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(54) Title: PURIFIED LASOFOXIFENE AND A METHOD FOR PURIFICATION OF RACEMIC LASOFOXIFENE BY RECRYSTALLIZATION

(57) Abstract: A method for removing impurities from racemic *cis*-6-phenyl-5-[4-(2- pyrrolidin-1-ylethoxy) phenyl]-5, 6, 7, 8-tetrahydronaphthalen-2-ol and purified *cis*-6-phenyl-5-[4-(2- pyrrolidin-1-ylethoxy) phenyl]-5, 6, 7, 8- tetrahydronaphthalen-2-ol useful as an estrogen agonist/ antagonist.



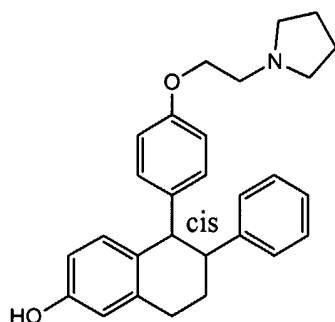
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PURIFIED LASOFOXIFENE AND A METHOD FOR PURIFICATION OF
RACEMIC LASOFOXIFENE BY RECRYSTALLIZATION

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BACKGROUND OF THE INVENTION

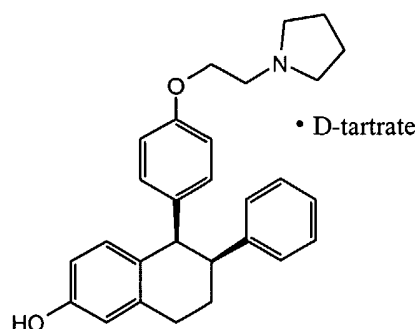
The present invention relates to a process for removing impurities from a racemic mixture of *cis* isomers of a compound of Formula I, *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, (hereinafter "racemic lasofoxifene" or "racemate").



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This invention also relates to a purified racemic lasofoxifene, *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, (hereinafter "purified racemic lasofoxifene" or "purified racemate"), and purified lasofoxifene D-tartrate, (-)-*cis*-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate, which is useful as an estrogen agonist/antagonist, also known as a selective estrogen receptor modulator ("SERM").

Racemic lasofoxifene is an intermediate in the syntheses of lasofoxifene D-tartrate, having the following structure:



Lasofoxifene, lasofoxifene D-tartrate, its racemate and processes for the preparation thereof, are disclosed in commonly assigned U.S. Patent No.

5 5,552,412, issued September 3, 1996, and U. S. Patent No. 5,948,809, issued September 7, 1999. The text of these patents and all other references cited in this specification are hereby incorporated by reference in their entirety.

Typically, drug substances preferably contain less than 0.2% impurities, most preferably less than 0.1% impurities. During the scale-up process for commercial production of lasofoxifene D-tartrate, however, it was determined that the
 10 resulting lasofoxifene D-tartrate compound contained undesirable impurities greater than 0.2%. It was also determined that purification of lasofoxifene D-tartrate to less than 0.1% impurities was not commercially feasible at the proposed scale-up. Consequently, there was a need to obtain an intermediate of Lasofoxifene D-tartrate,
 15 having a purity of less than 0.1% impurities. The process described within the instant invention resolves this issue.

SUMMARY OF THE INVENTION

20 This invention is directed to a method of purifying racemic, cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, which comprises:

- 25 a) suspending racemic cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in a mixture of ethanol and tetrahydrofuran to form a suspension;
- b) agitating and heating said suspension;

- c) cooling said suspension of step (b); and
- d) collecting a solid purified racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

In a preferred embodiment, said mixture of ethanol and tetrahydrofuran has about a 4:1 volume ratio

In a preferred embodiment, said mixture of ethanol and tetrahydrofuran has about a 3:1 volume ratio.

In a more preferred embodiment, said mixture of ethanol and tetrahydrofuran has about a 2:1 volume ratio.

In a more preferred embodiment, said mixture of ethanol and tetrahydrofuran has about a 1:1 volume ratio.

In a preferred embodiment, said suspension formed in step (a) is agitated and heated from ambient temperature up to about 70°C in step (b).

In a preferred embodiment, said suspension formed in step (a) is agitated and heated from ambient temperature up to about 65°C for about 30 minutes to about 12 hours (b).

