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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 January 2009 (22.01.2009)

PCT

(10) International Publication Number
WO 2009/010991 A2

(51) International Patent Classification:
C07D 249/08 (2006.01) *C07C 255/35* (2006.01)

(21) International Application Number:
PCT/IN2008/000455

(22) International Filing Date: 16 July 2008 (16.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1509/DEL/2007 17 July 2007 (17.07.2007) IN

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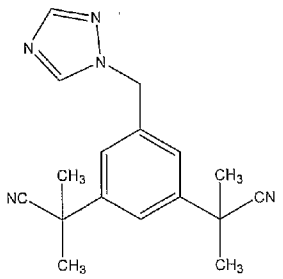
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, 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, 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),

[Continued on next page]

(54) Title: PURIFICATION PROCESS TO PREPARE HIGHLY PURE ANASTROZOLE



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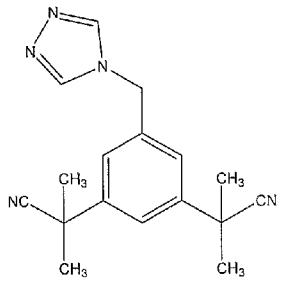

VI

(57) Abstract: The present invention relates to an industrially advantageous method for the purification of anastrozole of Formula (I), wherein isoanastrozole of Formula (VI), present in crude anastrozole as an impurity, is removed by using gel purification.

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European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report*

TITLE OF THE INVENTION

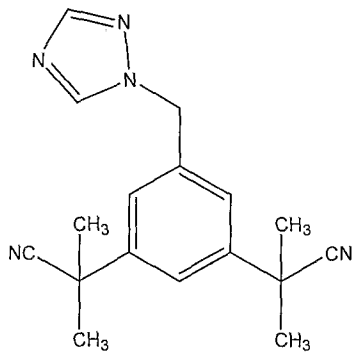
Purification Process to Prepare Highly Pure Anastrozole

FIELD OF THE INVENTION

The field of the invention relates to the preparation of highly pure anastrozole in good yields.

BACKGROUND OF THE INVENTION

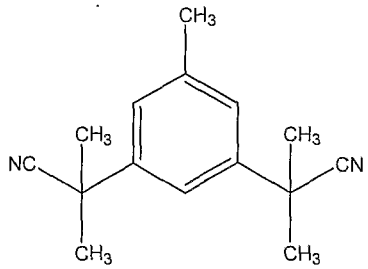
Anastrozole of formula I is a potent and selective non-steroidal inhibitor of the aromatase (oestrogen synthetase) system, which converts adrenal androgens to oestrogens in peripheral tissue.



Formula I

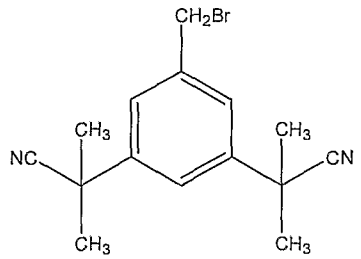
Anastrozole (INN, trade name: Arimidex®) is indicated in the treatment of breast cancer in post-menopausal women. It is used both in adjuvant therapy (i.e. following surgery) and in metastatic breast cancer. It has the effect of decreasing the amount of estrogen that the body makes and is chemically known as α,α,α,α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-benzenedi acetonitrile.

Anastrozole is first disclosed in US 4,935,437 and mainly two routes have been discussed to prepare anastrozole. According to first route, the process comprises bromination of compound of formula II namely 2,2'-(5-methyl-1,3-phenylene)-di-(2-methyl propionitrile)



Formula II

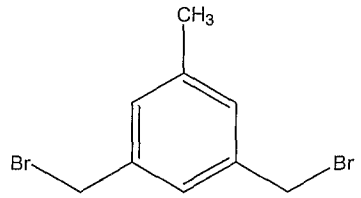
in carbon tetrachloride using *N*-bromosuccinimide in the presence of catalyst benzoyl peroxide to prepare bromomethyl derivative of formula III.



Formula III

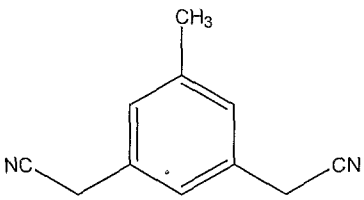
The bromomethyl derivative is further condensed with 1,2,4- triazole sodium in dimethylformamide to get crude anastrozole. The crude anastrozole is purified by flash column chromatography and further crystallized in ethyl acetate/cyclohexane to get pure anastrozole.

