Title: PROCESS FOR PREPARING TADALAFIL AND ITS INTERMEDIATES

Abstract: The present invention relates to two novel forms of Tadalafil which differ in their bulk densities. The invention also relates to an improved process for the preparation of Tadalafil and its intermediates.
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PROCESS FOR PREPARING TADALAFIL AND ITS INTERMEDIATES

Field of Invention:

The present invention relates to a novel form of Tadalafil (I) and improved process for the preparation of Tadalafil and its intermediates.

Background of the Invention:

Tadalafil, (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4b]indole-1,4-dione is an orally administered phosphodiesterase type 5 (PDE5) inhibitor. Tadalafil (I) has been developed as a treatment for erectile dysfunction and the treatment of female sexual dysfunction. The molecular structure of Tadalafil is represented by formula (I).

In WO 95/19978, Alain Daugan describes Tadalafil (I) as tetracyclic derivatives and the process for its preparation and their therapeutic use as PDE5 inhibitor.

James Butler in the patent WO 96/38131 also describes a process for the preparation of Tadalafil (I) and its intermediates.

In WO02/36593, Mark Orme describes the preparation of Tadalafil (I) as indole derivatives and their use as therapeutic agents.

Similarly, in the patents US 6140329, Alain Daugan et al. has described the uses of Tadalafil (I) and processes for its preparation.

J. Org. Chem (1998), 63, 2724-2727, reports a process for the preparation of compounds which are similar to the compounds used as intermediates in the preparation of Tadalafil (I).

The present invention discloses a novel form of Tadalafil (I) and improved processes for the preparation of Tadalafil (I) and its intermediates.
Summary of Invention:

It is an object of the present invention to disclose a simplified and improved process for preparing Tadalafil (I).

A further objective of the present invention is to disclose a novel form of Tadalafil (I) characterized by a different bulk density.

Another objective of the present invention is to provide a process to get higher yields of Tadalafil (I).

Still another objective of the present invention is to prepare Tadalafil (I) with high chiral purity from a racemic mixture of intermediates, without separation.

Another objective of the present invention is to provide improved processes for the preparation of the intermediates involved for preparing Tadalafil (I) according to the present invention.

Yet another objective of the present invention is to prepare the intermediates of Tadalafil (I) with good chiral purity and in higher yields, using milder and faster processes.

Still another objective of the present invention is to provide suitable pharmaceutical compositions containing Tadalafil (I) prepared according to the present invention and their use in medicine.

Description of the Figures:

Fig. 1: Microscopic view of the crushed sample of the novel heavy crystalline form of Tadalafil (I).

Fig. 2: Microscopic view of the crushed sample of known fluffy crystalline form of Tadalafil (I).

Description of the Invention:

The present invention relates to an improved process for the preparation of Tadalafil (I) and its intermediates. It also describes a novel form of Tadalafil characterized by its bulk density. The range of bulk density observed for the novel heavy crystalline form of Tadalafil (I) is 0.45-0.55 gm/cc (tapped) as compared to the known fluffy crystalline form, which has a bulk density in the range of 0.25-0.3 gm/cc (tapped).

The novel heavy crystalline form of Tadalafil (I) also differs from the well known fluffy crystalline form in its physical appearance as is evident from the microscopic view of the crushed samples of the two forms of Tadalafil (I) shown in Fig. 1 & 2.
These novel forms as well as other forms of Tadalafil (I) can be prepared according to the processes as described below.

1. **Preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-1- (3,4-methylene-dioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV):**

The preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-1- (3,4-methylene-dioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV) comprises of two steps.

**Step 1:**

WO 95/19978 and WO 02/36593, both describe similar processes for the production of a mixture of cis (IIIa) and trans (IIIb) isomers of methyl-1,2,3,4-tetrahydro-1- (3,4-methylene-dioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (III) involving the use of D-tryptophan methyl ester (V), piperonal (VI), anhydrous CH₂Cl₂ and trifluoroacetic acid.

The process has the following disadvantages:

1. All these processes are time consuming, requiring 4-5 days for completion.

2. Overall yield obtained is low (total yield of 70-84%), with 37-42 % cis isomer (IIIa), which is desired, and 27-47 % trans (IIIb) (undesired).

