Title: REGIOSELECTIVE SYNTHESIS OF LETROZOLE

Abstract: The present invention relates to an improved process for the preparation of letrozole (I) and its pharmaceutically acceptable salts, to compositions comprising letrozole or a pharmaceutically acceptable salt thereof, and to uses of such compositions. In particular it relates to a process and to novel intermediates for preparing letrozole and its salts substantially free from regioisomeric impurities.
REGIOSELECTIVE SYNTHESIS OF LETROZOLE

Field of the invention

The present invention relates to an improved process for the preparation of letrozole (I) and its pharmaceutically acceptable salts, to compositions comprising letrozole or a pharmaceutically acceptable salt thereof, and to uses of such compositions. In particular, it relates to a process and to novel intermediates for preparing letrozole and its salts substantially free from regioisomeric impurities.

Background of the invention

Letrozole (I), chemically named as 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile, is one of a new class of drugs, known as aromatase inhibitors, which function by reducing body levels of oestrogen in postmenopausal women. Many breast cancers increase in size by utilising the hormone oestrogen. In women who have undergone menopause, the main source of oestrogen is through changing androgens (sex hormones produced by the adrenal glands) into oestrogen, which is catalysed by an enzyme called aromatase. The conversion process is known as aromatisation and happens mainly in the fatty tissues of the body. Letrozole blocks this aromatisation process and reduces the amount of oestrogen in the body and, consequently, letrozole is marketed as a type of hormonal therapy that is used in the treatment of breast cancer in women who have undergone menopause.
Letrozole and processes to prepare it were first described in patent US 4,978,672. The synthesis of letrozole proceeded via treatment of intermediate 4-[(1,2,4-triazol-1-yl)methyl]benzonitrile (III) with 4-fluorobenzonitrile (IV) in the presence of a catalyst, potassium tert-butoxide. The preparation of intermediate (III) was achieved by reaction of α-bromotolunitrile with 1,2,4-triazole in a mixture of chloroform and acetonitrile at reflux, followed by the purification of the product (III) by column chromatography. It was found that during the preparation of intermediate (III), an undesired regioisomer, namely 4-[(1,3,4-triazol-1-yl)methyl]benzonitrile (V), was formed in about 20-25% yield. Consequently, this leads to an uneconomical loss of yield and to a difficult and inconvenient purification of intermediate (III), which was required to remove the regioisomeric impurity (V). In addition, complete purification was not possible and the impurity (V) was carried through the synthesis such that regioisomer (II) was formed in the synthetic step to prepare letrozole and purification of letrozole had to involve removal of impurity (II). These two purifications were very difficult and a substantial quantity of material was lost during the purifications by column chromatography. In addition, removal of the impurities by column chromatography vastly increased the solvent consumption of the process and purification using column chromatography is not a practical approach for the industrial production of letrozole or its intermediates.

Another process for the preparation of letrozole, disclosed in patent application WO 2005/047269, has recognised that the removal of the undesired regioisomers by column chromatography is a problem and discloses a method for the separation of the unwanted impurity (V) from the intermediate (III) by preparation of its hydrochloride salt which is
relatively less soluble in the solvent dichloromethane or chloroform and separation by filtration while the desired intermediate (III) hydrochloride salt remains in solution. The desired intermediate (III) is then isolated as free base and purified by crystallization. Although some control of the isomeric purity was achieved by this method, the loss of significant quantities of the desired product (III) could not be avoided and this route is not attractive for commercial production.

A regiospecific preparation of intermediate 4-\([1-(1,2,4\text{-triazol-1-yl})\text{methyl}]\)benzonitrile (III), was disclosed in patent application WO 2004/076409. The disclosed process afforded intermediate (III) with low levels of its regioisomeric impurity by using the 4-amino-derivative of 1,2,4-triazole so that regioselectivity in the reaction can be achieved. The desired intermediate 4-\([1-(1,2,4\text{-triazol-1-yl})\text{methyl}]\)benzonitrile (III) was obtained by de-amination of its 4-amino derivative with sodium nitrite and concentrated hydrochloric acid. However, this process suffers from the disadvantages that extra steps are involved in the synthesis and toxic nitrous acid is formed during the de-amination reaction.

Yet another approach to reduce the possible regioisomeric impurity was discussed in patent application WO 2007/039912, wherein the reaction of the alkali (preferably sodium or potassium) salt of 1,2,4-triazole with α-bromotolunitrile was disclosed. This process, although reducing the level of the 1,3,4-triazolyl isomeric impurity, did not totally eliminate the formation of the impurity. In addition, the formation of the alkali salt of 1,2,4-triazole also increases the time cycle of the process due to the additional step.

In another approach, disclosed in patent application, WO 2007/144896, the 4,4'-disubstituted diphenylmethane moiety was prepared and then the 1,2,4-triazole ring was introduced to afford letrozole. The process involved coupling of 4-fluorobenzonitrile (IV) with 4-tolunitrile in DMF using potassium tertiary butoxide as a catalyst. The resulting 4,4'-dicyanodiphenylmethane was brominated with N-bromosuccinimide to afford a bromomethyl intermediate, which was reacted with 1,2,4-triazole to afford letrozole.