The compound of formula II is prepared by treating 3,5-bis(bromomethyl) toluene of formula IV



Formula IV

with potassium cyanide in dichloromethane and in presence of tetrabutylammonium bromide to get diacetonitrile derivative of formula V.

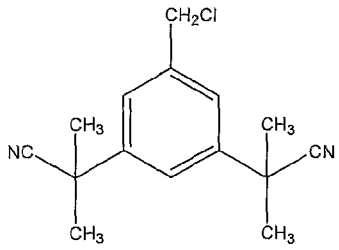


Formula V

The diacetonitrile derivative is purified by flash column chromatography and crystallized in carbon tetrachloride to get pure 2,2'-(5-methyl-1,3-phenylene) diacetonitrile.

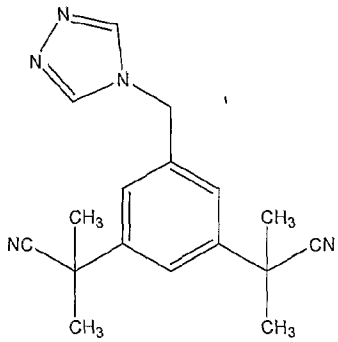
The compound of formula V is further methylated with methyl iodide in dimethylformamide and in presence of strong base such as sodium hydride and finally crystallized in carbon tetrachloride to get compound of formula II.

Furthermore, second route comprises reacting chloromethyl derivative of formula IIIa



Formula IIIa

with 1,2,4- triazole sodium in acetonitrile thereafter solvent is removed and the resulting residue is partitioned between ethyl acetate and aqueous potassium hydrogen carbonate. The organic phase is separated and dried to get a mixture of anastrozole and its isomer, i.e. isoanastrozole of formula VI.



Formula VI

The isomeric mixture is separated by flash column chromatography to get pure anastrozole.

US patent application 2006/0035950 discloses a process for the preparation of pure anastrozole by reacting bromomethyl derivative of formula III with sodium triazole under basic conditions and the resulting crude anastrozole is purified via anastrozole acid addition salt such as hydrochloride or hydrobromide salt. Generally crude anastrozole in toluene is treated with aqueous acidic solution of sodium sulfate and sulfuric acid, resulting phases are separated. The organic phase is treated with gaseous hydrochloric acid to crystallize anastrozole hydrochloride. Crystalline salt of anastrozole hydrochloride is further treated with sodium carbonate solution to get free base of anastrozole and crystallized in hydrophobic solvent such as cyclohexane to get purified anastrozole.

US patent application 2006/0276657 discloses preparation of anastrozole by treating bromomethyl derivative of formula III with 1,2,4- triazole sodium in dimethylformamide and in presence of

suitable base and resulting crude anastrozole is purified by selective extraction using mixture of solvents such as toluene, linear, branched or cyclic C_{5-8} hydrocarbon, water, *N*-methylpyrrolidine and C_{1-3} alcohol mixed with water. Particularly the quenched reaction mixture is selectively extracted and re-extracted with toluene, heptane and water followed by washing of organic layer with methanol and water. Thereafter heptane is added to organic layer to precipitate anastrozole which is isolated by filtration. It is further recrystallized in isopropyl alcohol and heptane to get pure anastrozole.

PCT publication WO 2005/105762 discloses the purification of crude anastrozole through anastrozole acid addition salt formation such as hydrochloride, fumarate and oxalate. Specifically crude anastrozole is treated with corresponding acid in acetone to get anastrozole acid salt which is recrystallized from acetone. The purified anastrozole acid salt is neutralized to anastrozole by using base such as potassium hydroxide, bicarbonate or carbonate in water and the resulting anastrozole is further recrystallized using solvent such as ethyl acetate, hexane, heptane, toluene, aqueous solvents such as methanol, ethanol, isopropanol, acetonitrile, acetone, tetrahydrofuran, dimethylformamide, dioxane or a combination thereof.

WO 2007/039913 publication discloses preparation of anastrozole wherein crude anastrozole is purified by column chromatography followed by recrystallization with a solvent preferably in ethyl acetate and hexane or acetone and water.

Recently a US patent application 2007/0100148 has published which discloses two processes for the purification of anastrozole. First process comprises crystallization of the anastrozole using isopropanol and water and in second process anastrozole is purified by column chromatography using ethylacetate as an eluting agent.