3. All these processes require either fractional crystallization or column chromatography of the reaction mixture in order to separate the isomers before epimerization to form pure cis (IIIa) isomer.

The above mentioned problems are overcome by the process of the present invention wherein a mixture of D-tryptophan methyl ester (V), piperonal (VI) and a suitable solvent was stirred at room temperature for 1-3 hrs. Thereafter molecular sieves and trifluoroacetic acid was added and the reaction mixture was stirred for 27-32 hrs to obtain a mixture of cis (IIIa) and trans (IIIb) isomers of methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (III). The suitable solvents were selected from the group consisting of dichloromethane, chloroform, ethylene dichloride and the like or mixtures thereof.

Alternatively, the mixture of cis (IIIa) and trans (IIIb) isomers of methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (III) can also be prepared by a process comprising reacting a mixture of D-tryptophan methyl ester (V), piperonal (VI) and a suitable solvent at room temperature for 1-3 hrs. Thereafter trifluoroacetic acid was added in lots during 0-30 hrs. The solvent was removed during the course of the reaction. This gives the desired compound (III). The suitable solvents were selected from the group consisting of dichloromethane, toluene, chloroform, ethylene dichloride and the like or mixtures thereof.
The process has the following advantages:

1. The process requires lesser time (32-36 hrs) for completion while even after 4-5 days a large portion of starting material remains in the prior art process.

2. The process gives higher yield (60 %) of desired cis isomer (IIIa) and 34 % trans (IIIb) isomer with lower content of starting material.

3. The crude reaction mixture can be used as such in the next epimerization step, without further purification or chromatographic separation of the isomers.

Step 2:

The process described in WO 95/19978 requires separation of cis (IIIa) and trans (IIIb) isomer from the reaction mixture obtained from Step 1. The trans (IIIb) isomer thereafter is converted into pure cis (IIIa) or cis.HCl (IV) form. The same application also describes another process where the separated cis (IIIa) and trans (IIIb) isomers are used in 1:1 proportion to form pure cis HCl (IV).

The process has the following disadvantages:

1. The process requires the cis (IIIa) and trans (IIIb) isomers to be separated before epimerization.

2. The process requires 24-72 hrs, after the separation of cis (IIIa) and trans (IIIb) isomers from the reaction mixture.

3. The process gives 46-77 % yield, with 77 % obtained in 72 hrs of the reaction.

An alternative process to obtain pure cis isomer (IIIa) is mentioned in patents WO 95/19978 and WO 02/36593 but the process has the following disadvantages:

1. It is a very lengthy route involving 4-5 steps.
2. It uses very pungent smelling Lawesson’s reagent making it less preferable for large scale application. Also Lawesson’s reagent, methyl iodide and borohydrides used in the reaction are hygroscopic in nature causing handling problems.

3. The process is not cost-effective.

In the present invention the crude reaction mixture containing cis (IIIa) and trans (IIIb), obtained from Step 1 above, is reacted as such with aqueous HCl at 40-60 °C for 24 hrs to obtain pure cis HCl (IV).

IIIa:IIIb

IV

The process overcomes the disadvantages of the above processes and has the following advantages:

1. The reaction mixture of Step 1 can as such be used for the process, without separation, reducing the number of steps involved.
2. The process gives higher (80 %) yield of the cis isomer (IIIa) in lesser time (24 hrs).
3. The process involves only 2 steps.
4. The process does not use any pungent smelling or hygroscopic chemicals making it more preferable for large scale application.

2. Preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II):

WO 95/19978 (Alain Daugan) reports a process for the preparation of cis-chloro (II) involving pure (1R,3R)-methyl-1,2,3,4-tetrahydro-l-(3,4-methylene-dioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (IIIa) (also referred here as 'cis base'). All the examples given in the application require the use of ether for crystallization.