However, formation of 1,3,4-triazolyl isomeric impurity (II) could not be totally avoided and, in addition, the reaction of 4-tolunitrile and 4-fluorobenzonitrile also leads to significant formation of tris-phenyl impurity (T) which is problematic to remove, particularly on a commercial scale.
Therefore the prior art processes described above for the preparation of letrozole and its intermediates have major disadvantages with respect to the formation and removal of process related impurities; poor commercial viability due to the use of hazardous reactants; expensive, time consuming separation methods such as column chromatography; and/or low yields of final product.

As the commercial production of letrozole is of great importance and in view of the above disadvantages associated with the prior art, there is a real need for alternative and improved processes for the preparation of letrozole which do not involve multiple steps and further eliminate the need for cumbersome purification techniques, particularly for the removal of the regioisomers (II) and (V). The alternative processes must be economical and high yielding and provide letrozole with a high degree of chemical purity.

Object of the invention

Therefore the object of the invention is to provide a process for the preparation of letrozole which eliminates formation of the regioisomeric impurity (II), uses relatively safe reagents and is economical to use on a commercial scale.

Summary of the invention

The difficulties encountered in the prior art in the preparation of letrozole have been successfully overcome in the present invention, wherein the 1,2,4-triazole ring is formed
during the reaction process, therefore completely eliminating the formation of any triazole regioisomers and the requirement to remove them in the purification process.

Therefore a first aspect of the present invention provides a process for the preparation of letrozole, or a pharmaceutically acceptable salt thereof, comprising converting 4,4'-dicyanodiphenyl methyl hydrazine, or a salt thereof, to letrozole.

Preferably the 4,4'-dicyanodiphenyl methyl hydrazine, or a salt thereof, is converted to letrozole by reaction with 1,3,5-triazine.

Preferably the salt of the 4,4'-dicyanodiphenyl methyl hydrazine is the hydrogen chloride salt.

Preferably the 4,4'-dicyanodiphenyl methyl hydrazine, or a salt thereof, is prepared by a process comprising the following steps:

(a) treating 4,4'-dicyanobenzophenone with hydrazine hydrate to obtain 4,4'-dicyanobenzophenone hydrazone;
(b) converting the 4,4'-dicyanobenzophenone hydrazone into its ketone adduct;
(c) reduction of the 4,4'-dicyanobenzophenone hydrazone ketone adduct into its corresponding 4,4'-dicyanodiphenyl methyl hydrazine ketone adduct; and
(d) converting the 4,4'-dicyanodiphenyl methyl hydrazine ketone adduct into 4,4'-dicyanodiphenyl methyl hydrazine, or a salt thereof.

Preferably step (a) is carried out under acidic conditions. Preferably step (a) is carried out in a polar solvent, wherein the polar solvent is preferably an alcohol, preferably an alkyl alcohol and most preferably is methanol.

Preferably the ketone adduct in step (b) is a dialkyl, an arylalkyl or a diaryl ketone. Most preferably the ketone is acetone.

Preferably in step (b) the ketone used to prepare the ketone adduct is the only solvent or the solvent is the ketone mixed with one or more additional solvents. Preferably the additional solvent comprises an alcohol, more preferably an alkyl alcohol and most
preferably methanol. Preferably the amount of ketone in the additional solvent mixture is 30-70%, more preferably 40-60% and most preferably 50-55%.

Preferably the reduction in step (c) is carried out using catalytic hydrogenation, wherein the catalyst is preferably palladium on charcoal.

Preferably step (d) is carried out using acid hydrolysis. Preferably in step (d), a salt of 4,4’-dicyanodiphenyl methyl hydrazine is prepared, preferably the hydrogen chloride salt.

Preferably the 4,4’-dicyanodiphenyl methyl hydrazine, or a salt thereof, is converted to letrozole by reaction with 1,3,5-triazine in a polar solvent. Preferably the polar solvent is an alcohol, preferably an alkyl alcohol, more preferably methanol, ethanol, isopropanol or a mixture thereof, and most preferably methanol. Optionally, the alcohol is mixed with one or more other solvents, which is/are preferably selected from cyclic ethers or halogenated alkanes or mixtures thereof. Preferably the cyclic ether is tetrahydrofuran. Preferably the halogenated alkane is dichloromethane.

Preferably in the process according to the first aspect of the present invention, the 4,4’-dicyanodiphenyl methyl hydrazine, or a salt thereof, is not isolated and used in-situ.

A second aspect of the present invention provides a process for the preparation of 4-[(1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III), comprising converting 4-cyanophenyl methyl hydrazine, or a salt thereof, to 4-[(1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III). Preferably the 4-cyanophenyl methyl hydrazine, or a salt thereof, is converted to 4-[(1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) by reaction with 1,3,5-triazine. Preferably the reaction is carried out in a polar solvent, wherein the polar solvent is preferably an alcohol, preferably an alkyl alcohol. Preferably the alkyl alcohol is selected from methanol, ethanol, isopropanol or a mixture thereof, most preferably methanol.

Preferably the 4-cyanophenyl methyl hydrazine salt is the hydrogen chloride salt.