In view of the above, it has turned out that it is difficult to manufacture anastrozole in the required quality by following simple crystallization. The known processes comprise reaction of bromo derivative of formula III with 1,2,4 triazole or its salt as described above have been found to give isoanastrozole isomer of formula VI in unacceptable amounts. This impurity along with other impurities is difficult to remove by usual working up procedures leading to extensive and expensive purification processes. Most of the processes disclose the purification of anastrozole to remove unwanted isoanastrozole impurity of formula VI using column chromatography and

crystallization or by selective extraction using large volumes of solvent. The use of column chromatography at commercial scale is tedious, cumbersome and time consuming, therefore there is an urgent need to develop a simple and efficient process to purify anastrozole which can be easily implemented on commercial scale.

It is an object of the present invention to devise a simple and commercially attractive process to remove isomer impurity and prepare highly pure anastrozole.

SUMMARY OF THE INVENTION

Accordingly, in one embodiment, the present invention provides a process to prepare highly pure anastrozole, comprising the steps of:

a) preparing a solution of crude anastrozole in a non polar solvent,
b) adding silica gel in to the solution,
c) stirring the reaction mixture for 30 to 60minutes,
d) filtering the solution,
e) concentrating the filtrate,
f) recrystallizing the residue in a suitable organic solvent or mixtures thereof,
g) optionally repeating steps a to f, and
h) isolating pure anastrozole.

In yet another embodiment, the present invention provides a process for preparing highly pure anastrozole comprising the steps of:

a) condensing 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) of formula III with alkali metal salt of 1,2,4 triazole in a polar aprotic solvent at -5 to -10°C,
b) quenching the reaction mixture with demineralized water and stirred,
c) isolating the crude anastrozole,
d) preparing a solution of crude anastrozole in a non polar solvent,
e) adding silica gel in to the solution,
f) stirring the reaction mixture for 30 to 60minutes,
g) filtering the solution,
h) concentrating the filtrate,
i) recrystallizing the residue in a suitable organic solvent or mixtures thereof,

j) optionally repeating steps d to i, and

k) isolating pure anastrozole.

DETAILED DESCRIPTION OF THE INVENTION

In one preferred embodiment, the present invention relates to a process for purifying anastrozole wherein, the removal of isomeric products such as isoanastrozole of formula VI and other impurities are minimized by treatment of crude anastrozole using gel purification and optionally recrystallizing anastrozole in an organic solvent or mixtures thereof.

In one embodiment, the present invention provides a process for preparing highly pure anastrozole by treating crude anastrozole with silica gel in non polar solvent such as toluene, hexane, heptane, xylene or mixtures thereof and preferably toluene is used. The solution can be further stirred at 0 to 80°C and more preferably at 25 to 45°C to get clear solution. To this clear solution silica gel (100-200mesh) is added and stirred for 5-120minutes at 25 to 45°C more preferably for 30-60minutes at 30 to 35°C followed by removing the silica gel by suitable technique such as filtration.
Toluene is evaporated from the filtrate under vacuum to get solid residue, which is then heated in diisopropyl ether for 1-3hours preferably for 2hours and thereafter product is isolated by filteration. Optionally the resulting product is recrystallized in suitable organic solvent or mixtures thereof to get highly pure anastrozole.
The organic solvent can be selected from alcohols such as ethanol, methanol, n-propanol, isopropanol, or mixtures thereof; ketones such as acetone, methyl isobutyl ketone, methylethylketone, or mixtures thereof; ethers such as diisopropyl ether, isopropyl ether or mixtures thereof; esters such as ethyl acetate; aliphatic or aromatic hydrocarbon solvents such as toluene, xylene or mixtures thereof or cyclic hydrocarbons such as cyclohexane or halogenated solvents such as methylene chloride or mixtures thereof or preferably the solvent is ethanol or cyclohexane and ethylacetate.

Anastrozole obtained by the described purification process may have a purity of at least 99.7% area by HPLC, more preferably, of at least 99.8%, and even more preferably, of at least 99.94% area by HPLC. Anastrazole obtained by the described purification process may contain at least one of the following impurities: not more than 0.15%, preferably not more than about 0.05% area by HPLC of

isoanastrazole, not more than about 0.05% area by HPLC of 2,2'-(5-methyl-1,3-phenylene)-di-(2-methyl propionitrile) of formula II.

