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(54) Title: PROCESS FOR PREPARING TADALAFIL

(57) Abstract: A process for preparing tadalafil.

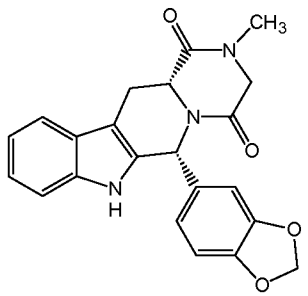
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PROCESS FOR PREPARING TADALAFIL

INTRODUCTION TO THE INVENTION

The present invention relates to a process for the preparation of tadalafil. In particular, it relates to a process for the preparation of (1R,3R)-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b] indole-3-carboxylic acid (hereinafter referred to as "beta-carboline acid") or salts thereof and its conversion to tadalafil.

Tadalafil is chemically known as (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3, 4-methylene dioxyphenyl)-pyrazino [2',1':6, 1] pyrido [3,4-b] indole-, 1,4-dione (hereinafter referred to by the adopted name "tadalafil"), and is structurally represented by Formula I.

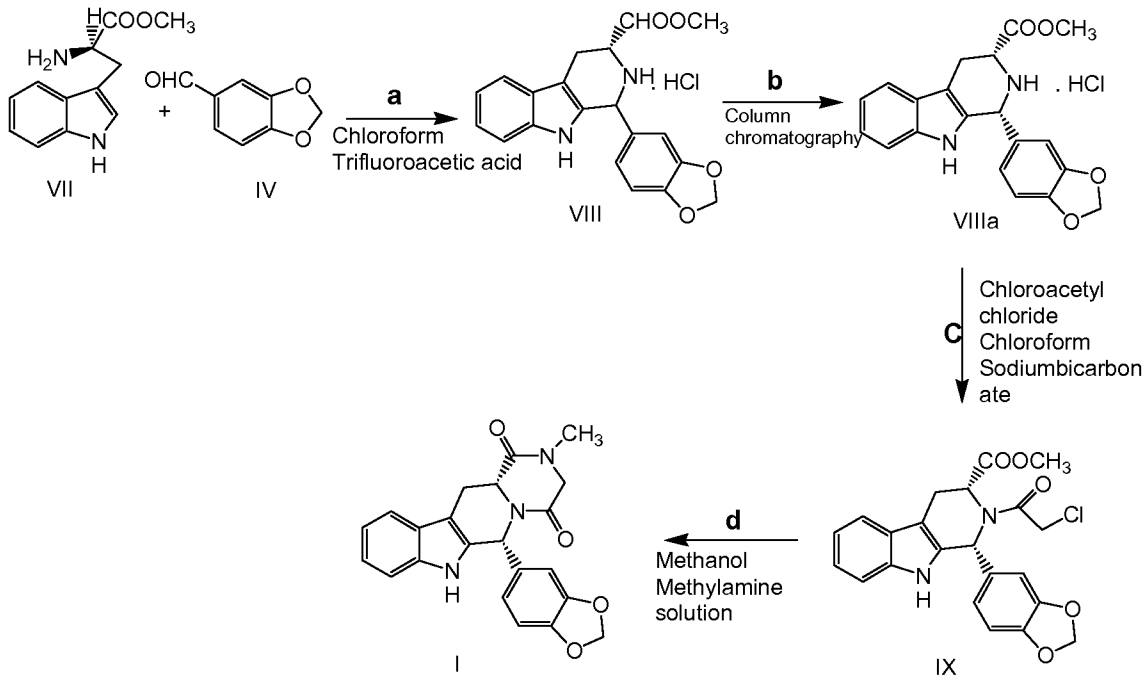


Formula I

Tadalafil is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Tadalafil is used in the treatment of erectile dysfunction. It is available in the market under the brand name CIALIS™ as tablets for oral administration, each tablet containing 5, 10, or 20 mg of tadalafil.

U.S. Patent No. 5,859,006 describes tadalafil, its related compounds, and methods for their synthesis.The patent describes the preparation of tadalafil as depicted by Scheme 1. Briefly, the process involves condensation of D-tryptophan methyl ester of Formula VII with piperonal of Formula IV to yield a mixture of isomers of the beta carboline ester of Formula VIII which are separated using column chromatography. Reacting the required isomer of beta-carboline ester of Formula VIIIa with a haloacetyl halide like chloroacetyl chloride in a suitable solvent in the presence of a base or an alkaline metal carbonate to give (1R,3R)-methyl 1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,

4-b] indole 3-carboxylate of Formula IX, which on treatment with a primary amine in a suitable solvent such as alcohol gives tadalafil of Formula I.



Scheme 1

The method described in the above patent employs toxic reagents like chloroacetyl chloride involves the purification of intermediates by column chromatography at various stages, the process is time consuming, taking 4-5 days for completion of the reaction, and the overall yield obtained is also very low. All these factors make the process uneconomical and difficult for scaling up.

International Application Publication No. WO 2005/068464 describes a process, which follows the same scheme, but involves the usage of molecular sieves in stage a, which makes the process less time consuming, and avoids fractional crystallization of the product. The process described in this application, although showing considerable advantages over the previous process, does not reduce the number of stages, and also does not avoid the use of hazardous reagents like chloroacetyl chloride.

Processes for the preparation of tadalafil have also been described in International Application Publication Nos. WO 2005/068464, WO 2006/091980, and WO2006/091975.

The processes described in the above mentioned documents do not reduce the number of stages, and also do not avoid use of the reagents like chloroacetyl chloride.

Thus there is a need to develop a process, which involves the use of safer reagents, avoids column chromatography of the intermediates and final product, and gives higher yields. A process, which involves a fewer number of stages, thereby reducing the process time cycle also would be helpful.

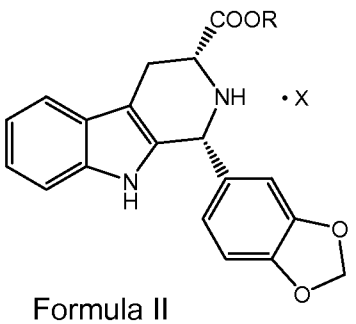
The present invention provides a process for the preparation of tadalafil having a reduced number of stages, which is easily scalable, cost effective, safe, and has a shorter time cycle.

SUMMARY OF THE INVENTION

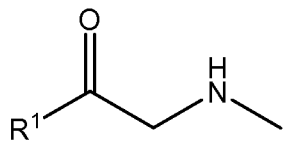
The present invention relates to a process for the preparation of tadalafil.

In one aspect, the present invention provides a process for the preparation of tadalafil of Formula I using beta-carboline acid, its derivatives and salts thereof.

In an embodiment, the process for the preparation of tadalafil of Formula I comprises condensation of beta-carboline acid, its derivatives or salts thereof of Formula II with sarcosine derivatives or salts thereof having Formula VI in the presence of a suitable reagent.



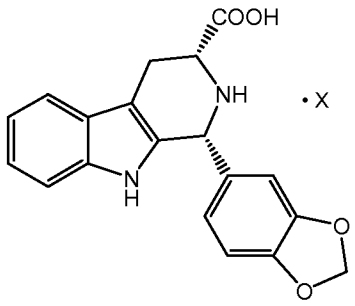
Formula II



Formula VI

where R is hydrogen, or a C_1 to C_6 straight chain branched or cyclic alkyl, C_1 to C_6 straight chain branched or cyclic alkoxy, or an aryloxy group and the like; R_1 is a halogen, C_1 to C_6 straight chain branched or cyclic alkoxy, aryloxy or hydroxy group, and X is an inorganic or organic acid.

In another aspect, the present invention provides substantially pure beta-carboline acid or its salts of Formula IIa.



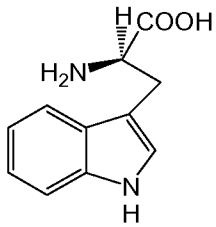
Formula IIa

where X is defined above.

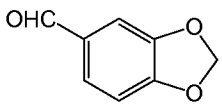
In yet another aspect, the present invention provides a process for preparation of the beta-carboline acid or its salts of Formula IIa.