This process has the following disadvantages:

1. Ether used for recrystallization is more inflammable so difficult to use in large scale.
This problem is solved by the present invention wherein (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV) (hereafter referred to as ‘cis-HCl’) was used instead of cis base. Here a mixture of a suitable solvent selected from the group consisting of dichloromethane, chloroform, ethylenedichloride and the like or mixtures thereof, and cis-HCl was cooled to 0-5 °C, suitable base and chloroacetyl chloride was added and the reaction mixture was stirred for 30 to 45 min at 0 °C. A slurry was prepared in a suitable solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol and the like or mixtures thereof. The desired compound (II) was obtained on filtering the slurry. The suitable base used in the reaction was selected from triethylamine or sodium carbonate.

The process has the following advantages:
1. Using methanol for purification gives the desired compound (II) with purity more than 99 %
2. Methanol is safer to be used in large scale, unlike ether.

3. Preparation of Tadalafil (I):

WO 95/19978 (Alain Daugan) reports a process for the preparation of Tadalafil (I) from (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) (also referred here as ‘cis-chloro’). The examples given for the
process use methylamine, methanol and nitrogen gas and require use of 2-propanol for recrystallization. The process has the following disadvantages:

1. The process requires longer time (16 hrs).
5 2. The process requires the use of nitrogen gas, increasing the overall cost.
3. Yield obtained is less (65 %) compared to that (84 %) obtained by the present invention.
4. Purification is done by recrystallization using 2-propanol, which requires prior removal of the methanol used during the reaction for crystallization.

The above problems were overcome by the modified process of the present invention which involved reacting a mixture of (1R,3R)-methyl-1,2,3,4-tetrahydro- 2-chloroacetyl- (3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) as described earlier, methylamine, and a suitable solvent. The mixture was heated at 40-60 °C for 10-12 hrs. Then the solids were filtered and washed with the same solvent used for the reaction to give Tadalafil (I) (84 % yield). The solvent used in the reaction was selected from the group consisting of methanol, ethanol, isopropyl alcohol and the like or mixtures thereof.

The present invention, has the following advantages as compared to the earlier described processes.

1. The process requires shorter time (10-12 hrs).
2. The process does not use nitrogen gas, which decreases the cost.
3. The yield obtained is also higher (84 %) than that obtained by the known processes.
4. The purification is done using the same solvent as is used for the reaction, so there is no need to distill out the solvent or to do tedious workup, after the reaction, reducing the number of steps.
5. Using aqueous methylamine in the above process has the advantage of being cheaper and easier to handle in large scale.

Tadalafil (I) obtained in above process is in the fluffy crystalline form.

4. Preparation of heavy crystalline form of Tadalafil (I):
The fluffy crystalline form of Tadalafil (I) was dissolved in DMSO and poured in water which results in white solid precipitate. These solids were filtered and washed with water to obtain the heavy crystalline form of Tadalafil (I).

Overall, this improved process of preparing Tadalafil (I) by a process described in the present invention involving the intermediates prepared by the above mentioned processes have the following advantages:

1. It is a faster process requiring lesser number of steps to prepare Tadalafil (I).
2. The process gives higher yields of Tadalafil (I).
3. It is a process comparatively simpler and more feasible at large scale.
4. Another benefit is that the process is cost effective and uses chemicals, which can be handled conveniently on a large scale.
5. Substantially pure intermediates are obtained.
6. Prior art states that racemates of compound of formula (I) are obtained when racemic mixture of intermediates (IIIa and IIIb) is used, which requires further purification step to separate them. In the present invention, a diastereomeric mixture (using D-tryptophan as a starting material) is used as such without separation to prepare chirally pure form of compound of formula (I), which requires no further purification.

During the process corresponding solvates are also formed for e.g. methanolates, ethanolates and so on, the process for preparing them are also encompassed in the present invention.

Various pharmaceutical compositions and formulations of both the novel heavy crystalline form of Tadalafil (I) and fluffy crystalline form of Tadalafil (I) prepared according to the present invention can be prepared in the manner known in the prior art.

The dosage of both the novel heavy crystalline form of Tadalafil (I) and fluffy crystalline form of Tadalafil (I) prepared according to the present process are suitably selected according to the usage, and may vary as per the requirement of the patient.

Both the novel heavy crystalline form of Tadalafil (I) and fluffy crystalline form of Tadalafil (I) prepared by the process described in the present invention are suitable as phosphodiesterase type 5 (PDE5) inhibitor, preferably for the treatment of erectile dysfunction, the treatment of female sexual dysfunction and other related disease conditions.