In a preferred embodiment, suspension so formed in step (b) is cooled and agitated for about 30 minutes to about 18 hours in step (c).

In a preferred embodiment, said suspension so formed in step (c) is collected by filtration, providing purified racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, having less than 0.1% impurities.

In another aspect, the invention is directed to purified racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.

The term "ambient temperature," as used here means about 15-25°C.

The terms "unpurified racemic lasofoxifene" or "racemate," as used herein, means the racemic mixture of *cis* isomers of *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol prior to performing the purification process (*i.e.* greater than 0.1% impurities).

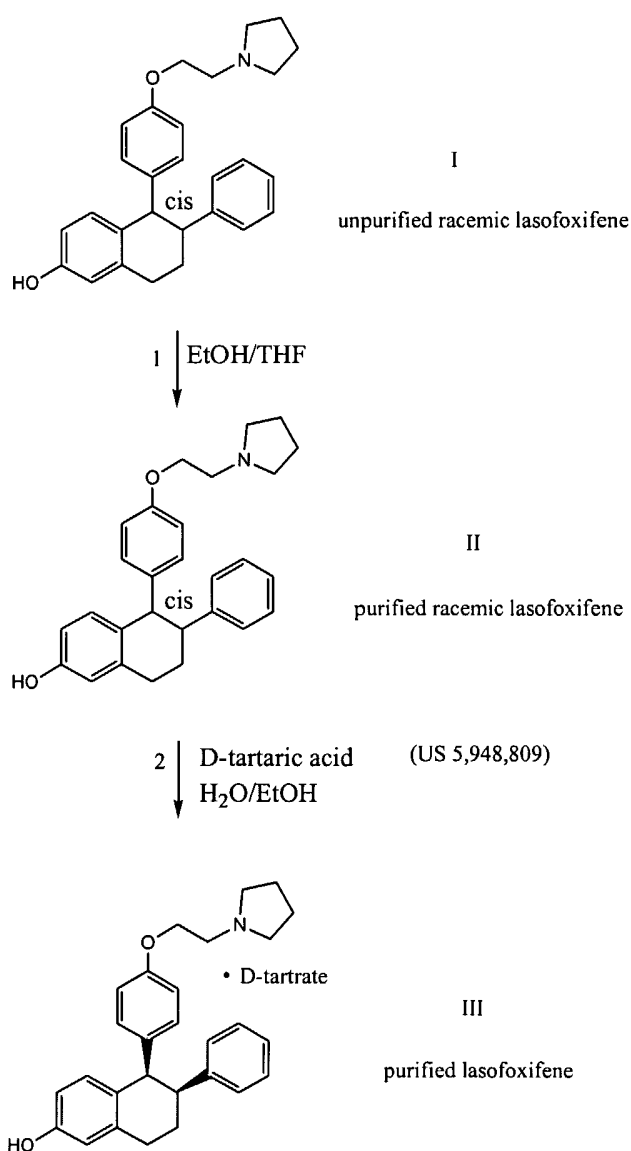
The terms "purified racemate lasofoxifene," or "purified racemate," as used herein, means racemic cis-6-phenyl-5[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, having less than 0.1% impurities.

The term "purified lasofoxifene D-tartrate," as used herein, means
5 (-)-cis-6(S)-phenyl-5(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate, having less than 0.2% impurities.

DETAILED DESCRIPTION OF THE INVENTION

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SCHEME I



Lasofloxifene is a valuable estrogen/antagonist and is useful for, *inter alia*, oral contraception; relief for the symptoms of menopause; prevention of threatened or habitual abortion; relief of dysmenorrhea, relief of dysfunctional uterine bleeding; relief of endometriosis; an aid in ovarian development; treatment of acne; diminution of excessive growth of body hair in women (hirsutism); the prevention and treatment of cardiovascular disease; prevention and treatment of arteriosclerosis; prevention and treatment of osteoporosis; treatment of benign prostatic hyperplasia and prostatic carcinoma obesity; and suppression of post-partum lactation.

Lasofloxifene also has a beneficial effect on plasma lipid levels and, as such, is useful in treating and preventing hypercholesterolemia. While lasofloxifene is an estrogen agonist in bone, it is an antiestrogen in breast tissue and, as such would be useful in the treatment and prevention of breast cancer.

