

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
19 April 2012 (19.04.2012)

PCT

(10) International Publication Number  
**WO 2012/050263 A1**

(51) International Patent Classification:

*C07C 213/08* (2006.01) *A61K 31/138* (2006.01)  
*C07C 217/70* (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:

PCT/KR2010/009037

(22) International Filing Date:

16 December 2010 (16.12.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

10-2010-0101006 15 October 2010 (15.10.2010) KR

(71) Applicant (for all designated States except US): **CJ CHEILJEDANG CORP.** [KR/KR]; CJ Bldg., 500, Namdaemunno 5-ga, Jung-gu, Seoul 100-749 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SONG, Seog-Beom** [KR/KR]; 105-1901 LG Village, Mangpo-dong, Yeongtong-gu, Suwon-si, Gyeonggi-do 443-400 (KR). **MOON, Jeong-Ju** [KR/KR]; 560-6, Sotae-dong, Dong-gu, Gwangju 501-828 (KR). **HONG, Hye-Suk** [KR/KR]; #203,194-6, Seohyeon-dong, Bundang-gu, Seongnam-si, Gyeonggi-do 463-820 (KR). **PARK, Mi-Kyung** [KR/KR]; 808-1006, Gangnam Maeul Jugong Apt., Sangha-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-719 (KR). **CHO, Il-Hwan** [KR/KR]; 106-303 Daea APT, Gayang-dong, Gangseo-gu, Seoul 157-200 (KR). **KWEON, Jae-Hong** [KR/KR]; #102, 164-15 Maetan-

dong, Yeongtong-gu, Suwon-si, Gyeonggi-do 443-370 (KR).

(74) Agent: **LEE, Duck-Rog**; YEIL Patent & Trademark International, YeilPAT Bldg., 669-17 Yeoksam 1-dong, Gangnam-gu, Seoul 135-915 (KR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: NOVEL METHOD OF PREPARING ENDOXIFEN

(57) Abstract: Provided is a method of preparing endoxifen by coupling 4,4-hydroxybenzophenone as a starting material with propiophenone. The method can be used to obtain an E/Z-form endoxifen mixture with a high yield compared to the conventional methods of preparing endoxifen, and provide Z-form endoxifen of at least 99% purity in the mixture to have a therapeutic effect.



WO 2012/050263 A1

## Description

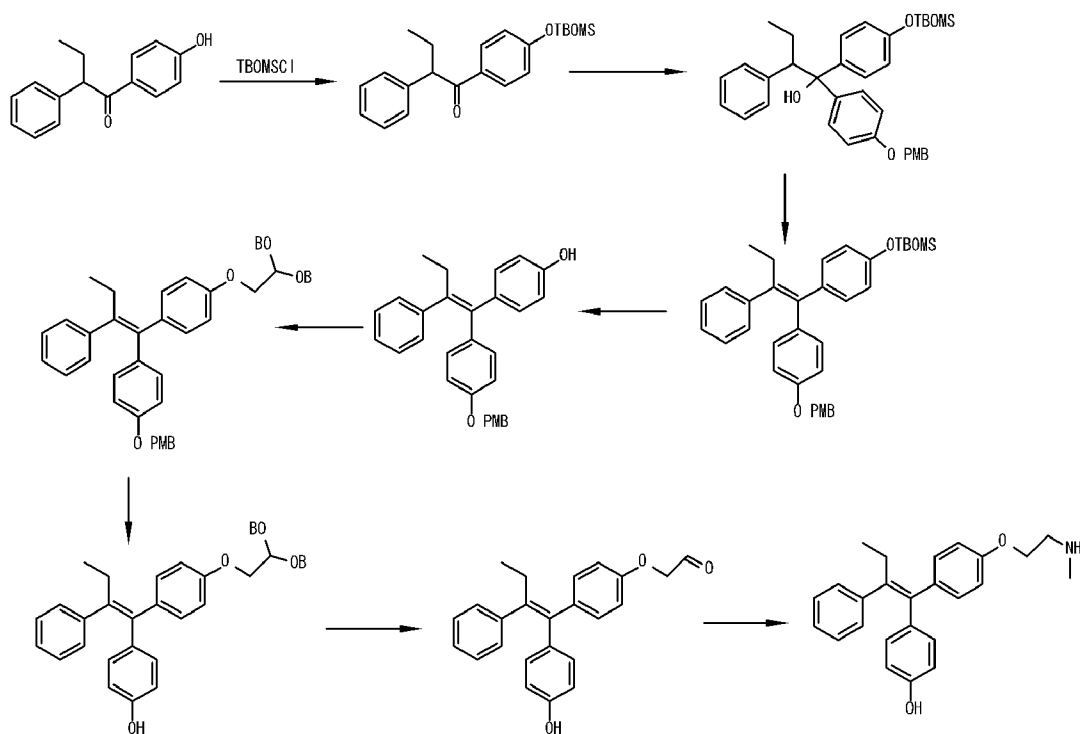
### Title of Invention: NOVEL METHOD OF PREPARING ENDOXIFEN

#### Technical Field

- [1] The present invention relates to a novel method of preparing endoxifen, and more particularly, to a method of preparing Z-form endoxifen having anti-breast cancer effects, with high purity and high yield using 4,4'-hydroxybenzophenone as a starting material.

