



- (51) International Patent Classification:
C07D 249/08 (2006.01)
- (21) International Application Number:
PCT/IB2014/061435
- (22) International Filing Date:
14 May 2014 (14.05.2014)
- (25) Filing Language: Italian
- (26) Publication Language: English
- (30) Priority Data:
RM2013A000285 14 May 2013 (14.05.2013) IT
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(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, BN, 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, IR, IS, JP, KE, KG, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))



WO 2014/184754 A1

(54) Title: METHOD FOR PREPARING ANASTROZOLE FOR PHARMACEUTICAL PURPOSES

(57) Abstract: A method for preparing anastrozole characterised in that it comprises; - a bromination step, wherein 2-2' (5-methyl-1, 3- phenylene) bis (2-methylpropanenitrile) is subject to a bromination reaction in the presence of an ester solvent so as to obtain 2-[3 -bromomethyl-5 - (cyano-dimethyl-methyl) -phenyl] - 2-methyl-propanenitrile; - a nucleophilic substitution step, wherein an organic mixture comprising unreacted 2-2' (5-methyl-1, 3 -phenylene) bis (2- methylpropanenitrile), the 2- [3 -bromomethyl-5- (cyano-dimethyl- methyl) -phenyl] -2 -methyl-propanenitrile formed and, if necessary, other reaction by-products is caused to react in dimethylformamide with 1-2-4-triazole or with its sodium salt at a temperature ranging from 0 to 25 °C for the formation of anastrozole; - an anastrozole purification step.

"METHOD FOR PREPARING ANASTROZOLE FOR PHARMACEUTICAL PURPOSES"**TECHNICAL FIELD**

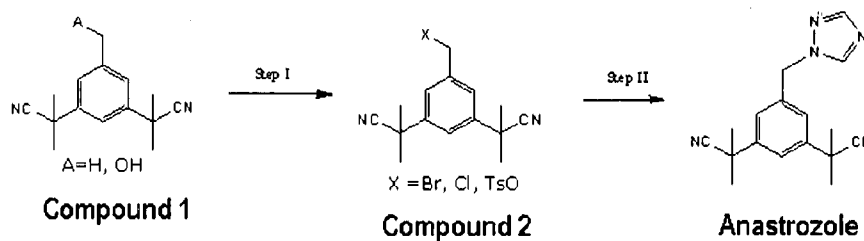
The present invention concerns a simple direct process for preparing pure anastrozole, with IUPAC name 2,2'-[5-(1H-1,2,4-triazol-1-yl-methyl)-1,3-phenylene]bis(2-methylpropanenitrile).

By means of the present process it is possible to synthesise and isolate anastrozole for pharmaceutical purposes from a commercially available starting material without having to isolate and purify other process intermediates.

BACKGROUND ART

Anastrozole is an active ingredient in the category of hormone drugs, able to inhibit the action of a specific enzyme for the regulation and control of female sex hormones. In medicine anastrozole is usually used in the treatment of advanced or recurrent breast cancer in post-menopausal women. The typical dosage for administration of the drug is 1 mg/day orally.

Although various procedures for the total synthesis of anastrozole have been described in literature, the most expedient one, from various points of view, including that of industrial production, consists in two consecutive and distinct process steps. The general reaction scheme is as follows:



In this regard, one of the synthesis approaches most widely used consists in reacting the 2,2'-[5-methyl-1,3-phenylene]bis(2-methylpropanenitrile) (A=H) [COMPOUND 1] with a brominating agent in the presence of a radical initiator to

form the intermediate 2-[3-bromomethyl-5-(cyano-dimethyl-methyl)-phenyl]-2-methyl-propanenitrile (X=Br) [COMPOUND 2]. Said intermediate, after being isolated and purified, in general by means of crystallization or chromatography, is
5 reacted with 1'-1-2-4-triazole or with its sodium salt to form anastrozole. This approach, described initially by the patent EP0296749, has been taken up and widened in many variations by subsequent patents which all claim different implementation conditions for the initial radical bromination reaction,
10 purification of the intermediate [COMPOUND 2], coupling of the same with the triazole (or a derivative thereof) and, above all, different methods of purifying raw quality anastrozole in order to isolate a finished product with purity grade suitable for pharmaceutical use.

