



(51) International Patent Classification:

C07D 513/16 (2006.01) **A61K 31/519** (2006.01)
C07D 513/22 (2006.01) **A61K 31/5025** (2006.01)
A61K 31/4738 (2006.01) **A61P 35/00** (2006.01)
A61K 31/433 (2006.01) **C07D 401/00** (2006.01)

(21) International Application Number:

PCT/GB2012/051134

(22) International Filing Date:

18 May 2012 (18.05.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

11382158.1 19 May 2011 (19.05.2011) EP
 12275024.3 9 March 2012 (09.03.2012) EP

(71) Applicant (for all designated States except US):
CENTRO NACIONAL DE INVESTIGACIONES ONCOLÓGICAS (CNIO) [ES/ES]; Melchor Fernández, Almagro 3, E-28029 Madrid (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PASTOR FERNÁNDEZ, Joaquín** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **ÁLVAREZ ESCOBAR, Rosa María** [ES/ES]; Centro Nacional de Investigaciones On-

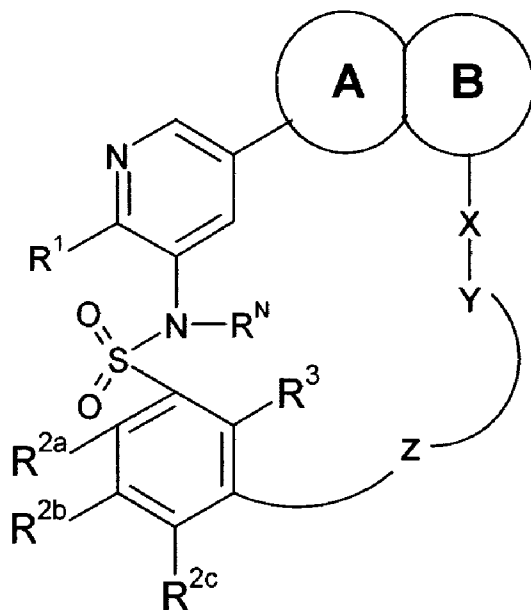
cológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **RIESCO FAGUNDO, Rosario Concepción** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **GARCÍA GARCÍA, Ana Belén** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **RODRÍGUEZ HERGUETA, Antonio** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **MARTÍN HERNANDO, Jose Ignacio** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **BLANCO APARICIO, Carmen** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES). **CEBRIÁN MUÑOZ, David Álvaro** [ES/ES]; Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández, Almagro 3, E-28029 Madrid (ES).

(74) Agent: **SNODIN, Michael D.**; Park View House, 58 The Ropewalk, Nottingham, Nottinghamshire NG1 5DD (GB).

(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,

[Continued on next page]

(54) Title: MACROCYCLIC COMPOUNDS AS PROTEIN KINASE INHIBITORS



(57) Abstract: There is provided compounds of formula I, wherein R¹, R^{2a}, R^{2b}, R^{2c}, X, Y, Z, R³ and ring A/B have meanings given in the description, and pharmaceutically-acceptable esters, amides, solvates or salts thereof, which compounds are useful in the treatment of diseases in which inhibition of a protein or lipid kinase (e.g. PI3-K, particularly class I PI3K, PIM family kinase and/or mTOR) is desired and/or required, and particularly in the treatment of cancer. The invention also relates to combinations containing such compounds.



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, 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))
- 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))
- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

10 January 2013