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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, 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,  
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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,  
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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: AMINOACID CONJUGATES OF BETA - LAPACHONE FOR TUMOR TARGETING

(57) Abstract: The present invention relates to quinone prodrug compositions and therapeutic methods using such prodrug compositions. Preferably, the quinone compounds of the invention are naphthoquinone compounds such as  $\beta$ -lapachone or  $\beta$ -lapachone analogs. The quinone prodrug compositions of the invention exhibit improved solubility, stability, bioavailability, and pharmacokinetic properties, as well as improved plasma half-life *in vivo*.



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**INTERNATIONAL SEARCH REPORT**

International application No

PCT/US2005/028438

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61K47/48 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

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, WPI Data, BIOSIS, EMBASE, 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.
X	WO 03/090710 A (CASE WESTERN RESERVE UNIVERSITY; BOOTHMAN, DAVID; GAO, JINMING; NASONG) 6 November 2003 (2003-11-06)  page 33, line 15 - page 34, line 8; claims 1,2,8,15 page 15, lines 17-23 -----	1,2, 10-12, 15-17, 19-22, 26-30,36
X	WO 03/011224 A (CYCLIS PHARMACEUTICALS, INC; JIANG, ZHIWEI; REDDY, DASHARATHA, G) 13 February 2003 (2003-02-13)  page 24, line 28 - page 25, line 4; claims 31,32,45,46,79,85,86,109,167-173; figure 12 ----- -/--	1,2, 10-12, 15-17, 20-46

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

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/028438

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 02/058694 A (DANA-FARBER CANCER INSTITUTE, INC; PARDEE, ARTHUR, B; ANDERSON, KENNET) 1 August 2002 (2002-08-01)</p> <p>page 18, paragraph 1; claims 3-9</p> <p>-----</p>	<p>1-3, 10-12, 15-36, 38-40, 43-46</p>
Y	<p>DI CHENNA P. H. ET AL: "Preparation and cytotoxicity toward cancer cells of mono(arylimino) derivatives of b-lapachone" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 44, 2001, pages 2486-2489, XP008068680 ISSN: 0022-2623 figure 1 see conclusion</p> <p>-----</p>	<p>1-6, 10-46</p>
E	<p>WO 2005/082357 A (ARQULE, INC; LI, CHIANG J; LI, YOUZHI) 9 September 2005 (2005-09-09)</p> <p>page 21, paragraph 3; claim 1 page 28, paragraph 5 - page 29, paragraph 1; claims 1,7,10</p> <p>-----</p>	<p>1-5, 10-12, 14-36, 38-40, 43-46</p>
E	<p>WO 2005/082356 A (ARQULE, INC; LI, CHIANG J; LI, YOUZHI; PARDEE, ARTHUR B) 9 September 2005 (2005-09-09)</p> <p>page 20, paragraph 3; claim 1 page 34, paragraph 2; claims 12,15,22,25,36,39</p> <p>-----</p>	<p>1-5, 10-12, 14-36, 43-46</p>
E	<p>WO 2006/020722 A (ARQULE INC [US]; ASHWELL MARK [US]; LI CHIANG J [US]; TANDON MANISH [U]) 23 February 2006 (2006-02-23) page 74, paragraph 2; claims 8-15,27-29,31 page 77 page 86, paragraph 3 - page 87, paragraph 1</p> <p>-----</p>	<p>1-3, 10-13, 15-46</p>
P,X	<p>POWIS G ET AL: "MOLECULAR PHARMACOLOGY AND ANTITUMOR ACTIVITY OF PALMARUMYCIN-BASED INHIBITORS OF THIOREDOXIN REDUCTASE" MOLECULAR CANCER THERAPEUTICS, AMERICAN ASSOCIATION OF CANCER RESEARCH, US, vol. 5, no. 3, 2006, pages 630-636, XP008071878 ISSN: 1535-7163 see discussion abstract; figure 1</p> <p>-----</p>	<p>1-6,10, 18-20, 26,27, 36,42</p>
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/028438

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	<p>KUMI-DIAKA JAMES ET AL: "Potential mechanism of phytochemical-induced apoptosis in human prostate adenocarcinoma cells: Therapeutic synergy in genistein and [beta]-lapachone combination treatment"            CANCER CELL INTERNATIONAL, BIOMED CENTRAL, LONDON, GB,            vol. 4, no. 1,            17 August 2004 (2004-08-17), page 5,            XP021007276            ISSN: 1475-2867            see conclusion            abstract</p>	1-6, 10-46
P,Y	<p>-----            REINICKE K E ET AL: "DEVELOPMENT OF BETA-LAPACHONE PRODRUGS FOR THERAPY AGAINST HUMAN CANCER CELLS WITH ELEVATED NAD(P)H:QUINONE OXIDOREDUCTASE 1 LEVELS"            CLINICAL CANCER RESEARCH, THE ASSOCIATION, DENVER, NJ, US,            vol. 11, no. 8,            15 April 2005 (2005-04-15), pages 3055-3064, XP008046994            ISSN: 1078-0432            abstract; figure 1            -----</p>	1-6, 10-46

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2005/028438

## 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 26-42 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:

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.:

1-3, 10-17, 26, 28-46 (all partially), 4-6, 18-25, 27

### 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: 4-6, 18-25, 27 complete; 1-3, 10-17, 26,28-46 in part.

A quinone prodrug composition comprising a quinone compound attached to one or two independently select pro-moieties wherein at least one of the pro-moieties is an amino-acid. Pharmaceutical composition and kit comprising the same and use for the treatment of cancer.  
Excluding the subject matter of inventions 2-4.

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2. claims: 1-3, 10-17,26,28-46 in part

A quinone prodrug composition comprising a quinone compound attached to one or two independently select pro-moieties wherein at least one of the pro-moieties is a water solubilizing moiety. Pharmaceutical composition and kit comprising the same and use for the treatment of cancer.  
Excluding the subject matter of inventions 1,3,4.

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3. claims: 7 complete; 1,2,10-17,26, 28-46 in part

A quinone prodrug composition comprising a quinone compound attached to one or two independently select pro-moieties wherein at least one of the pro-moieties is a peptide or protein. Pharmaceutical composition and kit comprising the same and use for the treatment of cancer.  
Excluding the subject matter of inventions 1,2,4.

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4. claims: 8,9 complete; 1,2,10-17,26,28-46 in part

A quinone prodrug composition comprising a quinone compound attached to one or two independently select pro-moieties wherein at least one of the pro-moieties is an carboxylic acid. Pharmaceutical composition and kit comprising the same and use for the treatment of cancer.  
Excluding the subject matter of inventions 1-3.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2005/028438
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Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
WO 03090710	A	06-11-2003	AU 2003228666 A1	10-11-2003
-----				
WO 03011224	A	13-02-2003	BR 0211613 A	09-11-2004
			CA 2455567 A1	13-02-2003
			CN 1561209 A	05-01-2005
			EP 1420777 A2	26-05-2004
			JP 2005507861 T	24-03-2005
			MX PA04000994 A	17-02-2005
			US 2003091639 A1	15-05-2003
-----				
WO 02058694	A	01-08-2002	CA 2428425 A1	01-08-2002
			EP 1387677 A2	11-02-2004
			JP 2004535363 T	25-11-2004
-----				
WO 2005082357	A	09-09-2005	CA 2556789 A1	09-09-2005
-----				
WO 2005082356	A	09-09-2005	CA 2556823 A1	09-09-2005
			EP 1729760 A2	13-12-2006
			EP 1722775 A1	22-11-2006
-----				
WO 2006020722	A	23-02-2006	WO 2006020719 A2	23-02-2006
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