A PROCESS FOR THE PREPARATION OF 6-HYDROXY-2-(4-HYDROXYPHENYL)-3-[4-(2-PIPERIDINO ETHOXY) BENZOYL]BENZO[B]THIOPHENE

(57) Abstract: The present invention relates to a process for preparing 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula (I), said process comprising: deprotecting compound of formula (II) with base in dimethyl sulfoxide to yield substantially pure compound of formula (I) with HPLC purity of 99% or more by area and optionally converting to its pharmaceutically acceptable salt.

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A PROCESS FOR THE PREPARATION OF 6-HYDROXY-2-(4-HYDROXYPHENYL)-3-[4-(2-PIPERIDINO ETHOXY)BENZOYL]BENZO[b]THIOPHENE

The present invention relates to a process for the preparation of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I, and its pharmaceutically acceptable salts. Compound of formula I commonly known as raloxifene (INN Name) is used in the treatment and prevention of osteoporosis in post-menopausal women.

![Formula I]

BACKGROUND OF THE INVENTION

United States Patent No.4,418,068 (Assigned to: Eli Lilly and company; referred to herein as '068) describes the preparation of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I, and its pharmaceutically acceptable salts by various methods.

One of the methods exemplified in this patent prepares compound of formula I by deprotection of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula II, with sodium hydroxide and denatured alcohol.
After completion of the reaction, alcohol is distilled out and the residue is dissolved in water followed by ether washing to remove unreacted starting materials/impurities. The aqueous layer is subjected to acid-base treatment to give crude 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I. The crude compound of formula I is then subjected to column purification to get an oil which is dissolved in acetone, seeded and chilled to get purified compound of formula I.

This patented process has several disadvantages

(a) It requires large amount of the alcoholic solvent (about 25 volumes per gram of compound of formula II) for the step of deprotection. The alcoholic solvent used generates ether impurities viz. compounds of formula IIIa to IIIc to the extent of about 25%. We have found that these side products once formed are very difficult to remove and require exhaustive washings and purifications which reduce the overall yield and purity of the final product.

(IIIa : R = C₁₋₄ linear or branched alkyl group; R₁ = H)
IIIb: \( R = H; R_1 = C_{1,4} \) linear or branched alkyl group

IIIc: \( R \& R_1 = C_{1,4} \) linear or branched alkyl group

(b) After completion of reaction the workup is tedious requiring series of purification steps. Firstly, large quantity of ether has to be used in the workup for washing out the impurities. Secondly, the crude product obtained after workup has to be subjected to column chromatography which is impractical on a large scale and commercially non feasible and requires large amounts of organic solvents. The fraction containing the product is then isolated as an oil and is dissolved in acetone to obtain the purified product. This process thus requires large amount of multiple organic solvents which evaporate and are environmentally harmful.


![Chemical Structure](image)

IIIc: \( R \& R_1 = CH_3 \)

The dealkylation is carried out in presence of Lewis acid like aluminum chloride and boron trichloride. Dealkylations with aluminum chloride require addition of mercaptan compounds which give an offensive odour. Also aluminum chloride produces large quantity of aluminum based by-products which are soluble in raloxifene processing.
solvents and are detected in the final product. Boron trichloride overcomes the disadvantages of aluminum chloride but is corrosive, toxic gas with pungent irritating odor and hence difficult to handle. Also the cost is prohibitive as it is six-fold expensive than aluminum trichloride. Further, the purity and yield of the compound of formula I obtained using these dealkylation methods are not reported.


![Formula IV](image)

After completion of the reaction, the workup involves ether wash, treatment with aqueous methanesulfonic acid followed by basification with ammonia to give crude 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I. The crude compound of formula I is then subjected to column purification to get compound of formula I as a yellow foam which is recrystallized from acetone, to get purified compound of formula I. This process is disadvantageous as the workup involves multiple purification steps using different solvents and results in lower yield of the compound of formula I.

Therefore there is need in the art for a commercially viable process for preparing 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I, which minimizes formation of impurities, drives the reaction to
completion and provides substantially pure compound of formula I directly without the need of cumbersome purification techniques such as column chromatography or recrystallization. The present invention provides such a process for preparing 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I from 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene compound of formula II.

We have tried various reaction conditions and solvent systems for preparing 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I, from compound of formula II. In some of the systems which we tried for example when deprotection was carried out with base in dimethyl formamide (DMF) or tetrahydrofuran, although alkyl ether impurities, (compounds of formula III a to III c) are not formed, the reaction was incomplete and compounds of formula V a and/or V b remained as impurities.
Surprisingly, we have now found that when the deprotection of compound of formula II is carried out with base in dimethyl sulfoxide the compound of formula I is obtained directly in substantially pure form without using column chromatography or recrystallization.