Preferably, in the process according to the second aspect of the present invention, the 4-cyanophenyl methyl hydrazine, or a salt thereof, is prepared by a process comprising
treating 4-halomethyl benzonitrile with hydrazine hydrate, wherein the halo group is chloro, bromo or iodo. Preferably the halo group is bromo.

Preferably, in the process according to the second aspect of the present invention, the 4-cyanophenyl methyl hydrazine, or a salt thereof, is not isolated and used in-situ.

Preferably, in the process according to the second aspect of the present invention, the 4-[(1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) is further converted to letrozole, or a pharmaceutically acceptable salt thereof.

A third aspect of the present invention provides letrozole when prepared by the process according to the first or second aspect of the present invention.

A fourth aspect of the present invention provides letrozole substantially free of the regioisomeric impurity (II).

A fifth aspect of the present invention provides letrozole when prepared by the process according to the first or second aspect of the present invention, substantially free of the regioisomeric impurity (II).

A sixth aspect of the present invention provides letrozole with an HPLC of purity more than 99.9%, substantially free of the regioisomeric impurity (II).

Preferably the letrozole according to the present invention has an HPLC of purity more than 99.9%, preferably more than 99.95%, preferably more than 99.98%.

A seventh aspect of the present invention provides 4-[(1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) when prepared by the process according to the second aspect of the present invention.

An eighth aspect of the present invention provides 4-[(1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) substantially free of the regioisomeric impurity (V).
A ninth aspect of the present invention provides 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) when prepared by the process according to the second aspect of the present invention, substantially free of the regioisomeric impurity (V).

A tenth aspect of the present invention provides 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) with an HPLC purity of more than 99.5%, preferably an HPLC purity of more than 99.9%, substantially free of the regioisomeric impurity (V).

An eleventh aspect of the present invention provides a pharmaceutical composition comprising letrozole, or a pharmaceutically acceptable salt thereof, according to the third, fourth, fifth or sixth aspect of the present invention.

A twelfth aspect of the present invention provides the use of letrozole, or a pharmaceutically acceptable salt thereof, according to the third, fourth, fifth or sixth aspect of the present invention, or the use of a pharmaceutical composition according to the eleventh aspect of the present invention, in the manufacture of a medicament for the treatment or prevention of breast cancer.

A thirteenth aspect of the present invention provides a method of treating or preventing breast cancer, comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of letrozole, or a pharmaceutically acceptable salt thereof, according to the third, fourth, fifth or sixth aspect of the present invention, or a therapeutically or prophylactically effective amount of a pharmaceutical composition according to the eleventh aspect of the present invention. Preferably the patient is a mammal, preferably a human.

The term "letrozole" as used herein throughout the description and claims means letrozole and/or any salt, solvate or polymorph thereof, unless otherwise specified.

For the purposes of the present invention, the letrozole or any of its intermediates, such as 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III), are "substantially free" of chemical or regioisomeric impurities, if they comprise less than 3% impurity, preferably less than 2%, preferably less than 1%, preferably less than 0.8%, preferably less than 0.5%, preferably less
than 0.3%, preferably less than 0.2%, preferably less than 0.1% and most preferably less than 0.05%.

For the purposes of the present invention, an "alkyl" group is defined as a monovalent saturated hydrocarbon, which may be straight-chained or branched, or be or include cyclic groups. An alkyl group may optionally be substituted and may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Preferably an alkyl group is straight-chained or branched. Preferably an alkyl group is not substituted. Preferably an alkyl group does not include any heteroatoms in its carbon skeleton. Examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, cyclopentyl, cyclohexyl and cycloheptyl groups. Preferably an alkyl group is a C\textsubscript{12} alkyl group, preferably a C\textsubscript{16} alkyl group. Preferably a cyclic alkyl group is a C\textsubscript{312} cyclic alkyl group, preferably a C\textsubscript{57} cyclic alkyl group.

An "aryl" group is defined as a monovalent aromatic hydrocarbon. An aryl group may optionally be substituted and may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Preferably an aryl group is not substituted. Preferably an aryl group does not include any heteroatoms in its carbon skeleton. Examples of aryl groups are phenyl, naphthyl, anthracenyl and phenanthrenyl groups. Preferably an aryl group is a C\textsubscript{14} aryl group, preferably a C\textsubscript{6} C\textsubscript{10} aryl group.

Detailed description of the invention

The inventors have found that letrozole can be regioselectively synthesized using hydrazines as key intermediates. The letrozole thus obtained is surprisingly substantially free from the regiosomeric impurity (II) and is a major advance over the various processes described in the prior art, as discussed above. The processes of the present invention comprise a unique formation of the 1,2,4-triazole ring from the key hydrazine intermediate in a reaction step.

The source of regiosomeric impurity in the prior art is the use of 1,2,4-triazole in the syntheses, as the 1,2,4-triazole will resonate while reacting and consequently the regioisomer is formed. Therefore, the processes according to the present invention
construct the 1,2,4-tmzole ring during the synthetic sequence and formation of any unwanted regioisomer is completely eliminated.

