



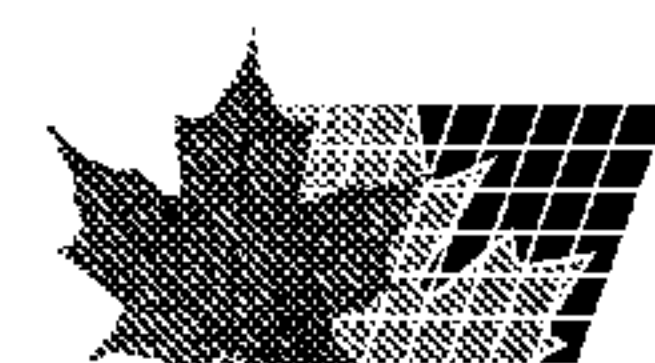
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(54) Title: IMPROVED SYNTHESIS AND PREPARATIONS OF DULOXETINE SALTS

(57) **Abrégé/Abstract:**

The invention relates to an improved process for preparing duloxetine hydrochloride. More particularly, the invention relates to the preparation of duloxetine hydrochloride by a process that provides a maximum yield of desired product with a minimum amount of undesired by-products.



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(54) Title: IMPROVED SYNTHESIS AND PREPARATIONS OF DULOXETINE SALTS

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tion relates to the preparation of duloxetine hydrochloride by a process that provides a maximum yield of desired product with a
minimum amount of undesired by-products.



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IMPROVED SYNTHESIS AND PREPARATIONS OF DULOXETINE SALTS**CROSS REFERENCE TO RELATED APPLICATIONS**

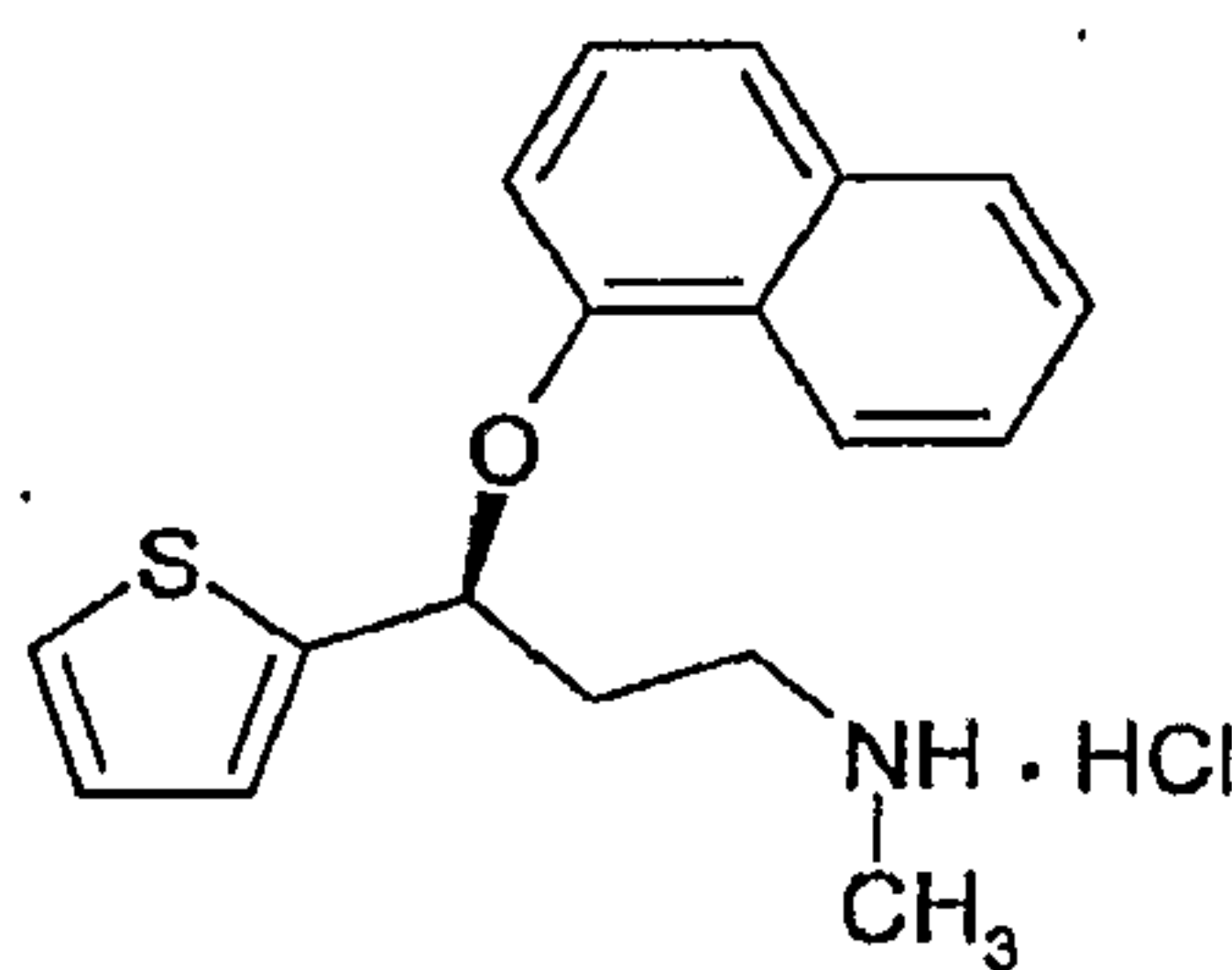
This application claims priority to United States Provisional Application Nos. 60/749,095; 60/749,096 and 60/749,097 filed December 12, 2005, and 60/815,835; 60/815,854 and 60/815,856 filed June 23, 2006, as well as the International Applications filed concurrently herewith under attorney docket numbers 23087-0022-1 PCT and 23087-0022-3 PCT, which applications are expressly incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION**Field of the Invention**

The invention relates to an improved process for preparing duloxetine hydrochloride. More particularly, the invention relates to the preparation of duloxetine hydrochloride by a process that provides a maximum yield of desired product with a minimum amount of undesired by-products.