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OBJECT OF THE INVENTION

An object of the invention is to provide a simple and commercially feasible process for the preparation of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I, in high yields in substantially pure form from compound of formula II using lower volumes of solvent, without the need for chromatographic methods of purification.

SUMMARY OF THE INVENTION

A process for preparing 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I, said process comprising

20 deprotecting compound of formula II with base in dimethyl sulfoxide
to yield substantially pure compound of formula I with HPLC purity of 99% or more by area and optionally converting to its pharmaceutically acceptable salt.

The substantially pure 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl] benzo[b]thiophene compound of formula I, or its hydrochloride salt referred to herein has HPLC purity 99% or more, preferably 99.5% or more.

DETAILED DESCRIPTION OF THE INVENTION

We have conceived that deprotection of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula II, with base to obtain substantially pure 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I, requires selection of appropriate solvent. To our surprise when the deprotection is carried out in dimethyl sulfoxide it resulted in substantially pure compound of formula I, without column chromatography in high yields.
According to one embodiment of the present invention substantially pure compound of formula I may be prepared by deprotecting compound of formula II with base in dimethyl sulfoxide.

The base for deprotection reaction may be selected from aqueous solution of alkali metal alkoxides such as sodium methoxide, potassium methoxide, potassium tertiary butoxide and the like; alkali metal hydroxide such as sodium hydroxide, potassium hydroxide and the like; alkali metal amide such as sodium amide and the like; ammonia, hydroxylamine, hydrazine, dimethylamine and the like.

The deprotection reaction may be carried out by heating at 50 °C or above, preferably at about 50 -100°C. The deprotection reaction may be carried out for 3 or more hours, preferably 3 -7 hours. The volume of dimethyl sulfoxide for deprotection reaction may range from 3 to 8 volumes per gram of compound of formula II.
After completion of the reaction, the reaction mixture may be subjected to simple acid base purification. The acid for purification may be selected from inorganic acid like hydrochloric acid, sulfuric acid and the like or organic acid like acetic acid and the like. The base for purification maybe selected from inorganic base like sodium carbonate, sodium bicarbonate and the like; or organic base such as ammonia and the like. Isolation of the 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b] thiophene, compound of formula I, may be achieved by using techniques such as filtration/centrifugation and drying.

The process of the present invention yields substantially pure 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I, by deprotecting compound of formula II with base in dimethyl sulfoxide without chromatographic purification.

The substantially pure 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]thiophene, compound of formula I, obtained by following the process of the present invention is substantially free of compounds of formula III a to III c.

![Chemical Structure](image)

**formula III**

(IIIa : \( R = C_{1-4} \) linear or branched alkyl group; \( R_1 = H \)

IIIb: \( R = H; R_1 = C_{1-4} \) linear or branched alkyl group

IIIc : \( R \) and \( R_1 = C_{1-4} \) linear or branched alkyl group)
The substantially pure 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]thiophene, compound of formula I, obtained by following the process of the present invention is substantially free of compound of formula V a and V b.

\[ \text{V a} \]

\[ \text{V b} \]

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy) benzoyl]benzo[b]thiophene, compound of formula I, may be converted to its pharmaceutically acceptable salts by using appropriate acid.

The pharmaceutically acceptable salts may be selected from mineral acid salts such as hydrochloride, hydrobromide, sulfate and the like; organic acid salts such as acetate, oxalate, citrate, succinate, maleate, fumarate, malate, tartrate, and the like; and sulfonates such as methanesulfonate, benzenesulfonate, toluenesulfonate and the like; preferably hydrochloride.

For instance, the hydrochloride salt of compound of formula I may be prepared by dissolving hydrochloric acid in alcoholic solvent like methanol, ethanol, isopropanol, n-
propanol, n-butanol, t-butanol, isobutanol or by passing HCl gas at a temperature ranging from about -10 to 100°C.

The hydrochloride salt of compound of formula I obtained, if required, may be recrystallized from polar aprotic solvent and water so as to remove any residual solvents.