#### Background Art

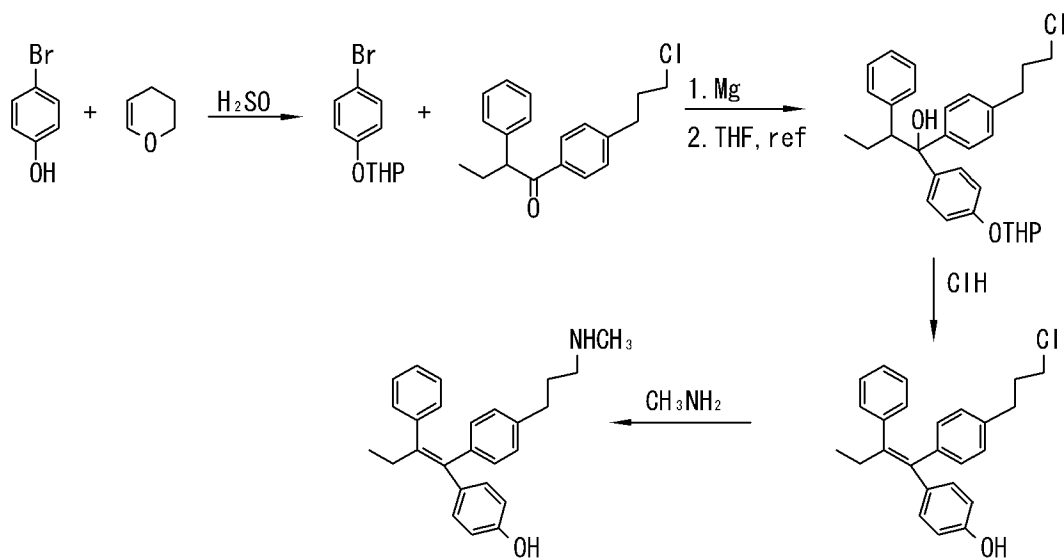
- [2] Breast cancer is the second most frequent carcinoma among Korean women, and 60 to 70% of all breast cancer patients are objects of hormone therapies.
- [3] Tamoxifen is a representative hormone drug which has been used to treat pre- and post-menopausal breast cancer patients for more than 3 decades. Although tamoxifen itself does not have therapeutic effects, tamoxifen can be converted into its active metabolite, endoxifen, by a metabolic enzyme, CYP2D6, present in the liver and endoxifen offers anti-hormone effects. However, there are about 30% of patients with estrogen receptor-positive breast cancer who are genetically deficient in CYP2D6. In case of them, even if tamoxifen is administered, the tamoxifen is not converted into its active form, endoxifen, and, therefore, therapeutic effects cannot be offered.
- [4] Recently, third-generation aromatase inhibitors have been frequently used for hormone therapies, but they have many side-effects and should not be administered to premenopausal patients. Hence, it is necessary to develop novel hormone drugs.
- [5] Compared to the aromatase inhibitors, tamoxifen has been proven to be stable for a long time and has advantages of having cardioprotective effects and increasing bone density. Accordingly, if novel hormone drugs reducing individual difference of therapeutic effects while retaining the advantages of tamoxifen could be developed, it would be very helpful to many breast cancer patients in therapeutic aspects.
- [6] Methods of synthesizing endoxifen which is the active metabolite of tamoxifen are disclosed in many literatures. For example, U. S. Patent No. 2009/0291124A1 discloses a method of preparing endoxifen starting from 4-hydroxybromobenzene.
- [7] Further, International Publication No. WO2009/120999A2 discloses the following method of preparing endoxifen:
- [8]



[9] However, in both of the literatures, the methods starts from expensive materials resulting in raising production costs and do not suggest any proper technique of separating pure Z-form endoxifen.

[10] International Publication No. WO2008/070463 discloses the following method of preparing endoxifen.

[11]



[12]

[13] In Bioorganic & Medical Chemistry Letters (2010), a method of preparing endoxifen including separating Z-form endoxifen by RP-HPLC is disclosed. However, this

method is not suitable for mass production.

- [14] As seen from the above, the prior methods of preparing endoxifen have problems of not preparing pure Z-form endoxifen, requiring high production costs, or using separation and purification techniques unsuitable for mass production. Further, none of prior literatures in the art has disclosed a method of preparing endoxifen starting from 4,4'-hydroxybenzophenone.

## Disclosure of Invention

### Technical Problem

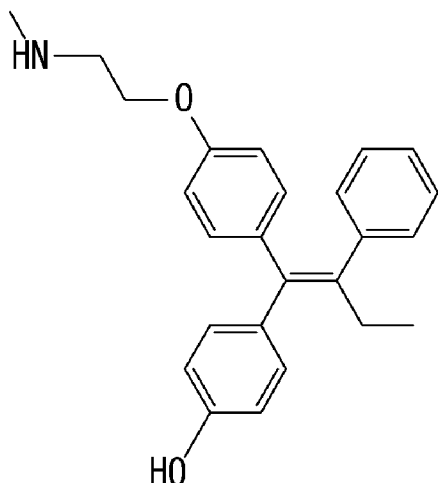
- [15] The present invention is directed to a method of preparing endoxifen using 4,4'-hydroxybenzophenone as a starting material, which reduces production costs, yields Z-form endoxifen with high purity and high yield and is suitable for mass production.

### Solution to Problem

- [16] In one aspect, the present invention provides a method of preparing Z-form endoxifen of Formula 1 or a salt thereof using 4,4'-hydroxybenzophenone as a starting material.

- [17] [Formula 1]

[18]



- [19] In another embodiment, the present invention may include a first step of protecting a hydroxy group in 4,4'-hydroxybenzophenone with a protecting group.
- [20] In another embodiment, the present invention may further include a second step of coupling a compound obtained from the first step with propiophenone.
- [21] In another embodiment, the present invention may further include a third step of O-alkylating a hydroxy group in a compound obtained from the second step.
- [22] In another embodiment, the present invention may further include a fourth step of de-protecting the protecting group binding to the hydroxy group.
- [23] In another embodiment, the present invention may further include a fifth step of de-

protecting a protecting group of an alkyl residue bound through O-alkylation.

[24] In another embodiment, the present invention may further include a sixth step of fractionally crystallizing materials obtained in the fifth step using an organic solvent.

[25] In another embodiment, the organic solvent used in the sixth step is selected from the group consisting of ethyl acetate, methanol, ethanol, propanol, benzene, acetone, acetonitrile, toluene, dichloromethane, 1,2-dichloroethane and chloroform and can be used alone or in combination with hexane, water or diethyl ether.

[26] Further, in another embodiment, the present invention provides a method of converting E-form endoxifen into Z-form endoxifen by treating the E/Z endoxifen mixture with an acid or base.