Discussion of the Related Art

Duloxetine hydrochloride (Compound I) is the international commonly accepted name for N-methyl-N-[(3S)-(3-(1-naphthyloxy)-3-thien-2-yl)propyl]amine hydrochloride (which is also known as methyl-[(S)-3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine hydrochloride) and has an empirical formula of $C_{18}H_{19}NOS \cdot HCl$ and a molecular weight of 333.88. Duloxetine hydrochloride is a commercially marketed pharmaceutically active substance known to be useful for the treatment of major depressive disorder.



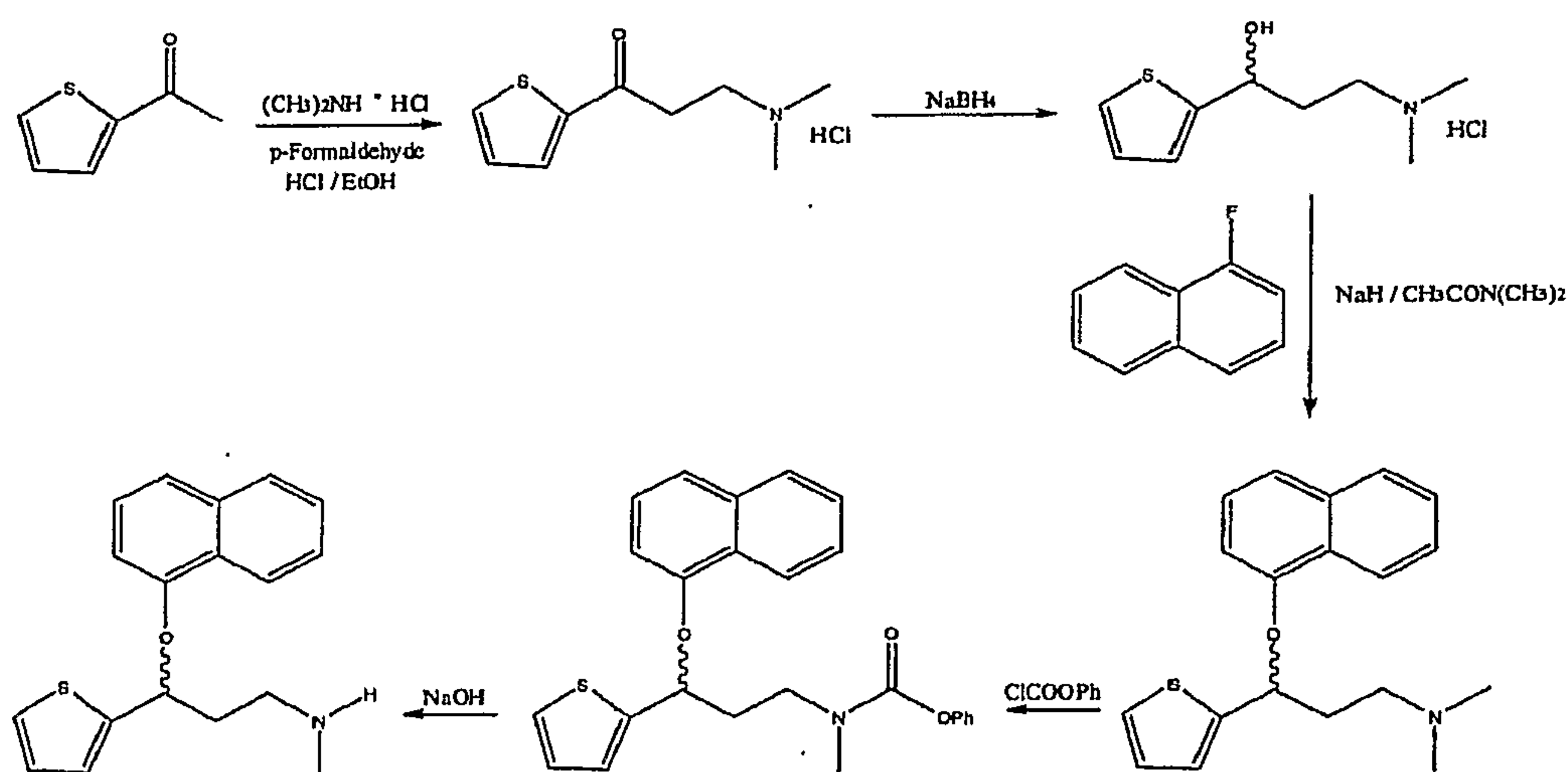
(I)

Duloxetine hydrochloride is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. In the United States, duloxetine hydrochloride is

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marketed under the name Cymbalta[®] for the treatment of major depressive disorder and diabetic peripheral neuropathic pain. In Europe, duloxetine hydrochloride has been approved for the treatment of major depressive disorder and also for the treatment of moderate to severe stress urinary incontinence.

5 Duloxetine and its pharmaceutically acceptable salts are disclosed in U.S. Patent No. 5,023,269 ("the '269 patent"). No examples related to the preparation of (S)-duloxetine, or one of its pharmaceutically acceptable salts (*e.g.*, the hydrochloride salt), are disclosed. In the '269 patent, racemic duloxetine was prepared by demethylating the corresponding N,N-dimethylpropanamine derivative using phenyl chloroformate to yield the corresponding
10 carbamate as an intermediate. The carbamate was then hydrolyzed to afford racemic duloxetine as an oil, and was subsequently isolated as the oxalate salt. The process disclosed in the '269 patent for obtaining racemic duloxetine is shown in Scheme 1.



