(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 October 2012 (04.10.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/131656 A3

(51) International Patent Classification:
A61K 31/4164 (2006.01) *A61P 35/00* (2006.01)
A61K 31/4192 (2006.01) *A61P 29/00* (2006.01)
A61K 31/44 (2006.01) *A61P 25/00* (2006.01)
C07D 213/74 (2006.01) *A61P 1/16* (2006.01)
C07D 233/54 (2006.01) *A61P 21/00* (2006.01)
C07D 249/06 (2006.01) *A61P 9/00* (2006.01)
C07D 401/12 (2006.01)

(21) International Application Number:
PCT/IB2012/051603

(22) International Filing Date:
2 April 2012 (02.04.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11305385.4 1 April 2011 (01.04.2011) EP
61/470,564 1 April 2011 (01.04.2011) US

(71) Applicants *(for all designated States except US)*: **SOCIÉTÉ SPLICOS** [FR/FR]; Campus du CNRS, 1919 route de Mende, F-34293 Montpellier Cedex 5 (FR). **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE** [FR/FR]; 3 rue Michel-Ange, F-75794 Paris Cedex 16 (FR). **INSTITUT CURIE** [FR/FR]; 26 rue d'Ulm, F-75248 Paris Cedex 05 (FR). **UNIVERSITE DE MONTPELLIER 2** [FR/FR]; Place Eugène Bataillon, F-34000 Montpellier (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SCHERRER, Didier** [FR/FR]; 26 avenue des Sabines, F-34170 Castelnau Le Lez (FR). **TAZI, Jamal** [FR/FR]; 4 rue Condorcet, F-34380 Clapiers (FR). **NAJMAN, Romain** [FR/FR]; 4 rue de la Corsade, Bâtiment A2, F-94240 L'Hay-Les-Roses (FR). **MAHUTEAU, Florence** [FR/FR]; 36 avenue Hoche, F-78470 Saint Remy Les Chevreuses (FR). **ROUX, Pierre** [FR/FR]; 700 rue des Erables, F-34980 Saint-Gely-Du-Fesc (FR).

(74) Agent: **LE COUPANEC, Pascale**; Nony, 3 rue de Penthièvre, F-75008 Paris (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, 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.

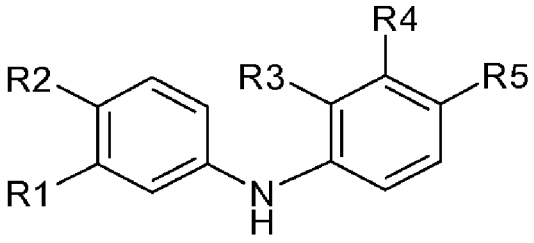
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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))*

[Continued on next page]

(54) Title: COMPOUNDS FOR USE AS THERAPEUTIC AGENTS AFFECTING P53 EXPRESSION AND/OR ACTIVITY



(I)

(57) Abstract: The present invention relates to compound (I) wherein R1 and R2 independently represent a hydrogen atom, a (C_1-C_4)alkoxy group, a fluoro(C_1-C_4)alkoxy group, a hydroxyl group, a benzyloxy group, a di(C_1-C_4)alkylamino group, a pyridyl- vinyl group, a pyrimidinyl- vinyl group, a styryl group, or a -NHCOphenyl group; R3, R4 and R5 independently represent a hydrogen atom, a (C_1-C_4)alkyl group, a CONHR6 group, a -CONR7R8 group, a -SO_2NHR6 group, or a heteroaryl group optionally substituted by a halogen atom, a -(CH2)nNR7R8 group or a hydroxy(C_1-C_4)alkyl group; R6 represents a hydrogen atom, a -$(CHR9)_m(CH_2)_n$NR7R8 group or a (C_1-C_6)alkyl group optionally substituted by a hydroxyl group; or anyone of its pharmaceutically acceptable salt, for use in a method for preventing, inhibiting or treating a disease in a patient suffering thereof, said disease involving a deregulated p53. Some of said compounds are new and also form part of the invention.

