



(51) International Patent Classification:
C07D 249/08 (2006.01)

(21) International Application Number:
PCT/EP2009/004958

(22) International Filing Date:
2 July 2009 (02.07.2009)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): **SYN-
THON B.V.** [NL/NL]; Microweg 22, NL-6545 CM Ni-
jmegen (NL).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **SMRZ, Rudolf**
[CZ/CZ]; Basteckeho 2543/14, CZ-155 00 Praha 5 (CZ).

(74) Agents: **PRINS, Hendrik, Willem** et al.; Bird & Bird
LLP, Van Alkemadelaan 700, 2597 AW The Hague (NL).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

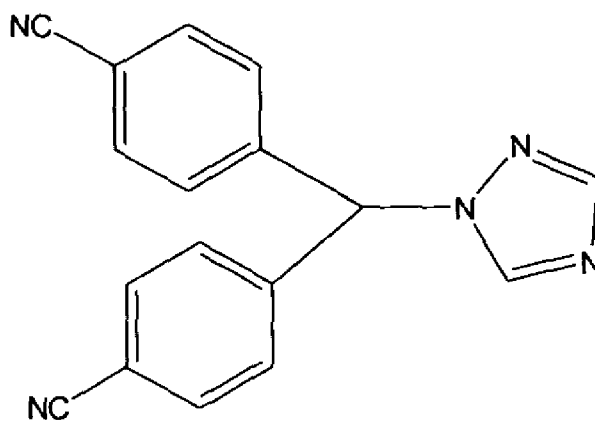
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD,
SE, SG, SK, SL, SM, ST, SV, SY, 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,
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))

(54) Title: PURIFICATION OF LETROZOLE



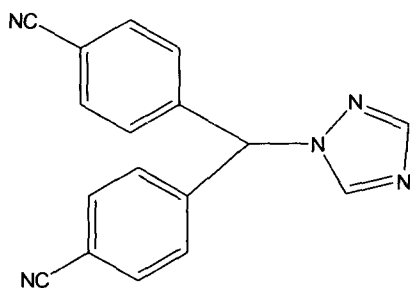
(57) Abstract: The present invention relates to a process for purification of letrozole of the formula (I) which comprises: combin-
ing crude letrozole with an aqueous acid solution to form an acidic solution; and precipitating letrozole base from said acidic solu-
tion, preferably by crystallization.

PURIFICATION OF LETROZOLE

5 [0001] The present invention relates to a process for purifying the compound letrozole, such as to a pharmaceutically acceptable grade of purity.

BACKGROUND OF THE INVENTION

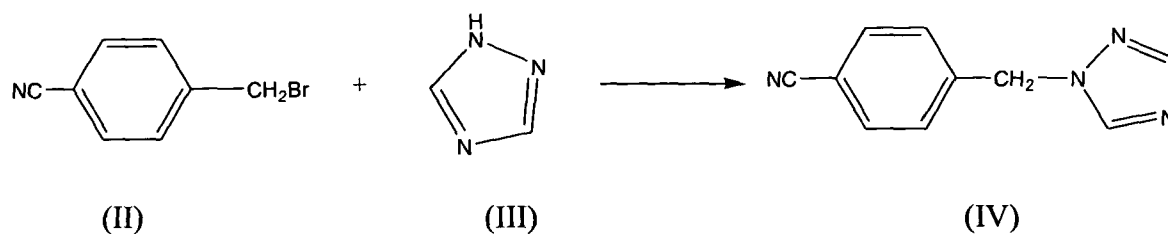
10 [0002] Letrozole, 4,4'-(1H-1,2,4-triazol-1-ylmethylene)-dibenzonitrile of the formula (I)



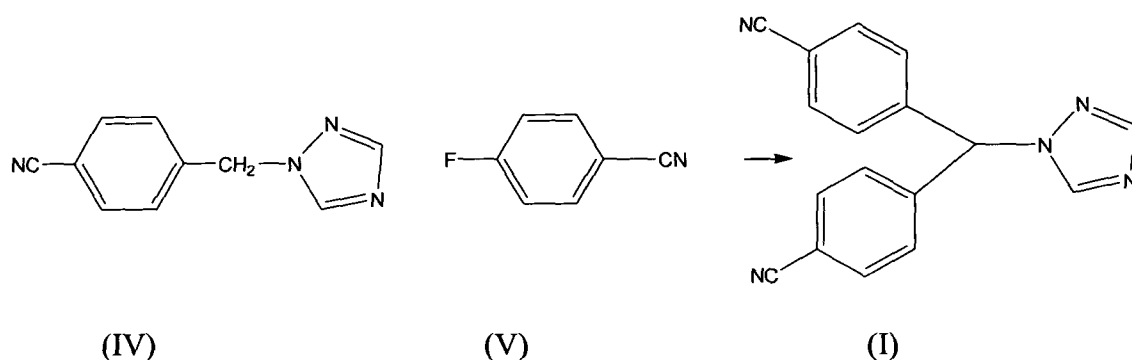
(I)

is a known compound used as a pharmaceutically active substance in the pharmaceutical industry. Letrozole is indicated for, inter alia, treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy. It is a non-steroidal competitive inhibitor of the aromatase enzyme system. Letrozole is marketed under the brand name FEMARA[®] by Novartis Pharmaceuticals as a film coated tablet containing 2.5 mg of letrozole as the free base.