Scheme 1

15 Methods for producing duloxetine and/or its salts are disclosed in various references, including: U.S. Patent No. 5,362,886; WO 04/056795; WO 03/062219; WO 00/61540; WO 03/070720; WO 04/011452; WO 04/024708; WO 04/005307; JP 2004123596; WO 04/13123; and WO 04/005220. Preparation of duloxetine hydrochloride is specifically described in the following references: U.S. Patent No. 5,362,886, U.S. Patent No. 5,491,243; WO 04/056795; *J. Labelled Compd. Radiopharm.*, 36, 213 (1995); and *Zhongguo Xinyao Zazhi*, 14(1), 74-76 (2005).
20

In U.S. Patent Nos. 5,362,886 and 5,491,243, concentrated hydrochloric acid is added to a solution of duloxetine base dissolved in ethyl acetate. The solution is then

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seeded with a crystal, and additional ethyl acetate is added. The solution is then stirred, concentrated and filtered to yield duloxetine hydrochloride.

In *J. Labelled Compd. Radiopharm*, 36, 213 (1995), duloxetine base was dissolved in ethyl acetate and treated with HCl/ethyl acetate. After stirring for 1 hour and chilling to -
5 20° C for an additional hour, the mixture was diluted with ether, filtered, washed with fresh ether and dried to yield duloxetine hydrochloride.

Potential impurities in duloxetine hydrochloride include those described in *J. Liq. Chrom. & Rel. Technol.*, 19(12), 1993-2007 (1996) and *Synth. Appl. Isotop. Lab. Compounds*, 597-603 (1994), though neither describes the characterization of such
10 impurities.

As with other pharmaceutical products, it is desirable to prepare duloxetine hydrochloride of a high grade and having a minimum amount of impurities present in order to minimize the occurrence of adverse side effects and to facilitate formulation and formulation shelf life.

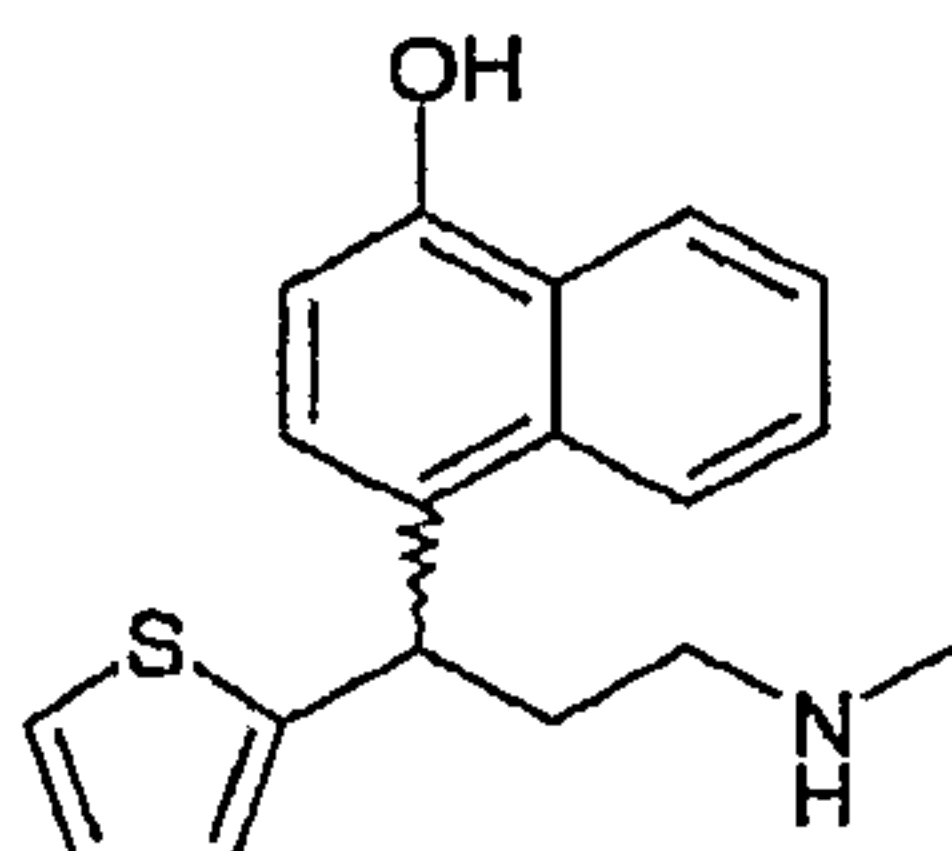
SUMMARY OF THE INVENTION

15 The invention relates to an improved process for preparing duloxetine hydrochloride. More particularly, the invention relates to the preparation of duloxetine hydrochloride by a process that provides a maximum yield of desired product with a minimum amount of undesired by-products.

20 In particular, it has been observed that duloxetine degrades upon contact with an acidic medium. Contact with an acidic medium, however, is necessary to form an acid addition salt. Thus, careful control of the reaction conditions for the conversion of duloxetine base into an acid addition salt is required. Additionally, the temperature, the molar ratio of the different reagents, the reaction media and the presence of water may affect the synthesis of duloxetine hydrochloride from duloxetine base.

25 The main degradation impurity when treating duloxetine with acid has here been isolated and identified as 4-(3-methylamino-1-thiophen-2-yl-propyl)-naphthalen-1-ol (Compound II, below) or salts thereof. One aspect of the invention includes the synthesis of Compound II as its hydrochloride salt and its use as a marker for measuring the purity of duloxetine salts.

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**Compound II**

Another aspect of the invention includes a process for monitoring the reaction products obtained during the preparation of duloxetine hydrochloride for the presence of undesirable by-products. Preferably, the monitoring process includes monitoring the products for the presence of 4-(3-methylamino-1-thiophen-2-yl-propyl)-naphthalen-1-ol (Compound II) or salts thereof (Compound II salt, *e.g.*, Compound II hydrochloride).

Another aspect of the invention includes the use of Compound II or salts thereof as a reference marker for the analysis of duloxetine and its pharmaceutically acceptable salts.