[27] Furthermore, in another embodiment, the present invention provides a method of obtaining endoxifen citrate by reacting endoxifen with water and citric acid.

### Advantageous Effects of Invention

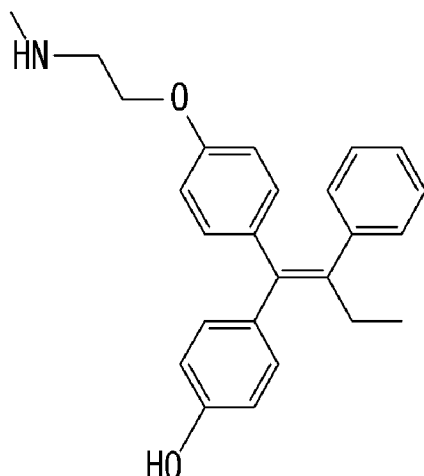
[28] According to a preparation method of the present invention, production costs can be reduced by means of using an inexpensive starting material, 4,4'-hydroxybenzophenone, and endoxifen can be obtained with high purity, for example, more than 99% purity, compared to the conventional method of preparing endoxifen. Particularly, Z-form endoxifen having anticancer effects can be obtained with high yield.

### Mode for the Invention

[29] According to the present invention, Z-form endoxifen of Formula 1 is prepared according to a following Scheme 1.

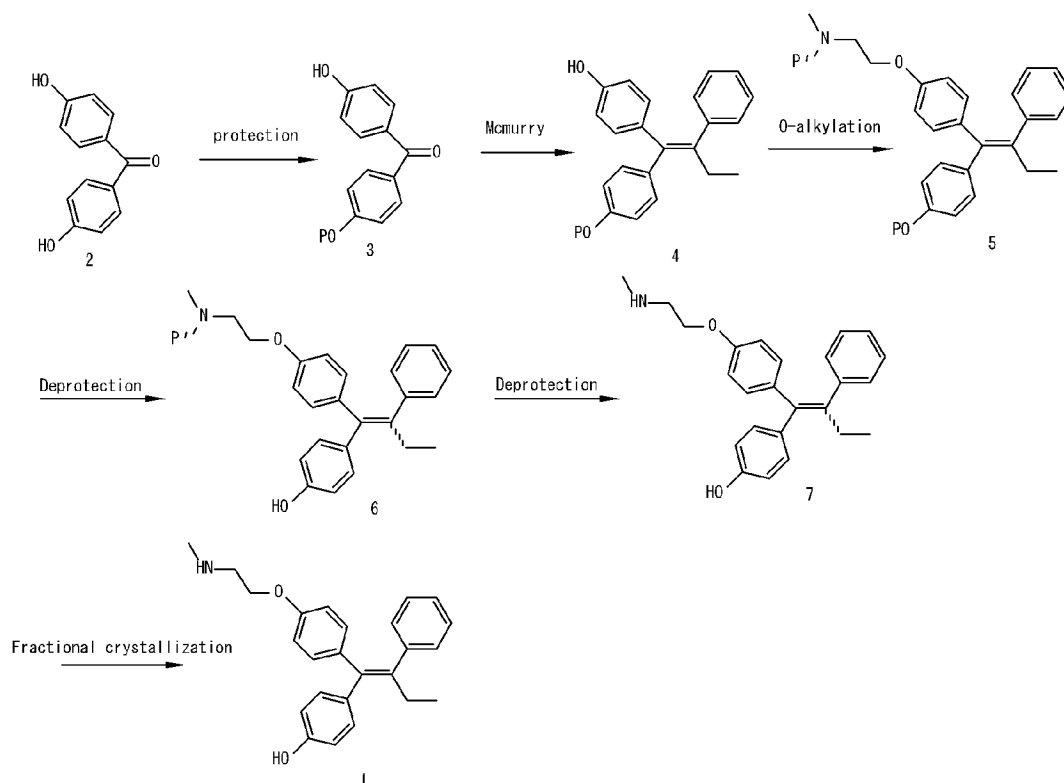
[30] [Formula 1]

[31]



[32] [Scheme 1]

[33]



[34]

[35] wherein P is benzyl, p-methoxybenzyl, acetate, tetrahydropyran or pivalate, and P' is ethyl carbamate or t-butyl carbamate.

[36] In the preparation method of the present invention, 4,4'-hydroxybenzophenone (a compound of Formula 2) is used as a starting material.

[37] One of two hydroxy groups binding to the compound of Formula 2 is protected by introducing a protecting group such as benzyl, p-methoxybenzyl, acetate, tetrahydropyran or pivalate, thereby a compound of Formula 3 is obtained.

[38] Preferably, after the compound of Formula 2 is dissolved in acetone, potassium carbonate and a protecting group-containing compound are added. Then, the reaction mixture is heated at 60°C for 48 hours with stirring, cooled to ambient temperature, and filtered. The pH of the reaction mixture is adjusted to 1 to 2 using hydrochloric acid, filtered with ethyl acetate, and washed with water and saline. Subsequently, the reaction mixture is dried, filtered, and dried by distillation under reduced pressure to obtain a compound of Formula 3.

[39] The compound of Formula 3 is coupled with propiophenone through the McMurry reaction wherein zinc and titanium chloride are used, to obtain a compound of Formula 4.

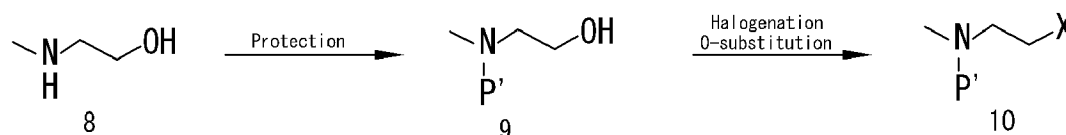
[40] Preferably, zinc is added to tetrahydrofuran, and the resulting mixture is then stirred at -10°C. After titanium chloride is added, the resulting mixture is heated at 80°C for 2

hours with stirring, and then cooled to 0°C. After the compound of Formula 3 and propiophenone are added and dissolved, the resulting mixture is heated at 80°C for 16 hours with stirring and cooled to ambient temperature and a potassium carbonate aqueous solution is added thereto. After extraction using ethyl acetate, the resulting materials is washed with saline, dried, filtered, and dried by distillation under reduced pressure. As a result, a compound of Formula 4 is obtained.

