total synthesis and having the following general formula (I) in which the groups are as defined in the description here below. Said compounds, though chemically related to the structure of cis/trans-combretastatin, do not always bind tubulin, but nevertheless exhibit cytotoxic activity of interest in the oncological field as anticancer and/or antiangiogenic agents.



WO 2005/007635 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT2004/000373

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D261/12	C07D261/08	C07D307/79	C07D333/54	C07C43/215
	C07C43/23	C07D231/56	C07D307/71	C07D333/44	C07F9/655
	C07F9/6553	C07F7/18	A61K31/09	A61K31/41	A61K31/343
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	C07D	C07C	C07F	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, CHEM ABS Data, BEILSTEIN 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	<p>LI Q. ET AL.: "Synthesis and biological evaluation of 2-indolyloxazolines as a new class of tubulin polymerization inhibitors. Discovery of A-289099 as an orally active antitumor agent" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 12, no. 3, 2002, pages 465-469, XP002268020 OXFORD, GB ISSN: 0960-894X cited in the application the whole document</p> <p style="text-align: center;">----- -/--</p>				1-11
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> 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		
24 February 2005			08. 07. 2005		
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 Seitner, I		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT2004/000373

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>SANGHEE K. ET AL.: "Comparative molecular field analysis study of stilbene derivatives active against A549 lung carcinoma"</p> <p>CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 51, no. 5, May 2003 (2003-05), pages 516-521, XP002268021</p> <p>PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO., JP</p> <p>ISSN: 0009-2363</p> <p>cited in the application</p> <p>the whole document</p> <p>figures 1,2</p> <p>table 1</p> <p>examples 11,1m</p>	1-11
X	<p>-----</p> <p>CUSHMAN M ET AL: "SYNTHESIS AND EVALUATION OF ANALOGUES OF (Z)-1-(4-METHOXYPHENYL)-2-(3,4,5-TRIMETHOXYPHENYL)ETHENE AS POTENTIAL CYTOTOXIC AND ANTIMITOTIC AGENTS"</p> <p>JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 12, 12 June 1992 (1992-06-12), pages 2293-2306, XP000571677</p> <p>ISSN: 0022-2623</p> <p>cited in the application</p> <p>the whole document</p> <p>Scheme II,table I</p>	1-11
X	<p>-----</p> <p>CUSHMAN M ET AL: "SYNTHESIS AND EVALUATION OF STILBENE AND DIHYDROSTILBENE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS THAT INHIBIT TUBULIN POLYMERIZATION"</p> <p>JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 8, 1 August 1991 (1991-08-01), pages 2579-2588, XP000571676</p> <p>ISSN: 0022-2623</p> <p>cited in the application</p> <p>the whole document</p> <p>tables I,II</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-11

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT2004/000373

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAYA A B S ET AL: "Design, synthesis and cytotoxic activities of naphthyl analogues of combretastatin A-4" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 22, 20 November 2000 (2000-11-20), pages 2549-2551, XP004224261 ISSN: 0960-894X cited in the application the whole document examples 3,4b,5b	1-11
X	----- MOLANDER, GARY A. ET AL: "Suzuki-Miyaura Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates" JOURNAL OF ORGANIC CHEMISTRY , 67(24), 8424-8429 CODEN: JOCEAH; ISSN: 0022-3263, 2002, XP002318998 example 6e; table 3	1
X	----- TEN HAVE R ET AL: "A Novel Synthesis of 3-Nitroindoles via Electrocyclization of 2,3-(Dialk-1-enyl)-4-nitropyrroles" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 9, 26 February 1998 (1998-02-26), pages 1913-1920, XP004107494 ISSN: 0040-4020 examples 11c-e; table 3	1
X	----- WO 92/04321 A (RHONE-POULENC RORER INTERNATIONAL INC) 19 March 1992 (1992-03-19) example 85	1
X	----- KNEFELI, FRANK ET AL: "Electron impact induced loss of C-5/C-8 substituents of 1,2,3,4-tetrahydroisoquinolines. VI. Synthesis and mass spectrometric fragmentation of dihydroindole derivatives" ARCHIV DER PHARMAZIE (WEINHEIM, GERMANY) , 323(3), 145-55 CODEN: ARPMAS; ISSN: 0365-6233, 1990, XP008043565 page 147; example 22	1
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT2004/000373

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>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CHUPINA, L. N. ET AL: "Indole derivatives. 135. 5-[2-(4-Methoxyphenyl)ethenyl]indolines and indoles" XP002319001 retrieved from STN Database accession no. 1990:35623 CAS RN: 124548-86-3; 124567-97-1 abstract & KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII , (7), 911-14 CODEN: KGSSAQ; ISSN: 0453-8234, 1989,</p>	1
X	<p>----- DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KASAHARA, AKIRA ET AL: "Palladium-catalyzed vinylation and carbonylation of bromoindoles and N-acetyl bromoindoline" XP002319002 retrieved from STN Database accession no. 1989:480291 CAS RN: 122001-33-6; 122001-34-7 abstract & YAMAGATA DAIGAKU KIYO, KOGAKU , 20(2), 141-6 CODEN: YDKKAR; ISSN: 0513-465X, 1988,</p>	1
X	<p>----- EP 0 150 139 A (ROUSSEL-UCLAF) 31 July 1985 (1985-07-31) claim 12</p>	1
X	<p>----- DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CHUPINA, L. N. ET AL: "Indole derivatives. 124. 5-(2-Phenylethenyl)indolines and indoles" XP002319003 retrieved from STN Database accession no. 1984:490714 CAS RN; 91459-38-0; 91459-39-1 abstract & KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII , (4), 466-9 CODEN: KGSSAQ; ISSN: 0453-8234, 1984,</p> <p>----- -/--</p>	1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT2004/000373