Another aspect of the invention includes methods for preparing duloxetine hydrochloride having reduced levels of Compound II or salts thereof. These methods provide high quality and purity duloxetine hydrochloride without requiring complicated separation procedures.

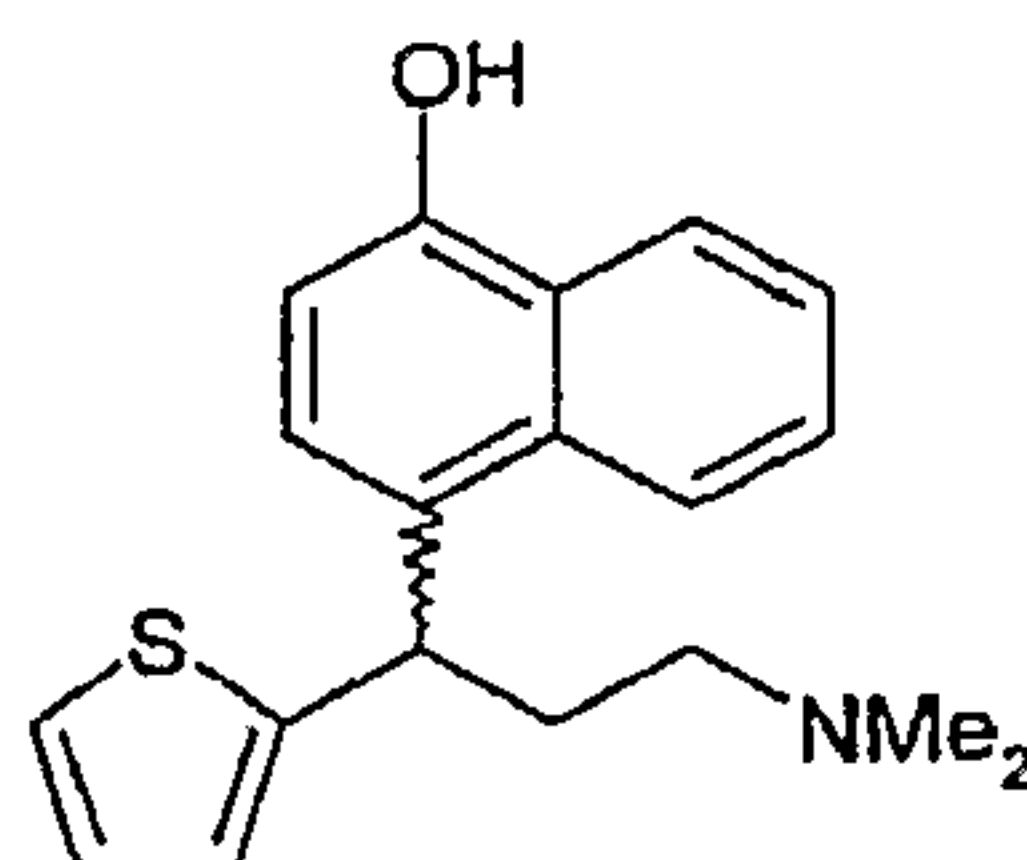
Another aspect of the invention includes the production of duloxetine hydrochloride having less than approximately 0.1% area by HPLC of Compound II and/or salts thereof.

Another aspect of the invention includes the production of duloxetine hydrochloride having less than approximately 0.1% area by HPLC of Compound II and/or salts thereof, wherein the production of duloxetine hydrochloride does not require procedures to separate Compound II and/or salts thereof from the crude duloxetine hydrochloride reaction product.

Another aspect of the invention includes formulating duloxetine hydrochloride having less than approximately 0.1% area by HPLC of Compound II and/or salts thereof into readily usable dosage units for the therapeutic treatment of mammals, including humans.

Another aspect of the invention includes producing Compound II from 4-[3-dimethylamino-1-(2-thienyl)-1-propyl]naphthol (Compound III, below) and/or its salts:

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**Compound III**

Another aspect of the invention includes the Compound III and salts thereof (Compound III salt, *e.g.*, Compound III hydrochloride).

5 Another aspect of the invention includes the use of Compound III as a reference marker.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reference will now be made in detail to the preferred embodiments of the invention. This invention may, however, be embodied in many different forms and should not be
10 construed as limited to the embodiments set forth herein. In addition, and as will be appreciated by one of skill in the art, the invention may be embodied as a method, system or process.

The invention relates to an improved process for preparing duloxetine hydrochloride. More particularly, the invention relates to the preparation of duloxetine hydrochloride by a process that provides a maximum yield of desired product with a minimum amount of
15 undesired by-products.

One aspect of the invention includes a compound obtained during the production of duloxetine hydrochloride named 4-(3-methylamino-1-thiophen-2-yl-propyl)-naphthalen-1-ol (Compound II), characterized as its hydrochloride salt by ¹H and ¹³C NMR, mass spectroscopy, IR and elemental analysis.

20 Another aspect of the invention includes a process of using Compound II and/or salts thereof as a marker in the production of duloxetine and its pharmaceutically acceptable salts.

Another aspect of the invention includes producing Compound II from 4-[3-dimethylamino-1-(2-thienyl)-1-propyl]naphthol (Compound III) and/or its salts. Compound III can be obtained as a degradation impurity when treating the duloxetine intermediate (S)-
25 N,N-dimethyl-(3-(1-naphthyloxy)-3-(thien-2-yl)propylamine with acid.

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Another aspect of the invention includes the Compound III and salts thereof (Compound III salt, *e.g.*, Compound III hydrochloride).

Another aspect of the invention includes the use of Compound III as a reference marker in the synthesis of (S)-N,N-dimethyl-(3-(1-naphthyloxy)-3-(thien-2-yl)propylamine and salts thereof, and, in particular, the oxalate salt.

Another aspect of the invention includes duloxetine hydrochloride containing less than approximately 0.1% of Compound II and/or salts thereof.

