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kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, 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,

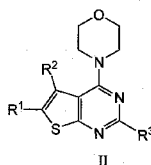
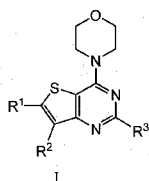
[Continued on next page]

(54) Title: COMBINATIONS OF PHOSPHOINOSITIDE 3-KINASE INHIBITOR COMPOUNDS AND CHEMOTHERAPEUTIC AGENTS, AND METHODS OF USE

in vitro Cell Proliferation Assays of Combinations of
Formula Ia Compound (GDC-0941) and Various Chemotherapeutic Agents

Expt.	Cell Line	Tumor Type	Gene Mutation	Chemotherapeutic	Chemo. EC50	Compound Ia EC50	Combination Index (CI)	Synergy
1	MDA-MB-361	Breast	PI3K E545K	5-FU	>40	0.48	0.048	++++
2	MT3	Breast	K-ras G12D	5-FU	>40	0.58	0.954	+/-
3	MDA-MB-436	Breast	PTEN neg	5-FU	>40	0.82	0.757	++
4	MDA-MB-468	Breast	PTEN neg	5-FU	20	0.87	0.674	+++
5	ZR75-1	Breast	PTEN neg	5-FU	20	0.3	0.682	+++
6	Cal-120	Breast		5-FU	1.33	1.38	1.33	-
7	HCC-1569	Breast	PTEN neg	carboplatin	>40	0.322	1.1	-
8	HCC-1569	Breast	PTEN neg	docetaxel	0.0004	0.322	0.737	++
9	MDA-MB-361	Breast	PI3K E545K	docetaxel	0.0016	0.48	0.11	++++
10	MDA-MB-468	Breast	PTEN neg	docetaxel	0.005	0.87	0.136	++++
11	ZR75-1	Breast	PTEN neg	docetaxel	0.0025	0.3	0.901	+/-
12	MT3	Breast	K-ras G12D	docetaxel	0.001	0.58	0.278	++++
13	MCF7	Breast	PI3K E545K	docetaxel	0.005	0.17	0.866	+
14	MDA-MB-436	Breast	PTEN neg	docetaxel	0.005	0.82	0.346	+++
15	Cal-120	Breast		docetaxel	0.85	1.38	0.85	+
16	MDA-MB-231	Breast	K-ras G13G	docetaxel	0.0001	6.5	0.96	-
17	MDA-MB-361	Breast	PI3K E545K	doxorubicin	0.148	0.48	0.137	++++
18	Cal-51	Breast	PI3K E542K	gemcitabine	0.002	0.76	0.189	++++
19	Cal-120	Breast	PTEN neg	gemcitabine	0.4	1.38	0.4	+++
20	MDA-MB-361	Breast	PI3K E545K	gemcitabine	0.006	0.48	0.421	+++

Figure 1-A



(57) Abstract: Combinations of PI3K inhibitor compounds having Formulas (I) and (II) and chemotherapeutic agents, including stereoisomers, geometric isomers, tautomers, metabolites and pharmaceutically acceptable salts thereof, are useful for treating hyperproliferative disorders such as cancer. Methods of using such combinations for *in vitro*, *in situ*, and *in vivo* diagnosis, prevention or treatment of such disorders in mammalian cells, or associated pathological conditions, are disclosed.



NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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- *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:

19 November 2009

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/075883

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/505 A61P35/00 G01N33/50

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 G01N

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, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 2007/127175 A (PIRAMED LTD [GB]; GENENTECH INC [US]; GOLDSMITH RICHARD [US]; FOLKES A) 8 November 2007 (2007-11-08) page 93, last paragraph to page 94, first paragraph claim 1	
Y	WO 2004/065391 A (ALMIRALL PRODESFARMA SA [ES]; TERRICABRAS BELART EMMA [ES]; SEGARRA MA) 5 August 2004 (2004-08-05) claims 1,17,20 ----- -/--	1-56



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

18 September 2009

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02/10/2009

Name and mailing address of the ISA/

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Baurand, Petra

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAYAKAWA M, KAIZAWA H, MORITOMO H, KOIZUMI T, OHISHI T, YAMANO M, OKADA M, OHTA M, TSUKAMOTO S, RAYNAUD F I ET AL.: "Synthesis and biological evaluation of pyrido[3',2':4,5]furo[3,2-d]pyrimidine derivatives as novel PI3 kinase p110alpha inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 17, no. 9, 3 April 2007 (2007-04-03), XP022015320 page 2441, right-hand column, 2nd paragraph	1-56
A	TUMKEVICIUS S ET AL: "First Example of Synthesis of Thieno[2,3-d]pyrimidine-6-carbaldehydes by Oxidation of Thieno[2,3-d]pyrimidin-6-yl Methanols with Molecular Iodine" CHEMISTRY OF HETEROCYCLIC COMPOUNDS, KLUWER ACADEMIC PUBLISHERS-CONSULTANTS BUREAU, NE, vol. 41, no. 6, 1 June 2005 (2005-06-01), pages 800-801, XP019276371 ISSN: 1573-8353 the whole document	
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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.
Y	YU DIHUA; HUNG MIEN-CHIE: "Role of erbB2 in breast cancer chemosensitivity" BIOESSAYS, vol. 22, no. 7, July 2000 (2000-07), pages 673-680, XP002546485 page 677, right-hand column, paragraph 1 page 677, right-hand column, last paragraph	57-61
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T	MENDOZA NERISSA; PHILLIPS GAIL LEWIS; SILVA JOHNNY; SCHWALL RALPH; WICKRAMASINGHE DINELI: "Inhibition of ligand-mediated HER2 activation in androgen-independent prostate cancer" CANCER RESEARCH, vol. 62, no. 19, 1 October 2002 (2002-10-01), pages 5485-5488, XP002546487 the whole document	
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Y	LOPREVITE MAURA ET AL: "In vitro study of farnesyltransferase inhibitor SCH 66336, in combination with chemotherapy and radiation, in non-small cell lung cancer cell lines" ONCOLOGY REPORTS, NATIONAL HELLENIC RESEARCH FOUNDATION, ATHENS, GR, vol. 11, no. 2, 1 February 2004 (2004-02-01), pages 407-414, XP009091362 ISSN: 1021-335X page 407, abstract	62,63

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/075883

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 2005/094358 A (ROSWELL PARK CANCER INST [US]) 13 October 2005 (2005-10-13) claim 19 example 1 page 4, paragraph 13 -----	64
Y	BIANCO R, SHIN I, RITTER CH A, YAKES F M, BASSO A, ROSEN N, TSURUTANI J, DENNIS P A, MILLS G B, ARTEAGA C L: "Loss of PTEN/MMAC1/TEP in EGF receptor-expressing tumor cells counteracts the antitumor action of EGFR tyrosine kinase inhibitors" ONCOGENE, vol. 22, no. 18, 8 May 2003 (2003-05-08), pages 2812-2822, XP002546490 page 2813, left-hand column, last paragraph -----	64

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/075883

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.:

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: 1-56

Condensed pyrimidines for formula (I) or (II) in combination with a chemotherapeutic agent and the use thereof for the treatment of hyperproliferative disorders

2. claims: 57-64

Method for determining compounds to be used in combination for the treatment of cancer

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/075883

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007127175 A	08-11-2007	AR 060633 A1	02-07-2008
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