

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 January 2007 (25.01.2007)

PCT

(10) International Publication Number
WO 2007/010013 A3

(51) International Patent Classification:
A61K 31/506 (2006.01) **A61P 35/00** (2006.01)

(74) Agent: **ROTH, Peter, R.**; NOVARTIS AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(21) International Application Number:
PCT/EP2006/064430

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, 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, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 19 July 2006 (19.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/701,103 20 July 2005 (20.07.2005) US

(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, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for AE, AG, AL, AM, AU, AZ, BA, BB, BE, BF, BG, BJ, BR, BW, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GQ, GR, GW, HN, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MC, MD, MG, MK, ML, MN, MR, MW, MX, MZ, NA, NE, NG, NI, NL, NO, NZ, OM, PG, PH, PL, PT, RO, RS only*): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

Declaration under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

(71) Applicant (*for AT only*): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1239 Vienna (AT).

Published:

— *with international search report*

(72) Inventors; and

(88) Date of publication of the international search report:
3 May 2007

(75) Inventors/Applicants (*for US only*): **MANLEY, Paul, W.** [GB/CH]; Bruggweg 12, CH-4144 Arlesheim (CH).
ROESEL, Johannes [DE/CH]; Unterm Schellenberg 211, CH-4125 Riehen (CH).

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: COMBINATION COMPRISING A PYRIMIDYLAMINO BENZAMIDES AND A FLT-3 INHIBITOR FOR TREATING PROLIFERATIVE DISEASES

(57) Abstract: The invention provides a pharmaceutical combination comprising: a) a pyrimidylaminobenzamide compound; and b) a Flt-3inhibitor, and a method for treating or preventing a proliferative disease using such a combination.



WO 2007/010013 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/064430

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/506 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 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, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/005281 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; BREITENSTEIN WERNER [CH];) 15 January 2004 (2004-01-15) cited in the application page 9, paragraph 3 - paragraph 5 page 2 page 13, paragraph 2	1-12
Y	WO 03/037347 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; DANA FARBER CANCER INST I) 8 May 2003 (2003-05-08) cited in the application page 37, paragraphs 3,4 page 42	1-12
	----- -/-- -----	

☒ 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

3 November 2006

Date of mailing of the international search report

19/12/2006

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

Büttner, Ulf

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/064430

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCUTO A ET AL: "Synergistic cytotoxic effects of a combination of a novel tyrosine kinase inhibitor AMN107 and histone deacetylase inhibitor LBH589 against Bcr-Abl expressing human leukemia cells" BLOOD, W.B.SAUNDERS COMPANY, ORLANDO, FL, US, vol. 104, no. 11, Part 1, November 2004 (2004-11), page 546A, XP002378080 ISSN: 0006-4971 abstract	1-12
Y	NEMOTO A ET AL: "INTERLEUKIN-7 AND FLT-3 LIGAND SYNERGISTICALLY SUPPORT CELL PROLIFERATION AND SURVIVAL OF PHILADELPHIA-CHROMOSOME POSITIVE B-PRECURSOR LEUKEMIA CELLS BY COOPERATIVELY STIMULATING JAK/STAT, RAS/RAF/MAPK, AND PI3K PATHWAYS" BLOOD, W.B.SAUNDERS COMPANY, ORLANDO, FL, US, vol. 102, no. 11, 16 November 2003 (2003-11-16), page 236B, XP009065939 ISSN: 0006-4971 abstract	1-12
A	GUO FEI ET AL: "Molecular characterization of human AML cells with resistance to growth-inhibitory and apoptotic effects of hydroxamic acid analogue histone deacetylase inhibitors." BLOOD, vol. 104, no. 11, Part 1, November 2004 (2004-11), page 332A, XP009074480 & 46TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; SAN DIEGO, CA, USA; DECEMBER 04 -07, 2004 ISSN: 0006-4971 abstract	1-12
A	WEISBERG E ET AL: "Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl" CANCER CELL, XX, US, vol. 7, no. 2, February 2005 (2005-02), pages 129-141, XP002396353 ISSN: 1535-6108 the whole document	1-12

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/064430

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	COOLS J ET AL: "PKC412 OVERCOMES RESISTANCE TO IMATINIB IN A MURINE MODEL OF FIP1L1-PDGFR-ALPHA-INDUCED MYELOPROLIFERATIVE DISEASE" CANCER CELL, XX, US, vol. 3, no. 5, May 2003 (2003-05), pages 459-469, XP008039395 ISSN: 1535-6108 page 467, column 1, paragraph 4 - column 2, paragraph 1	1-12
P,X	GLEIXNER KAROLINE V ET AL: "PKC412 inhibits in vitro growth of neoplastic human mast cells expressing the D816V-mutated variant of KIT: comparison with AMN107, imatinib, and cladribine (2CdA) and evaluation of cooperative drug effects" BLOOD, vol. 107, no. 2, January 2006 (2006-01), pages 752-759, XP002405519 ISSN: 0006-4971 page 758, column 2	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/064430

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 4-12 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:

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.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/064430

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004005281 A1	15-01-2004	CA 2491632 A1	15-01-2004
		EP 1532138 A1	25-05-2005
		JP 2005533827 T	10-11-2005
		MX PA05000328 A	31-03-2005
WO 03037347 A	08-05-2003	AT 335490 T	15-09-2006
		BR 0213739 A	19-10-2004
		CA 2462657 A1	08-05-2003
		CN 1582150 A	16-02-2005
		EP 1441737 A1	04-08-2004
		HU 0401642 A2	29-11-2004
		JP 2005507412 T	17-03-2005
		MX PA04004137 A	25-01-2005
		NZ 532136 A	31-08-2006