Racemic lasofloxifene is the *cis*-racemate of lasofloxifene, containing two asymmetric carbons corresponding to two optically active compounds. Resolution of the racemate has been accomplished by crystallization of the salt with R-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ("R-binap"), as described in commonly owned U.S. Pat. No. 5,552,412. Resolution of the racemate was also accomplished by the addition of D-tartaric acid to the racemic or partially optically enriched *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)-5,6,7,8-tetrahydronaphthalene-2-ol, forming a 1:1 salt in aqueous ethanol, as described in U.S. Pat. No. 5,948,809. Upon cooling the (-) isomer is separated as a solid and is collected, providing the desired pharmaceutically acceptable salt of the (-) *cis*-D-tartrate isomer in high yield.

Several purification methods were explored to reduce the amount of impurities in lasofloxifene D-tartrate to less than 0.2%, including recrystallization and chromatography. These methods were unsatisfactory, either because of loss in yield or insufficient purity of lasofloxifene D-tartrate. It was determined that the desired level of purification (less than 0.1%) and optimal yield were obtained by the purification techniques described herein.

As set forth in Scheme I and the examples, unpurified racemic lasofloxifene is combined with a mixture of ethanol and tetrahydrofuran in Step 1(a). A person of ordinary skill in the art will appreciate that the ratio of ethanol to tetrahydrofuran may vary. Preferably, however, the volume ratio is 1:1 to 4:1.

In step 1(b), the resulting suspension was heated from about ambient temperature up to about 70°C and agitated for a time period between about 30 minutes and up to about 12 hours. Preferably, however, the suspension is agitated for about 8 to about 12 hours. One of ordinary skill in the art will appreciate that the duration of agitation of the above suspension may be extended beyond 12 hours. In step 1(c), the heated suspension is then cooled to about ambient temperature with agitation for a time period from about 30 minutes to about 18 hours. Finally, in step 1(d), the solids may be collected by means known to those skilled in the art (e.g. filtration) and washed with an appropriate solvent (e.g. ethanol) and dried (e.g. *in vacuo*), providing purified racemic lasofoxifene.

The purified racemic lasofoxifene may be resolved, as depicted in Step II and described in U.S. 5,948,809, providing purified lasofoxifene D-tartrate.

A person of ordinary skill in the art would appreciate that the ratios of ethanol to tetrahydrofuran, the temperature, and the duration of heating and agitating may be varied. These variations are within the scope of this invention.

EXAMPLES

The examples below are intended to illustrate particular embodiments of the invention and are not intended to limit the specification, including the claims, in any manner.

EXAMPLE 1

Purification of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with 2:1 Ethanol:Tetrahydrofuran

60 grams of unpurified racemic lasofoxifene was combined with 150 mL ethanol and 76.8 mL tetrahydrofuran. The resulting suspension was heated at about 65-70°C and agitated for about 3 hours, cooled to ambient temperature and agitated for about an additional 18 hours. The solids were collected by filtration, washed twice with 25 mL ethanol, and dried *in vacuo* at about 45°C to provide 49.36 grams of purified racemic lasofoxifene (82.3% yield).

The impurity profile of both the unpurified and purified racemic lasofoxifene were analyzed by reverse-phase High Pressure Liquid Chromatography (hereinafter "HPLC"), using a HPLC system with an ultraviolet ("UV") detector set at 230 nm and a Symmetry C18 cartridge column (50 mm length x 3.9 mm I.D. at 40°C).

- 5 The mobile phase consisted of 1400:600:5:4 ratio v/v/v/v water:acetonitrile:trifluoroacetic acid:ammonium hydroxide, having a pH of 3.0 with a 2.0 mL/min flow rate. The retention time of racemic lasofoxifene is 5.7 minutes. The results are tabulated below and reported in percent (%) area.

10 TABLE 1: Percent impurities in unpurified and purified racemic lasofoxifene

Relative Retention Times	0.91	1.9	2.19	2.3	2.34
Unpurified Racemic Lasofoxifene	0.19	0.38	0.2	0.38	0.42
Purified Racemic Lasofoxifene	<0.02	0.09	<0.02	<0.02	<0.02

Example 2

15 Large Scale Purification of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-
5,6,7,8-tetrahydronaphthalen-2-ol with 2:1 Ethanol:Tetrahydrofuran

- 20 24.9 kilograms of unpurified racemic lasofoxifene was combined with 62 liters of ethanol and 31 liters of tetrahydrofuran. The resulting suspension was heated at about 60-65°C and agitated for about 12 hours, cooled to ambient temperature and agitated for about an additional two hours. The solids were collected by filtration, washed with 22 liters of ethanol, and dried *in vacuo* at about 45°C to provide 20.5 kg purified racemic lasofoxifene (82.3 % yield).