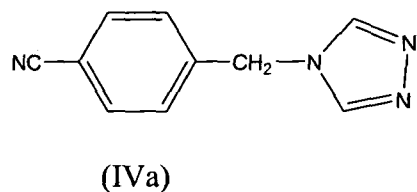
20 [0003] US patent 4,978,672 (EP 236,940) describes the synthesis of letrozole by reacting 4-(bromomethyl)benzonitrile of the formula (II) and 1H-1,2,4-triazole of the formula (III) in a presence of a base to provide 4-[1-(1,2,4-triazolyl)methyl]benzonitrile of the formula (IV),



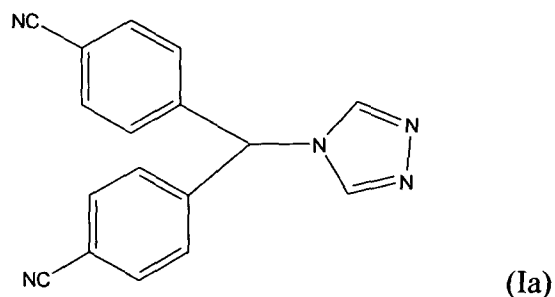
which is then purified by column chromatography and subsequently converted to letrozole of the formula (I) by the reaction with 4-fluorobenzonitrile of the formula (V) in a presence of a strong base.



[0004] According to WO 2004/076409, the purification of the compound (IV) by column chromatography is necessary as the raw product is contaminated with approx. 20 to 40% of the side product of the reaction of (II) and (III), which is 4-[1-(1,3,4-triazolyl)methyl]benzonitrile (IVa).



If not removed, this side product reacts with the compound (V) in the letrozole synthesis pathway to yield 4,4'-(1H-1,3,4-triazol-1-ylmethylene)bisbenzonitrile (Ia),



which is a site isomer of letrozole (and is called hereinunder as isoletrozole), the presence of which in the final product of pharmaceutical grade is undesirable. US Pharmacopoeia monograph restricts the maximum allowable amount of isoletrozole in the letrozole to max. 0.3 %.

5 **[0005]** The presence of isoletrozole in letrozole represents a serious problem and therefore various purification processes were developed. One of the purification possibilities is based on purification of the intermediate compound (IV) with the aim to minimize the content of the compound (IVa) therein, as the compound (IVa) is the source of forming the compound (Ia) in the letrozole product (see, e.g., US appl. 2005/0209294, WO 2005-047269, 10 WO 2007-100346, WO 2007-054964) . The second purification possibility, which the present invention relates to, is based on the purification of the crude letrozole itself. Such purification is conventionally represented by a crystallization from a suitable solvent system.

[0006] So far, any of the prior art publications, e.g. WO 2007/100346 (US 2007-066831), GB 2435283 (US 2007-112202), WO 2004/076409, WO 2007/039912, WO 15 2007/090464, WO 2007/107733, suggest crystallization of crude letrozole from an organic solvent. As the preferred solvents, suggested are dimethylformamide, acetone, methanol, isopropanol, toluene, xylene etc., optionally with an admixture with water.

[0007] It is apparent from the above that obtaining the compound (I) with a low content of its regioisomer (Ia) is a key issue in any process of making pharmaceutical grade 20 letrozole, particularly in the process employing the compound (IV) as the intermediate. The formation of the certain amount of the iso-product (Ia) may never be excluded, particularly in an industrial scale, and purification processes should be readily available. If a purification process is efficient and cheap, then the need to use special reaction conditions and expensive reagents may be avoided.

[0008] While the above purification processes are available for making the compound (I) essentially free from the compound (Ia), there is still a need of an improvement in the matter. In particular, purification processes, which do not employ organic solvents, are desirable from safety, economy and ecology aspects.

5

BRIEF DESCRIPTION OF THE PRESENT INVENTION

[0009] The present invention is based on the discovery that letrozole of the formula (I) can be precipitated from a diluted aqueous acidic solution in a form of a free base and that such precipitation can dramatically increase the purity of the product.

[0010] Accordingly, a first aspect of the invention provides a process for purification of letrozole of the formula (I), comprising combining crude letrozole with an aqueous acid solution, to form an acidic solution and precipitating the letrozole base from the solution, preferably by crystallization.