In an embodiment, the process for preparation of beta-carboline acid or its salts of Formula IIa comprises:

a) reacting D-tryptophan of Formula III with piperonal of Formula IV in the presence of an acid and a suitable solvent to afford a mixture of cis- and trans-isomers of 1,2,3,4-tetrahydro-1- (3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylic acid represented by Formula V;

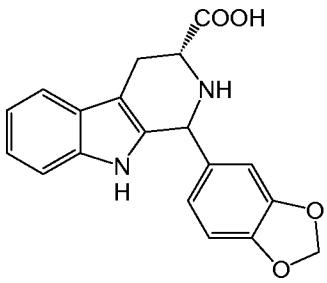


Formula III

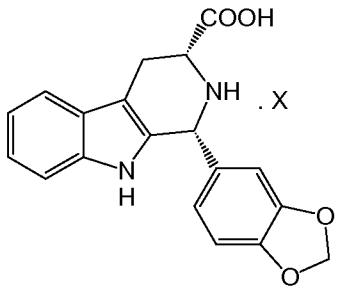


Formula IV

b) conversion of mixture of cis- and trans-isomers of Formula V into the cis-isomer of Formula IIa, optionally followed by purification by recrystallization or slurrying in a suitable solvent.



Formula V

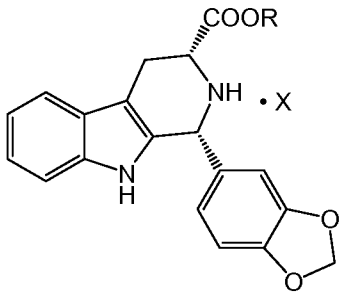


Formula IIa

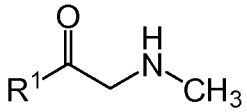
Still another aspect of the present invention provides a pharmaceutical composition comprising substantially pure tadalafil or its pharmaceutically

acceptable salts along with one or more pharmaceutically acceptable carriers, excipients or diluents.

An embodiment of the invention includes a process for preparing tadalafil, comprising reacting a compound having a formula:



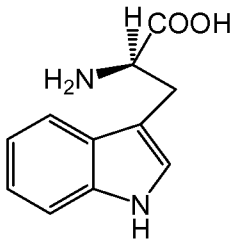
wherein R is hydrogen, a C_1 to C_6 straight chain branched or cyclic alkyl group, a C_1 to C_6 straight chain branched or cyclic alkoxy group, or an aryloxy group, and X is an inorganic or organic acid, with a compound having a formula:



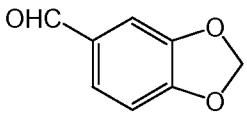
wherein R^1 is a halogen, a C_1 to C_6 straight chain branched or cyclic alkoxy group, or an aryloxy or hydroxy group, or a salt thereof, to form tadalafil.

Another embodiment of the invention includes a process for preparing tadalafil, comprising:

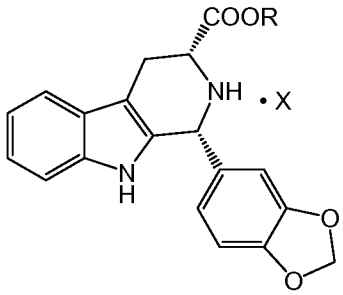
a) reacting a compound having a formula:



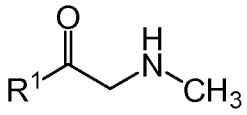
with a compound having a formula:



to form an intermediate, then further reacting with an acid to form a compound having a formula:

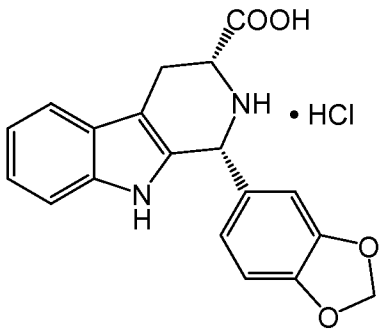


wherein R is hydrogen, a C_1 to C_6 straight chain branched or cyclic alkyl group, a C_1 to C_6 straight chain branched or cyclic alkoxy group, or an aryloxy group, and X is an inorganic or organic acid, and further reacting with a compound having a formula:



wherein R^1 is a halogen, a C_1 to C_6 straight chain branched or cyclic alkoxy group, or an aryloxy or hydroxy group, or a salt thereof, to form tadalafil.

A further embodiment of the invention includes a compound having a formula:



and being substantially free of isomeric impurities.

A still further embodiment of the invention includes tadalafil, containing about 0.005 to about 0.2, or about 0.005 to about 0.1, or about 0.005 to about 0.05, percent by weight of piperonal.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic representation of an embodiment of a process for the preparation of tadalafil.

Fig. 2 is an X-ray powder diffraction pattern of beta-carboline acid hydrochloride prepared in Example 6.

Fig. 3 is an infrared absorption spectrum of beta-carboline acid hydrochloride prepared in Example 6.

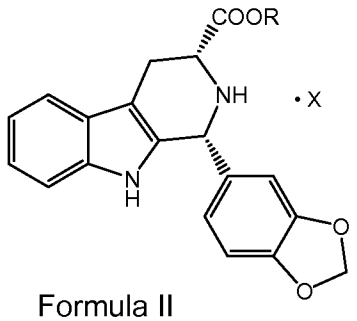
Fig. 4 is a differential scanning calorimetric curve of beta-carboline acid hydrochloride prepared in Example 6.

DETAILED DESCRIPTION OF THE INVENTION

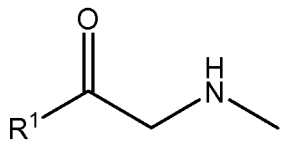
The present invention relates to a process for the preparation of tadalafil.

One aspect of the present invention provides a process for the preparation of tadalafil of Formula I using beta-carboline acid, its derivatives or salts thereof of Formula II.

In an embodiment, the process for the preparation of tadalafil of Formula I comprises condensation of beta-carboline acid, its derivatives or salts thereof of Formula II with sarcosine derivatives or salts thereof having Formula VI in the presence of a suitable reagent.



Formula II



Formula VI

where R is hydrogen, or a C_1 to C_6 straight chain branched or cyclic alkyl, C_1 to C_6 straight chain branched or cyclic alkoxy, or an aryloxy group and the like; R_1 is a halogen, or a C_1 to C_6 straight chain branched or cyclic alkoxy, or an aryloxy or hydroxy group, and X is an inorganic or organic acid.

Suitable solvents which can be used for the above reaction include but are not limited to: alcoholic solvents such as methanol, ethanol, isopropanol, n-butanol, tertiary butanol, and the like; ethers such as diethyl ether, dimethyl ether, diisopropyl ether, tetrahydrofuran, 1,4 dioxane, and the like; hydrocarbon solvents such as toluene, xylene, and the like; polar aprotic solvents like dimethylformamide, dimethylsulphoxide, diemthylacetamide, and the like; chlorinated solvents like dichloromethane, chloroform, carbon tetrachloride,

chlorobenzene and the like; and mixtures of such solvents and aqueous solvents in various proportions.

Suitable temperatures for conducting the reaction range from about -20 to about 100°C, or from about -10 to about 40°C.

Suitable reagents which can be used for condensation include but are not limited to bases like alkali metal alkoxides such as potassium alkoxide, sodium methoxide; alkali metal hydroxides such as sodium hydroxide, potassium hydroxide; alkali metal carbonates such as sodium carbonate, sodium bicarbonate; alkali metal hydrides comprising sodium hydride and the like; organic bases such as triethylamine, trimethyl amine, di-isopropylethylamine and the like; and mixtures thereof; and coupling agents like 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), dicyclohexyl carbodiimide (DCC), and diisopropylcarbodiimide (DIPCDI).

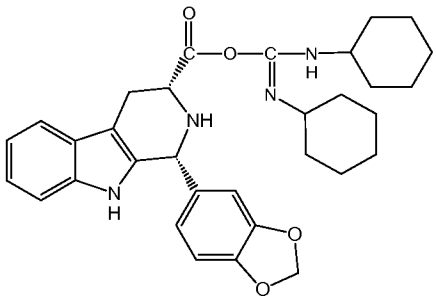
In an embodiment, the compound of Formula II is the beta-carboline acid of Formula IIa.

Optionally, in addition to the coupling agent, a catalytic auxiliary nucleophile may be used to activate the carboxyl group. Suitable catalytic auxiliary nucleophiles which can be used to promote the reaction include, but are not limited to 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimede (HOSu), and N-hydroxy-5-norbene-endo-2,3-dicarboxamide (HONB). The amount of the catalytic auxiliary nucleophile may range from 0.5 to 2 moles per mole of the compound of Formula VI, or it can be used in equimolar quantities.

It is desirable to use from about 1 to 5 moles, or from about 1 to about 3 moles, of coupling agent per mole of the acid of Formula IIa.

In an embodiment, the activation of carboxyl group of the compound of Formula IIa is carried out with dicyclohexyl carbodiimide (DCC), in the presence of the auxillary nucleophile 1-hydroxybenzotriazole (HOBt).