Another aspect of the invention includes a method for preparing duloxetine hydrochloride from duloxetine base that includes contacting duloxetine base with ammonium chloride

Another aspect of the invention includes a method for preparing duloxetine hydrochloride from (S)-N-methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid 1-chloroethyl ester, wherein the duloxetine hydrochloride has less than approximately 0.1% area by HPLC of Compound II and/or salts thereof.

Another aspect of the invention includes a method for preparing duloxetine hydrochloride from duloxetine base, wherein the duloxetine hydrochloride has less than approximately 0.1% area by HPLC of Compound II and/or salts thereof.

Another aspect of the invention includes formulating duloxetine hydrochloride having less than approximately 0.1% area by HPLC of Compound II and/or salts thereof into readily usable dosage units for the therapeutic treatment of mammals, including humans. Such formulations are normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. According to this aspect of the invention, there is provided a pharmaceutical composition that includes the compounds of the invention in association with a pharmaceutically acceptable diluent or carrier.

The formulations of the invention can also include alternative equivalent excipients (*i.e.*, other release control agents, fillers, lubricants and/or binders) having the same and/or similar functions and/or properties may be readily substituted and used in the above illustrative formulation. Additional suitable pharmaceutically-acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium

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stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention and specific examples provided herein without departing from the spirit or scope of the invention. Thus, it is intended that the present invention covers the modifications and variations of this invention that come within the scope of any claims and their equivalents.

Specific Examples

The following examples are for illustrative purposes only and are not intended, nor should they be interpreted to, limit the scope of the invention.

General Experimental Conditions:

HPLC Method

a. Chromatographic Purity HPLC Method

The chromatographic separation is carried out in a Phenomenex Luna C18, 5 μ m, 4.6 x 150 mm column at room temperature (20-25° C).

The mobile phase was prepared by mixing 500 mL of acetonitrile with 500 mL of buffer (pH = 2), which was prepared by dissolving 18.40 g of hexafluorophosphate in 1000 mL of water. The pH was adjusted to 2 with phosphoric acid. The mobile phase is mixed and filtered through 0.22 μ m nylon membrane under vacuum.

The chromatograph was equipped with a 220 nm detector and the flow rate was 1 mL per minute. Test samples (10 μ L) were prepared by dissolving the appropriate amount of sample in the mobile phase in order to obtain 0.5 mg per mL. The chromatogram was run for at least 30 minutes.

b. HPLC Chiral Method

The chromatographic separation was carried out in a Daicel CHIRALCEL OD-RH, 5 μ m, 4.6 x 150 mm column at room temperature (20-25° C).

The mobile phase was prepared by mixing 600 mL of acetonitrile with 400 mL of buffer (pH = 2), which was prepared from 18.40 g of hexafluorophosphate dissolved in

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1000 mL of water. The pH was adjusted to 2 with phosphoric acid. The mobile phase was mixed and filtered through a 0.22 μ m nylon membrane under vacuum.

The chromatograph was equipped with a 216 nm detector and the flow rate was 0.5 mL per minute. Test samples (5 μ L) were prepared by dissolving the appropriate amount of sample in the mobile phase in order to obtain 0.5 mg of sample per mL. The chromatogram was run for at least 25 minutes.

EXAMPLE 1: Preparation of (S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine hydrochloride (Duloxetine hydrochloride) starting from (S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine

Duloxetine base (10 g, 90% ee) was dissolved in acetone (100 mL) and stirred with cooling in an ice-water bath. Hydrogen chloride in diethyl ether (2M, 15.9 mL) was added, and a precipitate formed within 15 minutes. The mixture was then stirred at 0° C for 165 minutes, filtered and the collected solid washed with acetone (10 mL). The resulting white solid was dried under vacuum at 45° C to yield 8.16 g of duloxetine hydrochloride (Yield: 77%). The product was analyzed by chiral HPLC and determined to be 97% ee. The level of Compound II was < 0.05% peak area at 220 nm.

EXAMPLE 2: Preparation of (S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine hydrochloride (Duloxetine hydrochloride) starting from (S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine

Duloxetine base (99% ee, 0.5 g) was dissolved in acetone (5 mL) and stirred with cooling in an ice-water bath. Hydrogen chloride in diethyl ether (2M, 0.8 mL) was added, and a precipitate formed within 2 minutes. The mixture was stirred at ambient temperature for 16 hours, filtered, and the collected solid was washed with acetone (0.5 mL). The resulting white solid was dried under vacuum at ambient temperature to yield 0.485 g of duloxetine hydrochloride (Yield: 91%). The product was analyzed by chiral HPLC and determined to be 99.5% ee. The level of Compound II was < 0.007% peak area at 220 nm.

EXAMPLE 3: Preparation of (S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine hydrochloride (Duloxetine hydrochloride) starting from (S)-N-Methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid 1-chloroethyl ester

(S)-N-Methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid 1-chloroethyl ester (6.42 g, 60% ee) was stirred in methanol (3.2 mL) at ambient temperature for

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16 hours. Acetone (30 mL) was added, and the mixture was seeded with 5 mg of duloxetine hydrochloride. The mixture was stirred at ambient temperature for 1 hour, and then kept at 6° C for 16 hours. The resulting solid was filtered, washed with acetone (5 mL), and dried in a vacuum at ambient temperature for 24 hours to yield 1.56 g of duloxetine hydrochloride (Yield: 29%; 98% ee). The liquors were concentrated and dissolved in acetone (5 mL). After being maintained at 5° C for 16 hours, a second crop of duloxetine hydrochloride was obtained (0.486 g; Yield: 9%; 94% ee). Analysis of the liquors indicated < 5% ee.

