

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
6 June 2002 (06.06.2002)

PCT

(10) International Publication Number
WO 02/44132 A1

- (51) International Patent Classification⁷: **C07C 237/46**, 231/02
- (74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).
- (21) International Application Number: PCT/EP01/13939
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date:
29 November 2001 (29.11.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
MI2000A002601 1 December 2000 (01.12.2000) IT
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): **BRACCO IMAGING S.P.A.** [IT/IT]; Via E. Folli, 50, I-20134 Milano (IT).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **ANELLI, Pier, Lucio** [IT/IT]; Via E. Folli, 50, I-20134 Milano (IT). **BROCCHETTA, Marino** [IT/IT]; Via E. Folli, 50, I-20134 Milano (IT). **LUX, Giovanna** [IT/IT]; Via E. Folli, 50, I-20134 Milano (IT). **CAPPELLETTI, Enrico** [IT/IT]; Via E. Folli, 50, I-20134 Milano (IT).
- Published:**
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: A PROCESS FOR THE PREPARATION OF IOPAMIDOL AND THE NEW INTERMEDIATES THEREIN

(57) Abstract: A process for the preparation of (S)-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxo-propyl)amino]-2,4,6-triiodo-1,3-benzendicarboxamide (iopamidol) starting from 5-amino-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-1,3-benzendicarboxamide (II) which process comprises a) reacting the compound of formula (II) with a suitable protecting agent, to give a compound of formula (III) wherein R is a group of formula A or B wherein R₁ is a hydrogen atom, a C₁-C₄ straight or branched alkoxy group, R₂ is hydrogen, a C₁-C₄ straight or branched alkoxy group and R₃ is a C₁-C₄ straight or branched alkyl group, a trifluoromethyl or a trichloromethyl group; b) acylating the amino group in position 5 of the intermediate compound of formula (III), by reaction with a (S)-2-(acetyloxy)propanoyl chloride to give a compound of formula (IV) wherein R is as defined above; and c) removing all the acyl groups present in the compound of formula (IV) under basic conditions, with prior cleavage of the cyclic protections of the hydroxy groups in the carboxamido substituents under acidic conditions, when R is a group of formula A carboxamido hydroxy groups under acidic conditions. The invention also refers to the new intermediates of formula (III) and (IV) wherein -R is a group A.