Therefore, the present invention provides simple, convenient and inexpensive methods for the preparation of letrozole, and its pharmaceutically acceptable salts. The products obtained from the processes of the present invention are surprisingly very pure without the need for cumbersome purification techniques, such as column chromatography. In particular, the present invention provides letrozole and its pharmaceutically acceptable salts substantially free of regioisomeric impurities. The inventors have found that letrozole can be prepared in very high yield and purity without the regioisomeric impurity (II) by reacting the intermediate 4,4'-dicyanodiphenyl methyl hydrazine, preferably as its hydrohalide salt, with 1,3,5-tiazine.

A preferred embodiment of the first aspect of the present invention is outlined in Scheme 1.

![Scheme 1](attachment:Scheme_1.png)
The reagents and solvents illustrated in Schemes 1-3 are merely illustrative of the present invention and the reaction schemes are not limited by these reagents and solvents. Any suitable alternatives can be used.

The first step of the preferred embodiment outlined in Scheme 1 is the preparation of 4,4'-dicyanodiphenyl hydrazone from 4,4'-dicyanobenzophenone. The second step is to reduce the 4,4'-dicyanodiphenyl hydrazone to 4,4'-dicyanodiphenyl methyl hydrazine or its ketone adduct. The third step is to prepare an acid salt of the 4,4'-dicyanodiphenyl methyl hydrazine by treatment with suitable organic or inorganic acids including mineral acids. The hydrazine acid salt, which can also be used in-situ, is then treated with 1,3,5-triazine (S-triazine) in a suitable organic medium to prepare letrozole.

Optionally the letrozole can be further purified, if required, to obtain letrozole with more than 99.9% to 99.95% purity and completely free of any regioisomeric impurity.

Another embodiment of the first aspect of the present invention is a process for the preparation of letrozole comprising the following steps:

(a) preparation of 4,4'-dicyanobenzophenone hydrazone (herein also called 4,4'-dicyanodiphenyl hydrazone) by treatment of 4,4'-dicyanobenzophenone with hydrazine hydrate under acidic conditions;

(b) reduction of the 4,4'-dicyanobenzophenone hydrazone to the corresponding 4,4'-dicyanodiphenyl methyl hydrazine and in-situ protection of the free amino group as its acetone adduct;

(c) preparation of the hydrazine acid addition salt from the protected 4,4'-dicyanodiphenyl methyl hydrazine;

(d) preparation of letrozole from the 4,4'-dicyanodiphenyl methyl hydrazine acid addition salt; and

(e) crystallization of letrozole prepared as above by suitable crystallization methods to obtain letrozole with more than 99.90% HPLC purity.

The processes of the present invention provide a commercially viable process for the preparation of letrozole resulting in a greater than 60% molar overall yield and an HPLC
purity of greater than 99.90%, preferably greater than 99.95% and more preferably greater than 99.98%.

Preferred embodiments according to the first aspect of the invention include a process for the preparation of letrozole, comprising the reaction of 4,4'-dicyanodiphenyl methyl hydrazine acid salt, preferably inorganic acid salts, with 1,3,5-triazine (S-triazine) in one or more polar solvents, which are preferably alkyl alcohols.

A preferred preparation process for the intermediate hydrazine or its salt comprises the following steps:

(i) dissolution of 4,4'-dicyanobenzophenone into one or more polar organic solvents, preferably alcohols, and an organic acid, preferably alkanoic acids like acetic acid;
(ii) addition of hydrazine hydrate in the reaction mixture heated at 55-75°C;
(iii) isolation of the corresponding hydrazone from the reaction mixture;
(iv) dissolving the isolated hydrazone in a solvent mixture comprising an alcohol, such as methanol, and a ketone, such as acetone;
(v) hydrogenation of this solution using as catalyst 10% Pd/C at atmospheric pressure;
(vi) isolating the corresponding reduced product 2-(propan-2-ylidine)-1-[di-(4-cyanophenyl)methyl] hydrazine (VIII) after removal of the solvent; and
(vii) reacting it with inorganic acid to obtain the 4,4'-dicyanodiphenyl methyl hydrazine acid salt.

Preferably letrozole can be prepared from 4,4'-dicyanodiphenyl methyl hydrazine or its acid salt using the following steps:

(i) dissolving the 4,4'-dicyanodiphenyl methyl hydrazine acid salt in a suitable polar solvent, preferably aliphatic alcohols;
(ii) slow addition of a 1,3,5-triazine solution prepared in the same solvent as above, into the solution;
(iii) refluxing the reaction mixture as above for 6-7 hours until completion of the reaction as monitored by TLC;
(iv) removal of the solvent by distillation at reduced pressure;
(v) addition of water in the reaction mass and extraction with a suitable water immiscible halogenated and/or non-halogenated polar solvent; and
(vi) isolation of letrozole from the organic layer and treatment of the crude product with a mixture of ethyl acetate and hexane to obtain solid product.

Preferably the preparation of 4,4’-dicyanobenzophenone hydrazone is carried out in a polar solvent comprising a straight or branched aliphatic alcohol containing 1 to 5 carbon atoms. In addition, an acid is optionally also used, selected from an inorganic mineral acid or an organic 1 to 5 carbon chain alkanoic acid, preferably acetic acid.