The present invention is illustrated by the following examples, which should not be construed as limiting the scope of the invention in any way.
EXAMPLE 1

Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer (IIIa) and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer (IIIb):

Trifluoroacetic acid (30.2 g) was added dropwise to a stirred solution of D-tryptophan methyl ester (V) (124 g), piperonal (VI) (94 g) and molecular sieves (240 g) in cooled anhydrous CH₂Cl₂ (1.75 L) and the solution allowed to react at ambient temperature. After 30-34 hrs, the solution was diluted with CH₂Cl₂ (1.0 L), filtered and washed with CH₂Cl₂. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and water and then dried over anhydrous Na₂SO₄. The organic layer was evaporated under reduced pressure. The desired product (mixture of IIIa and IIIb) was obtained as a residual oil (199 g), with greater than 99% total yield and the HPLC purity of 60.4% cis (IIIa) and 26.9% trans (IIIb).

EXAMPLE 2

Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer (IIIa) and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer (IIIb):

To a stirred solution of D-tryptophan methyl ester (V) (0.5 g), piperonal (VI) (0.38 g) and molecular sieves (1 g) in cooled anhydrous CHCl₃ (14 mL), was added trifluoroacetic acid (0.34 mL) dropwise over 0 to 30 hrs and the solution was allowed to react at low temperature. The reaction was monitored by TLC. After 95-98 hrs, the solution was diluted with CHCl₃, filtered and washed with CHCl₃. The organic layer was washed with a saturated aqueous solution of NaHCO₃ then with water and dried over Na₂SO₄. After evaporation under reduced pressure, the desired product (mixture of IIIa and IIIb) was obtained as a residual oil (0.6g) with 75% total yield and the HPLC purity of 74.4% cis isomer (IIIa) and 22.3% trans isomer (IIIb).

EXAMPLE 3

Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer (IIIa) and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer (IIIb):

To a mixture of D-tryptophan methyl ester (V) (5 g) and piperonal (VI) (3.8 g) in cooled
dicloromethane (140 mL) was added dropwise trifluoroacetic acid (3.4 mL) in lots over 0-30 hrs. The reaction mixture was allowed to react at ambient temperature. Dicloromethane was distilled off at atmospheric pressure and fresh dicloromethane (140 mL) was added during the course of the reaction. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was diluted with dicloromethane & washed with aqueous solution of NaHCO₃, then washed with water and dried over Na₂SO₄. On concentrating the organic layer, it gave 8.0 g of desired product (mixture of IIIa and IIIb) with a total yield more than 99 %.

Mass spectrum (m/z) : 351 (M+H)+

% Purity by HPLC : 39.0 % (cis isomer)
51.7 % (trans isomer)

EXAMPLE 4

Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1- (3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer (IIIa) and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1- (3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer (IIIb):

Trifluoroacetic acid was added dropwise in lots over 0-30 hrs to a mixture of D-tryptophan methyl ester (V) (2 g) and piperonal (VI) (1.5 g) in cooled dicloromethane (56 mL) and the reaction mixture was allowed to react at ambient temperature. Dicloromethane was distilled off and fresh dicloromethane was added during course of the reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was, diluted with dicloromethane (50 mL), washed with aqueous solution of NaHCO₃, then washed with water and dried over Na₂SO₄. On concentrating the organic layer, it gave 3.2 g of desired product (mixture of IIIa and IIIb) with a total yield more than 99.7 %.

Mass spectrum (m/z) : 351 (M+H)+

% Purity by HPLC : 43.7 % (cis isomer)
51.1 % (trans isomer)

EXAMPLE 5

Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1- (3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer (IIIa) and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1- (3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer (IIIb):

Trifluoroacetic acid (0.036 g) was added dropwise in lots over 0-25 hrs. to a stirred solution of D-tryptophan methyl ester (V) (0.15 g), piperonal (VI) (0.113 g) and molecular sieves (0.1 g) in cooled anhydrous CH₂Cl₂ (2 ml) and the solution allowed to react at ambient temperature. The progress of the reaction was monitored by TLC. After 25-30 hrs, the solution was diluted with
CH₂Cl₂, filtered and washed with CH₂Cl₂. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and water and then dried over anhydrous Na₂SO₄. The organic layer was evaporated under reduced pressure. The desired product (mixture of IIIa and IIIb) was obtained as a residual oil (0.2 g) with a total yield of 83% the HPLC purity of 42.6% cis (IIIa) and 34.6% trans (IIIb).