15 Many of the works reported in literature detail the different synthesis methods used and the methods of isolation and purification of anastrozole, by way of example we cite:

- US2007/010048: describes a purification process of the
20 product by passage through silica gel followed by crystallization in water/isopropanol.

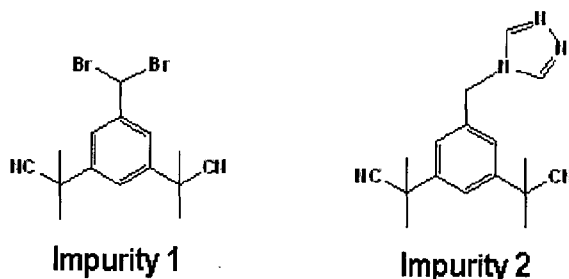
- US2007/028192: describes a purification process of raw anastrozole to pure anastrozole by means of a crystallization/recrystallization sequence in water/alcohol,
25 regulating the pH and the temperature.

- US2006/0035950 and US2009/0286989: describe anastrozole purification methods which eliminate the use of chromatography; from a raw product in solution, by addition of strong acid, an anastrozole salt is isolated which, after
30 being treated with water base, is extracted in organic solvent and then crystallized with high purity.

- US2010/0099887 claims purification conditions of the intermediate [COMPOUND 2] which, after being isolated with a high purity level, is treated with 1,2,4-triazole, a base and
35 a phase transfer catalyst. The product obtained is isolated by crystallization from ethyl acetate/diethyl ether.

The main characteristic common to all the methods of preparation of anastrozole described above is the different approach aimed at removing from the product the unreacted substrates, the by-products and the isomers formed in the general sequence of the two reaction steps.

Two of the main reaction by-products, widely described and reported in literature, are characterised by the following structures:



[IMPURITY 1]: by-product of dibromination of [COMPOUND 1]

[IMPURITY 2]: regioisomer of anastrozole (isoanastrozole)

The procedures described above, which entail either the use of chromatographic techniques or isolation and purification of the [compound 2], or isolation and purification of an anastrozole salt or the use of multiple crystallization/recrystallization sequences, although they are able to guarantee a degree of pharmaceutical purity of the end product, necessarily also involve drawbacks both in terms of applicability in the industrial field and productivity with the inevitable loss of overall yield and lengthening of the process times due to the isolation of an intermediate reaction product.

The need was therefore felt for an anastrozole preparation procedure that was easily applicable on an industrial scale, that reduced the operational complexity thereof, at the same time maximising the final yield and, above all, was able to rapidly guarantee the obtaining of a product with high purity,

compatible with a pharmaceutical use.

DISCLOSURE OF INVENTION

The subject of the present invention is a method for the
5 preparation of anastrozole, the essential characteristics of
which are described in claim 1, and the preferred and/or
auxiliary characteristics of which are described in claims 2-
10.

BEST MODE FOR CARRYING OUT THE INVENTION

For a better understanding of the invention, embodiments are
described below purely by way of non-limiting example.

Example

15 10.0 g of [COMPOUND 1] and 100 ml of tert-butyl acetate are
loaded in a flask. The resulting suspension is kept under
stirring at ambient temperature.

20 8.30 g of N-bromosuccinimide (NBS) followed by 220 mg of
catalyst azobisisobutyronitrile (AIBN) are then added. At this
point, the resulting mixture is heated and kept at a
temperature of 65°-75°C for 2-4 hours.

25 The reaction quenching is performed by lowering first the
temperature of the reaction mixture to 30°-40°C and then
adding 50 ml of a 5% solution of sodium metabisulphite.

30 At this point the organic rich phase is separated from the
water phase and then washed with distilled water.

80 ml of dimethylformamide (DMF) are added to the rich
solution, after the latter has been concentrated in a vacuum.
The solution thus obtained is re-distilled to eliminate the
35 residual t-butylacetate solvent.