[0011] The aqueous acid is preferably hydrochloric acid. The aqueous acid solution preferably has a concentration of between 2 to 20 % (w/v).

[0012] In a particular aspect, 1 weight part of letrozole is combined with 2.5- 25 volume parts of the aqueous solution of the acid, preferably the hydrochloric acid.

[0013] In another particular aspect, the relative molar amount of the acid in respect to letrozole is 1.5:1 to 2.5 :1 .

[0014] In another particular aspect, the letrozole comprising acidic solution is formed by heating the mixture of the crude letrozole and the aqueous acid to a temperature of above 30 °C, particularly of between 40 and 80 °C.

[0015] In yet another aspect, letrozole precipitates from the solution at a temperature of below 25 °C, particularly between 0 and 15 °C.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The present invention relates to a process for the purification of letrozole
5 which comprises combining crude letrozole with an aqueous acid solution to form an acidic solution and crystallizing letrozole base from the acidic solution.

[0017] The purification process of the present invention is based on the finding that the letrozole base is not converted into the equivalent amount of the isolateable letrozole salt when placed into an aqueous environment comprising a diluted acid. Instead, although an acid
10 is present, letrozole preferably precipitates from such system as a base. Without wishing to be bound by any theory, it is believed that the acid forms a salt with letrozole allowing for better water solubility, particularly at enhanced temperature, but due to hydrolytic instability of the salt and the severe water insolubility of the base, the equilibrium between the salt and base is so shifted that the base can precipitate instead of the letrozole salt unless a large excess
15 of acid is present. Accordingly, even though the solution may contain letrozole salt (e.g. ionic letrozole), letrozole can be crystallized from the diluted aqueous acidic solutions as the base and not as the corresponding salt as one would expect.

[0018] Surprisingly, the precipitation, preferably by crystallization, of letrozole under these conditions is accompanied with a substantive purification effect. The use of an
20 aqueous acid solution as the solvent system allows for significant purity increase in the letrozole crystallization, especially with respect to the isoletrozole impurity. More than 75% of the original isoletrozole present may be removed within a single precipitation or crystallization. The process allows decreasing not only the content of the isoletrozole but also other impurities arisen from the synthesis, without the use of an organic solvent. As a result, a
25 pharmaceutical grade letrozole, i.e. a product having the content of the title compound of at

least 99.7% and the content of any single structurally related impurity of less than 0.1 %, may be obtained in a simple and reliable process on an industrial scale.

[0019] In essence, the purification process of the present invention is based on a precipitation or crystallization of crude letrozole from a diluted aqueous acid. In particular, no organic solvent is employed in the process, which represents an advantage in terms of safety, economy and ecology. A typical example of the diluted aqueous acid is diluted hydrochloric acid, but it should be understood that hydrochloric acid is only an example of a suitable inorganic or organic acid useful in the inventive process and the invention is by no way limited thereto.

[0020] The “crude letrozole”, i.e. the starting letrozole to be purified, is a letrozole compound of whatever grade of purity obtained by corresponding chemical process. Such processes are well known in the art. Typically, the crude letrozole is the isolated product of the chemical synthesis after necessary removal of the solvents and rests of reagents. It may be in a form of a free base or in a form of an acid addition salt. Typically, it may comprise more than 0.5 % of the isoletrozole impurity and may also comprise various amounts of structurally related impurities arising from the synthesis in the last and/or preceded synthetic steps.

[0021] The crude letrozole is combined with a diluted aqueous acid, advantageously diluted hydrochloric acid. The amount of the acid is so selected that it typically comprises less than 3 molar equivalents, more typically 1.5 to 2.5 molar equivalents, of the acid in respect to letrozole, and that the concentration of the acid is less than 25%, preferably from 2 to 20 %, based on the amount of water present in the system. In terms of volume, the amount of the diluted aqueous acid is typically within the range of 2.5- 25 volume parts per 1 weight part of the crude letrozole to be purified. The order of the combination of components is not particularly important. For instance, water and acid may be combined together to form a

diluted acid and the crude letrozole may be added thereto, or letrozole may be first mixed with water and the acid may be added to the mixture.

[0022] The mixture of crude letrozole and the diluted acid is then heated to dissolution. The temperature of heating is typically above 30 °C, more typically from 35 °C to the reflux temperature, yet more typically between 40 and 80°C. It may happen that a clear solution cannot be obtained even after heating. This may happen, e.g., if water insoluble impurities are present in the starting crude letrozole. If this occurs, it is useful to filter the reaction mixture at enhanced temperature through a suitable filter, optionally after adding a small amount of a surface active material, e.g. activated charcoal, to enhance the speed of the filtration and the purification effect. The surface active material may also remove the colour-forming impurities from the synthesis.