Preferably the reduction and preparation of the ketone adduct of the 4,4'-dicyanobenzophenone hydrazone is carried out in an appropriate dialkyl ketone alone or in a mixture of dialkyl ketone and an aliphatic alcohol containing 1 to 5 carbon atoms in a straight or branched chain. Preferably the ratio of dialkyl ketone in the solvent mixture is 30-70%, preferably 40-60% and most preferably 50-55%.

Preferably the catalytic hydrogenation is carried out using 10% palladium on charcoal catalyst, preferably in a concentration of 2-10% with respect to the weight of the substrate 4,4'-dicyanobenzophenone hydrazone.

Preferably the acid used in the preparation of the acid addition salt of 4,4'-dicyanodiphenyl methyl hydrazine is an organic or inorganic acid and preferably the solvent used in the preparation is a polar solvent, such as an aliphatic alcohol, preferably a 1 to 5 carbon chain straight or branched chain alcohol. Preferably the acid used in the preparation of the acid addition salt of 4,4'-dicyanodiphenyl methyl hydrazine is hydrochloric acid and preferably the solvent used is either methanol, ethanol, isopropanol or a mixture thereof.

Preferably the reaction of 1,3,5-triazine with 4,4'-dicyanodiphenyl methyl hydrazine hydrochloride is carried out in a polar solvent, such as a 1 to 5 carbon atom containing straight or branched chain alcohol, alone or their mixture, preferably with one or more other solvents, preferably cyclic ethers or halogenated alkanes. The polar solvents used for the reaction are preferably methanol, ethanol or isopropanol, preferably mixed with tetrahydrofuran or dichloromethane. Preferably the reaction temperature is kept at between 25 to 80°C, preferably between 55 to 80°C, or more preferably 65 to 75°C.
Preferably the letrozole is isolated from the reaction mixture by concentration of the reaction mixture, dissolving the residue in water and extraction of the aqueous layer with a water immiscible polar solvent like dichloromethane or ethyl acetate.

Preferably the letrozole is purified by a solvent mixture. Preferably the letrozole is purified in a single solvent such as an alcohol or in a solvent mixture comprising an aliphatic hydrocarbon like pentane, n-hexane, n-heptane or their mixture and an aliphatic ester like ethyl, propyl, butyl or amyl acetate or propionate and mixtures thereof.

A second aspect of the present invention is the regioselective synthesis of intermediate 4-[(1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) free from regiosomeric impurity (V) via reacting 4-cyanophenyl methyl hydrazine with 1,3,5-triazine (S-triazine) in a suitable organic medium (Scheme 2).

Preferred embodiments of the second aspect of the present invention are outlined below:

(i) preparation of 4-cyanophenyl methyl hydrazine by reacting 4-bromomethyl benzonitrile with hydrazine hydrate in an alkyl alcohol, preferably methanol, and using a suitable organic/inorganic base like triethylamine or potassium carbonate;

(ii) preparation of a hydrohalide salt of 4-cyanophenyl methyl hydrazine by treatment with a suitable acid solution preferably in organic medium like alcohols; and

(iii) reaction of the hydrohalide salt of 4-cyanophenyl methyl hydrazine with S-triazine in an appropriate organic medium at a temperature of about 50 to 75°C.
Preferably letrozole is prepared from intermediate (III), prepared according to the second aspect of the present invention, by its reaction with 4-fluorobenzonitrile (IV) in the presence of strong base like potassium tert-butoxide as described in patent US 4,978,672 and other prior art processes described above (see also Scheme 3).

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\begin{align*}
\text{Scheme 3} \\
\text{In relation to the processes of the first and second aspects of the present invention, preferably the letrozole is prepared with an HPLC purity of more than 99.95\%, substantially free of the regioisomeric impurity (II).}
\end{align*}
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Preferably the products are obtained in a yield of 70\% or more, preferably 80\% or more, preferably 90\% or more, preferably 95\% or more.

Preferably the letrozole is obtained substantially free of chemical impurities.

Preferably the letrozole is obtained on a commercial scale, preferably in batches of 1kg or more, 10kg or more, 100kg or more, 500kg or more, or 1000kg or more.

The pharmaceutical composition according to the eleventh aspect of the present invention can be a solution or suspension form, but is preferably a solid oral dosage form. Preferred dosage forms in accordance with the invention include tablets, capsules and the like which, optionally, may be coated if desired. Tablets can be prepared by conventional techniques,
including direct compression, wet granulation and dry granulation. Capsules are generally formed from a gelatine material and can include a conventionally prepared granulate of excipients in accordance with the invention.

5 The pharmaceutical composition according to the present invention typically comprises one or more conventional pharmaceutically acceptable excipient(s) selected from the group comprising a filler, a binder, a disintegrant, a lubricant and optionally further comprises at least one excipient selected from colouring agents, adsorbents, surfactants, film-formers and plasticizers.