EXAMPLE 6
Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer (IIIa) and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer (IIIb):
Trifluoroacetic acid (2.1ml) was added dropwise in lots over 0-25 hrs. to a stirred solution of D-tryptophan methyl ester (V) (3 g), piperonal (VI) (2.2 g) and molecular sieves (3 g) in cooled anhydrous CH₂Cl₂ (84 ml) and the solution allowed to react at ambient temperature. The progress of the reaction was monitored by TLC. After 28-32 hrs, the solution was diluted with CH₂Cl₂, filtered and washed with CH₂Cl₂. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and water and then dried over anhydrous Na₂SO₄. The organic layer was evaporated under reduced pressure. The desired product (mixture of IIIa and IIIb) was obtained as a residual oil (4.8 g), with a total yield more than 99% and the HPLC purity of 20.1% cis (IIIa) and 46.6% trans (IIIb).

EXAMPLE 7
Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer (IIIa) and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer (IIIb):
Trifluoroacetic acid (2 M) was added dropwise in lots over 0-25 hrs. to a stirred solution of D-tryptophan methyl ester (V) (1 g), piperonal (VI) (0.68 g) and molecular sieves (2 g) in cooled anhydrous CH₂Cl₂ (28 ml) and the solution allowed to react at 0 °C for 56 hrs. The progress of the reaction was monitored by TLC. After 55-60 hrs, the solution was diluted with CH₂Cl₂, filtered and washed with CH₂Cl₂. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and water and then dried over anhydrous Na₂SO₄. The organic layer was evaporated under reduced pressure. The desired product (mixture of IIIa and IIIb) was obtained as a residual oil (1.4 g), with a total yield of 87% and HPLC purity of 69.9% cis (IIIa) and 18.8% trans (IIIb).

EXAMPLE 8
Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer (IIIa) and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer (IIIb):

Trifluoroacetic acid (2 M) was added dropwise in lots over 0-25 hrs. to a stirred solution of D-tryptophan methyl ester (V) (1 g), piperonal (VI) (0.74 g) and molecular sieves (2 g) in cooled anhydrous CH₂Cl₂ (28 ml) and the solution allowed to react at ambient temperature. The progress of the reaction was monitored by TLC. After 31 hrs, the solution was diluted with CH₂Cl₂, filtered and washed with CH₂Cl₂. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and water and then dried over anhydrous Na₂SO₄. The organic layer was evaporated under reduced pressure. The desired product (mixture of IIIa and IIIb) was obtained as a residual oil (1.49 g), with a total yield of 93 % and HPLC purity of 11.56 % cis (IIIa) and 30.5 % trans (IIIb).

EXAMPLE 9
Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate hydrochloride (IV):
Crude oily mixture of the cis (IIIa) and trans (IIIb) isomers (196 g) obtained above was heated in a mixture of hydrochloric acid and water at 50 to 55 °C. The progress of the reaction was monitored by TLC. A white solid precipitated. The mixture was then allowed to cool to 0 °C. and the solids filtered. The solids were then washed with water and then with diisopropyl ether and dried to give the hydrochloride salt of the title compound (IV) (174 g) as a pale yellow to yellow solid. (m.p.: 208-210 °C (dec.); Yield: 81 %; Purity by HPLC: cis.HCl: 98.1 %)

Characterization
Mass spectrum (m/z) : 351 (M+H)+
¹H NMR (DMSO) δ
: 2.5 (dd,2H), 3.8 (s,3H), 4.7 (s,1H), 5.8 (s,1H), 6.1 (s,2H),
: 6.9-7.1 (5H,m), 7.27 (d,2H), 7.5 (d,2H), 10.7 (s,1H).
¹³C (DMSO)
: 22, 52.9, 55.15, 57.5, 101.5, 106.3, 108.23, 110,111.2,
: 118.2, 119.1, 122, 125, 125.5, 127.1, 128.9, 136.7,
: 147.1, 148.4, 168.5.