WO 2012/131656 A3

— *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:
22 November 2012

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051603

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4164 A61K31/4192 A61K31/44 C07D213/74 C07D233/54
C07D249/06 C07D401/12 A61P35/00 A61P29/00 A61P25/00
A61P21/00 A61P9/00 A61P1/16

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 C07D

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, BIOSIS, CHEM ABS Data, EMBASE, 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	US 2011/053975 A1 (TAZI JAMAL [FR] ET AL) 3 March 2011 (2011-03-03) pages 10-11, paragraph 319-327 compounds C20, C30-C33, C36, C40, C42-C43, C46-47, C49, C51-C60, C62, C64-69, C76-78, C81-83, C85-91, C93, FMB008, MB228, FMMB15.4, FMMB22.16, FMMB31.11-12, FMMB41.2, FMMB57.1-10, FMMB53.1-2, FMMB53.5, FMMB53.8, FMMB53.10 ----- -/--	1-6,9-13

[X] Further documents are listed in the continuation of Box C.

[X] 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 application or patent 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 September 2012	28/09/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lemarchand, Aude

5

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NAYAK S K ET AL: "p53-Induced apoptosis and inhibitors of p53", CURRENT MEDICINAL CHEMISTRY 2009 BENTHAM SCIENCE PUBLISHERS B.V. NLD LNKD-DOI:10.2174/092986709788681976, vol. 16, no. 21, 2009, pages 2627-2640, XP007919173, ISSN: 0929-8673 the whole document	1-5,9-13
A	HARDCASTLE IAN R: "Inhibitors of the MDM2-p53 interaction as anticancer drugs", DRUGS OF THE FUTURE, vol. 32, no. 10, October 2007 (2007-10), pages 883-896, XP007919174, ISSN: 0377-8282 the whole document	1-5,9-13
X	US 3 409 668 A (GIUSEPPE PALAZZO ET AL) 5 November 1968 (1968-11-05) Compound of formula (I), wherein R=H, R'=Ph/Cl-Ph, R''=Et, Me; page 1, column 1, lines 20-42	1,6,9, 10,13
X	US 2 671 805 A (PETER KRIMMEL CARL) 9 March 1954 (1954-03-09) page 1, column 1, lines 1-41 page 1, column 2, lines 3-5	1,6,9, 10,13
X	JP 50 095285 A (HISAMITSU PHARM CO LTD) 29 July 1975 (1975-07-29) compound (II)	1,6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/051603

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011053975 A1	03-03-2011	CA 2711652 A1	16-07-2009
		CN 101965341 A	02-02-2011
		EP 2235000 A2	06-10-2010
		FR 2926297 A1	17-07-2009
		JP 2011509280 A	24-03-2011
		US 2011053975 A1	03-03-2011
		WO 2009087238 A2	16-07-2009
US 3409668 A	05-11-1968	GB 1057667 A	08-02-1967
		US 3409668 A	05-11-1968
US 2671805 A	09-03-1954	NONE	
JP 50095285 A	29-07-1975	NONE	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/051603

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.:

2-6, 11(completely); 1, 9, 10, 12, 13(partially)

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: 2-5(completely); 1, 9-13(partially)

   A compound of formula (Iab), (Ia), (Ib) or I(c)and its use as agent for preventing, inhibiting or treating a disease involving a deregulated p53 e.g. as listed in claim 10 (cancer, inflammation, fibrosis, neurodegenerative diseases, ischemia, atherosclerosis, hepatic disorders, cholestasis, autoimmune diseases, ethanol-induced injuries, ribosome biogenesis disorders, HIV-associated pathologies, such as dementia, diabetes, or myocardial infarction).

   ---

2. claims: 6(completely); 1, 9-13(partially)

   A compound of formula (Id) and its use as agent for preventing, inhibiting or treating a disease involving a deregulated p53 e.g. as listed in claim 10.

   ---

3. claims: 7(completely); 1, 9, 10, 12, 13(partially)

   A compound of formula I(e) and its use as agent for preventing, inhibiting or treating a disease involving a deregulated p53, e.g. as listed in claim 10.

   ---

4. claims: 8(completely); 1, 9, 10, 12, 13(partially)

   A compound of formula (If) and its use as agent for preventing, inhibiting or treating a disease involving a deregulated p53, e.g. as listed in claim 10.

   ---

5. claims: 1, 10, 13(all partially)

   A compound of formula (I) not encompassed by inventions 1-4 and its use as agent for preventing, inhibiting or treating a disease involving a deregulated p53, e.g. as listed in claim 10.