In yet another embodiment, the present invention provides a process for preparing highly pure anastrozole of formula I by condensing 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) of formula III with alkali metal salt of 1,2,4-triazole in a polar aprotic solvent at 10 to -25°C, more preferably at 0 to -15°C and most preferably at -5 to -10°C.

The alkali metal salts of 1,2,4-triazole can be selected from 1,2,4- triazole sodium, 1,2,4- triazole potassium, and the like.

The polar aprotic solvent can be selected from tetrahydrofuran, acetone, acetonitrile, dimethylformamide, dimethylsulfoxide or mixtures thereof. More preferably the solvent is dimethylformamide, dimethylsulfoxide or mixtures thereof and most preferably the solvent is dimethylformamide.

Particularly, the condensation is carried out by suspending 1,2,4- triazole sodium in dimethylformamide followed by addition of a solution of 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) in dimethylformamide. The resulting reaction mixture is maintained at a temperature of 10 to -25°C for 2-3hrs hrs and more preferably at -5 to -10°C for 1hr.

After completion of the reaction, the reaction mixture is quenched with demineralized water and finally stirred for 3-4 hrs at 10-15°C, preferably for 2-3hrs. The progress of reaction is monitored by thin layer chromatography (TLC) or by high pressure liquid chromatography (HPLC). The amount of starting material should be less than 0.5% w/v by HPLC. The precipitated crude anastrozole is isolated by filtration followed by washing with water.

The resulting anastrozole is analysed by high performance liquid chromatography and two major impurities along with other unknown impurities have been detected in the analysis. The two major impurities are isoanastrozole of formula VI which is present in 1-10% area by HPLC and 2,2'-(5-methyl-1,3-phenylene)-di-(2-methyl propionitrile) of formula II which is present in 0.3-10% area by HPLC.

Hence, anastrozole is purified to remove these impurities along with some unknown impurities to get the desired purity of anastrozole which should comply with the regulatory agencies.

Particularly, the crude anastrozole is dissolved in non polar solvent such as toluene, hexane, heptane, xylene or mixtures thereof and more preferably toluene is used. The solution can be further stirred at 0 to 80°C and more preferably at 25 to 45°C to get clear solution. To this clear

solution silica gel is added and reaction mixture is stirred for sufficient time so that impurities can get adsorbed on silica gel. Specifically the reaction mixture is stirred for 5-120minutes at 25 to 45°C and more preferably for 30-60 minutes at 30 to 35 °C. Thereafter silica gel is removed by suitable technique such as filtration. The solvent is evaporated under vacuum to get solid residue which is then heated in diisopropyl ether for 1-3hours preferably for 2hours and thereafter product is isolated by filtration.

Optionally the resulting product is recrystallized in a suitable organic solvent or mixtures thereof to get highly pure anastrozole.

The organic solvent can be selected from alcohols such as ethanol, methanol, n-propanol, isopropanol, or mixtures thereof; ketones such as acetone, methyl isobutyl ketone, methylethylketone, or mixtures thereof; ethers such as diisopropyl ether, isopropyl ether or mixtures thereof; esters such as ethyl acetate; aliphatic or aromatic hydrocarbon solvents such as toluene, xylene or mixtures thereof or cyclic hydrocarbons such as cyclohexane or halogenated solvents such as methylene chloride or mixtures thereof or preferably the solvent is ethanol or cyclohexane and ethyl acetate.

The silica gel used for purification can have particle size range from 60-400mesh, 240 400 mesh, 100-200 mesh, or 60-120 mesh etc. The ratio of crude anastrozole to silica gel can be 1:0.1 to 1:20, more preferably 1:0.4 to 1:3 and most preferably the ratio of crude anastrozole to silica gel is about 1:0.5 to 1:1.

Anastrozole obtained by the described purification process may have a purity of at least 99.7% area by HPLC, more preferably, of at least 99.8%, and even more preferably, of at least 99.94% area by HPLC. Anastrazole obtained by the described purification process may contain at least one of the following impurities: not more than 0.15%, preferably not more than about 0.05% area by HPLC of isoanastrazole, not more than about 0.05% area by HPLC of 2,2'-(5-methyl-1,3-phenylene)-di-(2-methyl propionitrile) of formula II.

In preferred embodiment of the present invention, the treatment of crude anastrozole with silica gel is not limited for single use but the crude product can be treated with silica gel for more than once if the desired purity of the anastrozole is not attained. Generally, the treatment of crude anastrozole with silica gel is repeated two times to get the highly pure anastrozole.