10 As described above, the pharmaceutical composition of the invention typically comprises one or more fillers, such as microcrystalline cellulose, lactose, sugars, starches, modified starches, mannitol, sorbitol and other polyols, dextrin, dextran or maltodextrin; one or more binders, such as lactose, starches, modified starch, maize starch, dextrin, dextran, maltodextrin, microcrystalline cellulose, sugars, polyethylene glycols, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, gelatin, acacia gum, tragacanth, polyvinylpyrrolidone or crospovidone; one or more disintegrating agents, such as croscarmellose sodium, cross-linked polyvinylpyrrolidone, crospovidone, cross-linked carboxymethyl starch, starches, microcrystalline cellulose, polyacrylin potassium; one or more different glidants or lubricants, such as magnesium stearate, calcium stearate, zinc stearate, calcium behenate, sodium stearyl fumarate, talc, magnesium trisilicate, stearic acid, palmitic acid, carnauba wax or silicon dioxide. If required, the pharmaceutical composition of the present invention may also include surfactants and other conventional excipients.

25 If the solid pharmaceutical formulation is in the form of coated tablets, the coating may be prepared from at least one film-former such as hydroxypropyl methyl cellulose, hydroxypropyl cellulose or methacrylate polymers which optionally may contain at least one plasticizer such as polyethylene glycols, dibutyl sebacate, triethyl citrate, and other pharmaceutical auxiliary substances conventional for film coatings, such as pigments, fillers and others.
The twelfth aspect of the present invention provides the use of a pharmaceutical composition according to the eleventh aspect of the present invention in the manufacture of a medicament for the treatment of cancer, in particular for the treatment of breast cancer in postmenopausal women.

Further aspects of the present invention include the intermediates:
- 4,4'-dicyanobenzophenone hydrazone (VII);
- 2-(propan-2-ylidene)-1-[di-(4-cyanophenyl)methyl]hydrazine (VIII);
- 4,4'-dicyanodiphenyl methyl hydrazine, or a salt or ketone adduct thereof; and
- 4-cyanophenyl methyl hydrazine.

Further aspects of the present invention include the preparation of letrozole, or its pharmaceutically acceptable salts, comprising a process involving one or more of the following intermediates:
- 4,4'-dicynanobenzophenone;
- 4,4'-dicyanobenzophenone hydrazone (VII);
- 2-(propan-2-ylidene)-1-[di-(4-cyanophenyl)methyl]hydrazine (VIII);
- 4,4'-dicyanodiphenyl methyl hydrazine, or a salt or ketone adduct thereof; and
- 4-cyanophenyl methyl hydrazine.

The details of the invention, its objects and advantages are explained hereunder in greater detail in the following non-limiting examples.

Examples

Example 1: 4,4'-dicynanobenzophenone hydrazone (VII)
In a reaction vessel, 100 g (0.430 mol) of 4,4'-dicyanobenzophenone (VI) was dissolved in 2500 ml of methanol by heating the solution at 55-65°C. To this solution, 500 ml of glacial acetic acid was slowly added. Then 17 g (8.0 mol) of hydrazine hydrate was slowly added and the reaction mixture was heated under reflux for 4 to 5 hours. After completion of the reaction, the excess solvent from the reaction mixture was distilled and the reaction was cooled. The crystallized hydrazone was filtered and washed with methanol and sucked dry. Finally the product was dried at 50-55°C under low pressure for 3 to 4 hours.
Yield: 95 g (89.6% molar)
Melting point: 206-209°C
HPLC purity: 97%

Example 2: 2-(propan-2-ylidene)-1-[di-(4-cyanophenyl)methyl]hydrazine (VIII)
In a suitable reaction vessel, a solution of 100 g (0.406 mol) of 4,4'-dicyanobenzophenone hydrazone (VII) was added to 3600 ml equal volume mixture of methanol and acetone at 25-30°C. In this solution, 7.5 g of palladium 10% on carbon was suspended under an inert (preferably nitrogen) atmosphere. In the reaction mixture, hydrogen gas was bubbled at atmospheric pressure. After completion of the reaction, the mixture was filtered through a Celite® bed and the filtrate solution was concentrated by distillation at 50-55°C under reduced pressure to afford a semi-solid mass which was suspended in 2-propanol and stirred for 1 hour to obtain the title product as an off-white solid.

Yield: 90 g (76.9% molar)
HPLC purity: > 95%

Example 3: 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile (letrozole)
In a suitable glass reaction vessel, a solution of 100 g (0.35 mol) of 2-(propan-2-ylidene)-1-[di-(4-cyanophenyl)methyl]hydrazine (VIII) in 1000 ml of methanol was charged. To this solution, 440 ml (11.0 mol) of hydrochloric acid was slowly added at ambient temperature and the reaction mixture was stirred for 3 to 4 hours. To this reaction mixture, a solution of 225 g (8.0 mol) of 1,3,5-triazine in 500 ml of methanol was added under stirring. After completion of the addition, the reaction mixture was heated at reflux for 6 to 7 hours. After completion of the reaction, the reaction mixture was concentrated by distillation under reduced pressure and the solvent removed to afford a sticky semi-solid mass. To this residue 1000 ml of water and 1000 ml of dichloromethane were added under stirring. The aqueous layer was separated and was extracted with more dichloromethane. The combined organic layers were washed with water and then dried on anhydrous sodium sulphate and concentrated by distillation under reduced pressure to obtain letrozole (crude) as a free flowing solid. The crude letrozole was further purified by crystallization in methanol or a
mixture of ethyl acetate and hexane (7:3) and dried at 50-55°C under reduced pressure (100-150 mmHg) to afford purified letrozole.