[41] The compound of Formula 4 is a mixture of E and Z forms, which are geometrical isomers containing alkene bonds. The compound of Formula 4 is alkylated using a compound of Formula 10 obtained from the following Scheme 2.

[42] [Scheme 2]

[43]



[44] wherein P is the same as described in the above, and X is chloro, bromo, iodio, methane sulfonyl, toluene sulfonyl, or trifluorotoluene sulfonyl.

[45] A compound of Formula 8 is protected by ethyl carbamate or t-butyl carbamate, thereby a compound of Formula 9 is obtained.

[46] Preferably, after the compound of Formula 8 is dissolved in dichloromethane, triethylamine is added and the resulting mixture is cooled to 0°C with stirring. Ethyl chloroformate is added, and the resulting mixture is then stirred at ambient temperature for 1 hour. The pH of the reaction mixture is adjusted to 1 to 2 using 1M hydrochloric acid, and the reaction mixture is extracted using dichloromethane. The resulting materials is washed with water and saline, dried, filtered, and dried by distillation under reduced pressure to obtain the compound of Formula 9.

[47] A hydroxy group in the compound of Formula 9 is converted into a leaving group by halogenation such as chlorination, bromination or iodination, or sulfonylation such as methane sulfonylation, toluene sulfonylation, or trifluorotoluene sulfonylation, thereby a compound of Formula 10 is obtained.

[48] Preferably, the compound of Formula 9 is dissolved in tetrahydrofuran and the resulting mixture is cooled to 0°C with stirring. Imidazole is added and dissolved, and triphenylphosphine is then added and dissolved. Subsequently, iodine is added and dissolved, and then the resulting mixture is stirred at ambient temperature for 1 hour. A sodium hydrogen carbonate saturated solution is added in order to adjust the pH of the reaction mixture to 7 to 8, and then the reaction mixture is extracted with ethyl acetate. Subsequently, an organic layer is washed with a sodium thiosulfate saturated solution, dried, filtered, and distilled under reduced pressure, thereby the compound of Formula

10 is obtained.

[49] A hydroxy group in the compound of Formula 4 is O-alkylated by the compound of Formula 10, thereby a compound of Formula 5 is obtained.

[50] Preferably, the compound of Formula 4 is dissolved in N,N-dimethylformamide, cesium carbonate is added, and then the resulting mixture is stirred at ambient temperature. The compound of Formula 10 is added, and then the resulting mixture is heated at 70°C for 2 hours with stirring. An ammonium chloride saturated solution is added in order to adjust the pH of the reaction mixture to 7 to 8, and the reaction mixture is extracted with diethyl ether. The resulting materials is washed with saline, dried, filtered, and dried by distillation under reduced pressure to obtain the compound of Formula 5.

[51] The compound of Formula 5 is deprotected (e.g., debenzylated) into a compound of Formula 6 using borontribromide.

[52] Preferably, the compound of Formula 5 is dissolved in dichloromethane, and the resulting mixture is stirred at -40°C. Subsequently, borontribromide is added and the resulting mixture is stirred. The pH of the reaction mixture is adjusted to 7 to 8 by adding a sodium carboxylate saturated solution. The reaction mixture is extracted with dichloromethane. The resulting materials is washed with saline, dried, filtered, and dried by distillation under reduced pressure to obtain the compound of Formula 6.

[53] Otherwise, the compound of Formula 5 is deprotected into the compound of Formula 6 by hydrogenation using palladium as a catalyst.

[54] Preferably, the compound of Formula 5 is dissolved in ethyl acetate, a 5% palladium/carbon catalyst is added, and the resulting mixture is then stirred under hydrogen pressure of 1 atm. Afterwards, the resulting mixture is filtered with celite, dried, filtered, and dried by distillation under reduced pressure to obtain the compound of Formula 6.

[55] Otherwise, the compound of Formula 5 is deprotected into the compound of Formula 6 using an acid.

[56] The compound of Formula 6 is deprotected into a compound of Formula 7 by using hydrazine.

[57] Preferably, the compound of Formula 6 is added to ethyleneglycol and then the reaction mixture is stirred. Then, hydrazine monohydrate and potassium hydroxide are sequentially added and the resulting mixture is heated at 160°C for 2 hours with stirring. Water is added, and the resulting mixture is extracted twice with diethyl ether. An organic layer is washed with water and saline, dried, filtered, and dried by distillation under reduced pressure. And, the resulting materials is recrystallized using ethanol/water to obtain the compound of Formula 7.

[58] The compound of Formula 7 is obtained with higher yield by fractional crystal-

lization using organic solvents alone or in combination.

[59] Preferably, the compound of Formula 7 is added to an organic solvent, dissolved therein at a certain temperature, and stirred at room temperature for 1 hour. The obtained solid is filtered and dried under reduced pressure, thereby Z-form endoxifen is obtained.

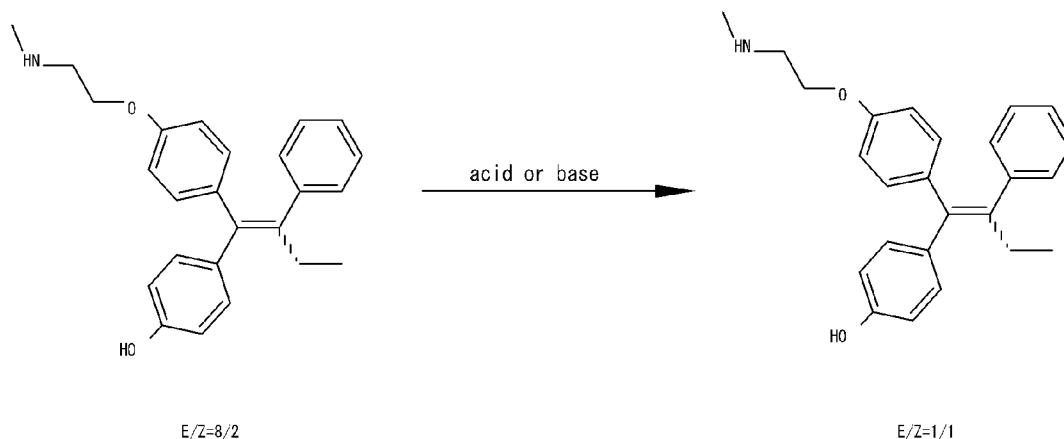
[60] As the organic solvent, ethyl acetate, methanol, ethanol, propanol, benzene, acetone, acetonitrile, toluene, dichloromethane, 1,2-dichloroethane or chloroform may be used, and an E/Z ratio of endoxifen is varied depending on the kind of solvents used.