The polar aprotic solvent may be selected from dimethyl sulfoxide, dimethyl formamide, ethylacetate, acetone and the like. The recrystallization of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride may be carried out by dissolving in polar aprotic solvent followed by addition of water to facilitate crystallization. The dissolution may be carried at 50-80 °C followed by addition of water. The preferred ratio of volume of polar aprotic solvent to volume of water may be selected from the range of 1: 20 to 1: 80. The resulting mixture is stirred for 0.5 to 5 hours to crystallize the hydrochloride of compound of formula I having HPLC purity 99% or more, preferably 99.5% or more.

According to another embodiment of the present invention the hydrochloride salt of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thiophene may be prepared by reacting 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thiophene with ammonium chloride.

Preferably, the reaction of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thiophene with ammonium chloride is carried out in water.

The hydrochloride salt of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2piperidinoethoxy)benzoyl]benzo[b]thiophene obtained is substantially pure.
The substantially pure hydrochloride salt of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]thiophene compound of formula I, referred to herein, has HPLC purity 99% or more, preferably 99.5% or more.

The 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride, compound of formula II, may be prepared by any method known to those skilled in the art such as United States Patent No 4,418,068.

The examples that follow do not limit the scope of the present invention and are included as illustrations.

15 Example 1

Preparation of hydrochloride of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]thiophene, compound of formula I

To 4.0g of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride, compound of formula II, in a round bottom flask, a solution of 2.72g potassium hydroxide in 4.5 ml of DM water and 16ml dimethyl sulfoxide was added. The reaction mixture was heated at 60-62° C for 4.0 hours. After completion of the reaction, it was diluted with DM water at room temperature and acidified with aqueous HCl. The reaction mixture was stirred at room temperature for 1.0 hour and basified using aqueous ammonia, and stirred overnight at room temperature, filtered and dried to get 2.84g of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene HPLC purity > 99% by area. The
above material was dissolved in methanol and filtered to remove undissolved solid. Aqueous HCl was added to the filtrate at room temperature. The precipitated solid was filtered at room temperature, washed with methanol and dried to give the hydrochloride salt of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene compound of formula I. Yield = 2.03g (66.33 %) HPLC purity 99.67%.

Example 2

Preparation of hydrochloride of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I

To 7.6 kg of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene hydrochloride, compound of formula II, in a round bottom flask, a solution of 5.19 kg potassium hydroxide in 8.6 L of DM water and 30.4 L dimethyl sulfoxide were added. The reaction mixture was heated at 60-62°C for 4.0 hours. After completion of the reaction, it was diluted with DM water at room temperature and acidified with acetic acid. The reaction mixture was stirred at room temperature and basified using aqueous ammonia, and stirred at room temperature, filtered and dried to get compound of formula I, 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene HPLC purity > 99% by area. The above material was dissolved in methanol and filtered to remove undissolved solid. Aqueous HCl was added to the filtrate at room temperature. The precipitated solid was filtered at room temperature, washed with methanol and dried to give the hydrochloride salt of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene.
compound of formula I (HPLC purity 99.64% by area). The hydrochloride salt was recrystallized by dissolving in 7.0 L of dimethyl sulfoxide at 60-70° C followed by addition of 456 L water. The resulting product was stirred for 1 to 2 hours filtered and dried to give hydrochloride of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]thiophene compound of formula I. Yield = 4.1 kg(70.5%) HPLC purity = 99.81% by area.

**Example 2**

**Preparation of hydrochloride of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]thiophene, compound of formula I**

In a round bottom flask to 3.0 gm of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl] benzo[b]thiophene, 17 gm ammonium chloride and 50 ml of demineralised water were added. The reaction mixture was heated to 70-75°C and stirred at that temperature for 8.45 hrs and then cooled to room temperature, filtered, washed with 100 ml demineralised water, suck dried and dried at 55-60°C under vacuum to obtain 2.9 gm of hydrochloride salt of compound of formula I. m.p. 267-282°C, HPLC purity 99.68%. XRD analysis of the product matched with the non-solvated form of United States Patent No. 5,731,327.

**COMPARATIVE EXAMPLES**

**Comparative Example 1: Preparation of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy) benzoyl] benzo[b]thiophene, compound of formula I**
In a round bottom flask to 1g of 6-methanesulfonyloxy-2-(4- methanesulfonyl oxyphenyl)-3[4-(2-piperidinoethoxy)-benzoyl]benzo[ b] thiophene hydrochloride, compound of formula II, a solution of 1g sodium hydroxide in DM water and 10 ml dimethyl formamide was added. The reaction mixture was heated at 80-90° C for 3.0 hrs. The reaction mixture was diluted with DM water at room temperature and acidified using concentrated HCl. The reaction mixture was stirred at room temperature for 1.0 hour and basified with liquor ammonia, and stirred overnight at room temperature, filtered and sucked dried to get a crude solid.