For activation of the carboxyl group, the acid of Formula IIa, is treated with dicyclohexyl carbodiimide (DCC) which leads to the formation of an active ester compound 2-[(1R,3R)-1,2,3,4-tetrahydro-1-(3,4-methylene dioxyphenyl)-9H-pyrido [3,4-b]indole-3-carbonyl]-1,3-dicyclohexyl-isourea of Formula IIi, which may or may not be isolated as an intermediate following the reaction of the present invention.



Formula IIi

Suitably, a catalytic auxiliary nucleophile 1-hydroxybenzotriazole (HOBt) is added to promote the reaction. The catalytic auxillary nucleophiles are introduced in carodiimide mediated couplings to reduce possible side reactions, including racemization, and to increase reaction rate when active esters are used. In addition to providing excellent leaving groups, all the additives are capable of acting as proton acceptors aiding deprotonation of the ammonium ion intermediate and thereby greatly increasing reaction rate. The cyclohexylurea formed during the course of the reaction as a byproduct can be separated by filtration.

Alternatively, the active ester can be generated through use of a phosphonium reagent like benzotriazole-1-yloxy-trisphosphonium hexafluorophosphate (PyBOP). This reagent is used in tandem with a tertiary amine base, which abstracts the acidic carboxyl proton.

The pH of the reaction mixture can range from about 5 to about 14.

The reaction will be conducted to completion, frequently requiring time periods ranging from about 10 hours to about 60 hours, or longer, depending upon the reactants and conditions chosen.

Suitably, the product is extracted into an organic solvent such as: chlorinated solvents like dichloromethane, chloroform, carbon tetrachloride, chlorobenzene and the like; and hydrocarbon solvents such as toluene, xylene, and the like. The organic layer is then suitably washed with water to wash out the water soluble salts.

Optionally, an alcohol such as methanol may be added for clearing any emulsions formed during extractions or water washings.

In another embodiment, the compound of Formula II where R is a C_1 to C_6 straight chain branched or cyclic alkyl, C_1 to C_6 straight chain branched or cyclic

alkoxy, or aryloxy group and the like may be prepared from the corresponding acid of Formula IIa using processes known to one skilled in the art.

The process used for condensation of the derivatives of Formula II with the compound of Formula VI is similar to the process described above for the condensation of the beta-carboline acid or a salt thereof of Formula II with the compound of Formula VI.

Tadalafil obtained above may be further purified by recrystallization or slurrying in a suitable solvent.

Recrystallization involves providing a solution of tadalafil in a suitable solvent and then crystallizing the solid from the solution.

Suitable organic solvents which can be used for recrystallization or slurrying include but are not limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, and the like; halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketonic solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ether solvents such as diethyl ether,dimethyl ether, di-isopropyl ether, methyl tertiary-butyl ether, tetrahydrofuran, 1,4-dioxane and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; nitrile solvents such as acetonitrile, propionitrile and the like; and mixtures thereof in various proportions.

The concentration of tadalafil in the solvent can range from 40 to 80% or more. For recrystallization, a solution can be prepared at an elevated temperature if desired to achieve a desired concentration. Any temperature is acceptable for the dissolution as long as a clear solution of the tadalafil is obtained and is not detrimental to the drug substance chemically or physically. The solution may be brought down to room temperature for further processing if required or an elevated temperature may be used. A higher temperature will allow the precipitation from solutions with higher concentrations of tadalafil resulting in better economies of manufacture.

The compound obtained can be further dried suitably using a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying can be carried out at temperatures of about 35° C to about 70° C.

The drying can be carried out for any desired time periods to achieve the desired product purity, times from about 1 to 20 hours, or longer, frequently being sufficient.

In another aspect, the present invention provides substantially pure beta-carboline acid of Formula IIa or its salts.

The beta-carboline acid is capable of forming a wide variety of mono or di-acid salts with various inorganic and organic acids. The acids that may be used include, but are not limited to, those that form anions like acetate, benzoate, bicarbonate, bitartarate, citrate, iodide, chloride, bromide, mesylate, tartarate, and the like.

The beta-carboline acid is also capable of forming base salts with various cations. Examples of such salts include alkali metal, alkaline earth metal, and transition metal salts like salts of calcium, magnesium, sodium, lithium, zinc, potassium and the like.

In one embodiment the acid is hydrochloric acid and the salt obtained is hydrochloride salt of the beta-carboline acid.

Crystalline beta-carboline acid hydrochloride obtained using the above process is characterized by any of its X-ray powder diffraction ("XRPD") patterns, infrared absorption ("IR") spectra, and differential scanning calorimetry ("DSC") curves.

Crystalline beta-carboline acid hydrochloride obtained in the present invention is characterized by its XRPD pattern. The XRPD data reported herein was obtained using Cu Kα radiation, having the wavelength 1.541 Å and were obtained using a Bruker Axe D8 Advance Powder X-ray Diffractometer.

The crystalline beta-carboline acid hydrochloride is characterized by its XRPD pattern substantially in accordance with the pattern of Fig. 2. It is also characterized by an XRPD pattern having significant peaks at about 6.6, 9.9, 11.2, 13.4, 13.7, 17.1, and 21.5, ± 0.2 degrees 2θ. It is also characterized by the additional XRPD peaks at about 22.7, 29.4, and 23.9, ± 0.2 degrees 2θ.

The infrared (IR) absorption spectrum of crystalline beta-carboline acid hydrochloride has been recorded on a Perkin Elmer System Spectrum 1 model spectrophotometer, between 450 cm^{-1} and 4000 cm^{-1}, with a resolution of 4 cm^{-1}, the test compound being at the concentration of 1% by mass in a potassium bromide pellet.

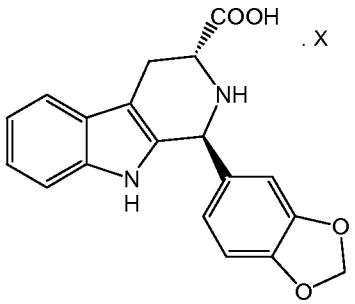
The crystalline beta-carboline acid hydrochloride is characterized by an infrared absorption spectrum in potassium bromide comprising peaks at about 753, 1040, 1205, 1252, 1757, 3226, 3621, and 1451, ± 5 cm^{-1}. Crystalline beta-carboline acid is also characterized by its infrared absorption spectrum in potassium bromide substantially in accordance with the spectrum of Fig. 3.

Differential scanning calorimetric analysis was carried out using a DSC Q1000 model from TA Instruments with a ramp of 10°C/minute. The starting temperature was 40°C and ending temperature was 300°C.

The crystalline beta-carboline acid hydrochloride has a characteristic differential scanning calorimetry curve substantially in accordance with Fig. 4, having an endotherm at about 217°C.

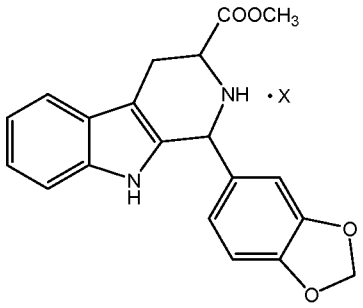
By "substantially pure beta-carboline acid" it is meant that the acid or its salts prepared according to the process of the present invention contain less than about 5%, or less than about 1%, of any process related impurities, especially, impurities like the trans-isomeric impurity of beta carboline, the ester impurity of beta carboline, D-tryptophan, N-acetyl D-tryptophan, and piperonal, as characterized by a high performance liquid chromatography ("HPLC") chromatogram obtained from a mixture comprising the desired compound and one or more of the said impurities. The percentage here is a weight percentage derived from the area-% of the peaks representing the said impurities.

As used herein: "trans isomeric impurity of beta-carboline" refers to (1S, 3R)-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylic acid represented by Formula IIb; and



Formula IIb

"ester impurity of beta-carboline" refers to methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate represented by Formula IIc



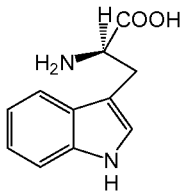
Formula IIc

where X is an inorganic or organic acid.

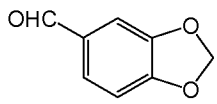
In yet another aspect, the present invention provides a process for the preparation of beta-carboline acid or its salts of Formula IIa.