- 25 The impurity profile of both unpurified and purified lasofoxifene was analyzed by HPLC, as described above. The results are tabulated below and reported in percent (%) area.

TABLE 2: Percent impurities in unpurified and purified racemic lasofoxifene

Relative Retention Times	0.91	1.9	2.19	2.3	2.34
Unpurified Racemic Lasofoxifene	0.19	0.38	0.2	0.38	0.42
Purified Racemic Lasofoxifene	<0.02	0.05	<0.02	<0.02	<0.02

5

Example 3**Purification of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with 2:1 Ethanol:Tetrahydrofuran**

8.14 grams of unpurified racemic lasofoxifene was combined with 20 mL of ethanol and 10 mL of tetrahydrofuran. The resulting suspension was heated at about 60-65°C and agitated for about 8 hours, cooled to ambient temperature and agitated for about two additional hours. The solids were collected by filtration, washed with 2 mL of ethanol, and dried *in vacuo* at about 40°C to provide 6.81 grams of purified racemic lasofoxifene (83.7 % yield).

The impurity profile of both unpurified and purified racemic lasofoxifene was analyzed by HPLC, as described above. The results are tabulated below and reported in percent (%) area.

TABLE 3: Percent impurities in unpurified and purified racemic lasofoxifene

Relative Retention Times	0.92	1.93	2.08	2.25	2.36	2.43
Unpurified Racemic Lasofoxifene	0.54	0.49	0.2	0.07	0.12	0.25
Purified Racemic Lasofoxifene	<0.02	0.03	0.05	0.01	<0.02	<0.02

20

Example 4**Purification of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with 2:1 Ethanol:Tetrahydrofuran**

25

8.2 grams of unpurified racemic lasofoxifene was combined with 41.1 mL of ethanol and 20.6 mL of tetrahydrofuran. The resulting suspension was heated at about 60-65°C and agitated for about 8 hours, cooled to ambient temperature and

agitated for about an additional two hours. The solids were collected by filtration, washed with 2 mL of ethanol and dried *in vacuo* at about 40°C to provide 6.76 grams purified racemic lasofoxifene (82.5 % yield).

The impurity profile of both unpurified and purified racemic lasofoxifene was analyzed by HPLC, as described above. The results are tabulated below and reported in percent (%) area.

TABLE 4: Percent impurities in unpurified and purified racemic lasofoxifene

Relative Retention Times	0.92	1.93	2.08	2.25	2.36	2.43
Unpurified Racemic Lasofoxifene	0.18	0.29	0.38	<0.02	0.03	0.19
Purified Racemic Lasofoxifene	<0.02	0.05	0.1	<0.02	<0.02	<0.02

Example 5

Purification of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with 2:1 Ethanol:Tetrahydrofuran

8.2 grams of unpurified racemic lasofoxifene was combined with 13.7 mL of ethanol and 6.8 mL of tetrahydrofuran. The resulting suspension was heated at about 60-65°C and agitated for about 8 hours, cooled to ambient temperature and agitated for about an additional two hours. The solids were collected by filtration, washed with 2 mL of ethanol, and dried *in vacuo* at about 40°C to provide 7.65 grams of purified racemic lasofoxifene (93.3 % yield).

The impurity profile of both unpurified and purified racemic lasofoxifene was analyzed by HPLC, as described above. The results are tabulated below and reported in percent (%) area.

TABLE 5: Percent impurities in unpurified and purified racemic lasofoxifene

Relative Retention Times	0.92	1.93	2.08	2.25	2.36	2.43
Unpurified Racemic Lasofoxifene	0.18	0.29	0.38	<0.02	0.03	0.19
Purified Racemic Lasofoxifene	<0.03	0.07	0.16	<0.02	<0.02	0.02

Example 6**Purification of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with 1:1 Ethanol:Tetrahydrofuran**

5 4.0 grams of unpurified racemic lasofoxifene was combined with 7.5 mL of ethanol and 7.5 mL of tetrahydrofuran. The resulting suspension was heated at about 60-65°C and agitated for about 8 hours, cooled to ambient temperature and agitated for about an additional two hours. The solids were collected by filtration, washed with 0.5 mL of ethanol, and dried *in vacuo* at about 40°C to provide 3.31
10 grams of purified racemic lasofoxifene (82.8 % yield).