4.47 g sodium 1,2,4-triazole are added to the same solution, after the latter has been brought to a temperature of 0°-25°C (preferably 5°-10°C). The reaction mixture thus obtained is kept under stirring for 1-2 hours.

5

The reaction is quenched by the addition of 100 ml toluene and 125 ml distilled water. After separation of the phases, the rich organic phase is treated with a water solution HCl 0.1M.

10 After separation of the phases, 1 g of carbon is added to the resulting organic phase and it is kept under stirring at ambient temperature.

After filtering, the clarified organic phase is extracted 15 twice with 100 ml of HCl 2M. The rich water phase, containing high purity dissolved anastrozole, is lastly back-washed with toluene.

Maintaining a temperature below 15°C, a solution of NaOH at 20 30% by weight is added to the rich acid solution in 60-90 minutes until pH 1 is reached. The mixture is then left in crystallization break at 0°-5°C for 2 hours. A solution of NaOH 0.5 M is then added until a pH of between 2.5 and 3.5 is obtained. The resulting suspension is then left in break at 25 0°-5°C for a further 2 hours. A last quantity of NaOH 0.5 M solution is then added until a final pH of between 5 and 7 is reached, followed by a last break at 0°-5°C.

The product is lastly filtered, washed with distilled water 30 and then dried in a vacuum at a temperature of 50°C.

In this way 6.3-6.6 g of pharmaceutical grade anastrozole are obtained from 10 g of commercial grade ANA-3.

35 In particular, the product has:
anhydrous titre: 99.16% + 101.10%;

KF<0.1%;

total impurities: 0.21% + 0.26%

In conclusion, the method subject of the present invention
5 offers the important advantages of not requiring the use of
purification by column chromatography, which is costly and
difficult to apply on an industrial scale, of not requiring
the step of isolation and purification of the bromoderivative
intermediate or other intermediates, therefore facilitating
10 operation and productivity of the process, of using ester
solvents readily available on the market, with low toxicity
and environmental impact, and lastly of not requiring multiple
processes of crystallization/isolation/recrystallization but
of allowing anastrozole to be obtained for pharmaceutical
15 purposes by means of one single crystallization from purely
water solvent by control of the pH.

CLAIMS

1. A method for preparing anastrozole characterised in that it comprises:

- 5 - a bromination step, in which 2-2' (5-methyl-1,3-phenylene)bis(2-methylpropanenitrile) is subject to a bromination step in the presence of an ester solvent so as to obtain 2-[3-bromoethyl-5-(cyano-dimethyl-methyl)-phenyl]-2-methyl-propanenitrile;
- 10 - a nucleophilic substitution step, in which an organic mixture comprising unreacted 2-2' (5-methyl-1,3-phenylene)bis(2-methylpropanenitrile), the 2-[3-bromoethyl-5-(cyano-dimethyl-methyl)-phenyl]-2-methyl-propanenitrile formed and, if necessary, other reaction by-products is caused to
- 15 react in dimethylformamide with 1-2-4-triazole or with its sodium salt at a temperature ranging from 0 to 25°C for the formation of anastrozole;
- an anastrozole purification step comprising, in sequence, the following sub-steps:
- 20 a) a mixture of an organic solvent immiscible with water and water is added to the solution resulting from the nucleophilic substitution step;
- b) the organic phase is separated from the water phase;
- c) the organic phase is treated with a water solution with a
- 25 pH value ranging from 0.8 to 1.2 and subsequently separated;
- d) the organic phase is treated with a water solution with a pH value lower than or equal to 0 and subsequently the water phase is collected;
- e) the acid water phase resulting from step (d) is subject to
- 30 a crystallization operation by means of a gradual pH variation through the addition of an alkaline solution, at a temperature ranging from 0 to 15°C, until a final PH value ranging from 5 to 7 is reached.

35 2. A method for preparing anastrozole according to claim 1, characterised in that the purification step comprises a sub-

step (c'), which takes place between the sub-step (c) and the sub-step (d) and in which active carbon is added to the organic phase previously separated during sub-step (c) and later removed by means of filtration.