In an embodiment, a process for the preparation of beta-carboline acid or its salts of Formula IIa comprises:

a) reacting D-tryptophan of Formula III with piperonal of Formula IV in the presence of an acid and a suitable solvent to afford a mixture of cis- and trans-isomers of 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylic acid or its salts represented by Formula V;

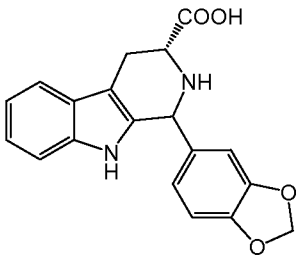


Formula III

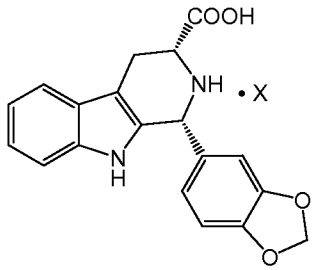


Formula IV

b) conversion of a mixture of cis- and trans-isomers of the compound of Formula V into the cis-isomer of beta-carboline acid hydrochloride of Formula IIa, optionally followed by purification by recrystallization or slurrying in a suitable solvent.



Formula V



Formula IIa

This process is shown schematically as the first two steps in Fig. 1.

Step a) involves the reaction of D-tryptophan of Formula III with piperonal of Formula V in the presence of an acid and optionally a suitable solvent to afford a mixture of cis- and trans-isomers represented by Formula V.

Suitable solvents which can be used for the reaction include, but are not limited to: halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketonic solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, and the like; hydrocarbon solvents such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; and mixtures thereof.

Suitable acids which can be used include but are not limited to: inorganic acids such as hydrochloric acid, sulphuric acid, and the like; organic acids such as oxalic acid, trifluoroacetic acid, tartaric acid, formic acid, acetic acid, para-toluene sulfonic acid and the like; and mixtures thereof.

Optionally, the reaction can be conducted with the acid being used as the medium of the reaction without the use of any solvent system.

The reaction temperatures can range from about 40 °C to about -20 °C, or at temperatures as high as about 40 °C or about 70 °C or more.

The time period required for the completion of reaction will vary depending on the conditions chosen, and frequently will range from about 5 hours to about 50 hours, or about 20 hours to about 30 hours.

The product obtained may contain a 1:9 to 9:1 mixture of the cis- and trans-isomers of the beta-carboline acid of Formula V.

Optionally, the isomeric mixture is used for the next step without isolating the product. The reaction medium containing the mixture of isomers can be taken directly into the next step, or it can be extracted into an organic layer and the solvent distilled off to form a residue.

Step b) involves the conversion of the cis- and trans-isomeric mixture of Formula V into the desired isomer of Formula IIa by treatment with an acid, optionally followed by purification by recrystallization or slurrying in a suitable solvent.

Suitable acids which can be used include but are not limited to: inorganic acids such as hydrochloric acid, sulphuric acid, and the like; organic acids such as oxalic acid, tartaric acid, acetic acid, para-toluene sulfonic acid, formic acid and the like; and mixtures thereof.

The mixture of isomers of Formula V may be taken into the aqueous or non-aqueous acid solution in the form of a residue, or in the form of a solution in a suitable solvent.

Suitable solvents which can be used for the dissolution of a residue include but are not limited to: ketonic solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, and the like; and mixtures thereof.

The treatment with acid is continued until the desired amount of conversion is achieved. This frequently involves stirring of the reaction mixture for a period of about 5 hours to about 50 hours, or about 25 hours to about 35 hours.

The quantity of acid which can be used for the reaction may range from about 1 to about 30 molar equivalents, per equivalent of the isomeric mixture compound of Formula V.

The pH of the mass may range from about 0.1 to about 5, or from about 0.1 to about 2.

Optionally, the required isomer of the acid obtained of Formula IIa may be further purified by recrystallization or slurrying in a suitable solvent to increase the purity of the compound.

Recrystallization involves providing a solution of the intermediate in a suitable solvent and then crystallizing the solid from the solution.

Suitable organic solvents which can be used for recrystallization or slurrying include but are not limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, and the like; halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketonic solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ether solvents such as diethyl ether,dimethyl ether, di-isopropyl ether, methyl tertiary-butyl ether, tetrahydrofuran, 1,4-dioxane and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane,

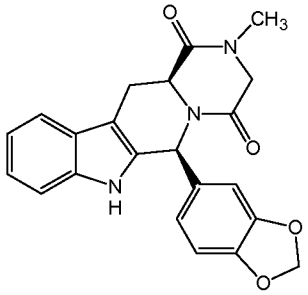
cyclohexane and the like; nitrile solvents such as acetonitrile, propionitrile and the like; and mixtures thereof in various proportions.

The concentration of the compound in the solvent can range from 40 to 80% or more. A solution can be prepared at an elevated temperature if desired to achieve a desired concentration. Any temperature is acceptable for the dissolution as long as a clear solution of the tadalafil is obtained and is not detrimental to the drug substance chemically or physically. The solution may be brought down to room temperature for further processing if required or an elevated temperature may be used. A higher temperature will allow the precipitation from solutions with higher concentrations, resulting in better economies of manufacture.

The compound obtained can be further dried suitably using a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying can be carried out at temperatures of about 35° C to about 70° C. The drying can be carried out for any desired time periods to achieve a desired purity, times from about 1 to 20 hours frequently being sufficient.

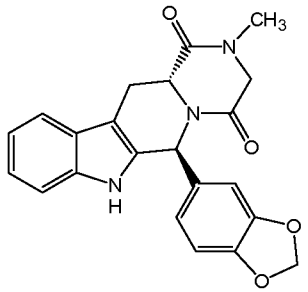
Tadalafil obtained by the process of the present invention is "substantially pure." By "substantially pure" it is meant that tadalafil or any of the pharmaceutically acceptable salts prepared in accordance with the present invention contains less than about 1%, or less than about 0.5%, of process related impurities as characterized by a high performance liquid chromatography ("HPLC") chromatogram obtained from a mixture comprising the desired compound and one or more of the said impurities. The percentage here is weight percent derived from the area-% of the peaks representing the said impurities. Substantially pure tadalafil is considered to be "substantially free" from these impurities.

Tadalafil prepared according to the process of the present invention has a low level of impurities as determined by HPLC. For example, it contains less than about 0.15%, or about 0.05%, of (6S,12aS)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino [2',1':6,1]pyrido[3,4-b]indole-1,4-dione represented by Formula 1a (hereinafter referred to as "tadalafil chiral impurity");



Formula Ia

it contains less than about 0.15%, or about 0.03%, of (6S,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione represented by Formula Ib (hereinafter referred to as "trans-tadalafil impurity"); and



Formula Ib

it contains about 0.005% to about 0.2%, about 0.005% to about 0.1%, or about 0.005% to about 0.05%, of piperonal.

Tadalafil obtained according to the process of the present invention has a particle size (D_{90}) of about 100 μm to about 200 μm and a bulk density of about 0.25 to 0.5 g/ml.

The D_{90} refers to the value for the particle size for which at least 90 volume percent of the particles have a size smaller than the value. Methods for determining D_{90} include laser diffraction, such as using Malvern Instruments Ltd. (of Malvern, Worcestershire, United Kingdom) equipment.

Tadalafil obtained by the process of the present invention has a D_{90} of about 100 μm to about 200 μm.

Tadalafil obtained by the process of the present invention has a bulk density of about 0.25 g/ml to about 0.5 g/ml. The bulk densities are determined using Test 616 "Bulk Density and Tapped Density," *United States Pharmacopeia 24*, pages 1913-4 (United States Pharmacopeial Convention, Inc., Rockville, Maryland, 1999).

Still another aspect of the present invention provides a pharmaceutical composition comprising pure tadalafil or its pharmaceutically acceptable salts along with one or more pharmaceutically acceptable carriers, diluents and/or other excipients.

The pharmaceutical composition may be formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as but not limited to syrups, suspensions, dispersions, and emulsions; and injectable preparations such as but not limited to solutions, dispersions, and freeze dried compositions. Formulations may be in the form of immediate release, delayed release or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared by direct blending, dry granulation or wet granulation or by extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated or modified release coated. Compositions of the present invention may further comprise one or more pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients that find use in the present invention include, but are not limited to: diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, pregelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, crospovidone, croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins, resins; release rate controlling agents such as hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose, methyl cellulose, various grades of methyl

methacrylates, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but are not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

In the compositions of present invention tadalafil or its pharmaceutically acceptable salts is a useful active ingredient in the range of 0.5 mg to 50 mg, or 1 mg to 25 mg, per dosage form unit.

Certain specific aspects and embodiments of this invention are described in further detail by the examples below, which examples are only illustrative and not intended to limit the scope of the appended claims in any manner.