Purity data as given above have proved that the use of silica gel for the purification of crude anastrozole is very efficient to remove major impurity of anastrozole i.e. isoanastrozole. Further, the process does not employ tedious column chromatography to purify the crude anastrozole. The

process is cost effective, industrially feasible, simple and easy to carry out and furthermore time consumption is less.

The process of the invention is illustrated by the following examples, which is by way of illustration only and not to be considered to limit the scope of the invention in any manner.

EXAMPLES

Example 1

Preparation of Anastrozole

To a cooled suspension of 1,2,4- triazole sodium (7.5 g; 0.0824 moles) in *N,N* -dimethylformamide (40 ml), a solution of 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) (10.0 g; 0.033 moles) in *N,N*-dimethylformamide (25 ml) was added.. The reaction mixture was stirred at -5 to -10°C for 45 minutes then quenched with demineralized water (260 ml) and thereafter stirred for 2 hours at 10-15°C. The precipitated product was filtered, washed with water and dried to get the title compound. The HPLC purity was as follows:

anastrozole: 89.35%;

isoanastrozole: 7.14%;

2,2'-(5-methyl-1,3-phenylene)-di-(2-methyl propionitrile) of formula II : 0.54%.

Example 2

Purification of Anastrozole

To a clear solution of crude product (4.0 g) in toluene (30 ml), silica gel (100-200 mesh, 2.5 g) was added and stirred for 30 minutes. Thereafter silica gel was filtered off and toluene was evaporated to get residue. The resulting residue was further taken in diisopropylether (100 ml) and refluxed, thereafter stirred at 30-35°C for 2 hours. The reaction mixture was filtered to get crystalline residue. The HPLC purity was as follows: anastrozole : 93.44%; isoanastrozole : 4.28%; Compound of formula II : 0.50%. Yield: 2.0 g

To a clear solution of crystalline residue (2.0 g) in toluene (20 ml), silica gel (100-200 mesh, 1.0 g) was added, stirred for 30 minutes and filtered to remove silica gel. From the resulting filtrate toluene was evaporated to get solid residue. Solid residue was further dissolved in ethanol (3.6 ml) and stirred to get a clear solution. The reaction mixture was cooled and filtered to get the crystalline anastrozole. Yield: 1.0 g. The HPLC purity was as follows:

anastrozole: 99.93%;

isoanastrozole: 0.02%;

Compound of formula II: Not detected.

Example 3

Preparation of Anastrozole

To a cooled suspension of 1,2,4-triazole sodium (90.0g; 0.988 moles) in *N,N*-dimethylformamide (480 ml), a solution of 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) (120 g; 0.394 moles) in *N,N*-dimethylformamide (300ml) was added. The reaction mixture was stirred at -5 to -10°C for 45 minutes then quenched with demineralized water (3.1L) and stirred for 3 to 4 hours at 10-15°C. The precipitated solid product, thus obtained, was filtered, washed with water and dried to get the title compound (78g). The HPLC purity was as follows:

anastrozole: 83.28%; isoanastrozole : 1.85%;

Compound of formula II: 7.8%.

Example 4

Purification of Anastrozole

To a clear solution of crude anastrozole (78 g) obtained from example 3 in toluene(720 ml), silica gel (100-200 mesh, 36 g) was added and stirred for 30 minutes. Silica gel was filtered off and the filtrate was evaporated under reduced pressure to get solid residue. The solid residue was refluxed with diisopropyl ether then reaction mixture was cooled down to 30-35°C and further stirred for 2.5 hours. The reaction mixture was filtered to get crystalline residue. The HPLC purity was as follows:- anastrozole : 96.56%; isoanastrozole : 1.2%; Compound of formula II : 0.06%. Yield: 56.0g.

To a clear solution of crystalline residue (56 g) in toluene (560 ml), silica gel (100-200 mesh, 17.0g) was added and the reaction mass was stirred for 30 minutes. Silica gel was filtered out and toluene was removed by evaporation under reduced pressure. The resulting residue was dissolved in ethanol (100 ml) and stirred to get clear solution, which was cooled to 0-5°C and filtered to get crystals of pure anastrozole. Yield: 27.0 g

The HPLC purity was as follows:

anastrozole: 99.97%;

isoanastrozole: 0.01%;

Compound of formula II: Not detected.