Yield: 70 g (70.7% molar)

5 HPLC purity: >99.9% (Regioisomer impurity (II) could not be detected.)

Example 4: 4-[L-(1,2,4-triazol-1-yl)methyl]benzonitrile (III)

In a suitable glass reaction vessel, hydrazine hydrate (40.8 g, 1.02 mol) and triethylamine (26 g, 0.248 mol) were added to methanol (125 ml). To this mixture, a solution of 4-bromomethyl benzonitrile (25 g, 0.128 mol) in methanol (375 ml) was added slowly at 10-20°C. The reaction mixture was stirred at the same temperature for 5 to 7 hours. After completion of the reaction, the solvent was removed by distillation at 40-50°C under reduced pressure. To the residue, water (200 ml) and dichloromethane (100 ml) were added and the mixture stirred for 15 minutes. The organic layer was separated and the aqueous layer was extracted with another 75 ml of dichloromethane. Both dichloromethane layers were combined and washed with water (100 ml). The organic layer was dried on anhydrous sodium sulphate and the solvent was removed by distillation at 35-40°C under reduced pressure to yield off-white solid 4-cyanophenyl methyl hydrazine (20 g).

The 4-cyanophenyl methyl hydrazine (20 g, 0.14 mol) was dissolved in methanol (100 ml) and treated with a 35% aqueous solution of hydrochloric acid (12 ml) at 10-15°C under stirring to obtain 4-cyanophenyl methyl hydrazine hydrochloride. To this solution, 1,3,5-triazine (S-triazine) (66 g, 0.81 mol) dissolved in methanol (330 ml) was slowly added. The reaction mixture temperature was slowly increased to reflux and the reaction mixture refluxed for 5 to 6 hours. After completion of the reaction, the reaction mixture was concentrated by distillation of the solvent. To the residue, water was added and the reaction mixture was extracted with dichloromethane. After concentration of the dichloromethane layer, the product 4-[L-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) was isolated as an off-white solid and further purified by crystallization in solvents like methanol or isopropanol.

Yield: 17.5 g (74.5% molar)

HPLC purity: >99.5% (Regioisomer impurity (V) could not be detected.)
The 4-[l-(l,2,4-triazol-l-yl)methyl]benzonitrile (III) prepared in accordance with example 4 was converted into letrozole using 4-fluorobenzonitrile (IV) in the presence of strong base such as potassium tert-butoxide as described in the prior art, for example, in patent US 4,978,672. The HPLC purity of the letrozole obtained was >99.9%; the regioisomer impurity (II) could not be detected.

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope and spirit of the invention, which is defined by the following claims only.
Claims

1. A process for the preparation of letrozole, or a pharmaceutically acceptable salt thereof, wherein the 1,2,4-triazole ring of letrozole is formed during the preparation process.

2. A process for the preparation of letrozole, or a pharmaceutically acceptable salt thereof, comprising converting 4,4'-dicyanodi phenyl methyl hydrazine, or a salt thereof, to letrozole.

3. A process according to claim 2, wherein the 4,4'-dicyanodi phenyl methyl hydrazine, or a salt thereof, is converted to letrozole by reaction with 1,3,5-triazine.

4. A process according to claim 2 or 3, wherein the salt of the 4,4'-dicyanodi phenyl methyl hydrazine is the hydrogen chloride salt.

5. A process according to any of claims 2 to 4, wherein the 4,4'-dicyanodi phenyl methyl hydrazine, or a salt thereof, is prepared by a process comprising the following steps:
   (a) treating 4,4'-dicyanobenzo phenone with hydrazine (such as hydrazine hydrate) to obtain 4,4'-dicyanobenzo phenone hydrazone;
   (b) converting the 4,4'-dicyanobenzo phenone hydrazone into its ketone adduct;
   (c) reduction of the 4,4'-dicyanobenzo phenone hydrazone ketone adduct into its corresponding 4,4'-dicyanodi phenyl methyl hydrazine ketone adduct; and
   (d) converting the 4,4'-dicyanodi phenyl methyl hydrazine ketone adduct into 4,4'-dicyanodiphenyl methyl hydrazine, or a salt thereof.

6. A process according to claim 5, wherein step (a) is carried out:
   (i) under acidic conditions; and/or
   (ii) in a polar solvent; and/or
   (iii) in an alcohol; and/or
   (iv) in an alkyl alcohol; and/or
   (v) in methanol.
7. A process according to claim 5 or 6, wherein the ketone adduct is:
   (i) a dialkyl, an arylalkyl or a diaryl ketone; and/or
   (ii) acetone.

8. A process according to any of claims 5 to 7, wherein in step (b) the ketone is the only solvent or the solvent is the ketone mixed with one or more additional solvents.

9. A process according to claim 8, wherein:
   (i) the additional solvent comprises an alcohol; and/or
   (ii) the additional solvent comprises an alkyl alcohol; and/or
   (iii) the additional solvent comprises methanol; and/or
   (iv) the amount of ketone in the additional solvent mixture is 30-70%; and/or
   (v) the amount of ketone in the additional solvent mixture is 40-60%; and/or
   (vi) the amount of ketone in the additional solvent mixture is 50-55%.