EXAMPLE 4: Preparation of (S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine hydrochloride (Duloxetine hydrochloride) starting from (S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine

(S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine (1 g, 62% ee) was stirred in ethyl acetate (4 mL) at 0° C, and hydrogen chloride in methanol (1.25 M, 2.42 mL) was added. The mixture was stirred at this temperature for 4 hours and then at ambient temperature for an additional 16 hours. The mixture was then evaporated, and acetone (5 mL) was added, causing abundant precipitation. Additional acetone (7 mL) was added, and the mixture was stirred for 30 minutes and filtered. The resulting product was washed with acetone (2 × 5 mL) and dried under vacuum at 50° C to yield 0.43 g of duloxetine hydrochloride as a white solid. Analysis: 97.4% ee, >97 % peak area of duloxetine hydrochloride, < 0.01% (peak area) of Compound II.

EXAMPLE 5: Preparation of (S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine hydrochloride (Duloxetine hydrochloride)

(S)-N-methyl-(3-(1-naphthyloxy)-3-thien-2-yl)propylamine (1 g, 62% ee) was stirred in ethyl acetate (4 mL) at 0° C and aqueous hydrochloric acid (37%, 0.25 mL) was added. The mixture was stirred at this temperature for 4 hours and then at ambient temperature for an additional 16 hours. The mixture was then evaporated, and acetone (5 mL) was added. No precipitation was observed and the mixture was concentrated under reduced pressure to yield a brown oil. Analysis: 36% peak area of Compound II, 18% peak area of duloxetine hydrochloride.

EXAMPLE 6: Preparation of Duloxetine Hydrochloride with Ammonium Chloride Solution

Duloxetine base (0.5 g) was dissolved in acetone (2.5 mL) and water (2.5 mL). The mixture was cooled in ice, and a saturated solution of ammonium chloride (2.5 mL) was added.

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The mixture was stirred at ambient temperature for 16 – 24 hours. The acetone was then removed by evaporation under reduced pressure causing precipitation. The resulting suspension was then stirred at ambient temperature for 16 – 24 hours, filtered, washed with water (0.5 mL) and dried in a vacuum oven at ambient temperature overnight. Analysis: 99.5% ee, >99.2 % peak area of duloxetine hydrochloride, < 0.2% (peak area) of Compound II.

EXAMPLE 7: Preparation of 4-(3-methylamino-1-thiophen-2-yl-propyl)-naphthalen-1-ol hydrochloride (Compound II hydrochloride)

Duloxetine hydrochloride (5 g) was heated at reflux temperature in 0.1 N hydrochloric acid (50 mL) for 6 hours. The mixture was then concentrated under reduced pressure and slurried in 2-propanol (20 mL). The mixture was then filtered and dried to yield 4.16 g of a brown solid. A portion of this solid (3.7 g) was heated in 2-propanol to reflux temperature for 30 minutes, cooled, filtered, washed with 2-propanol (10 mL) and dried under vacuum at 40° C to yield 2.51g of Compound II as an off-white solid.

Analysis of Compound II hydrochloride: ¹H NMR (400 MHz, DMSO) 10.17 (1H, s), 9.1-8.8 (2H, br s), 8.16 (1H, d), 8.12 (1H, d), 7.48 (1H, t), 7.42 (1H, t), 7.33 (1H, d), 7.28 (1H, d), 7.04 (1H, d), 6.92 (1H, t), 6.89 (1H, d), 5.09 (1H, t, CHAr), 2.85 (2H, m), 2.56 (5H, m); ¹³C NMR (100 MHz, DMSO) 153.1, 149.5, 132.7, 129.8, 127.3, 127.0, 125.7, 125.2, 124.9, 124.9, 124.0, 123.3, 108.3, 47.6, 38.2, 33.2, 32.9; IR (KBr Disc) 3206, 2964, 2788, 1623, 1596, 1585, 1514, 1470, 1379, 1332, 1280, 1259, 1212, 1145, 1065, 1051, 848, 827, 806, 764, 711, 537, 424 cm⁻¹; MS (ESI+) 298.1, 100% (M+H); Elemental Analysis: C₁₈H₂₀ClNOS · ¼ H₂O requires C 63.89%, H 6.11, N 4.14%, Cl 10.48%, S 9.47%; Found C 63.82%, H 6.17, N 4.12%, Cl 10.44%, S 9.43%.

EXAMPLE 8: Preparation of 4-[3-dimethylamino-1-(2-thienyl)-1-propyl]naphthol hydrochloride (Compound III hydrochloride)

A mixture of *N,N*-3-dimethylamino-1-(2-thienyl)-1-propanol (50 g, 270 mmol) and 1-naphthol (38.9 g, 270 mmol) in 1M aqueous hydrochloric acid (1L) was heated at reflux for 20 hours. The mixture was cooled and adjusted to pH 7 by the addition of aqueous NaOH (50%). The mixture was then and extracted with dichloromethane (2 × 250 mL). Some solid remained suspended in the aqueous layer. The organic layers were combined, washed with water (2 × 5 mL) and concentrated under reduced pressure to yield 11.47 g of a brown solid. The two aqueous layers from above were then combined and filtered to give 54.4 g of a brown solid. This solid was combined with 7.8 g of the first brown solid obtained and then slurried in 2-propanol (200