The impurity profile of both unpurified and purified racemic lasofoxifene was analyzed by HPLC, as described above. The results are tabulated below and reported in percent (%) area.

15 **TABLE 6: Percent impurities in unpurified and purified racemic lasofoxifene**

Relative Retention Times	0.92	1.93	2.08	2.25	2.36	2.43
Unpurified Racemic Lasofoxifene	0.11	0.24	0.22	<0.02	0.05	0.12
Purified Racemic Lasofoxifene	>0.02	0.04	0.07	<0.02	<0.02	<0.02

Example 7

20 **Purification of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with 5:1 Ethanol:Tetrahydrofuran**

 4.0 grams of unpurified racemic lasofoxifene was combined with 12.5 mL of ethanol and 2.5 mL of tetrahydrofuran. The resulting suspension was heated at
25 about 60-65°C and agitated for about 8 hours, cooled to ambient temperature and agitated for about an additional two hours. The solids were collected by filtration, washed with 0.5 mL of ethanol and dried *in vacuo* at about 40°C to provide 3.69 grams of purified racemic lasofoxifene (92.3 % yield).

 The impurity profile of both unpurified and purified racemic lasofoxifene
30 was analyzed by HPLC, as described above. the results are tabulated below and reported in percent (%) area.

TABLE 7: Percent impurities in unpurified and purified racemic lasofoxifene

Relative Retention Times	0.92	1.93	2.08	2.25	2.36	2.43
Unpurified Racemic Lasofoxifene	0.11	0.24	0.22	<0.02	0.05	0.12
Purified Racemic Lasofoxifene	>0.02	0.08	0.13	<0.02	<0.02	<0.02

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Example 8**Attempted Purification of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with Ethanol**

4.0 grams of unpurified racemic lasofoxifene was combined with 15 mL of ethanol. The resulting suspension was heated at about 60-65°C and agitated for about 8 hours, cooled to ambient temperature and agitated for about an additional two hours. The solids were collected by filtration, washed with 0.5 mL of ethanol, and dried *in vacuo* at about 40°C to provide 3.31 grams of purified racemic lasofoxifene (82.8 % yield).

The impurity profile of both unpurified and purified racemic lasofoxifene was analyzed by HPLC, as described above. The results are tabulated below and reported in percent (%) area.

TABLE 8: Percent impurities in unpurified and purified racemic lasofoxifene

20

Relative Retention Times	0.92	1.93	2.08	2.25	2.36	2.43
Unpurified Racemic Lasofoxifene	0.11	0.24	0.22	<0.02	0.05	0.12
Purified Racemic Lasofoxifene	0.05	0.13	0.18	<0.02	<0.02	0.03

Example 9**Recrystallization of cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with Tetrahydrofuran**

25

4.0 grams of unpurified racemic lasofoxifene was combined with 15 mL of tetrahydrofuran. The resulting solution was heated at about 60-65°C and agitated for about 8 hours, cooled to ambient temperature upon which no crystallization

occurred. Crystallization commenced after seeding. The suspension was agitated at ambient temperature for about two hours. The solids were collected by filtration, washed with 0.5 mL of ethanol, and dried *in vacuo* at about 40°C to provide 2.65 g product (66.3% yield).

- 5 The impurity profile of both unpurified and purified racemic lasofoxifene was determined by HPLC, as described above. The results are tabulated below and reported in percent (%) area.

TABLE 9: Percent impurities in unpurified and purified racemic lasofoxifene

10

Relative Retention Times	0.92	1.93	2.08	2.25	2.36	2.43
Unpurified Racemic Lasofoxifene	0.11	0.24	0.22	<0.02	0.05	0.12
Purified Racemic Lasofoxifene	<0.02	<0.02	0.05	<0.02	<0.02	<0.02

Example 10

Attempted Purification of lasofoxifene D-tartrate, (-)-cis-6(S)-phenyl-5-(R)-[4-(2-pyrrolidin-1-ylethoxy)phenyl]5,6,7,8-tetrahydronaphthalen-2-ol D-tartrate by

15

Recrystallization from Ethanol/Water

- 8.28 grams of unpurified lasofoxifene D-tartrate was dissolved in 166 mL of a 1:1 mixture of ethanol and water by heating at about 50°C. After filtration, the solution was slowly cooled to about 0°C, upon which crystallization commenced. The mixture was stirred at ambient temperature for about 48 hours. The solid was collected by filtration and washed twice with 10 mL ethanol. It was then dried *in vacuo* at about 45°C to provide 6.37 grams of purified lasofoxifene D-tartrate (76.9% yield).