[0023] The obtained solution is cooled to a temperature not exceeding 25°C, preferably within the range of between 0 - 15°C. In accordance with the invented feature, letrozole does not remain in the solution under these conditions as a dissolved letrozole salt (e.g. letrozole hydrochloride), but precipitates as the letrozole base. To facilitate the crystallization, it is sometimes advantageous to seed the reaction mixture by a small amount of crystals of letrozole base and/or to dilute the mixture with water.

[0024] In the last step, the solid product is isolated from the mixture, typically by filtration or centrifugation, and optionally washed and dried.

[0025] The process may provide a product, i.e. letrozole, which generally comprises less than 0.1 % , sometimes less than 0.05%, of the iso-impurity of the formula (Ia). If the desired limit is not reached, it is advantageous to repeat the above purification process until the limit is reached or to combine the above purification process with another type of crystallization.

[0026] In general, the yield of the overall process, calculated on the amount of the starting material, is around 60 to 90%. The purification process does not require any extraction step and no organic solvent. It may be easily performed in multi-kilogram scale on a simple equipment.

5 [0027] The invention is further illustrated by the following example.

Example 1

[0028] 4 g of crude letrozole was suspended at ambient temperature in 40 ml of diluted aqueous hydrochloric acid (12.5 % w/v) and heated under stirring. The product
10 dissolved at 35-40 °C to form a pale yellow solution. The solution was heated to 50 °C, 0.15 g of activated carbon was added thereto and stirred for 15 minutes. Filtered and washed with 5 ml of the 12.5% HCl. The filtrate was cooled to 10 °C and diluted with 40 ml of water . A small amount of seed crystals was added in the time when stable opalescence occurred. The mixture was stirred for 1 hour without heating and allowed to stand overnight at ambient
15 temperature. Filtered , washed with 20 ml of water and dried at ambient temperature. Yield : 3.51 g .

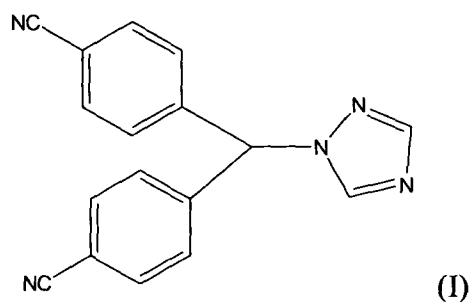
Impurities prior to purification: isoletrozole 0.25 %,

Impurities after the purification : isoletrozole 0.06 %

20 [0029] The invention having been described it will be obvious that the same may be varied in many ways and all such modifications are contemplated as being within the scope of the invention as defined by the following claims.

CLAIMS

- 5 1. A process for purification of letrozole of the formula (I)



which comprises:

- combining crude letrozole with an aqueous acid solution to form an acidic solution; and
 - 10 - precipitating letrozole base from said acidic solution, preferably by crystallization.
2. The process according to claim 1, wherein the acid is hydrochloric acid.
3. The process according to claim 1 or 2, wherein the concentration of the acid is between 2 to 20% (w/v).
- 15 4. The process according to claim 1-3, wherein 1 weight part of letrozole is combined with 2.5- 25 volume parts of the aqueous acid solution.
5. The process according to claim 1-4, wherein the relative molar amount of the acid is from 1.5 to 2.5 molar equivalents in respect to letrozole.

6. The process according to claims 1-5, wherein the letrozole comprising acidic solution is formed by heating the mixture of the crude letrozole and the aqueous acid solution to a temperature of above 30 °C, preferably to a temperature between 40 and 80 °C.

7. The process according to claims 1-6, wherein letrozole precipitates from the
5 solution at a temperature of below 25 °C, preferably between 0 and 15° C

8. The process according to claims 1-7, wherein the letrozole solution is treated with a surface active material, preferably with activated carbon, and filtered prior to the precipitation.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/004958

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D249/08

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 practical, 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.
Y	US 2007/112202 A1 (FRIEDMAN ODED [IL] ET AL) 17 May 2007 (2007-05-17) cited in the application paragraph [0037] - paragraph [0041]; example 6	1-8
Y	WO 2007/134846 A (SYNTHON BV [NL]; PIS JAROSLAV [CZ]; SMRZ RUDOLF [CZ]) 29 November 2007 (2007-11-29) Experimental example 1 on page 17 paragraph [0026]; claims 11,12	1-8

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

☒ 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
- *E* earlier document 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

24 November 2009

Date of mailing of the international search report

09/12/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/004958

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007112202	A1	17-05-2007	NONE
WO 2007134846	A	29-11-2007	AR 061016 A1 30-07-2008
			CN 101568526 A 28-10-2009
			EP 2024343 A2 18-02-2009
			US 2007281982 A1 06-12-2007