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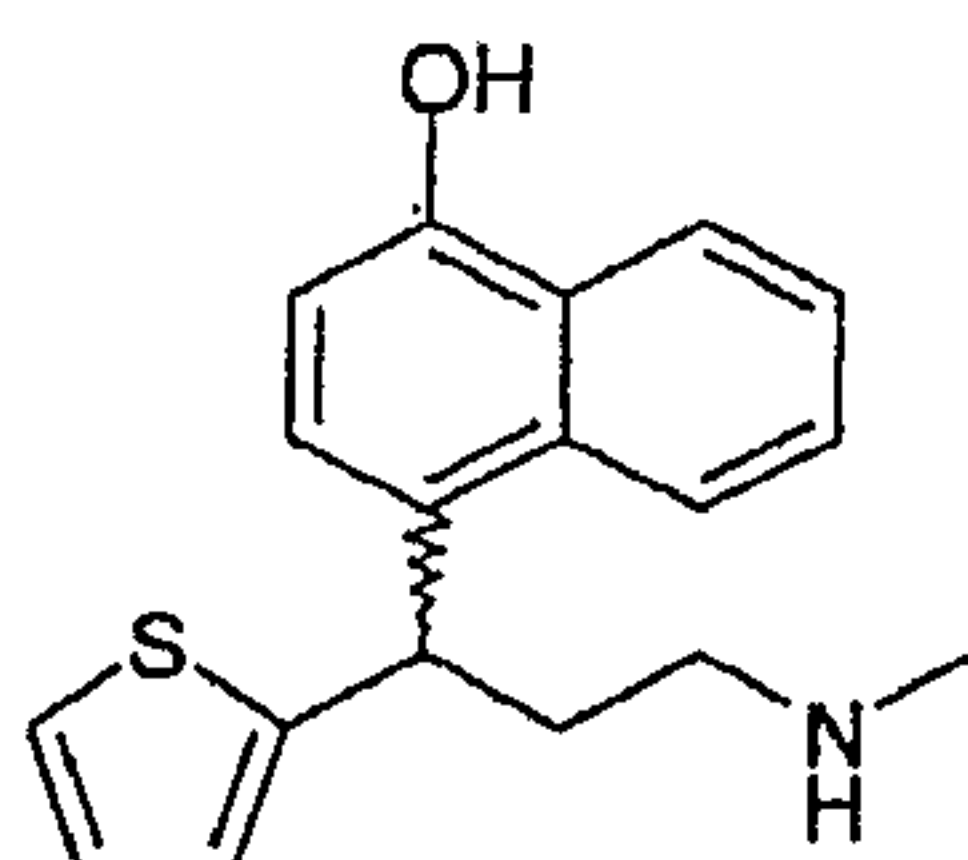
mL) at ambient temperature for 80 minutes. The resulting solid was filtered, washed with 2-propanol (20 mL) and dried under vacuum at 50° C to yield 38.75 g (Yield: 41%) of Compound III hydrochloride as a brown solid.

Analysis of Compound III hydrochloride: ¹H NMR (400 MHz, d6-DMSO, 25 °C)
5 10.25 (1H, s), 8.17 (1H, dd), 8.12 (1H, d), 7.5-7.4 (3H, m), 7.27 (1H, dd), 7.07 (1H, d), 6.93
(1H, d), 6.91 (1H, dd), 5.06 (1H, t), 2.93 (2H, m), 2.7-2.5 (8H, m); ¹³C NMR (100.6 MHz,
d6-DMSO, 25 °C) 152.6, 149.0, 132.2, 129.2, 126.8, 126.5, 125.2, 124.6, 124.4, 124.4,
123.3, 122.9, 107.8, 55.7, 42.3, 37.9, 31.3; IR (KBr Disc) 3428.2, 3106.8, 2960.3, 2646.7,
1624.6, 1594.1, 1583.2, 1517.6, 1747.1, 1442.4, 1386.5, 1347.0, 1278.6, 1248.6, 1215.8,
10 1158.8, 1148.0, 1058.8, 1011.7, 971.6, 838.6, 772.7, 713.3, 706.2; MS (ESI+) 312, 100%)
(M+H); Elemental Analysis: C₁₉H₂₂ClNOS · ¼ H₂O requires C 64.76%, H 6.44, N 3.97%,
Cl 10.06%, S 9.10%; Found C 64.76%, H 6.62, N 3.95%, Cl 10.05%, S 8.92%.

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What is claimed is:

1. 4-(3-methylamino-1-thiophen-2-yl-propyl)-naphthalen-1-ol ("Compound II") having the formula:

**Compound II**

- 5 and salts thereof, wherein the hydrochloride salt of Compound II is characterized by ¹H NMR (400 MHz, DMSO) having characteristic peaks at approximately 10.17 (1H, s), 9.1-8.8 (2H, br s), 8.16 (1H, d), 8.12 (1H, d), 7.48 (1H, t), 7.42 (1H, t), 7.33 (1H, d), 7.28 (1H, d), 7.04 (1H, d), 6.92 (1H, t), 6.89 (1H, d), 5.09 (1H, t, CHAr), 2.85 (2H, m) and 2.56 (5H, m).
2. Compound II and salts thereof according to claim 1, wherein the hydrochloride salt of Compound II is characterized by ¹³C NMR (100 MHz, DMSO) having characteristic peaks at approximately 153.1, 149.5, 132.7, 129.8, 127.3, 127.0, 125.7, 125.2, 124.9, 124.9, 124.0, 123.3, 108.3, 47.6, 38.2, 33.2 and 32.9.
3. A salt of Compound II according to claims 1 or 2, wherein said salt is the hydrochloride salt.
5. A method of measuring the purity of duloxetine and its pharmaceutically acceptable salts comprising measuring the quantity of at least one of Compound II and a salt thereof in at least one of a sample of duloxetine, its pharmaceutically acceptable salts and combinations thereof.
6. Duloxetine and its pharmaceutically acceptable salts containing less than approximately 0.1% area by HPLC of Compound II or a salt thereof.
7. Duloxetine hydrochloride containing less than approximately 0.1% area by HPLC of Compound II or a salt thereof.
8. A method for preparing duloxetine hydrochloride comprising converting (*S*)-*N*-methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid 1-chloroethyl ester

