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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 July 2010 (29.07.2010)

PCT

(10) International Publication Number
WO 2010/083975 A1

(51) International Patent Classification:
A61K 45/06 (2006.01) *A61K 31/44* (2006.01)
A61K 31/519 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/EP2010/000270

(22) International Filing Date:
19 January 2010 (19.01.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09382006.6 21 January 2009 (21.01.2009) EP

(71) Applicant *(for all designated States except US)*: **ALMIRALL, S.A.** [ES/ES]; Ronda del General Mitre 151, E-08022 Barcelona (ES).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GODESSART MARINA, Nuria** [ES/ES]; C/ Laureà Miró, 408-410, E-08980 Sant Feliu de Llobregat, (Barcelona) (ES). **PIZCUETA LALANZA, Maria, Pilar** [ES/ES]; C/ Laureà Miró, 408-410, E-08980 Sant Feliu de Llobregat, (Barcelona) (ES).

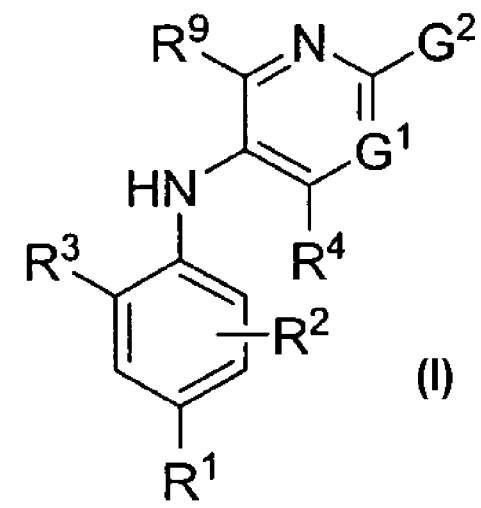
(74) Agents: **SRINIVASAN, Ravi, Chandran** et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5JJ (GB).

(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, 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, RO, RS, RU, 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.

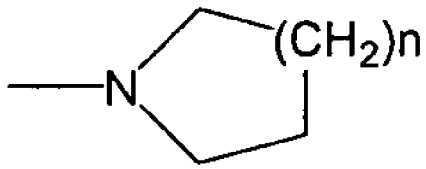
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,

[Continued on next page]

(54) Title: COMBINATIONS COMPRISING METHOTREXATE AND DHODH INHIBITORS



(I)



(57) Abstract: The present invention provides a combination which comprises (a) methotrexate and (b) a non-hepatotoxic DHODH inhibitor of formula (I): wherein: R^1 is selected from the group consisting of hydrogen atoms, halogen atoms, C_{1-4} alkyl, C_{3-4} cycloalkyl, $-CF_3$ and $-OCF_3$, R^2 is selected from the group consisting of hydrogen atoms, halogen atoms and C_{1-4} alkyl groups, R^3 is selected from the group consisting of $-COOR^5$, $-CONHR^5$, tetrazolyl, $-SO_2NHR^5$ and $-CONHSO_2R^5$ groups, wherein R^5 is selected from the group consisting of a hydrogen atom and linear or branched C_{1-4} alkyl groups, R^4 is selected from the group consisting of a hydrogen atom and a C_{1-4} alkyl group, R^9 is selected from the group consisting of a hydrogen atom and a phenyl group, G^1 represents a group selected from N and CR^6 wherein R^6 is selected from the group consisting of hydrogen atoms, halogen atoms, C_{1-4} alkyl, C_{3-4} cycloalkyl, C_{1-4} alkoxy, $-CF_3$, $-OCF_3$, monocyclic N-containing C_{5-7} heteroaryl, monocyclic N- containing C_{3-7} heterocyclyl groups and C_{6-10} aryl groups which C_{6-10} aryl groups are optionally substituted with one or more substituents selected from halogen atoms and C_{1-4} alkyl groups, G^1 represents a group selected from N and CR^6 wherein R^6 is selected from the group consisting of hydrogen atoms, halogen atoms, C_{1-4} alkyl, C_{3-4} cycloalkyl, C_{1-4} alkoxy, $-CF_3$, $-OCF_3$, monocyclic N-containing C_{5-7} heteroaryl, monocyclic N- containing C_{3-7} heterocyclyl groups and C_{6-10} aryl groups which C_{6-10} aryl groups are optionally substituted with one or more substituents selected from halogen atoms and C_{1-4} alkyl groups, G^2 represents a group selected from: • a hydrogen atom, a hydroxy group, a halogen atom, a C_{3-4} cycloalkyl group, a C_{1-4} alkoxy group and $-NR^aR^b$, wherein R^a represents a C_{1-4} alkyl group and Rb is selected from a group consisting of C_{1-4} alkyl group and C_{1-4}alkoxy-C_{1-4} alkyl group, or Ra and Rb together with the nitrogen atom to which they are attached form a saturated 6 to 8 membered heterocyclic ring optionally containing one oxygen atom as an additional heteroatom, • a monocyclic or bicyclic 5 to 10 membered heteroaromatic ring containing one or more nitrogen atoms which is optionally substituted by one or more substituents selected from halogen atoms, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-4} cycloalkyl, C_{3-4} cycloalkoxy,

[Continued on next page]

WO 2010/083975 A1

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, MK, MT, NL, NO, PL, PT, RO, 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))*

$-CF_3$, $-OCF_3$, and $-CONR^7R^8$, wherein R^7 and R^8 are independently selected from hydrogen atom, linear or branched C_{1-4} alkyl groups, C_{3-7} cycloalkyl groups, or R^7 and R^8 together with the nitrogen atom to which they are attached form a group of formula wherein n is an integer from 0 to 3, and • a phenyl group which is optionally substituted by one or more substituents selected from halogen atoms, C_{1-4} alkyl, hydroxyl, C_{1-4} alkoxy, C_{3-4} cycloalkyl, C_{3-4} cycloalkoxy, cyano, $-CF_3$, $-OCF_3$, $-CONR^7R^8$, oxadiazolyl, triazolyl, pyrazolyl and imidazolyl groups, which oxadiazolyl, triazolyl, pyrazolyl and imidazolyl groups are optionally substituted by C_{1-4} alkyl or C_{3-7} cycloalkyl groups and wherein R^7 and R^8 are independently selected from hydrogen atom, linear or branched C_{1-4} alkyl groups, C_{3-7} cycloalkyl groups, or R^7 and R^8 together with the nitrogen atom to which they are attached form a group of formula wherein n is an integer from 0 to 3 or, when G' represents CR^6, G^2 together with R^6 forms a non-aromatic C_{5-10} carbocyclic group or a C_{6-10} aryl group, and the pharmaceutically acceptable salts and N-oxides thereof.