EXAMPLE 1

PREPARATION OF (1R,3R)-1,2,3,4-TETRAHYDRO-1-(3,4-METHYLENE DIOXYPHENYL)-9H-PYRIDO[3,4-b]INDOLE-3-CARBOXYLIC ACID HYDROCHLORIDE (FORMULA IIa)

1500 ml of dichloromethane and 150 g of D-tryptophan were taken into a clean and dry round bottom flask followed by stirring for 10 minutes. 132.3 g of piperonal was added followed by cooling to 3 °C. 90 ml of trifluoroacetic acid was added followed by heating to 42 °C and stirring for about 25 hours. After the completion of the reaction, the reaction mass was cooled to 28 °C followed by addition of 1500 ml of dichloromethane and 750 ml of 10% aqueous sodium bicarbonate solution. The resultant suspension was stirred for 10 minutes followed by addition of 600 ml of methanol and then stirring for about 15 minutes. Organic and aqueous layers were separated and the aqueous layer was extracted with 300 ml of dichloromethane. The combined organic layer was taken into a clean and dry round bottom flask followed by addition of 750 ml of water.

The resultant suspension was stirred for about for 15 minutes followed by addition of 300 ml of methanol and stirring for about 15 minutes. Organic and aqueous layers were separated and the organic layer was taken into a clean and dry round bottom flask. The organic layer was distilled completely at 40 °C followed by addition of 1500 ml of 1 N hydrochloric acid. The resultant reaction mass was heated to 50 °C followed by stirring for about for 40 hours. The reaction mass was then slowly cooled to 5 °C and maintained for 10 minutes followed by

filtration of the separated solid. The solid was washed with pre-cooled (to 5°C) water. The solid was dried at 60 °C for 7 hours under a vacuum of about 600 mm Hg to afford 220 g of the title compound.

Purity by HPLC: 93.31%.

Ester impurity: 0.72%.

Trans-isomeric impurity: 0.74%.

EXAMPLE 2

PREPARATION OF (6R,12aR)-2,3,6,7,12,12a-HEXAHYDRO-2-METHYL-6-(3,4-METHYLENE DIOXYPHENYL)-PYRAZINO [2',1':6, 1] PYRIDO [3, 4-b] INDOLE-, 1,4-DIONE (FORMULA IIa)

Step A: Preparation of methylamino-acetic acid ethyl ester (Formula VI)

335 ml of dichloromethane was taken into a round bottom flask and 67 g of methylamino-acetic acid ethyl ester hydrochloride was added to it at 28 °C. A mixture of 67 ml of 20% aqueous ammonia solution and 67 ml of water was added to it at 28 °C. The mixture was stirred at 28 °C for 20 minutes. The organic layer was separated and washed with 134 ml of water. The organic layer was taken into a round bottom flask and distilled off under vacuum at 40 °C. To the residue obtained, 250 ml of dimethylformamide was added, and the solution was kept aside for further use during condensation.

Step B: Preparation Of (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-Methyl-6-(3,4-Methylene Dioxyphenyl)-Pyrazino [2',1':6, 1] Pyrido [3, 4-b] Indole-, 1,4-Dione; Tadalafil (Formula I)

2500 ml of dimethylformamide was taken into a dry round bottom flask and 50 g of the beta-carboline acid of Formula I obtained in Example 1 was added to it. The reaction mass was cooled to 4 °C. 24.4 g of triethylamine was added to the above reaction mass at the same temperature. The reaction mass was maintained at 4 °C for 20 minutes. 33.2 g of dicyclohexylcarbodiimide was added to the reaction mass, and stirred at 4°C for 1 hour. 27 g of 1-hydroxybenzotriazole was added to the reaction mass at 4 °C. The methylamino-acetic acid ethyl ester solution prepared above was added to the reaction mass at 2 °C over 20 minutes. After the addition was complete, the temperature of the reaction mass was raised to 28 °C. The reaction mass was maintained at 28 °C for 34 hours. The reaction

mass was then filtered and the separated solid washed with 100 ml of dichloromethane. The filtrate was taken into a round bottom flask and 500 ml of water and 500 ml of dichloromethane were added to it. The reaction mass was stirred at 28 °C for 10 minutes. The organic layer was separated. The aqueous layer was extracted into 100 ml of dichloromethane. The combined organic layer was washed with 100 ml of water followed by 400 ml of 10% sodium bicarbonate solution. The organic layer was then washed with 400 ml of 5% aqueous oxalic acid solution, followed by 400 ml of water. The organic layer was dried over sodium sulfate and 50% of the solvent was distilled off atmospherically at 46 °C. The remaining reaction mass was cooled gradually to 3 °C and maintained for 1 hour. The separated solid was filtered and washed with 25 ml of methanol. The compound was then suction dried under vacuum for about 30 minutes to yield 26 g of the title compound.

Purity by HPLC: 99.8%.

EXAMPLE 3

PROCESS FOR THE PURIFICATION OF TADALAFIL (FORMULA I)

25 g of the tadalafil from Example 2 and 4750 ml of methanol were charged into a clean and dry round bottom flask followed by heating to 65°C. 2400 ml of methanol were distilled off at about 65°C from the solution followed by cooling to about 4°C. The mass was stirred at 4°C for 45 minutes followed by filtration of separated solid. The solid was washed with 25 ml of methanol. 1201.5 ml of acetone was added to it, followed by heating to about 60°C for 2 hours. 600 ml of acetone was distilled from the reaction solution followed by cooling to 3 °C for 2.5 hours. The separated solid was filtered and the solid was washed with 20 ml of chilled acetone. The solid was dried at about 62°C for 5 hours under a vacuum of about 600 mm Hg to afford 16.3 g of the title compound.

Purity by HPLC: 99.98%.

Individual impurities: Less than 0.01%.

EXAMPLE 4

PREPARATION OF (1R,3R)-1,2,3,4-TETRAHYDRO-1-(3,4-METHYLENE DIOXYPHENYL) -9H-PYRIDO [3,4-b]INDOLE-3-CARBOXYLIC ACID (FORMULA IIa)

500 ml of dichloromethane was taken into a round bottom flask, and 100 g of (1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene dioxy phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate was added to it. The mixture was stirred at 30 °C for 15 minutes. A solution of 150 ml of aqueous ammonia and 150 ml water was added to the reaction mixture. The reaction mixture was stirred at 30 °C for another 20 minutes. The organic and aqueous layers were separated and the organic layer was distilled off under vacuum. To the obtained residue 500 ml of water was added. 20.8 g of sodium hydroxide flakes were added to the reaction mass and heated to 70 °C. The reaction mass was maintained at 70 °C for 4 hours. Reaction completion was monitored using thin layer chromatography. After the reaction was complete, the reaction mass was cooled to 3 °C. pH of the reaction mass was adjusted to 2.0 with hydrochloric acid at 3 °C. The reaction mass was stirred at 3 °C for 60 minutes. The separated solid was filtered and washed with 100 ml of chilled water. The solid was dried under vacuum for 30 to 60 minutes followed by drying at 60 to 70° C for 4 to 5 hours to yield 78 g of the title compound.

EXAMPLE 5

PREPARATION OF (6R,12aR)-2,3,6,7,12,12A-HEXAHYDRO-2-METHYL-6-(3,4-METHYLENE DIOXYPHENYL)-PYRAZINO [2',1':6, 1] PYRIDO [3, 4-b] INDOLE-1,4-DIONE (FORMULA I)

100 ml of dimethylformamide was taken into a dry round bottom flask and 10 g of the beta-carboline acid obtained in Example 4 was added to it. The reaction mass was cooled to 5 °C. 4.5 g of triethylamine was added to the reaction mass at the same temperature. 7.4 g of dicyclohexylcarbodiimide was added to the reaction mass, and stirred at 4 °C for 1 hour. 6.1 g of 1-hydroxybenzotriazole was added to the reaction mass, followed by addition of the methylamino-acetic acid ethyl ester, prepared by a process similar to Example 2, Step A, at 3 °C. The temperature of the reaction mass was raised to 28 °C. The reaction mass was

maintained at 28 °C for about 2 days. Reaction completion was checked using thin layer chromatography. After completion of the reaction, the reaction mass was filtered to separate the unwanted by-product. The filter cake was washed with 50 ml of dichloromethane. The combined filtrate was taken into a round bottom flask and 100 ml of water, and 50 ml of dichloromethane was added to it. The reaction mass was stirred for 20 minutes. The aqueous and organic layers were separated, and the aqueous layer was extracted into 20 ml of dichloromethane. The combined organic layer was washed with 50 ml of water followed by 50 ml of 10% aqueous sodium bicarbonate solution. Then the organic layer was washed with 40 ml of 5% oxalic acid solution, and finally it was washed with 50 ml of water. The organic layer was dried over sodium sulfate. The organic layer was distilled under vacuum. The obtained residue was cooled to 28°C, and 20 ml of methanol was added to it. The reaction mass was then cooled to 3°C. The reaction mass was stirred at 3°C for 60 minutes. The separated solid was filtered, and washed with 5 ml of chilled methanol. The compound was suction dried under vacuum for 30 minutes. The wet compound was taken into a round bottom flask and 50 ml of acetone was added to it. The reaction mass was heated to reflux, and checked for clear dissolution. After clear dissolution was obtained, 50% of the acetone was distilled from the reaction mass. The reaction mass was then cooled to 3°C, and stirred for 30 minutes. The solid was filtered and washed with 5 ml of chilled acetone. The solid was suction dried under vacuum followed by drying at 50 to 60°C for 1 to 2 hours to yield 1.2 g of the title compound.