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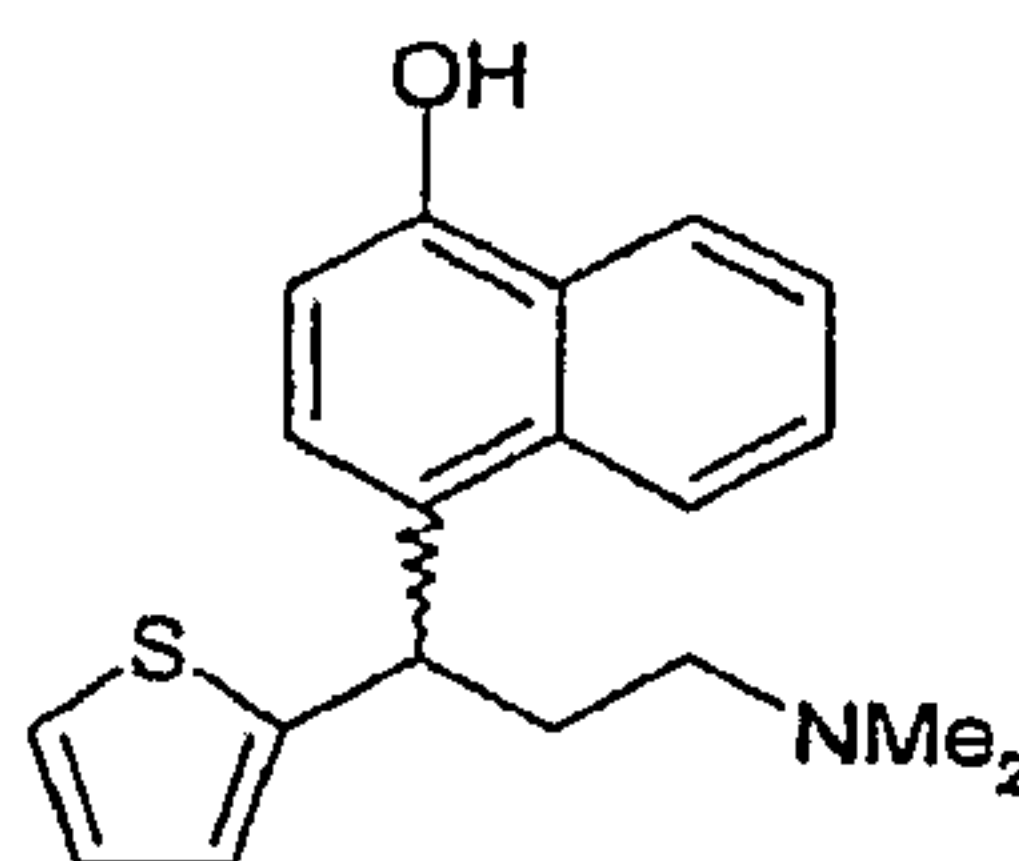
to duloxetine hydrochloride, wherein said duloxetine hydrochloride has less than approximately 0.1% area by HPLC of Compound II or a salt thereof.

9. A method for preparing duloxetine hydrochloride comprising converting duloxetine base to duloxetine hydrochloride, wherein said duloxetine hydrochloride has less than approximately 0.1% area by HPLC of Compound II or a salt thereof.
10. The of claim 9, wherein said conversion comprises contacting said duloxetine base with ammonium chloride to yield duloxetine hydrochloride.
11. A formulation comprising duloxetine hydrochloride, wherein said duloxetine hydrochloride has less than approximately 0.1% area by HPLC of Compound II or salt thereof.
12. The formulation of claim 11, further comprising at least one of a pharmaceutically acceptable diluent and a carrier.
13. The formulation of claim 11, further comprising at least one additional excipient material.
14. The formulation of claim 13, wherein said at least one additional excipient material is at least one of an inert diluent, a granulating and disintegrating agent, a binding agent, a lubricating agent, a preservative agent, an anti-oxidant and combinations thereof.
15. The formulation of claim 14, wherein said inert diluent is at least one of lactose, sodium carbonate, calcium phosphate, calcium carbonate and combinations thereof.
16. The formulation of claim 14, wherein said granulating and disintegrating agent is at least one of corn starch, algenic acid and combinations thereof.
17. The formulation of claim 14, wherein said binding agent is starch.
18. The formulation of claim 14, wherein said lubricating agent is at least one of magnesium stearate, stearic acid, talc and combinations thereof.
19. The formulation of claim 14, wherein said preservative agent is at least one of ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate and combinations thereof.
20. The formulation of claim 14, wherein said anti-oxidant is ascorbic acid.
21. A process for producing duloxetine hydrochloride having less than approximately 0.1% area by HPLC of Compound II or a salt thereof comprising converting duloxetine base

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to duloxetine hydrochloride, wherein said process does not require a procedure to separate Compound II or a salt thereof from said duloxetine hydrochloride.

22. 4-[3-dimethylamino-1-(2-thienyl)-1-propyl]naphthol (Compound III) having the formula:



and salts thereof, wherein said Compound III and its salts are obtained during the production of duloxetine hydrochloride.

23. A salt of Compound III according to claim 22, wherein said salt is the hydrochloride salt.

24. The hydrochloride salt of claim 23 characterized by ^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$, 25°C) having characteristic peaks at approximately 10.25 (1H, s), 8.17 (1H, dd), 8.12 (1H, d), 7.5-7.4 (3H, m), 7.27 (1H, dd), 7.07 (1H, d), 6.93 (1H, d), 6.91 (1H, dd), 5.06 (1H, t), 2.93 (2H, m), 2.7-2.5 (8H, m).

25. The hydrochloride salt of claim 23 characterized by ^{13}C NMR (100.6 MHz, $\text{d}_6\text{-DMSO}$, 25°C) having characteristic peaks at approximately 152.6, 149.0, 132.2, 129.2, 126.8, 126.5, 125.2, 124.6, 124.4, 124.4, 123.3, 122.9, 107.8, 55.7, 42.3, 37.9, 31.3.

26. A method of measuring the purity of duloxetine and its pharmaceutically acceptable salts comprising measuring the quantity of at least one of Compound III and a salt thereof in at least one of a sample of duloxetine, its pharmaceutically acceptable salts and combinations thereof.

27. A process for preparing Compound II and salts thereof comprising converting Compound III and salts thereof into Compound II and salts thereof.