[61] An endoxifen mixture obtained by the fractional crystallization and mainly consisted of E-form endoxifen is treated according to the following Scheme 3 and converted into a mixture having an E/Z ratio of 1:1. Subsequently, Z-form endoxifen is separated by the fractional crystallization. As a result, the Z-form endoxifen is obtained with higher yield.

[62]

[63] [Scheme 3]

[64]



[65]

[66] Preferably, the endoxifen mixture mainly consisted of E-form endoxifen is added to a mixture of dichloromethane and trifluoroacetic acid, and the resulting mixture is then stirred at ambient temperature for 1 hour. After a sodium hydrocarbonate saturated solution is added in order to adjust the pH of the reaction mixture to 7 to 8, the reaction mixture is extracted twice with dichloromethane. The resulting materials is washed with saline, dried, filtered, and dried under reduced pressure to obtain endoxifen having an E/Z ratio of 1:1.

[67] Hereinafter, the present invention will be described in further detail with reference to Examples. However, it is clearly understood by those of ordinary skill in the art that these Examples are merely to explain the present invention, not to limit the scope of the present invention.

[68]     Example 1: (4-benzyloxy-phenyl)-(4-hydroxy-phenyl)-methanone

[69]     After 50 g (233.4 mmol) of 4,4'-hydroxybenzophenone was dissolved in 500 ml of acetone, 35 g (252.1 mmol) of potassium carbonate and 30.5 ml (252.1 mmol) of benzyl bromide were sequentially added and the resulting mixture was heated at 60°C for 48 hours with stirring. After the resulting mixture was cooled to ambient temperature, the potassium carbonate was filtered and a 1M hydrochloric acid solution was added to adjust the pH of the reaction mixture to 1 to 2. After the reaction mixture was extracted twice with 200 ml of ethyl acetate, an organic layer was washed twice with 200 ml of water, washed with 200 ml of saline, dried on anhydrous magnesium sulfate, filtered, and dried by distillation under reduced pressure. After addition of 150 ml of ethanol and 50 ml of water, the resulting mixture was heated at 60°C for 1 hour with stirring, and then cooled to ambient temperature with stirring. The obtained solid was filtered and dried under reduced pressure to obtain 32 g (45%) of (4-benzyloxy-phenyl)-(4-hydroxy-phenyl)-methanone.

[70]     mp 169°C; IR(cm<sup>-1</sup>) 3347, 1600, 1249; <sup>1</sup>H NMR(400 MHz, DMSO) δ7.69(d, J = 8.0 Hz, 2H), 7.62(d, J = 8.0 Hz, 2H), 7.49-7.31(m, 5H), 7.16(d, J = 12.0 Hz, 2H), 6.89(d, J = 12.0 Hz, 2H), 5.21(s, 2H)

[71]     Example 2: 4-(1-(4-benzyloxy-phenyl)-2-phenyl-but-1-enyl)-phenol

[72]     58 g (887.0 mmol) of zinc was added to 600 ml of tetrahydrofuran, and the resulting mixture was stirred at -10°C. 44 ml of titanium tetrachloride was slowly added. After addition of titanium tetrachloride was completed, the resulting mixture was heated at 80°C for 2 hours with stirring and cooled to 0°C. A tetrahydrofuran solution prepared by dissolving 20 g (65.7 mmol) of (4-benzyloxy-phenyl)-(4-hydroxy-phenyl)-methanone and 28.2 g (210.2 mmol) of propiophenone in 900 ml of tetrahydrofuran was slowly added. The resulting mixture was heated at 80°C for 16 hours with stirring and cooled to room temperature. Subsequently, 500 ml of a 10% potassium carbonate aqueous solution was added. The resulting mixture was extracted with 700 ml of ethyl acetate, and the resulting materials was washed using 700 ml of saline, dried on anhydrous magnesium sulfate, filtered, and dried by distillation under reduced pressure. The obtained residue was separated and purified by column chromatography (ethyl acetate /n-hexane =1/10) to obtain 21.4 g (80%) of 4-(1-(4-benzyloxy-phenyl)-2-phenyl-but-1-enyl)-phenol.

[73]     mp 118°C; IR(cm<sup>-1</sup>) 3516, 1507, 1238; <sup>1</sup>H NMR(400 MHz, CDCl<sub>3</sub>) δ7.47-7.26(m, 5H), 7.18-7.07(m, 7H), 6.96(d, J = 8.0 Hz, 1.2H), 6.82-6.71(m, 2.8H), 6.62(d, J = 8.0 Hz, 0.8H), 6.47(d, J = 8.0 Hz, 1.2H), 5.07(s, 1.2H), 4.91(s, 0.8H), 2.48(m, 2H), 0.92(m, 3H)

[74]     Example 3: Ethyl-2-hydroxyethyl(methyl)carbamate

[75]     50 g (665.7 mmol) of 2-(methylamino) ethanol was dissolved in 500 ml of

dichloromethane, 92.5 ml (665.7 mmol) of triethylamine was added, and the resulting mixture was then cooled to 0°C with stirring. 65 ml (665.7 mmol) ethylchloroformate was slowly added, and the resulting mixture was then stirred at ambient temperature for 1 hour. A 1M hydrochloric acid solution was added to adjust the pH of the reaction mixture to 1 to 2, and the reaction mixture was extracted with 500 ml of dichloromethane. The resulting materials was washed using 500 ml of water and 500 ml of saline, dried on anhydrous magnesium sulfate, filtered, and dried by distillation under reduced pressure to obtain 83.3 g (85%) of ethyl-2-hydroxy ethyl(methyl)carbamate.