EXAMPLE 6

PREPARATION OF (1R,3R)-1,2,3,4-TETRAHYDRO-1-(3,4-METHYLENE DIOXYPHENYL) -9H-PYRIDO [3,4-b]INDOLE-3-CARBOXYLIC ACID HYDROCHLORIDE (FORMULA IIa)

500 ml of dichloromethane was taken into a round bottom flask and 50 g of D-tryptophan was added. 44.1 g of piperonal was added at 28°C. 36.2 ml of trifluoroacetic acid was then added and the reaction mass was heated to 40°C. The reaction mass was maintained at 40°C for 9 hours. Reaction completion was checked using thin layer chromatography. After the reaction was complete, the reaction mass was allowed to cool to 28°C and 250 ml of dichloromethane and

250 ml of methanol was added. The reaction mass was then quenched with 250 ml of 8% sodium bicarbonate solution. The organic layer was separated, and the aqueous layer was extracted into 100 ml of dichloromethane. The combined organic layer was distilled under atmospheric pressure at 45°C. 250 ml of 1 N hydrochloric acid was added to the residue obtained and the reaction mass was heated to 50°C. The reaction mass was maintained at 54°C for 14 hours. 150 ml toluene was added and the mass cooled to 17 °C. The reaction mass was maintained at 17°C for 30 minutes. The separated solid was filtered and washed with 100 ml of toluene followed by washing with 50 ml of water. The compound was dried at 67°C for 4 hours to yield 79 g of the title compound (yield: 86.5%).

Purity by HPLC: 98.45%.

Ester impurity: 0.5%.

Trans-isomeric impurity: 0.6%.

Piperonal: 0.05%

EXAMPLE 7

PREPARATION OF (6R,12AR)-2,3,6,7,12,12A-HEXAHYDRO-2-METHYL-6-(3,4-METHYLENE DIOXYPHENYL)-PYRAZINO [2',1':6, 1] PYRIDO [3,4-b] INDOLE-1,4-DIONE (FORMULA I)

25 g of (1R,3R)-1,2,3,4-tetrahydro-1-(3,4-methylene dioxyphenyl) -9H-pyrido [3,4-b]Indole-3-carboxylic acid hydrochloride obtained in Example 6 and 200 ml of dimethylformamide were taken into a round bottom flask and 10.15 g of triethylamine was added. 13.5 g of 1-hydroxybenzotriazole was added under stirring. 33 g of sarcosine ethyl ester, and 16.7 g of dicyclohexylcarbodiimide were added. The reaction mass was heated to 53 °C and maintained for 4 hours. Reaction completion was checked using thin layer chromatography. After the reaction was completed, the reaction mass was cooled to 12 °C and maintained for 60 minutes. The reaction mass was then filtered and the filter bed was washed with 50 ml of dichloromethane. To the combined filtrate 250 ml of dichloromethane and 250 ml of water were added and the layers separated. The aqueous layer was extracted with 50 ml of dichloromethane. To the combined organic layer another 75 ml of dichloromethane was added. The combined organic layer was washed with a solution of 16 g of sodium bicarbonate in 125 ml of water. 75 ml of

methanol was added to the organic layer and the organic layer was washed with 100 ml of water. The organic layer was distilled atmospherically at 44°C to distill off 50% of the solvent. The remaining solution was cooled to 3°C and maintained for 2 hours. The separated solid was filtered and washed with chilled methanol. The wet compound was dried under suction for 30 minutes to yield 19.4 g of the title compound (yield: 74.3%).

Purity by HPLC: 99.92%.

EXAMPLE 8

PREPARATION OF (6R,12aR)-2,3,6,7,12,12A-HEXAHYDRO-2-METHYL-6-(3,4-METHYLENE DIOXYPHENYL)-PYRAZINO [2',1':6, 1] PYRIDO [3,4-b] INDOLE-1,4-DIONE (FORMULA I)

625 ml of methanol and 625 ml of acetone were taken into a clean round bottom flask and 25 g of tadalafil was added to it. The mixture was heated to 55°C and maintained for 20 minutes. 50 % of the solvent was distilled off atmospherically at 56°C. The remaining mixture was cooled to 2°C and maintained for 1 hour. The separated solid was filtered and washed with 25 ml of methanol. The wet material was taken into another round bottom flask and 1500 ml of acetone was added to it. The mixture was heated to 50°C and maintained for 30 minutes. The solution was filtered in the hot condition through a celite bed and the bed was washed with 50 ml of acetone. 50% of the solvent was distilled off from the filtrate atmospherically at 55°C. The resulting solution was cooled to 2°C and maintained for 1 hour. The separated solid was filtered and washed with 12.5 ml of acetone. The wet compound was dried at 55°C for 5 hours to yield 14.6 g of the title compound (yield: 58.4%)

Purity by HPLC: 99.98%.

Piperonal: 0.01%

Other individual impurities: less than 0.01%.

EXAMPLE 9

DETERMINATION OF IMPURITIES IN TADALAFIL

The HPLC analysis conditions are as described in Table 1.

Table 1

<table>
<tr><td>Column and Packing:</td><td>Symmetry shield RP18, 250×4.6mm, 5 µm.</td></tr>
<tr><td>Buffer:</td><td>1.38 g of sodium dihydrogen orthophosphate monohydrate dissolved in 1000 ml water and the pH of the solution adjusted to 2.5 with dilute phosphoric acid.</td></tr>
<tr><td>Mobile Phase A:</td><td>A degassed mixture of buffer preparation and acetonitrile in the ratio of 80:20.</td></tr>
<tr><td>Mobile Phase B:</td><td>A degassed mixture of acetonitrile and water in the ratio of 80:20.</td></tr>
<tr><td>Gradient:</td><td>
<table>
<tr><th>Time (in minutes)</th><th>% B</th><th>% A</th></tr>
<tr><td>0.01</td><td>10</td><td>90</td></tr>
<tr><td>5.0</td><td>10</td><td>90</td></tr>
<tr><td>40</td><td>90</td><td>10</td></tr>
<tr><td>50</td><td>90</td><td>10</td></tr>
<tr><td>55</td><td>10</td><td>90</td></tr>
<tr><td>60</td><td>10</td><td>90</td></tr>
</table>
</td></tr>
<tr><td>Temperature:</td><td>27° C</td></tr>
<tr><td>Injection volume:</td><td>10 µL</td></tr>
<tr><td>Flow rate:</td><td>1.0 mL per minute</td></tr>
<tr><td>Wavelength:</td><td>220 nm</td></tr>
<tr><td>Diluent:</td><td>Acetonitrile:water (1:1)</td></tr>
<tr><td>Run time:</td><td>60 minutes</td></tr>
</table>

IMPURITY NAME	RRT
Piperonal	0.66
Beta carboline acid	0.39
Tadalafil	1.00

EXAMPLE 10

DETERMINATION OF IMPURITIES IN BETA-CARBOLINE ACID

The HPLC analysis conditions are described in Table 2.