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>SOUSA DE B F S E ET AL: "UEBER DIE HERSTELLUNG VON STYRYL-DERIVATEN DES 3-PHENYL-BENZISOXAZOLS PREPARATION OF STYRYL DERIVATIVES OF 3-PHENYL-BENZISOXAZOLE"</p> <p>HELVETICA CHIMICA ACTA, VERLAG HELVETICA CHIMICA ACTA. BASEL, CH, vol. 61, no. 275/276, 1978, pages 2904-2940, XP009031181</p> <p>ISSN: 0018-019X</p> <p>examples 33.1,33.2,33.3; table 33</p> <p>example 39.1; table 39</p> <p>-----</p>	1
P,X	<p>DATABASE WPI</p> <p>Section Ch, Week 200382</p> <p>Derwent Publications Ltd., London, GB;</p> <p>Class B02, AN 2003-903121</p> <p>XP002319006</p> <p>-& WO 03/087072 A1 (MOCHIDA PHARM CO LTD)</p> <p>23 October 2003 (2003-10-23)</p> <p>abstract</p> <p>example 39</p> <p>-----</p>	1-11
X	<p>WO 02/10137 A (SIGNAL PHARMACEUTICALS, INC; BHAGWAT, SHRIPAD, S; SATOH, YOSHITAKA; SA)</p> <p>7 February 2002 (2002-02-07)</p> <p>examples 133,136,137</p> <p>claims 24-26,31,50</p> <p>-----</p>	1-11
X	<p>WO 01/53268 A (AGOURON PHARMACEUTICALS, INC) 26 July 2001 (2001-07-26)</p> <p>page 35; example 1</p> <p>page 38; example 2</p> <p>claims 3,8</p> <p>-----</p>	1-11
X	<p>WO 95/29907 A (FUJISAWA PHARMACEUTICAL CO., LTD; KAWAI, YOSHIO; YAMAZAKI, HITOSHI; KA) 9 November 1995 (1995-11-09)</p> <p>page 1</p> <p>example 3</p> <p>-----</p>	1-11
X	<p>DATABASE CAPLUS [Online]</p> <p>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;</p> <p>LIU, JIE ET AL: "Synthesis and antitumor activity of 3-[(substituted phenyl)vinyl]indole derivatives"</p> <p>XP002319004</p> <p>retrieved from STN</p> <p>Database accession no. 2000:90981</p> <p>abstract</p> <p>CAS RN: 24620-45-9</p> <p>& YAOXUE XUEBAO, 34(12), 908-912 CODEN: YHHPAL; ISSN: 0513-4870, 1999,</p> <p>-----</p> <p>-/--</p>	1-11

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT2004/000373

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> DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ALONSO, DANIEL F. ET AL: "Effects of synthetic urokinase inhibitors on local invasion and metastasis in a murine mammary tumor model" XP002319005 retrieved from STN Database accession no. 1996:626348 CAS RN: 149732-37-6 abstract -& BREAST CANCER RESEARCH AND TREATMENT , 40(3), 209-223 CODEN: BCTRD6; ISSN: 0167-6806, 1996, XP008043503 ----- </p>	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IT2004/000373

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:

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:

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 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.:

1-11 (in part): 12-18

Remark on Protest

- ☐ 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

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

1. claims: 1-11 (in part); 12-18

Compounds according to formula (I) in which Y has the first definition and Ar has the first definition given in claim 1. The use of such compounds as medicines according to claims 3-11. Intermediates for the preparation of compounds of formula (I) according to claims 12-18.

2. claims: 1-11 (in part)

Compounds according to formula (I) in which Y has the first definition and Ar has the second definition given in claim 1. The use of such compounds as medicines according to claims 3-11.

3. claims: 1-11 (in part)

Compounds according to formula (I) in which Y has the first definition and Ar has the third definition given in claim 1. The use of such compounds as medicines according to claims 3-11.

4. claims: 1-11 (in part)

Compounds according to formula (I) in which Y has the first definition and Ar has the fourth definition given in claim 1. The use of such compounds as medicines according to claims 3-11.

5. claims: 1-11 (in part)

Compounds according to formula (I) wherein Y has the second definition given in claim 1. The use of such compounds as medicines according to claims 3-11.

6. claims: 1-11 (in part)

Compounds according to formula (I) wherein Y has the third definition given in claim 1. The use of such compounds as medicines according to claims 3-11.

7. claims: 1-11 (in part)

Compounds according to formula (I) wherein Y has the fourth definition given in claim 1. The use of such compounds as medicines according to claims 3-11.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IT2004/000373

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9204321	A	19-03-1992	AT 136026 T AU 8641991 A CA 2091257 A1 DE 69118388 D1 EP 0548250 A1 JP 3334087 B2 JP 6504520 T MX 9203775 A1 WO 9204321 A1 US 5468898 A	15-04-1996 30-03-1992 11-03-1992 02-05-1996 30-06-1993 15-10-2002 26-05-1994 01-07-1992 19-03-1992 21-11-1995
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