EXAMPLE 10
Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate hydrochloride (IV):
Crude oily mixture of the cis (IIIa) and trans (IIIb) isomers (0.2 g) was heated in hydrochloric acid and water at 50 to 55 °C. The progress of the reaction was monitored by TLC. After a
white solid precipitates, the mixture was allowed to cool to 0-5 °C and the solids filtered. The solids were then washed with water and then with diisopropyl ether and dried to give the hydrochloride salt of the title compound (IV) (0.15 g) as a pale yellow to yellow solid. (Yield 68 %; Purity by HPLC: cis.HCl : 95.2 %).

EXAMPLE 11
Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate hydrochloride (IV):
Crude oily mixture of the cis (IIIa) and trans (IIIb) isomers (1.5 g) was heated in hydrochloric acid and water at 50 to 55 °C. The progress of the reaction was monitored by TLC. After a white solid precipitates, the mixture was allowed to cool to 0-5 °C and the solids filtered. The solids were then washed with water and then with diisopropyl ether and dried to give the hydrochloride salt of the title compound (IV) (1.2 g) as a pale yellow to yellow solid. (Yield : 73 %; Purity by HPLC: cis.HCl : 94.18 % and trans.HCl : 2.0 %; m.p.: 208-210 °C)

EXAMPLE 12
Preparation of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate hydrochloride (IV):
Pure trans (IIIb) 98.8 % isomer (1.8 g) was heated in hydrochloric acid and water at 60 °C. The progress of the reaction was monitored by TLC. After a white solid precipitates, the mixture was allowed to cool to 25 °C and the solids filtered. The solids were then washed with water and then with diisopropyl ether and dried to give the hydrochloride salt of the title compound (IV) (0.15 g) as a pale yellow to yellow solid. (Yield :91 %; Purity by HPLC: cis.HCl : 97.6 %) m.p. 206 – 209°C (dec.). Sp. Rotation +82.25° (c=1 % in methanol).

EXAMPLE 13
Preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (II):
Chloroacetyl chloride (45.6 mL) was added dropwise to a solution of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate hydrochloride (IV) (170 g) and triethylamine (110mL) in anhydrous CH₂Cl₂ (2.38 L) at 0°C. The solution was stirred at 0 °C. for some time, then diluted with CH₂Cl₂ and the progress monitored by TLC. The solution was washed first with water and then with a saturated aqueous solution of NaHCO₃ and brine. After drying over Na₂SO₄ and evaporation under reduced pressure, the resulting solid (190 g) was washed with methanol to give the title compound as a pale yellow solid (II) (170 g).
Sp. Rotation at 30 °C (-125 °) (c=1.17 %, CHCl₃); m.p. : 226 °C; Yield:- 90 %
Purity by HPLC: 99.8%.

Characterization

Mass spectrum (m/z) : 427 (M+H)+

$^1$H NMR (DMSO) $\delta$

: 3.0 (s,3H), 3.4 (d,2H), 4.4 (d,1H), 4.8 (d,1H),

: 5.1 (d,1H), 5.9 (s,1H), 6.4 (d,2H), 6.6 (s,1H), 6.7 (d,2H),

: 7.0-7.29 (2H,m), 7.32 (d,1H), 7.5 (d,1H), 10.8 (s,1H).

$^{13}$C (DMSO)

: 22, 43.1, 51.2, 51.7, 52.3, 100, 106.2, 107.5,

: 109.1, 111, 118, 121.5, 122.3, 125.8, 129.8, 133,

: 136.3, 146.6, 146.9, 166, 170.35.

