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- (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, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, KM, ML, MR, NE, SN, TD, TG).

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**Previous Correction:**  
see Notice of 16 February 2017



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(54) **Title:** P38 INHIBITORS FOR THE TREATMENT AND PROPHYLAXIS OF LIVER CANCER

(57) **Abstract:** The present invention provides p38 inhibitors which are useful for the treatment and/or prophylaxis of liver cancer. In particular, the present invention provides compounds capable of inhibiting the intracellular expression of the p38 gamma protein in the hepatocytes of a subject relative to that observed in the absence of the compound, for use in the therapeutic treatment of liver cancer.

## INTERNATIONAL SEARCH REPORT

International application No  
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A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/5377 C07D231/40 A61P35/00 ADD.		
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 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, INSPEC, 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.
Y	YVONNE KUMA ET AL: "BIRB796 Inhibits All p38 MAPK Isoforms in Vitro and in Vivo", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 280, no. 20, 20 May 2005 (2005-05-20), pages 19472-19479, XP007913553, ISSN: 0021-9258, DOI: 10.1074/JBC.M414221200 [retrieved on 2005-05-08] the whole document figures; tables	1-3,11, 12
Y	WO 2005/063715 A1 (BOEHRINGER INGELHEIM PHARMA [US]; SMOLIGA JOHN A [US]; VITOUS JANA [US] 14 July 2005 (2005-07-14) the whole document page 6, lines 16-19	1-3,11, 12
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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	"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	
"E" earlier application or patent but published on or after the international filing date	"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	
"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)	"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	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Orlando, Michele	

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2016/063532

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARCIA GOETTERT ET AL: "Development of a p38 mitogen activated protein kinase ELISA assay for the quantitative determination of inhibitor activity", JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, NEW YORK, NY, US, vol. 66, 6 March 2012 (2012-03-06), pages 349-351, XP028490226, ISSN: 0731-7085, DOI: 10.1016/J.JPBA.2012.03.008 [retrieved on 2012-03-15] the whole document page 351	1-3,11, 12
Y	TATIANA EFIMOVA: "p38[delta] mitogen-activated protein kinase regulates skin homeostasis and tumorigenesis", CELL CYCLE, vol. 9, no. 3, 1 February 2010 (2010-02-01), pages 498-505, XP055227163, ISSN: 1538-4101, DOI: 10.4161/cc.9.3.10541 the whole document page 503	1-3,11, 12
A,P	Anonymous: "Useful new molecules for the treatment of liver cancer.",  21 October 2015 (2015-10-21), XP055303285, Retrieved from the Internet: URL:https://www.cnice.es/sites/default/files/ot44.en.pdf [retrieved on 2016-09-16] the whole document	1-3,11, 12
X	WO 2005/040758 A2 (INTERMUNE INC [US]; OZES OSMAN N [US]; BLATT LAWRENCE M [US]) 6 May 2005 (2005-05-06) the whole document	1-3,11, 12
Y	paragraphs [0104], [0390]; examples; table 2	1-3,11, 12
X	CN 103 550 242 A (SICHUAN GUOKANG PHARMACEUTICAL CO LTD) 5 February 2014 (2014-02-05) the whole document claims; examples	1-3,11, 12
X	CN 101 652 138 B (UNIV CENTRAL SOUTH) 6 July 2011 (2011-07-06) the whole document claims; examples	1-3,11, 12
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2016/063532

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>Y.-S. KEUM: "Mechanism of Action of Sulforaphane: Inhibition of p38 Mitogen-Activated Protein Kinase Isoforms Contributing to the Induction of Antioxidant Response Element-Mediated Heme Oxygenase-1 in Human Hepatoma HepG2 Cells", CANCER RESEARCH, vol. 66, no. 17, 1 September 2006 (2006-09-01), pages 8804-8813, XP055227130, US ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-05-3513 the whole document</p>	1-3,11, 12
A	<p>EP 2 727 596 A1 (FUNDACION CT NAC DE INVESTIGACIONES CARDIOVASCULARES CARLOS III CNIC []) 7 May 2014 (2014-05-07) the whole document</p>	1-3,11, 12
A	<p>EP 2 653 555 A1 (FUNDACION CT NAC DE INVESTIGACIONES CARDIOVASCULARES CARLOS III CINC []) 23 October 2013 (2013-10-23) the whole document</p>	1-3,11, 12
A	<p>A. BUDHU ET AL: "The role of cytokines in hepatocellular carcinoma", JOURNAL OF LEUKOCYTE BIOLOGY, vol. 80, no. 6, 18 August 2006 (2006-08-18), pages 1197-1213, XP055227184, US ISSN: 0741-5400, DOI: 10.1189/jlb.0506297 the whole document page 1201, left-hand column; table 1</p>	1-3,11, 12

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2016/063532

## 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.:
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.:

3(completely); 1, 2, 11, 12(partially)

### 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: 3(completely); 1, 2, 11, 12(partially)

A composition according to claim 1 for use in the treatment of hepatic cancer, wherein the compound is pirfenidone or a salt or derivative thereof capable of inhibiting p38 gamma and/or delta intracellular expression; a pharmaceutical composition comprising said compound.

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2. claims: 10(completely); 1, 2, 11, 12(partially)

A composition according to claim 1 for use in the treatment of hepatic cancer, wherein the compound is doramapimod (BIRB 796; BIRB-796; BIRB796) or a salt or derivative thereof capable of inhibiting p38 gamma and/or delta intracellular expression; a pharmaceutical composition comprising said compound.

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3. claims: 8(completely); 1, 2, 11, 12(partially)

A composition according to claim 1 for use in the treatment of hepatic cancer, wherein the compound is a p38-delta and/or p38-gamma gene silencer compound such as a siRNA (small interfering RNA of p38 delta and/or p38 gamma protein) and/or shRNA (small hairpin RNA of p38 delta and/or p38 gamma protein) and/or RNA-directed DNA cleavage by the cas9-crisp or talent based technology; a pharmaceutical composition comprising said compound.

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4. claims: 9(completely); 1, 2, 11, 12(partially)

A composition according to claim 1 for use in the treatment of hepatic cancer, wherein the compound is a peptide comprising SEQ ID NO 1 (YGRKKRRQRRRARVPKETAL); a pharmaceutical composition comprising said compound.

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5. claims: 4, 5(completely); 1, 2, 11, 12(partially)

A composition according to claim 1 for use in the treatment of hepatic cancer, wherein the compound is a compound represented by formula I of claim 2 (e); a pharmaceutical composition comprising said compound.

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6. claims: 6(completely); 1, 2, 11, 12(partially)

A composition according to claim 1 for use in the treatment of hepatic cancer, wherein the compound is a compound represented by formula (a.), (b.) or (c.) of claim 2 (f); a

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

pharmaceutical composition comprising said compound.

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7. claims: 7(completely); 1, 2, 11, 12(partially)

A composition according to claim 1 for use in the treatment of hepatic cancer, wherein the compound is selected among the structures listed in claim 2 (g); a pharmaceutical composition comprising said compound.

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8. claim: 13

Use in vitro of IL6 as a biomarker IL-6 for monitoring or determining the effectiveness of p38-gamma/delta inhibitor compounds, to evaluate the treatment with p38-gamma/delta inhibitors, or to identify p38-gamma/delta inhibitors in vitro.

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/EP2016/063532
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005063715 A1	14-07-2005	CA 2547837 A1 EP 1716121 A1 JP 2007514791 A US 2005137195 A1 WO 2005063715 A1	14-07-2005 02-11-2006 07-06-2007 23-06-2005 14-07-2005
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EP 2653555 A1	23-10-2013	NONE	