10. A process according to any of claims 5 to 9, wherein step (c) is carried out using:
    (i) catalytic hydrogenation; and/or
    (ii) catalytic hydrogenation, wherein the catalyst is palladium on charcoal.

11. A process according to any of claims 5 to 10, wherein step (d) is carried out using acid hydrolysis.

12. A process according to any of claims 5 to 11, wherein in step (d) 4,4'-dicyanodiphenyl methyl hydrazine hydrogen chloride is prepared.

13. A process according to any of claims 3 to 12, wherein the 4,4'-dicyanodiphenyl methyl hydrazine, or a salt thereof, is converted to letrozole by reaction with 1,3,5-triazine in:
    (i) a polar solvent; and/or
    (ii) an alcohol; and/or
    (iii) an alkyl alcohol; and/or
    (iv) methanol, ethanol, isopropanol or a mixture thereof; and/or
    (v) methanol; and/or
(vi) an alcohol mixed with one or more other solvents; and/or
(vii) an alcohol mixed with one or more other solvents, wherein the other solvent is selected from cyclic ethers or halogenated alkanes or mixtures thereof; and/or
(viii) an alcohol mixed with one or more other solvents, wherein the other solvent is selected from tetrahydrofuran or dichloromethane or a mixture thereof.

14. A process according to any of claims 2 to 13, wherein the 4,4'-dicyanodiphenyl methyl hydrazine, or a salt thereof, is not isolated and used in-situ.

15. A process for the preparation of 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III), comprising converting 4-cyanophenyl methyl hydrazine, or a salt thereof, to 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III).

16. A process according to claim 15, wherein the 4-cyanophenyl methyl hydrazine, or a salt thereof, is converted to 4-[1-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) by reaction with 1,3,5-triazine.

17. A process according to claim 15 or 16, wherein the salt of the 4-cyanophenyl methyl hydrazine is the hydrogen chloride salt.

18. A process according to any of claims 15 to 17, wherein the reaction is carried out in:
   (i) a polar solvent; and/or
   (ii) an alcohol; and/or
   (iii) an alkyl alcohol; and/or
   (iv) methanol, ethanol, isopropanol or a mixture thereof; and/or
   (v) methanol.

19. A process according to any of claims 15 to 18, wherein the 4-cyanophenyl methyl hydrazine, or a salt thereof, is prepared by a process comprising treating 4-halomethyl benzonitrile with hydrazine (such as hydrazine hydrate), wherein the halo group is chloro, bromo or iodo.
20. A process according to claim 19, wherein the halo group is bromo.

21. A process according to any of claims 15 to 20, wherein the 4-cyanophenyl methyl hydrazine, or a salt thereof, is not isolated and used in-situ.

22. A process according to any of claims 15 to 21, wherein the 4-[l-(1,2,4-triazol-1-yl)methyl]benzonitrile (III) is further converted to letrozole, or a pharmaceutically acceptable salt thereof.

23. Letrozole when prepared by a process according to any of claims 1 to 14 or 22.

24. Letrozole substantially free of the regioisomeric impurity (II).

25. Letrozole with an HPLC purity more than 99.9%.

26. Letrozole according to claim 23 or 24, having an HPLC purity more than 99.9%.

27. Letrozole according to claim 23 or 25, substantially free of the regioisomeric impurity (II).

28. Letrozole according to any of claims 23 to 27, for use in medicine.

29. Letrozole according to any of claims 23 to 28, for treating or preventing breast cancer.

30. 4-[l-(1,2,4-Triazol-1-yl)methyl]benzonitrile (III) when prepared by a process according to any of claims 15 to 21.

31. 4-[l-(1,2,4-Triazol-1-yl)methyl]benzonitrile (III) substantially free of the regioisomeric impurity (V).

32. 4-[l-(1,2,4-Triazol-1-yl)methyl]benzonitrile (III) with an HPLC purity more than 99.5%.
33. 4-[(1,2,4-Triazol-1-yl)methyl]benzonitrile (III) according to claim 30 or 31, having an HPLC purity more than 99.5%.

34. 4-[(1,2,4-Triazol-1-yl)methyl]benzonitrile (III) according to claim 30 or 32, substantially free of the regioisomeric impurity (V).

35. A pharmaceutical composition comprising letrozole, or a pharmaceutically acceptable salt thereof, according to any of claims 23 to 29.

36. Use of letrozole, or a pharmaceutically acceptable salt thereof, according to any of claims 23 to 29, or use of a pharmaceutical composition according to claim 35, in the manufacture of a medicament for the treatment or prevention of breast cancer.

37. A method of treating or preventing breast cancer, comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of letrozole, or a pharmaceutically acceptable salt thereof, according to any of claims 23 to 29, or a therapeutically or prophylactically effective amount of a pharmaceutical composition according to claim 35.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/GB2010/050993

**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 database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 2005/047269 Al (NATCO PHARMA LTD [IN]); AMALA KOMPELLA [IN]; RACHAKONDA SREENIVAS [IN];) 26 May 2005 (2005-05-26) cited in the application examples 1, 2</td>
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**D. Further documents are listed in the continuation of Box C**

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