

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

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number  
WO 02/100339 A3

- (51) International Patent Classification<sup>7</sup>: C07C 69/675, 255/49, 255/50, 317/14
- (74) Agents: BRAINARD, Charles, R. et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).
- (21) International Application Number: PCT/US02/18329
- (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, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 13 June 2002 (13.06.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/298,009 13 June 2001 (13.06.2001) US  
60/371,069 9 April 2002 (09.04.2002) US
- (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 BB, US*): TEVA PHARMACEUTICAL INDUSTRIES LTD. [IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petah Tiqva (IL).
- (71) Applicant (*for BB only*): TEVA PHARMACEUTICALS USA, INC. [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).
- Published:  
— with international search report
- (72) Inventors; and
- (88) Date of publication of the international search report:  
16 October 2003
- (75) Inventors/Applicants (*for US only*): DOLITZKY, Ben-Zion [IL/IL]; Lohame HaGhetto 32, Petach Tiqva 49651 (IL). REANY, Ofer [IL/IL]; House No. 70, Chitim Village, Lower Gallilee, 15280 Israel (IL). SHAMMAI, Jenny [IL/IL]; 18/2 Etzel Str, Kiryat Yam 29061 (IL).
- 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.*



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(54) Title: NOVEL PROCESS FOR PREPARING RAC-BICALUTAMIDE AND ITS INTERMEDIATES

(57) Abstract: The present invention relates to a new process for the synthesis of racemic and optically active bicalutamide starting from ethyl pyruvate and methyl methacrylate. The present invention discloses processes of preparing bicalutamide intermediates including ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionate, 1,2-epoxy-2-methyl propionate and 2-hydrox-2-methyl-3-(4-fluorophenylthio) propionic acid. The present invention further discloses micronized *rac*-bicalutamide and the preparation thereof.

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| <b>A. CLASSIFICATION OF SUBJECT MATTER</b>  |  |  |
|---|--|--|
| IPC(7) : C07C 69/675, 255/49, 255/50, 317/14  |  |  |
| US CL : 560/8, 9; 558/303, 411, 413, 414, 418, 425, 426; 568/28; 514/618/ 622   |  |  |
| According to International Patent Classification (IPC) or to both national classification and IPC   |  |  |
| <b>B. FIELDS SEARCHED</b>   |  |  |
| Minimum documentation searched (classification system followed by classification symbols)   |  |  |
| U.S. : 560/8, 9; 558/303, 411, 413, 414, 418, 425, 426; 568/28; 514/618/ 622  |  |  |
| 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)<br>Please See Continuation Sheet |  |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>   |  |  |
| Category *  | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.  |
| A   | US 4,554,381 A ( DESBOIS) 19 November 1985 ( 19.11.1985), columns 3 and 4.   | 1-7  |
| A   | US 5,723,485 A (GUNGOR et al) 03 March 1998 (03.03.1998), column 8 example 1.  | 1-7  |
| A   | Database CAPLUS on STN, Chem. Abstracts ( Columbus Ohio, USA), CA:129:244921, FRESKOS et al, ' Preparation of aromatic sulfonyl alpha,-hydroxy hydroxamic acid compounds as matrix metalloprotease inhibitors', WO 9839326, 11 September 1998. | 8-12   |
| A   | Database CAPLUS on STN Chem. Abstracts ( Columbus Ohio, USA) CA:128:75188, TAKAHASHI et al, ' Preparation and formulation of aryl sulfides , sulfoxides and sulfones as matrix metalloproteinases inhibitors', WO9749679 , December 31, 1997.  | 8-12   |
| A   | Database CAPLUS on STN Chem. Abstracts (Columbus Ohio, USA) CA:136:12767, SLUSAREK et al, ' Color photographic thermally processable film comprising blocked developer compound', EP 1158359 28 November 2001.                                 | 8-12   |
| A   | US 3,254,094 A (ROSS et al) 31 May 1966 (31.05.1966), columns 3-4.   | 13-19  |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input 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 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   |  |
| Date of the actual completion of the international search   | Date of mailing of the international search report   |  |
| 23 October 2002 (23.10.2002)  | 03 JUL 2003  |  |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703)305-3230          | Authorized officer<br>Jean F. Vollano<br>Telephone No. 703-308-1235  |  |

