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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 August 2012 (23.08.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/111027 A3

(51) International Patent Classification:
C07D 487/04 (2006.01)

(21) International Application Number:
PCT/IN2012/000103

(22) International Filing Date:
14 February 2012 (14.02.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
434/CHE/2011 15 February 2011 (15.02.2011) IN

(71) Applicant *(for all designated States except US)*: **HETERO RESEARCH FOUNDATION** [IN/IN]; Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhrapradesh, Hyderabad 500018 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PARTHASARADHI REDDY, Bandi** [IN/IN]; Hetero Research Foundation, Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhra pradesh, Hyderabad 500018 (IN). **RATHNAKAR REDDY, Kura** [IN/IN]; Hetero Research Foundation, Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhra pradesh, Hyderabad 500018 (IN). **MURALIDHARA REDDY, Dasari** [IN/IN]; Hetero Research Foundation, Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhra pradesh, Hyderabad 500018 (IN). **RAMACHANDRA, Puranik** [IN/IN]; Hetero Research Foundation, Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Hyderabad 500018 (IN). **VAMSI KRISHNA, Bandi** [IN/IN]; Hetero Research Foundation, Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad, Andhra pradesh, Hyderabad 500018 (IN).

(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).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

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))*

(88) Date of publication of the international search report:
11 October 2012

(54) Title: PROCESS FOR PEMETREXED DISODIUM

(57) Abstract: The present invention provides a process for the preparation of N-[4-[2-(2-amino-4, 7 -dihydro-4-oxo-1 H-pyrrolo[2,3-d]pyrimidin-5-yl) ethyf]benzoyl]-L-glutamic acid dimethyl ester1 or salts thereof. The present invention also provides a process for the preparation of pemetrexed disodium substantially free of enatiomeric impurity. In another aspect, the present invention provides a process for the preparation of pemetrexed disodium substantially free of enantiomeric impurity, which comprises: a) stirring a solution of N-[4-[2-(2-amino-4,7-dihydro-4-oxo-IH-pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid dimethyl ester 4- methylbenzenesulfonic acid with a mixture of sodium hydroxide and water at below 30°C; b) adjusting the pH of the reaction mass to above 7.2 with an acid; c) adding an organic solvent to the solution obtained in step (b) at below 30°C; and d) isolating the pemetrexed disodium substantially free of enantiomeric impurity.

WO 2012/111027 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2012/000103

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 487/04 (2012.01)
USPC - 544/280
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)
IPC(8) - A61K 31/513, 31/519; C07D 487/04 (2012.01)
USPC - 514/265.1; 544/279, 280

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)
PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2001/14379 A2 (CHELIUS et al) 01 March 2001 (01.03.2001) entire document	1-6
A	EP 2,301,909 A1 (LI et al) 30 March 2011 (30.03.2011) entire document	1-15
A	WO 2010/030598 A2 (KOCHERLAKOTA et al) 18 March 2010 (18.03.2010) entire document	1-15
A	US 5,403,843 A (AKIMOTO et al) 04 April 1995 (04.04.1995) entire document	1-15
A	US 2010/0305319 A1 (LUO et al) 02 December 2010 (02.12.2010) entire document	1-15

☐ Further documents are listed in the continuation of Box C. ☐

* 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
07 August 2012	17 AUG 2012

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)