Example 5

Preparation of Anastrozole

To a cooled suspension of 1,2,4-triazole sodium (88.5g; 0.972 moles) in *N,N*-dimethylformamide (472 ml), a solution of 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) (118 g; 0.387 moles) in *N,N*-dimethylformamide (295ml) was added. The reaction mixture was stirred at -5 to -10°C for 45 minutes then quenched with demineralized water (3.0L) and stirred for 2 hours at 10-15°C.

The precipitated solid product, thus obtained, was filtered, washed with water and dried to get the title compound (74.4 g). The HPLC purity was as follows: anastrozole: 84.35%; isoanastrozole: 1.38%; Compound of formula II: 8.66%.

Example 6

Purification of Anastrozole

To a clear solution of crude anastrozole (74.4 g) obtained from example 5 in toluene (687ml) ,silica gel (100-200 mesh, 34.3 g) was added and stirred for 30 minutes. Silica gel was filtered off and the filtrate was evaporated under reduced pressure to get solid residue. Solid residue was further refluxed with diisopropyl ether, thereafter cooled down to 30-35°C and stirred for 2.0 hours. The reaction mixture was filtered to get crystalline product. The HPLC purity was as follows: anastrozole: 96.5%; isoanastrozole : 1.2%; Compound of formula II : 0.06%. Yield: 45.0g.

To a clear solution of crystalline product (45g) in toluene (450 ml), silica gel (100-200 mesh ,13.5 g) was added and the reaction mass was stirred for 30 minutes. Silica gel was filtered off and toluene was removed by evaporation under reduced pressure. The resulting residue was further dissolved in ethanol (80.0 ml) and stirred to get clear solution. The reaction mixture was cooled to 0-5°C and filtered to get pure anastrozole. The HPLC purity was as follows: anastrozole: 99.86%; isoanastrozole: 0.02%; Compound of formula II: 0.01%. Yield: 25.5g.

Example 7

Preparation of Anastrozole

To a cooled suspension of 1,2,4-triazole sodium (89.17g; 0.979 moles) in N,N-dimethylformamide (298.0 ml), a solution of 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) (118.9 g; 0.389 moles) in N,N-dimethylformamide (298ml) was added. The reaction mixture was stirred at -5 to -10°C for 45 minutes then quenched with demineralized water (3.1L) and stirred for 2 hours at 10-15°C.

The precipitated solid product, thus obtained, was filtered, washed with water and dried to get the title compound (83.3 g). The HPLC purity was as follows: anastrozole: 79.34%; isoanastrozole: 4.7%; Compound of formula II: 6.78%.

Example 8

Purification of Anastrozole

To a clear solution of crude anastrozole (83.3g) obtained from example 7 in toluene (714 ml), silica gel (100-200 mesh, 35.7 g) was added and stirred for 30 minutes. Silica gel was filtered off and the filtrate was evaporated under reduced pressure to get solid residue. The solid residue was further refluxed with diisopropyl ether thereafter cooled down to 30-35°C and stirred for 2.0 hours. The reaction mixture was filtered to get crystalline product. The HPLC purity was as follows: anastrozole: 88.62%; isoanastrozole: 4.39%; Compound of formula II : 0.75%. Yield: 39.23g.

To a clear solution of crystalline product (39.23 g) in toluene (400 ml), silica gel (100-200 mesh,12.0g) was added and the reaction mass was stirred for 30 minutes. Silica gel was filtered out and toluene was removed by evaporation under reduced pressure. The resulting residue was further dissolved in ethanol (72 ml) and stirred to get clear solution. The reaction mixture was cooled to 0-5°C and filtered to get pure anastrozole. The HPLC purity was as follows: anastrozole: 99.82%; isoanastrozole: 0.04 %; Compound of formula II: Not detected. Yield: 24.5g.

Example 9

Preparation of Anastrozole

To a cooled suspension of 1,2,4-triazole sodium (15.9g; 0.175moles) in *N,N*-dimethylformamide (53.0 ml), a solution of 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) (20 g; 0.065 moles) in *N,N*-dimethylformamide (50ml) was added. The reaction mixture was stirred at -5 to -10°C for 45 minutes then quenched with demineralized water (520 ml) and stirred for 2 hours at 10-15°C.

The precipitated solid product, thus obtained, was filtered, washed with water and dried to get the title compound (16.0 g). HPLC purity was as follows:

anastrozole: 87.34%;

isoanastrozole: 3.23%;

Compound of formula II: 7.83%.