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## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| A          | Database CAPLUS on STN Chem. Abstracts (Columbus Ohio, USA) CA:86:171116<br>BUETTNER et al, 'Trifluoromethyl-substituted aminobrenzonitriles', DE2537288, 03<br>March 1977.  | 13-19                 |
| A          | Database CAPLUS on STN Chem. Abstracts (Columbus Ohio, USA) CA:108:150026<br>TUCKER et al, 'Resolution of the non-steroidal antiandrogen 4'-cyano-3-(4-<br>fluorophenylsulfonyl)-2-hydroxy-2-methyl-3'-trifluoromethyl)propionanilide and the<br>determination of the absolute configuration of the active enantiomer', J. Med Chem.,<br>1988 31(4) pages 885-7. | 20-24                 |
| A,P        | Database CAPLUS on STN Chem. Abstracts (Columbus Ohio, USA) CA: 2002:414656<br>JAMES et al, 'A two step synthesis of the anti-cancer drug (R,S)-bicalutamide', Synthesis,<br>2002, (7) pages 850-852.  | 20-24                 |
| A          | US 4,636,505 A (TUCKER et al) 13 January 1987 (13.01.1987) columns 13 and 14.  | 20-24, 44-49          |
| A          | Database CAPLUS on STN Chem. Abstracts (Columbus Ohio, USA) CA:120:191513<br>HORCHLER VON LOCQUENGHEN et al 'Preparation of oxiranecarboxylates and<br>analogues', DE4218765 09 December 1993.   | 27-34                 |
| A          | Database CAPLUS on STN Chem. Abstracts (Columbus Ohio, USA) CA:89:90113<br>RASTETTER et al '3,5-dinitroperoxybenzoic acid. A crystalline storable substitute for<br>peroxytrifluoroacetic acid' J. Org. Chem., 1978, 43(16) pages 3163-6.  | 27-34                 |
| A          | Database CAPLUS on STN Chem. Abstracts (Columbus Ohio, USA) CA: 134:326279,<br>EKWURIBE, N. 'Asymmetric synthesis and antiandrogenic use of enantiomers of Casodex<br>(bicalutamide) and derivatives from enantiomers of citramalic acid or proline" WO<br>2001028990, 26 April 2001.  | 35-43                 |

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## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claim Nos.: 25 and 26  
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:  
Please See Continuation Sheet
  
3.  Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation 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 fee, this Authority did not invite payment of any additional fee.
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.:

Remark on Protest

  

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**Continuation of Box I Reason 2:**

Claims 25 and 26 recite the limitation of "wherein the rac-bicalutamide is an R isomer" and wherein the rac-bicalutamide is an S isomer", respectively. The term rac-bicalutamide is referring to the racemic mixture which is a 50-50 mixture of an R and S isomer. It is unclear how a mixture can then be an R isomer or an S isomer solely.

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-7, drawn to a compound of formula X which is the lithium salt of 4-fluorophenyl methyl sulfone and the method of preparing compound X.

Group 2, claim(s) 8-12, drawn to a process for preparing ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionate.

Group 3, claim(s) 13-19, drawn to a compound of formula Y which is a salt of 5-amino-2-cyano-benzotrifluoride and the method of preparing the salt.

Group 4, claim(s) 20-24, drawn to a process for preparing rac-bicalutamide.

Group 5, claim(s) 27-34, drawn to a process for preparing 1,2-epoxy-2-methyl proprionate.

Group 6, claim(s) 35-43, drawn to a process for preparing 2-hydroxy-2-methyl-3-(fluorophenyl thio) proprionic acid.

Group 7, claim(s) 44-49, drawn to a micronized rac-bicalutamide and a pharmaceutical compositions of the rac-bicalutamide .

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Groups 1-7 do not have unity of invention as described in paragraph (b) below:

(a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

(b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

- (1) A product and a process specially adapted for the manufacture of said product; or
- (2) A product and a process of use of said product; or
- (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
- (4) A process and an apparatus or means specifically designed for carrying out the said process; or
- (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

The seven groups do not form unity of invention described by the five categories above.

Group 1 is drawn to a compound of formula X and the method of preparation of the compound which is 4-fluorophenyl methyl sulfone. Group 2 is a process of the preparation of ethyl [2-{4-fluorophenyl sulfone}]-2-hydroxy propionate which is an ethyl ester. The process does not fit with the unity of invention for Group 1 nor does it fit the unity of invention for Groups 3-7. Group 3 is drawn to a compound of formula Y which is an amine benzonitrile and the method of making the compound. Group 4 is drawn to a

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process for making the known compound rac-bicalutamide and does not have unity of invention with any of the Groups. It could have unity of invention with group 7. However since Group 7 is drawn to the bicalutamide compound which is a known compound and there are other methods of making the compound and therefore Group 4 and 7 lack a special technical feature which unites them. The compound is disclosed, for example in US 4,636,505 and a method of preparation is given. For there not to be lack of unity the Groups must possess a special technical feature and unity of invention. Groups 4 and 7 lack a "special technical feature". Group 5 is drawn to the process of preparing methyl 1,2-epoxy-2-methyl propionate which is not found in any other process or compound. Group 6 is a process for the preparation of 2-hydroxy-2-methyl-3-(4-fluorophenylthio) propionic acid. This lacks unity of invention with the other groups and a special technical feature which unites them.

### Continuation of B. FIELDS SEARCHED Item 3:

CAS ONLINE, EAST, Beilstein

search terms: structure drawings for each compound, bicalutamide, sulfone, lithium salt, propanoic acid ester