[76] IR( $\text{cm}^{-1}$ ) 3398, 2936, 1679;  $^1\text{H}$  NMR(400 MHz,  $\text{CDCl}_3$ )  $\delta$ 4.16 (q, 2H,  $J = 7.0$  Hz), 3.76 (brs, 2H), 3.44 (brs, 2H), 2.97 (s, 3H), 1.27 (t, 3H,  $J = 7.0$  Hz)

[77] Example 4: Ethyl-2-iodized ethyl(methyl)carbamate

[78] 30 g (203.8 mmol) of ethyl-2-hydroxyethyl(methyl) carbamate was dissolved in 1500 ml of tetrahydrofuran, and the resulting mixture was cooled to 0°C with stirring. 77.6 g (1019.3 mmol) of imidazole and 69.4 g (305.7 mmol) of triphenylphosphine were added and dissolved. After addition and dissolution of 80.2 g (305.7 mmol) of iodine was completed, the resulting mixture was stirred at ambient temperature for 1 hour. A sodium hydrocarbonate saturated solution was added to adjust the pH of the reaction mixture to 7 to 8, and the reaction mixture was then extracted with 2000 ml of ethyl acetate. An organic layer was washed using 500 ml of a sodium thiosulfate saturated solution, dried on anhydrous magnesium sulfate, filtered, and dried by distillation under reduced pressure. The obtained residue was purified by column chromatography (ethyl acetate/n-hexane=1/3) to obtain 41.9 g (80%) of ethyl-2-iodized ethyl(methyl) carbamate.

[79] IR( $\text{cm}^{-1}$ ) 2979, 1697, 1194;  $^1\text{H}$  NMR(400 MHz,  $\text{CDCl}_3$ )  $\delta$ 4.15 (brd,  $J = 4.0$  Hz, 2H), 3.61 (brd,  $J = 4.0$  Hz, 2H), 3.25-3.20 (brm, 2H), 2.95 (s, 3H), 1.28 (t,  $J = 12.0$  Hz, 3H)

[80] Example 5: (2-(4-(1-(4-benzyloxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester

[81] 20 g (49.2 mmol) of 4-(1-(4-benzyloxy-phenyl)-2-phenyl-but-1-enyl)-phenol was dissolved in 500 ml of N,N-dimethylformamide, cesium carbonate (48 g, 147.7 mmol) was added, and the resulting mixture was then vigorously stirred at ambient temperature. 37.8 g (147.7 mmol) of ethyl-2-iodized ethyl(methyl)carbamate was added, and the resulting mixture was heated at 70°C for 2 hours with stirring. An ammonium chloride saturated solution was added to adjust the pH of the reaction mixture to 7 to 8, and the reaction mixture was extracted twice with 500 ml of diethyl ether. An organic layer was washed with 500 ml of saline, dried on anhydrous magnesium sulfate, filtered, and dried by distillation under reduced pressure. The obtained residue was recrystallized with ethyl acetate/n-hexane (=5/95) to obtain 21.9

g (83%) of

(2-(4-(1-(4-benzyloxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester.

- [82] mp 91°C; IR( $\text{cm}^{-1}$ ) 1689, 1508, 1238;  $^1\text{H}$  NMR(400 MHz,  $\text{CDCl}_3$ )  $\delta$ 7.46-7.29(m, 5H), 7.16-7.10(m, 7H), 6.96(d,  $J = 8.0$  Hz, 1.5H), 6.86(d,  $J = 8.0$  Hz, 0.5H), 6.77(d,  $J = 8.0$  Hz, 2H), 6.62(d,  $J = 8.0$  Hz, 0.5H), 6.52(d,  $J = 8.0$  Hz, 1.5H), 5.07(s, 1.5H), 4.91(s, 0.5H), 4.13(brs, 0.5H), 3.96(brs, 1.5H), 3.66(brs, 0.5H), 3.55(brs, 1.5H), 3.05(s, 0.7H) 2.97(s, 2.3H), 2.49(q,  $J = 8.0$  Hz, 2H), 1.33-1.24(m, 5H), 0.94(t,  $J = 8.0$  Hz, 3H)

- [83] Example6:

(2-(4-(1-(4-hydroxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester

- [84] 20 g (37.3 mmol) of (2-(4-(1-(4-benzyloxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester was dissolved in 140 ml of dichloromethane, and the resulting mixture was stirred at -40°C. 74.6 ml (74.6 mmol) of a 1.0 M borontribromide solution in dichloromethane was slowly added, and the resulting mixture was stirred for 1 hour. A sodium hydrocarbonate saturated solution was added to adjust the pH of the reaction mixture to 7 to 8, and the reaction mixture was extracted twice with 200 ml of dichloromethane. An organic layer was washed with 200 ml of saline, dried on anhydrous magnesium sulfate, filtered, and dried by distillation under reduced pressure. The obtained residue was crystallized with diethyl ether/hexane (=5/95) to obtain 14.1 g (85%) of (2-(4-(1-(4-hydroxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester.