EXAMPLE 14

Preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4b]indole-3-carboxylate (II):

Chloroacetyl chloride (0.4 ml) was added dropwise at 0 °C to a stirred solution of (1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4b]indole-3-carboxylate hydrochloride (IV) (0.72 g) and NaHCO$_3$ (0.29 g) in anhydrous CHCl$_3$ (15 ml). The resulting mixture was stirred for 1 hour at the same temperature and diluted with CHCl$_3$. Water was then added dropwise with stirring to the mixture, followed by a saturated aqueous solution of NaHCO$_3$. The organic layer was washed with water until neutral and dried over Na$_2$SO$_4$. After evaporation of the solvent under reduced pressure, the desired yellow solid compound (II) (0.65 g) was obtained. (Yield: 82%; m.p. 221-224 °C; Purity by HPLC: 93.7%)

EXAMPLE 15

Preparation of (6R,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 (I):

A solution of methylamine (33% in methanol) (148 mL) was added at room temperature to a stirred suspension of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4b]indole-3-carboxylate (II) (168 g) in methanol (2.52 L) and the resulting mixture was heated at 50 °C for 10 hrs. The reaction was monitored by TLC. The reaction mixture was cooled, the solids filtered, washed with methanol, dried in a vacuum oven to obtain Tadalaflil (I) in the form of a crystalline fluffy powder (135 g). (Yield: 88%; Purity by HPLC: 99.97%; m.p.: 290-292 °C (dec.); Bulk density=0.25-0.3 g/cc).

EXAMPLE 16

Preparation of (6R,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 (I):
A solution of methylamine in ethanol (0.44 mL) was added at room temperature to a stirred suspension of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl- (3,4-methyleneedioxyphenyl)-9H-pyrido[3,4b]indole-3-carboxylate (II) (0.5 g) in methanol and the resulting mixture was heated at 50 °C for 7 hrs. The reaction was monitored by TLC. The solids were filtered, washed with methanol and dried in a vacuum oven to obtain Tadalafil (I) as crystalline fluffy powder (0.33g) (Yield: 66 %; Purity by HPLC: 99.8 %; m.p.: 290-292°C (dec.)).

EXAMPLE 17
Preparation of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methyleneedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (I):
An aqueous solution of methylamine was added at room temperature to a stirred suspension of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methyleneedioxyphenyl)-9H-pyrido-[3,4b]indole-3-carboxylate (II) (25 g) in methanol (375 mL) and the resulting mixture was heated at 50 °C. The reaction was monitored by TLC and upon completion was cooled, the solids filtered, washed with methanol and dried in a vacuum oven to obtain Tadalafil (I) in the form of crystalline fluffy powder (Yield: 84 %; Purity by HPLC: 99.9 %; m.p.: 290°C (dec.)).

EXAMPLE 18
Preparation of heavy crystalline form of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methyleneedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (I):
Fluffy Tadalafil (I) (25 g) was dissolved in DMSO (75 mL) at 30 to 35°C. Tadalafil (I) was precipitated by adding D.M. water (150 mL) under stirring. Then the precipitates were filtered, washed with D.M. water and dried in a vacuum oven under reduced pressure to obtain heavy crystalline form of Tadalafil (I) (22g). (m.p. 286 °C (dec.), Yield : 88 %, Bulk density:0.45-0.55 g/cc).

EXAMPLE 19
Preparation of heavy crystalline form of (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methyleneedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione (I):
Fluffy Tadalafil (I) (30 g) was dissolved in DMSO (90 mL) at 20 to 25 °C. Tadalafil (I) was precipitated by adding D.M. water (180 mL) under stirring. Then the precipitates were filtered, washed with D.M. water and dried in a vacuum oven under reduced pressure to obtain heavy crystalline form of Tadalafil (I) (26g). (m.p. 286 °C(dec.); Yield : 87 %)
We claim:

1. A process for the preparation of Tadalafil (I) comprising, heating a mixture of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II), methyamine and a suitable solvent at 40-60 °C for 10-12 hrs, filtering and washing with the same solvent.

2. A process for the preparation of Tadalafil (I) as claimed in claim 1 wherein, suitable solvent is selected from the group consisting of methanol, ethanol, isopropyl alcohol or mixtures thereof.

3. A process for the preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) comprising
   (a) reacting a mixture of (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV), suitable solvent selected from the group consisting of dichloromethane, chloroform, ethylendichloride or mixtures thereof, a suitable base and chloroacetyl chloride at 0-5 °C and
   (b) purifying using suitable solvent selected from the group consisting of methanol, ethanol, isopropyl alcohol or mixture hereof.

4. A process for the preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) as claimed in claim 3, wherein the suitable base is selected from triethylamine and sodium carbonate.