- 20 The impurity profile of both unpurified and purified lasofoxifene D-tartrate was analyzed by HPLC, as described above. The results are tabulated below and reported in percent (%) area.

TABLE 10: Percent impurities in unpurified and purified lasofoxifene D-tartrate

Relative Retention Times	0.92	2.06	2.14	2.26	2.38
Unpurified Lasofoxifene	0.21	0.16	0.07	0.28	0.11
Purified Lasofoxifene	<0.02	0.14	0.04	0.32	0.09

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Example 11**Large Scale Purification of Unpurified Racemic Lasofoxifene, cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol with Ethanol/Tetrahydrofuran**

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20.4 kilograms of unpurified racemic lasofoxifene was combined with 50 liters of ethanol and 25 liters of tetrahydrofuran. The resulting suspension was heated at about 55-65°C and agitated for about 8 hours, cooled to ambient temperature and agitated for about an additional four hours. The solids were collected by filtration, washed twice with 40 liters of ethanol, and dried *in vacuo* at about 40°C, providing 16.8 kilograms of purified racemic lasofoxifene (82.3% yield).

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The impurity profile of both unpurified and purified racemic lasofoxifene was analyzed by HPLC, as described above. Results are tabulated below and reported in percent (%) area.

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TABLE 11: Percent impurities in unpurified and purified lasofoxifene

Relative Retention Times	0.92	1.93	2.08	2.25	2.36	2.43
Unpurified Racemic Lasofoxifene	1.60	0.22	<0.02	<0.02	0.06	0.11
Purified Racemic Lasofoxifene	0.07	<0.02	<0.02	<0.02	<0.02	<0.02

CLAIMS

1. A method of purifying racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol comprising:
 - 5 (a) suspending racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in a mixture of ethanol and tetrahydrofuran to form a suspension;
 - (b) agitating and heating said suspension;
 - (c) cooling said suspension of step (b); and
 - 10 (d) collecting a solid purified racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol.
2. A method according to Claim 1, wherein said mixture of ethanol and tetrahydrofuran has a 4:1 volume ratio.
- 15 3. A method according to Claim 1, wherein said mixture of ethanol and tetrahydrofuran has a 3:1 volume ratio.
4. A method according to Claim 1, wherein said mixture of ethanol and tetrahydrofuran has a 2:1 volume ratio.
5. A method according to Claim 1, wherein said mixture of ethanol and tetrahydrofuran has a 1:1 volume ratio.
- 20 6. A method according to Claims 1, 2, 3, 4 or 5, wherein said suspension formed in step (a) is agitated and heated from ambient temperature up to 70°C in step (b).
7. A method according to Claim 6, wherein said suspension formed in step (a) is agitated and heated from ambient temperature up to 65°C for up to 12 hours in step (b).
- 25 8. A method according to Claim 7 wherein said suspension so formed in step (b) is cooled and agitated up to 18 hours in step (c).
9. A method according to Claim 8, wherein a solid, purified racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, in said suspension so formed in step (c) is collected by filtration, having less than 0.2% impurities.
- 30 10. A method according to Claim 8, wherein a solid, purified racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, in

said third suspension formed in step (c) is collected by filtration, having less than 0.1% impurities.

11. A method of purifying racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol comprising:

- 5 (a) suspending racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol in a mixture of ethanol and tetrahydrofuran in a 2:1 volume ratio to form a suspension;
- 10 (b) agitating and heating said suspension from ambient temperature up to 65°C for up to 12 hours;
- (c) cooling said suspension so formed with agitation for up to 18 hours; and
- (d) collecting a solid racemic *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol by filtration.

15 12. A purified *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalen-2-ol, having an impurity level less than 0.1%.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	examples 1,8	1-11
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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