5

3. A method for preparing anastrozole according to claim 1 or 2, characterised in that, during the bromination reaction, the ester solvent is comprised in the group consisting of tert-butyl acetate, isopropyl acetate, isobutyl acetate, ethyl acetate.

10

4. A method for preparing anastrozole according to claim 1, characterised in that said crystallization operation comprises, in sequence, a first alkalinization, in 30+60 minutes, up to a pH value ranging from 0.8 to 1.2, keeping the temperature lower than 15°C; a crystallization break at a temperature ranging from 0 to 5°C for an amount of time ranging from 2 to 3 hours; a second alkalinization, in 15+30 minutes, up to a pH value ranging from 2.5 to 3.5; a crystallization break at a temperature ranging from 0 to 5°C for an amount of time ranging from 1 hour to 2 hours; a third alkalinization, in 5+15 minutes, up to a pH value ranging from 5 to 7; a crystallization break at a temperature ranging from 0 to 5°C for an amount of time ranging from 1 hour to 2 hours.

25

5. A method for preparing anastrozole according to claim 4, characterised in that said first, second and third alkalinization involve the use of a basic solution selected among sodium hydroxide solution, potassium hydroxide solution, lithium hydroxide solution and ammonia solution.

30

6. A method for preparing anastrozole according to claim 5, characterised in that said first alkalinization uses a sodium hydroxide solution at 30% by weight and said second and third alkalinization use a sodium hydroxide solution at 2% by weight.

35

7. A method for preparing anastrozole according to any of the previous claims, characterised in that the nucleophilic substitution reaction takes place at a temperature ranging from 0 to 10°C.

8. A method for preparing anastrozole according to any of the previous claims, characterised in that it comprises a solvent change step, which is interposed between said bromination step and said nucleophilic substitution step and in which the solution resulting from the bromination reaction is subject to at least one extraction with water and subsequently to a distillation for the removal of the ester solvent; the organic mixture comprising unreacted 2-2' (5-methyl-1,3-phenylene)bis(2-methylpropanenitrile), the 2-[3-bromoethyl-5-(cyano-dimethyl-methyl)-phenyl]-2-methyl-propanenitrile formed and other reaction by-products being subsequently dissolved in dimethylformamide.

9. A method for preparing anastrozole according to any of the previous claims, characterised in that, during said sub-step (c) and said sub-step (d), the respective acid solution used is selected among water solution of HCl, water solution of sulphuric acid and water solution of hydrobromic acid.

10. A method for preparing anastrozole according to any of the previous claims, characterised in that, during said anastrozole purification step, a mixture of toluene and water is added to the solution resulting from the nucleophilic substitution reaction.

INTERNATIONAL SEARCH REPORT

International application No PCT/IB2014/061435
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A. CLASSIFICATION OF SUBJECT MATTER INV. C07D249/08 ADD.				
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) C07D				
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) EPO-Internal, WPI Data, CHEM ABS Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
A	US 2006/035950 A1 (ALNABARI MOHAMMED [IL] ET AL) 16 February 2006 (2006-02-16) cited in the application claim 3 -----	1-10		
A	WO 2007/105231 A1 (SHILPA MEDICARE LTD [IN]; VISHNUKANT B; PUROHIT PRASHANT; PAPAARAO K; V) 20 September 2007 (2007-09-20) claim 1 -----	1-10		
A	WO 2007/054963 A2 (CADILA HEALTHCARE LTD [IN]; SOLANKI KIRTIPALSINH SAIJANSIN [IN]; PAL G) 18 May 2007 (2007-05-18) claim 1 -----	1-10		
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
* Special categories of cited documents : <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> "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 </td> </tr> </table>			"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
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Date of the actual completion of the international search	Date of mailing of the international search report			
20 August 2014	02/09/2014			
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/061435

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/010991 A2 (IND SWIFT LAB LTD [IN]; SAXENA RAHUL [IN]; VERMA NARESH KUMAR [IN]; JA) 22 January 2009 (2009-01-22) claim 1 -----	1-10

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Information on patent family members

International application No PCT/IB2014/061435

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