5. A process for the preparation of a mixture of cis (IIIa) and trans (IIIb) isomers of methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate
(III) comprising reacting a mixture of D-tryptophan methyl ester (V), piperonal (VI), suitable solvent, molecular sieves and trifluoroacetic acid.

6. A process for the preparation of a mixture of cis (IIIa) and trans (IIIb) isomers of a compound of formula (III) comprising,
   (a) reacting a mixture of D-tryptophan methyl ester (V), piperonal (VI), a suitable solvent and trifluoroacetic acid and
   (b) removing the solvent.

7. A process for the preparation of a mixture of cis (IIIa) and trans (IIIb) isomers of a compound of formula (III) as claimed in claim 5 and 6, wherein suitable solvent is selected from the group consisting of dichloromethane, toluene, chloroform, ethylene dichloride or their mixtures thereof.

8. A process for the preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV) comprising reacting the crude reaction mixture containing cis (IIIa) and trans (IIIb) prepared by the process claimed in claims 5, 6 and 7, with aqueous HCl at 40-60°C.

9. A process for the preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) comprising,
   (a) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV) from a mixture of cis (IIIa) and trans (IIIb) isomers of compound of formula (III), by a process claimed in claims 8.
   (b) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) from (1R,3R)-
methyl-1,2,3,4-tetrahydro-1- (3,4-methylene-dioxynaphthy1)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV), by a process as claimed in claim 3 and 4.

10. A process for the preparation of (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) comprising,

(a) Preparing a mixture of cis (IIIa) and trans (IIIb) isomers of compound of formula (III) from D-tryptophan methyl ester (V) and piperonal (VI), by a process claimed in claims 5, 6 & 7.

(b) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxynaphthy1)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV) from a mixture of cis (IIIa) and trans (IIIb) isomers of compound of formula (III), by a process as claimed in claim 8.

(c) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) from (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxynaphthy1)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV), by a process as claimed in claim 3 and 4.

12. A process for the preparation of Tadalafil (I) comprising,

(a) Preparing a mixture of cis (IIIa) and trans (IIIb) isomers of compound of formula (III) from D-tryptophan methyl ester (V) and piperonal (VI), by a process claimed in claims 5, 6 & 7.

(b) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxynaphthy1)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV) from a mixture of cis (IIIa) and trans (IIIb) isomers of compound of formula (III) by a process as claimed in claim 8.

(c) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) from (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxynaphthy1)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV), by a process as claimed in claim 3 and 4.

(d) Preparing Tadalafil (I) from (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II), by a process claimed in claims 1 & 2.

13. A process for the preparation of Tadalafil (I) comprising,

(a) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxynaphthy1)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV) from a mixture of cis (IIIa) and trans (IIIb) isomers of compound of formula (III) by a process as claimed in claim 8.

(b) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) from (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxynaphthy1)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV), by a process as claimed in claim 3 and 4.
(c) Preparing Tadalafil (I) from (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II), by a process claimed in claims 1 & 2.

14. A process for the preparation of Tadalafil (I) comprising,
   (a) Preparing (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II) from (1R,3R)-methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate hydrochloride (IV), by a process as claimed in claim 3 and 4.
   (b) Preparing Tadalafil (I) from (1R,3R)-methyl-1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4b]indole 3-carboxylate (II), by a process claimed in claims 1 & 2.

15. Pharmaceutical compositions comprising Tadalafil (I), prepared by the process of the present invention.

16. Method of treatment and use of Tadalafil (I) prepared by the process of the present invention for erectile dysfunction, female sexual dysfunction and other related diseases conditions.

17. A novel heavy crystalline form of Tadalafil (I) characterized by a bulk density in the range of 0.20-0.22 gm/mL (tapped).

18. A process of preparing heavy crystalline form of Tadalafil (I) comprising dissolving the fluffy crystalline form of Tadalafil (I) in DMSO and washing with water.

19. Pharmaceutical compositions comprising the novel form of Tadalafil (I) of the present invention.

20. Method of treatment and use of the novel form of Tadalafil (I) of the present invention for erectile dysfunction, female sexual dysfunction and other related disease conditions.
Fig 1.

Fig 2.