Example 10

Purification of Anastrozole

To a clear solution of crude anastrozole (16g) obtained from example 9 in toluene(60ml) ,silica gel (100-200 mesh, 5.0 g) was added and stirred for 30 minutes. Silica gel was filtered off and the filtrate was evaporated under reduced pressure to get solid residue. The solid residue was further refluxed with diisopropyl ether thereafter cooled down to 30-35°C and stirred for 2.0 hours. The solution was filtered to get crystalline residue (7.0g).

To a clear solution of crystalline residue (7.0g) in toluene (40 ml), silica gel (100-200 mesh ,2.0 g) was added and the reaction mass was stirred for 30 minutes. Silica gel was filtered out and toluene was removed by evaporation under reduced pressure.

The resulting residue was further dissolved in ethyl acetate (7.0 ml) at 40-45°C and stirred to get clear solution. To this clear solution cyclohexane (14ml) was added at 40-45°C then cooled down to 20-25°C and further stirred for 2.0 hours. The reaction mixture was further cooled to 5-10°C and stirred for 2.0 hours then filtered to get pure anastrozole. Yield: 4.0g. HPLC purity was as follows: anastrozole: 99.94%; isoanastrozole: 0.01%; Compound of formula II: Not detected.

Example 11

Preparation of Anastrozole

To a cooled suspension of 1,2,4-triazole sodium (96g; 1.05moles) in *N,N*-dimethylformamide (512 ml), a solution of 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) (128 g; 0.42 moles) in *N,N*-dimethylformamide (320ml) was added. The reaction mixture was stirred at -5 to -10°C for 45 minutes then quenched with demineralized water (3.3L) and stirred for 2 hours at 10-15°C.

The precipitated solid product, thus obtained, was filtered, washed with water and dried to get the title compound (94.0g). The HPLC purity was as follows: anastrozole: 89.06%; isoanastrozole: 1.99%; Compound of formula II: 7.78%.

Example 12

Purification of Anastrozole

To a clear solution of crude anastrozole (94.0g) obtained from example 11 in toluene (564ml), silica gel (100-200 mesh, 28.2 g) was added and stirred for 30 minutes. Silica gel was filtered off and the filtrate was evaporated under reduced pressure to get solid residue. The solid residue was further refluxed with diisopropyl ether thereafter cooled down to 30-35°C and stirred for 2.0 hours.

The solution was filtered to get crystalline residue (60.0g). The HPLC purity was as follows: anastrozole: 98.06%; isoanastrozole: 1.33%; Compound of formula II : 0.56%.

To a clear solution of crystalline residue (60.0g) in toluene (600ml) silica gel (100-200 mesh, 18.0g) was added and the reaction mass was stirred for 30 minutes. Silica gel was filtered off and toluene was removed by evaporation under reduced pressure. The resulting residue is further dissolved in ethanol (120ml) and stirred to get a clear solution. The solution was cooled down to 0 to 5°C and filtered to get crystalline anastrozole (36g). The HPLC purity was as follows: anastrozole: 99.02%; isoanastrozole: 0.44%; Compound of formula II : 0.24%.

To a clear solution of crystalline anastrozole (36g) in toluene (360ml), silica gel (100- 200 mesh, 10.8g) was added and the reaction mass was stirred for 30 minutes. Silica gel was filtered off and the filtrate was evaporated under reduced pressure. The resulting residue is recrystallized in ethanol (72 ml) to get highly pure anastrozole. Yield: 23.4g. HPLC purity was as follows:

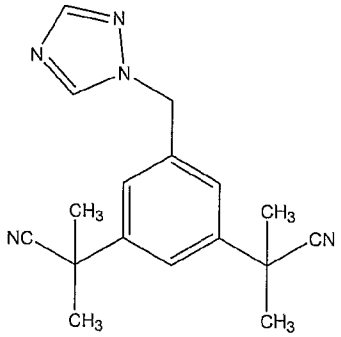
anastrozole: 99.76%;

isoanastrozole: 0.11%;

Compound of formula II: Not detected.

WE CLAIM

1) A process to prepare highly pure anastrozole of formula I,



Formula I

comprising the steps of:

a) preparing a solution of crude anastrozole in a non polar solvent,

b) adding silica gel in to the solution,

c) stirring the reaction mixture for 5 to 120 minutes,

d) filtering the solution,

e) concentrating the filtrate,

f) recrystallizing the residue in a suitable organic solvent or mixtures thereof,

g) optionally repeating steps a to f, and

h) isolating pure anastrozole.