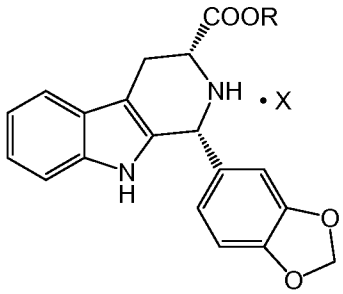
Table 2

<table>
<tr><td>Column and Packing:</td><td>KROMASIL 100 C18 250×4.6, 5 µm.</td></tr>
<tr><td>Buffer:</td><td>1.38 g of sodium-di-hydrogen orthophosphate monohydrate dissolved in 1000 ml water and the pH of the solution adjusted to 2.5 with dilute phosphoric acid.</td></tr>
<tr><td>Mobile Phase A:</td><td>A degassed mixture of buffer preparation and acetonitrile in the ratio of 80:20 v/v.</td></tr>
<tr><td>Mobile Phase B:</td><td>A degassed mixture of acetonitrile and water in the ratio of 80:20 v/v.</td></tr>
<tr><td>Gradient:</td><td>
<table>
<tr><th>Time (in minutes)</th><th>% B</th><th>% A</th></tr>
<tr><td>0.01</td><td>5</td><td>95</td></tr>
<tr><td>5.0</td><td>5</td><td>95</td></tr>
<tr><td>20</td><td>30</td><td>70</td></tr>
<tr><td>40</td><td>60</td><td>40</td></tr>
<tr><td>50</td><td>60</td><td>40</td></tr>
<tr><td>55</td><td>5</td><td>95</td></tr>
<tr><td>60</td><td>5</td><td>95</td></tr>
</table>
</td></tr>
<tr><td>Temperature:</td><td>27°C</td></tr>
<tr><td>Injection volume:</td><td>5 µL</td></tr>
<tr><td>Flow rate:</td><td>1.0 mL per minute</td></tr>
<tr><td>Wavelength:</td><td>220 nm</td></tr>
<tr><td>Diluent:</td><td>Buffer:Acetonitrile (7:3)</td></tr>
<tr><td>Run time:</td><td>60 minutes</td></tr>
</table>

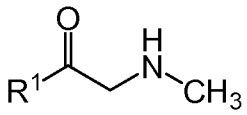
IMPURITY NAME	RRT
Piperonal	1.47
Trans isomeric impurity	1.14
D-Tryptophan	0.24
N-Acetyl D-Tryptophan	0.73
Beta-carboline acid	1.00

CLAIMS:

1. A process for preparing tadalafil, comprising reacting a compound having a formula:



wherein R is hydrogen, a C_1 to C_6 straight chain branched or cyclic alkyl group, a C_1 to C_6 straight chain branched or cyclic alkoxy group, or an aryloxy group, and X is an inorganic or organic acid, with a compound having a formula:



wherein R^1 is a halogen, a C_1 to C_6 straight chain branched or cyclic alkoxy group, or an aryloxy or hydroxy group, or a salt thereof, to form tadalafil.

2. The process of claim 1, wherein reacting occurs in the presence of a coupling agent.

3. The process of claim 1, wherein reacting occurs in the presence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole.

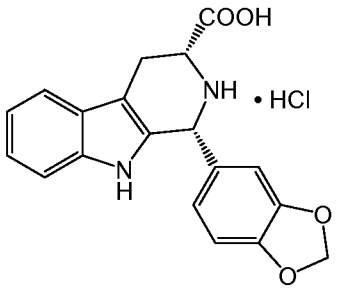
4. The process of claim 1, wherein reacting occurs in the presence of a chlorinated solvent.

5. The process of claim 1, wherein reacting occurs in the presence of dichloromethane.

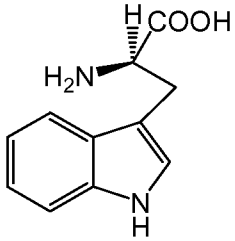
6. The process of claim 1, wherein tadalafil obtained is further purified in a solvent or a mixture of solvents.

7. The process of claim 6, wherein a solvent comprises a ketone, or an alcohol.

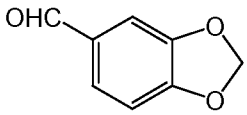
8. The process of claim 1, wherein a compound having a formula:



is prepared by reacting a compound having a formula:



with a compound having a formula:



to form an intermediate, then reacting with an acid.

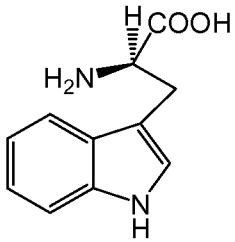
9. The process of claim 8, wherein reacting to form an intermediate occurs in the presence of an organic solvent.

10. The process of claim 8, wherein reacting to form an intermediate occurs in the presence of dimethylformamide.

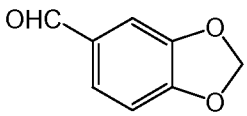
11. The process of claim 8, wherein an intermediate is not isolated before reacting with an acid.

12. A process for preparing tadalafil, comprising:

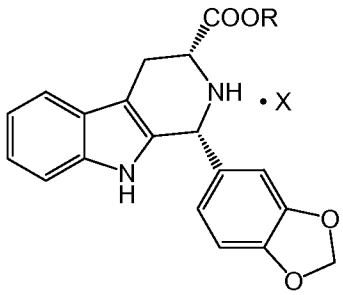
a) reacting a compound having a formula:



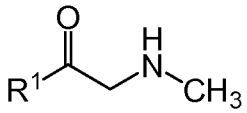
with a compound having a formula:



to form an intermediate, then further reacting with an acid to form a compound having a formula:



wherein R is hydrogen, a C_1 to C_6 straight chain branched or cyclic alkyl group, a C_1 to C_6 straight chain branched or cyclic alkoxy group, or an aryloxy group, and X is an inorganic or organic acid, and further reacting with a compound having a formula:



wherein R^1 is a halogen, a C_1 to C_6 straight chain branched or cyclic alkoxy group, or an aryloxy or hydroxy group, or a salt thereof, to form tadalafil.

13. The process of claim 12, wherein reacting to form an intermediate occurs in the presence of an organic solvent.

14. The process of claim 12, wherein reacting to form an intermediate occurs in the presence of dimethylformamide.

15. The process of claim 12, wherein an intermediate is not isolated before reacting with an acid.

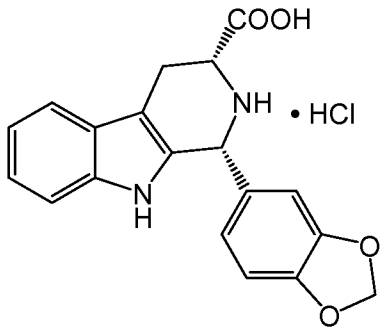
16. The process of claim 12, wherein reacting to form tadalafil occurs in the presence of a coupling agent.

17. The process of claim 12, wherein reacting to form tadalafil occurs in the presence of dicyclohexylcarbodiimide and 1-hydroxybenzotriazole.

18. The process of claim 12, wherein reacting to form tadalafil occurs in the presence of a chlorinated solvent.

19. The process of claim 12, wherein reacting to form tadalafil occurs in the presence of dichloromethane.

20. A compound having a formula:



and being substantially free of isomeric impurities.