- [85] IR( $\text{cm}^{-1}$ ) 3520, 2972, 1675, 1508, 1240, 1172;  $^1\text{H}$  NMR(400 MHz,  $\text{CDCl}_3$ )  $\delta$ 7.18-7.08(m, 7H), 6.91-6.70(m, 4H), 6.53-6.46(m, 2H), 4.13(brs, 0.8H), 3.96(brs, 1.2H), 3.66(brs, 0.8H), 3.55(brs, 1.2H), 3.06(s, 1.2H) 2.97(s, 1.8H), 2.48(q,  $J = 8.0$  Hz, 2H), 1.34-1.21(m, 5H), 0.92(t,  $J = 8.0$  Hz, 3H)

- [86] Example7:

(2-(4-(1-(4-hydroxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester

- [87] 20 g (37.3 mmol) of (2-(4-(1-(4-benzyloxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester was dissolved in 400 ml of ethyl acetate, and 15.9 g (3.7 mmol) of a 5% palladium/carbon catalyst was then added. The resulting mixture was stirred for 10 minutes under hydrogen pressure of 1 atm, filtered with cellite, dried on anhydrous magnesium sulfate, filtered, and dried by distillation under reduced pressure. The obtained residue was crystallized with diethyl ether/hexane (=5/95) to obtain 14.1 g

(85%) of

(2-(4-(1-(4-hydroxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester.

- [88] IR( $\text{cm}^{-1}$ ) 3520, 2972, 1675, 1508, 1240, 1172;  $^1\text{H}$  NMR(400 MHz,  $\text{CDCl}_3$ )  $\delta$ 7.18-7.08(m, 7H), 6.91-6.70(m, 4H), 6.53-6.46(m, 2H), 4.13(brs, 0.8H), 3.96(brs, 1.2H), 3.66(brs, 0.8H), 3.55(brs, 1.2H), 3.06(s, 1.2H) 2.97(s, 1.8H), 2.48(q,  $J = 8.0$  Hz, 2H), 1.34-1.21(m, 5H), 0.92(t,  $J = 8.0$  Hz, 3H)

- [89] Example8: 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol

- [90] 20 g (44.9 mmol) of (2-(4-(1-(4-hydroxy-phenyl)-2-phenyl-but-1-enyl)-phenyloxy)-ethyl)-methyl-carbamic acid ethyl ester was added to 500 ml of ethyleneglycol, and the resulting mixture was stirred. 76.2 ml (1.57 mol) of hydrazine monohydrate and 120.7 g (2.15 mol) of potassium hydroxide were sequentially added, and the resulting mixture was heated at  $160^\circ\text{C}$  for 2 hours with stirring. 500 ml of water was added, and then the resulting mixture was extracted twice with 500 ml of diethyl ether. An organic layer was washed with 500 ml of water and 500 ml of saline, dried on anhydrous magnesium sulfate, filtered, and dried by distillation under reduced pressure. The obtained residue was re-crystallized with ethanol/water (=5/5) to obtain 16.0 g (95%) of 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol.

- [91] mp  $141^\circ\text{C}$ ; IR( $\text{cm}^{-1}$ ) 3516, 1507, 1238;  $^1\text{H}$  NMR(400 MHz,  $\text{CDCl}_3$ )  $\delta$ 7.18-7.05(m, 7H), 6.85(d,  $J = 8.0$  Hz, 1.3H), 6.77(d,  $J = 8.0$  Hz, 0.7H), 6.75(d,  $J = 8.0$  Hz, 0.7H), 6.70(d,  $J = 8.0$  Hz, 1.3H), 6.51(d,  $J = 8.0$  Hz, 0.7H), 6.44(d,  $J = 8.0$  Hz, 1.3H), 4.09(t,  $J = 4.0$  Hz, 1.3H), 3.94(t,  $J = 4.0$  Hz, 0.7H), 3.00(t,  $J = 4.0$  Hz, 1.3H), 2.90(t,  $J = 4.0$  Hz, 0.7H), 2.53(s, 1.8H), 2.47(m, 3.2H), 0.92(t,  $J = 8.0$  Hz, 3H)

- [92] Example9:Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol

- [93] After 10 g (26.7 mmol) of 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol was added to 100 ml of methanol, the resulting mixture was heated to  $40^\circ\text{C}$  to dissolve the solutes completely, and then stirred for 1 hour at ambient temperature. The obtained solid was filtered and dried under reduced pressure to obtain 4.7 g (47%) of Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol having an E/Z ratio of 1/99 (an E/Z ratio of the filtrate was 63/37).

- [94] mp  $141^\circ\text{C}$ ; IR( $\text{cm}^{-1}$ ) 3516, 1507, 1238;  $^1\text{H}$  NMR(400 MHz,  $\text{CDCl}_3$ )  $\delta$ 7.18-7.05(m, 7H), 6.85(d,  $J = 8.0$  Hz, 2H), 6.70(d,  $J = 8.0$  Hz, 2H), 6.44(d,  $J = 8.0$  Hz, 2H), 4.09(t,  $J = 4.0$  Hz, 2H), 3.00(t,  $J = 4.0$  Hz, 2H), 2.53(s, 3H), 2.47(m, 2H), 0.92(t,  $J = 8.0$  Hz, 3H)

- [95] Example 10: Z-

4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol

- [96] After 10 g (26.7 mmol) of 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol was added to 100 ml of ethyl acetate, the resulting mixture was heated to 40°C to dissolve the solute completely and stirred at ambient temperature for 1 hour. The obtained solid was filtered and dried under reduced pressure to obtain 6.0 g (60%) of Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol having an E/Z ratio of 5/95 (an E/Z ratio of the filtrate was 87/13).
- [97] Example 11: Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol
- [98] After 10 g (26.7 mmol) of 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol was added to 100 ml of ethanol, the resulting mixture was heated to 40°C to dissolve the solute completely and stirred at ambient temperature for 1 hour. The obtained solid was filtered and dried under reduced pressure to obtain 2.3 g (23%) of Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol having an E/Z ratio of 1/99 (an E/Z ratio of the filtrate was 61/39).
- [99] Example 12: Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol
- [100] After 10 g (26.7 mmol) of 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol was added to 100 ml of isopropanol, the resulting mixture was heated to 40°C to dissolve the solute completely and stirred at ambient temperature for 1 hour. The obtained solid was filtered and dried under reduced pressure to obtain 4.1 g (41%) of Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol having an E/Z ratio of 4/96 (an E/Z ratio of the filtrate was 75/25).
- [101] Example 13: Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol
- [102] After 10 g (26.7 mmol) of 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol was added to 100 ml of acetonitrile, the resulting mixture was heated to 40°C to dissolve the solute completely and stirred at ambient temperature for 1 hour. The obtained solid was filtered and dried under reduced pressure to obtain 6.7 g (67%) of Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol having an E/Z ratio of 37/63 (an E/Z ratio of the filtrate was 84/16).
- [103] Example 14: 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol
- [104] After 50 ml of trifluoroacetic acid was added to 50 ml of dichloromethane and dissolved, 10 g (26.7 mmol) of 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol having an E/Z ratio of 87/13 was added. The resulting mixture was stirred at ambient temperature for 1 hour. A sodium hydrocarbonate saturated solution was added to adjust the pH of the