**HPLC Analysis of the crude solid revealed incomplete reaction**

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy) benzoyl]benzo[b]thiophene compound of formula I = 20.99 %

compounds of formula V a and V b = 66.23 %

compound of formula II = 4.53%

**Comparative Example 2: Preparation of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2- piperidinoethoxy)benzoyl] benzo[b]thiophene, compound of formula I**

In a round bottom flask to 5.0 g of 6-methanesulfonyloxy-2-(4- methanesulfonyl oxyphenyl)-3[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene hydrochloride a solution of 4g sodium hydroxide in DM water and 50ml tetrahydrofuran were added. The reaction mixture was heated at 60-62° C for 14.0 hrs. The reaction mixture was diluted with tetrahydrofuran and DM water at room temperature and acidified using acetic acid. The reaction mixture was stirred at room temperature for 20 minutes and basified with liquor ammonia, and stirred overnight at room temperature, filtered and dried.
HPLC Analysis of the crude solid revealed incomplete reaction

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy) benzoyl]benzo[b]thiophene

compound of formula I = 19.27%

compounds of formula V a and V b = 75%

compound of formula II = 4.94%

Comparative Example 3: Preparation of hydrochloride of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidino ethoxy) benzoyl]benzo[b]thiophene, compound of formula I

To 4.0 g of 6-methanesulfonyloxy-2-(4-methanesulfonyloxyphenyl)-3[4-(2-piperidino ethoxy)-benzoyl]benzo[b] thiophene hydrochloride, compound of formula II, in a round bottom flask, a solution of 10 ml of 5N sodium hydroxide and 100ml of denatured alcohol was added. The reaction mixture was refluxed for 1.5 hours under nitrogen atmosphere. The reaction mixture was evaporated to dryness under vacuum. The residue on HPLC analysis revealed 72.3 % compound of formula I with impurities of compounds of formula III a to c. The residue is dissolved in water and washed with diethyl ether. The water layer was degassed under vacuum and nitrogen was bubbled to remove traces of ether. The aqueous mixture was acidified and followed by basification with excess sodium bicarbonate. The crude product (2.4 gm, HPLC analysis of 98.86% by area) was filtered and purified by column chromatography to get 1.78 g yellow oil, which is dissolved in 6.0 ml acetone, cooled and filtered to get 1.2 g (42.2% theory) purified product.
Above purified material was dissolved in THF and HCl gas was bubbled through the solution. The yellow solid precipitated out was filtered and washed with diethyl ether and dried to give hydrochloride of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, compound of formula I. Yield = 1.26 g (41.18%, HPLC analysis of 99.76% by area).
We claim:

1. A process for preparing 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidino ethoxy)benzoyl]benzo[b]thiophene, compound of formula I, said process comprising
deprotecting compound of formula II with base in dimethyl sulfoxide
to yield substantially pure compound of formula I with HPLC purity of 99% or more by area and optionally converting to its pharmaceutically acceptable salt.

2. A process as claimed in claim 1 wherein the pharmaceutically acceptable salt is hydrochloride.
3. A process as claimed in claim 2 wherein the hydrochloride salt is prepared by adding hydrochloric acid to compound of formula I.

4. A process as claimed in claim 2 wherein the hydrochloride salt is prepared by reacting compound of formula I with ammonium chloride.

5. A process as claimed in claim 2 wherein the hydrochloride salt is prepared by reacting compound of formula I with ammonium chloride in water.

6. A process as claimed in claim 2 wherein the hydrochloride salt of compound of formula I is further subjected to one or more crystallizations to obtain the substantially pure hydrochloride salt of compound of formula I having HPLC purity greater than 99.6% by area.

7. A process as claimed in claim 6 wherein substantially pure compound of formula I is substantially free of compounds of formulae IIIa to IIIc.

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IIIa : R = C_{1-4} linear or branched alkyl group; R_1 = H
IIIb : R = H; R_1 = C_{1-4} linear or branched alkyl group
IIIc : R and R_1 = C_{1-4} linear or branched alkyl group
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Formula III
8. A process as claimed in claim 6 wherein the compound of formula I is substantially free of compound of formula V a and/or V b.

![Formula V a]

![Formula V b]

9. A process for the preparation of compound of formula I as claimed in claims 1 to 8 substantially as herein described and illustrated by examples 1 to 4.