21. Tadalafil, containing about 0.005 to about 0.2 percent by weight of piperonal.

22. Tadalafil, containing about 0.005 to about 0.1 percent by weight of piperonal.

23. Tadalafil, containing about 0.005 to about 0.05 percent by weight of piperonal.

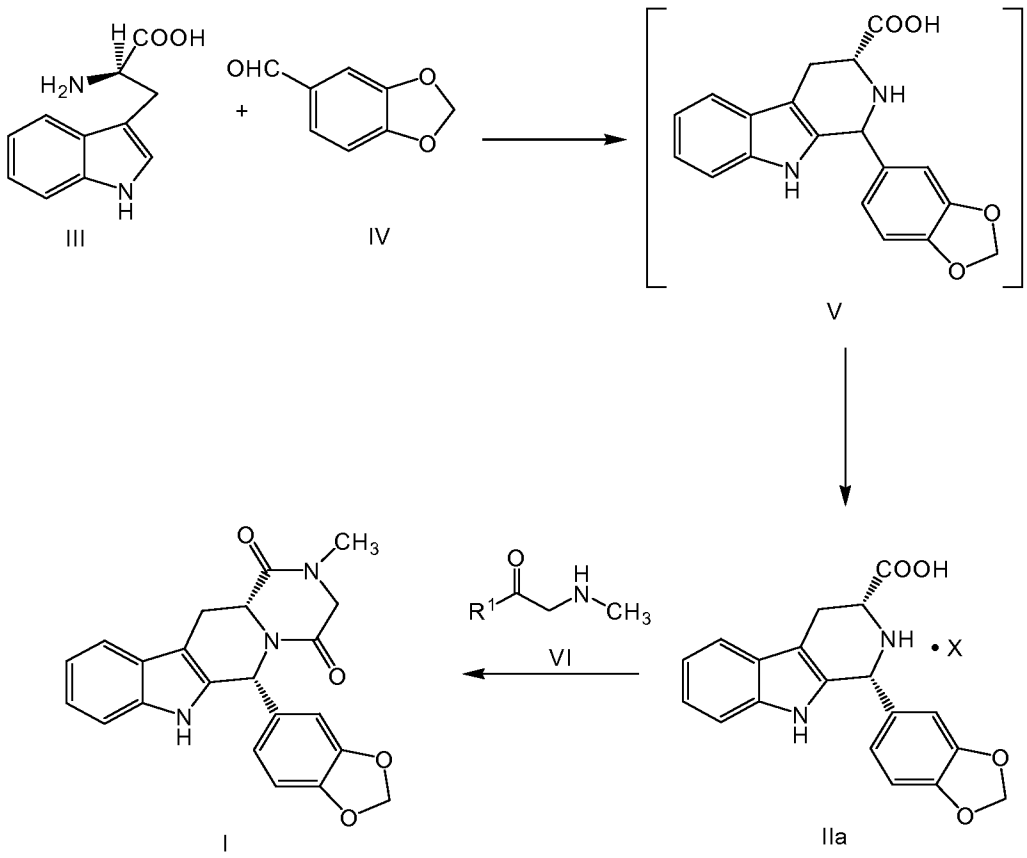
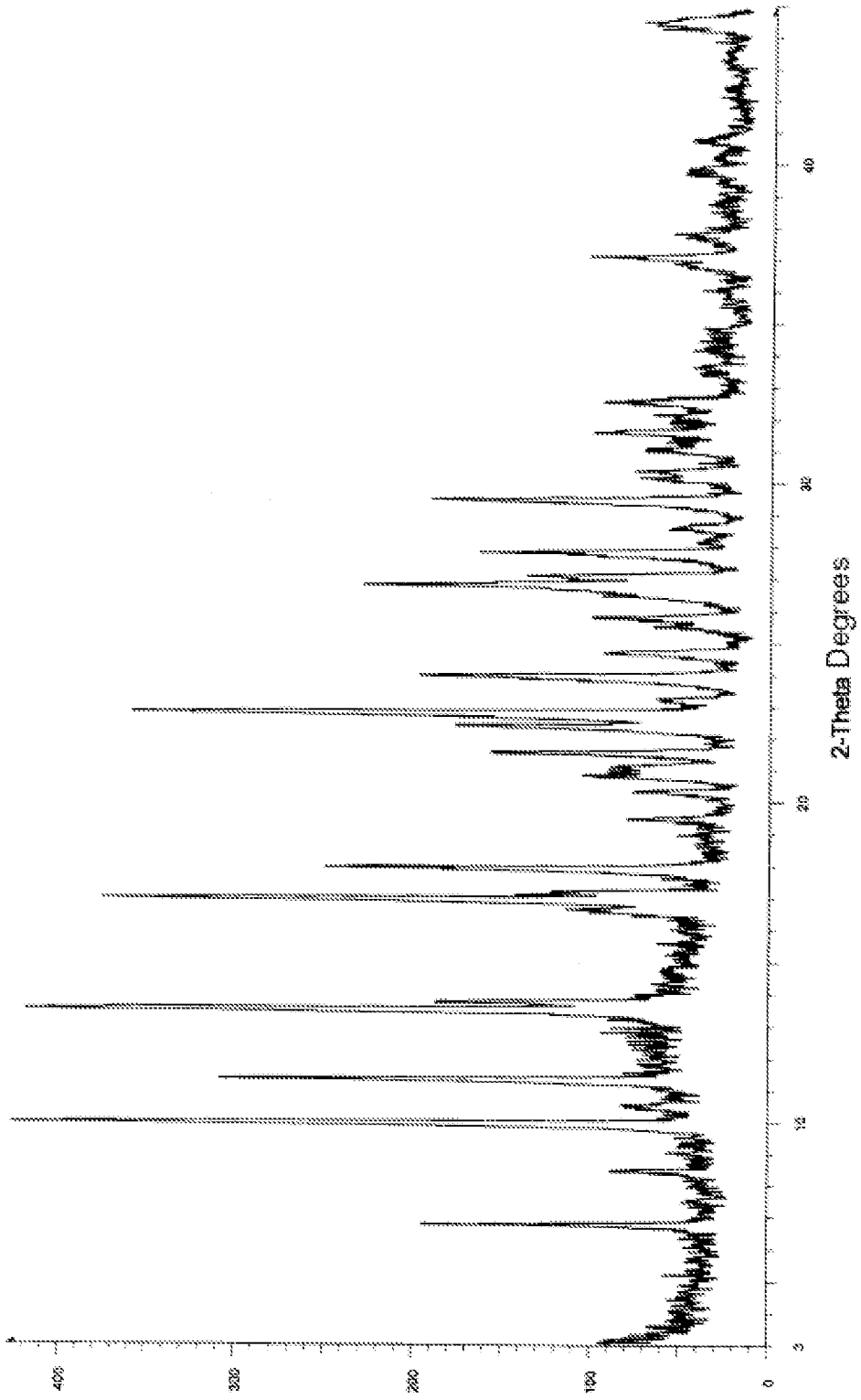

H
COOH
H2N
N
H
III
OHC
+
O
O
IV
COOH
NH
N
H
O
O
V
O
N
CH3
N
O
N
H
O
O
I
R1
O
H
N
CH3
VI
COOH
NH
• X
N
H
O
O
IIa

Fig. 1 of 4

Fig - 2 of 4



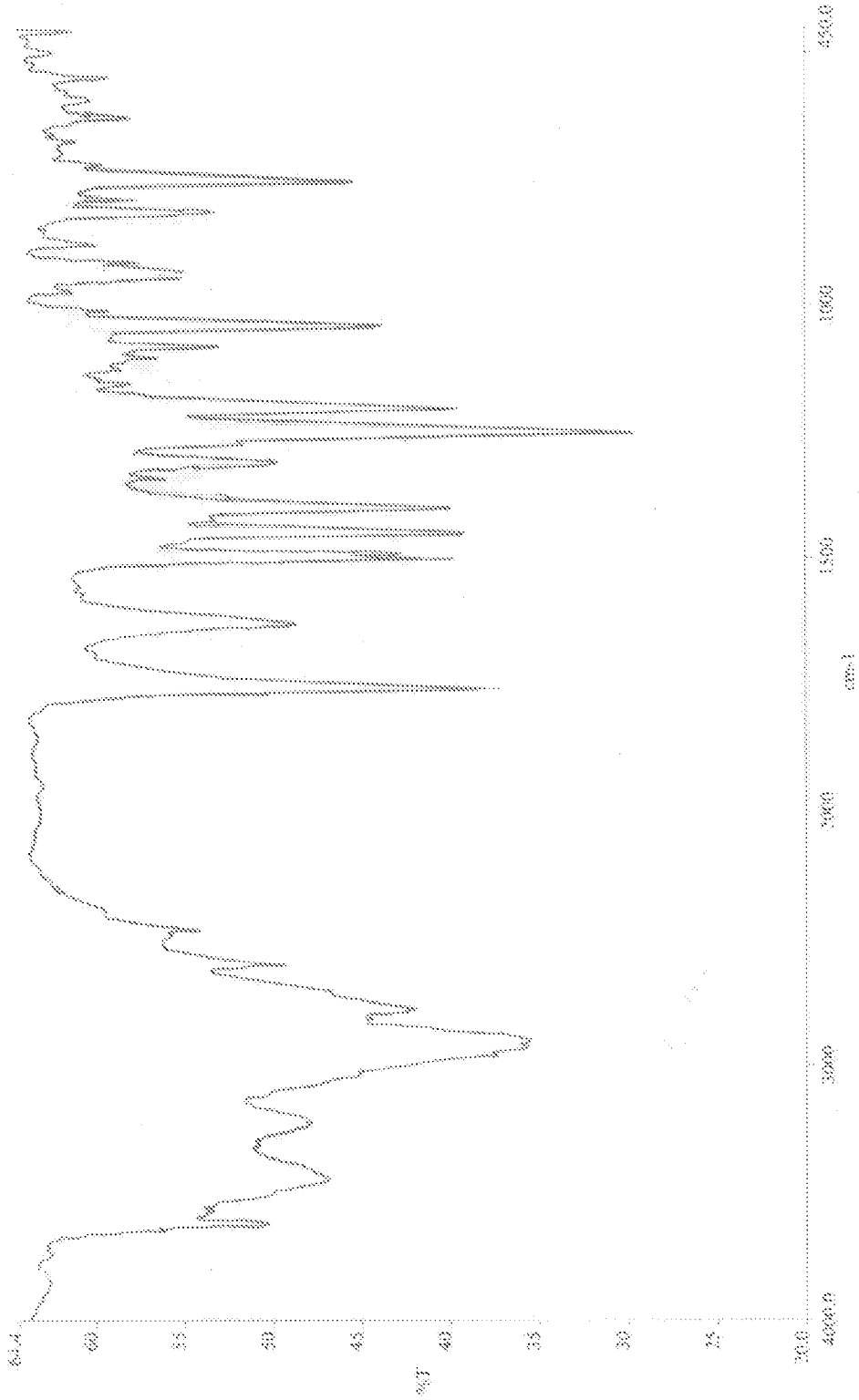


FIG. 3

Fig - 4 of 4