2) The process according to claim 1, wherein in step a), non polar solvent is selected from toluene, hexane, heptane, xylene or mixtures thereof.

3) The process according to claim 1, wherein in step a), non polar solvent is selected from toluene.

4) The process according to claim 1, wherein in step b), silica gel is used in ratio of 1:0.1 to 1:20, more preferably 1:0.4 to 1:2 and most preferably 1:0.5 to 1:1.

5) The process according to claim 1, wherein in step c), reaction mixture is stirred preferably for 30 minutes.

6) The process according to claim 1, wherein in step f), suitable organic solvent is selected from alcohols ; ketones; ethers; esters; aliphatic or aromatic hydrocarbon solvents or cyclic hydrocarbons or halogenated solvents.

7) The process according to claim 1, wherein in step f), alcohols include ethanol, methanol, n-propanol, isopropanol, or mixtures thereof.

8) The process according to claim 1, wherein in step f), ketones include acetone, methyl isobutyl ketone, methylethylketone, or mixtures thereof.

9) The process according to claim 1, wherein in step f), ethers include diisopropyl ether, isopropyl ether or mixtures thereof.

10) The process according to claim 1, wherein in step f), esters include ethyl acetate.

11) The process according to claim 1, wherein in step f), aromatic hydrocarbon solvents include toluene, xylene or mixtures thereof.

12) The process according to claim 1, wherein in step f), cyclic hydrocarbons include cyclohexane.

13) The process according to claim 1, wherein in step f), halogenated solvents include methylene chloride.

14) The process according to claim 1, wherein in step f), suitable organic solvent is selected from ethanol or a mixture of cyclohexane and ethyl acetate.

15) A process for preparing highly pure anastrozole comprising the steps of:

a) condensing 2,2'-(5-bromomethyl-1,3-phenylene)-di-(2-methyl propionitrile) of formula III with alkali metal salt of 1,2,4 triazole in a polar aprotic solvent at -25 to 10°C,

b) quenching the reaction mixture with demineralized water and stirred,

c) isolating the crude anastrozole,

d) preparing a solution of crude anastrozole in a non polar solvent,

e) adding silica gel in to the solution,

f) stirring the reaction mixture for 20 to 120minutes,

g) filtering the solution,

h) concentrating the filtrate,

i) recrystallizing the residue in a suitable organic solvent or mixtures thereof,

j) optionally repeating steps d to i, and

k) isolating pure anastrozole.

16) The process according to claim 15, wherein in step a), polar aprotic solvent is selected from tetrahydrofuran, acetone, acetonitrile, dimethylformamide, dimethylsulfoxide or mixtures thereof.

17) The process according to claim 15, wherein in step a), polar aprotic solvent is selected from dimethylformamide.

18) The process according to claim 15, wherein in step d), non polar solvent is selected from toluene, hexane, heptane, xylene or mixtures thereof.

19) The process according to claim 15, wherein in step d), non polar solvent is selected from toluene.

20) The process according to claim 15, wherein in step e), silica gel is used in ratio of 1:0.1 to 1:20, more preferably 1:0.4 to 1:2 and most preferably 1:0.5 to 1:1.

21) The process according to claim 15, wherein in step f), the stirring is preferably carried out for 30-60 minutes.

22) The process according to claim 15, wherein in step i), suitable organic solvent is selected from suitable organic solvent is selected from alcohols; ketones; ethers; esters; aliphatic or aromatic hydrocarbon solvents or cyclic hydrocarbons or halogenated solvents.

23) The process according to claim 15, wherein in step i), alcohols include ethanol, methanol, n-propanol, isopropanol, or mixtures thereof

24) The process according to claim 15, wherein in step i), ketones include acetone, methyl isobutyl ketone, methylethylketone, or mixtures thereof.

25) The process according to claim 15, wherein in step i), ethers include diisopropyl ether, isopropyl ether or mixtures thereof

26) The process according to claim 15, wherein in step i), esters include ethyl acetate.

27) The process according to claim 15, wherein in step i), aromatic hydrocarbon solvents include toluene, xylene or mixtures thereof.

28) The process according to claim 15, wherein in step i), cyclic hydrocarbons include cyclohexane.

29) The process according to claim 15, wherein in step i), halogenated solvents include methylene chloride.

30) The process according to claim 15, wherein step i), suitable organic solvent is selected from ethanol or a mixture of cyclohexane and ethyl acetate.