reaction mixture to 7 to 8, and the reaction mixture was extracted twice with 100 ml of dichloromethane. An organic layer was washed with 100 ml of saline, dried on anhydrous magnesium sulfate, filtered, and dried under reduced pressure to obtain 9.5 g (95%) of 4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol having an E/Z ratio of 1/1.

[105]     Example 15: Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol citrate

[106]     31 g (160.2 mmol) of anhydrous citric acid was added to 60 ml of water and completely dissolved and 10 g (26.7 mmol) of Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol was added. The resulting mixture was heated to 40°C for complete dissolution. Then, the resulting mixture was stirred at ambient temperature for 12 hours. The obtained solid was filtered and dried under reduced pressure to obtain 9.1 g (60%) of Z-4-(1-(4-(2-methylamino-ethoxy)-phenyl)-2-phenyl-but-1-enyl))-phenol citrate.

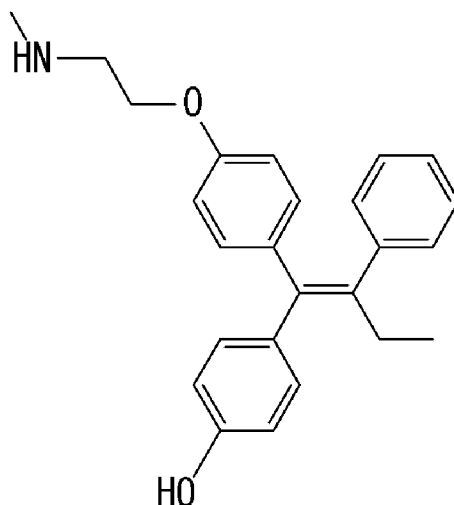
[107]     While the invention has been shown and described with reference to certain exemplary embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

[108]

## Claims

[Claim 1] A method of preparing Z-form endoxifen of Formula 1 or a salt thereof using 4,4'-hydroxybenzophenone as a starting material:

[Formula 1]



[Claim 2] The method according to claim 1, comprising a first step of protecting a hydroxy group in 4,4'-hydroxybenzophenone with a protecting group.

[Claim 3] The method according to claim 2, further comprising a second step of coupling a compound obtained from the first step with propiophenone.

[Claim 4] The method according to claim 3, further comprising a third step of O-alkylating a hydroxy group in a compound obtained from the second step.

[Claim 5] The method according to claim 4, further comprising a fourth step of deprotecting the protecting group binding to the hydroxy group.

[Claim 6] The method according to claim 5, further comprising a fifth step of deprotecting a protecting group of an alkyl residue bound through the O-alkylation.

[Claim 7] The method according to claim 6, further comprising a sixth step of fractionally crystallizing materials obtained in the fifth step using an organic solvent.

[Claim 8] The method according to claim 7, wherein the organic solvent is selected from the group consisting of ethyl acetate, methanol, ethanol, propanol, benzene, acetone, acetonitrile, toluene, dichloromethane, 1,2-dichloroethane and chloroform and is used alone or in combination with hexane, water or diethyl ether.

[Claim 9] A method of converting E-form endoxifen into Z-form endoxifen by

treating an E/Z endoxifen mixture obtained according to claim 7 with an acid or base.

[Claim 10]

A method of obtaining endoxifen citrate by reacting the endoxifen obtained according to claim 1 with water and citric acid.

## INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/KR2010/009037****A. CLASSIFICATION OF SUBJECT MATTER***C07C 213/08(2006.01)i, C07C 217/70(2006.01)i, A61K 31/138(2006.01)i, A61P 35/00(2006.01)i*

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)

C07C 213/08; A61K 31/075; A61K 31/35; A61K 31/415; A61K 31/445; C07C 41/01

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) &amp; Keywords: endoxifen, tamoxifen, Mcmurry

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                        | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | ABDUL H. FAUQ et al. "A convenient synthesis of (Z)-4-hydroxy-N-desmethyiltamoxifen (endoxifen)." Bioorganic & Medicinal Chemistry Letters. 3 April 2010, Vol. 20, pages 3036-3038.<br>See the whole document(especially, abstract, right column in p. 3036, 8a in Figure 1, and left column in p. 3038). | 1-3,9                 |
| Y         | See the whole document(especially, right column in p. 3036, and left column in p. 3038).                                                                                                                                                                                                                  | 4-8,10                |
| Y         | US 6576645 B1 (MARJA-LIISA SODERVALL et al.) 10 June 2003<br>See column 5, line 61-column 7, line 40; column 18, line 5-column 19, line 17.                                                                                                                                                               | 4-8,10                |
| A         | US 2005-0096384 A1 (BARRY FORMAN et al.) 05 May 2005<br>See the whole document.                                                                                                                                                                                                                           | 1-10                  |
| A         | US 7812197 B2 (MARJA SODERVALL et al.) 12 October 2010<br>See the whole document.                                                                                                                                                                                                                         | 1-10                  |

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

20 OCTOBER 2011 (20.10.2011)

Date of mailing of the international search report

**20 OCTOBER 2011 (20.10.2011)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office  
Government Complex-Daejeon, 189 Cheongsu-ro,  
Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

JWA, Seung Kwan

Telephone No. 82-42-481-5405



**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/KR2010/009037**

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)                                                                                                                                                                                                                   | Publication<br>date                                                                                                                                                  |
|-------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| US 6576645 B1                             | 10.06.2003          | US 2003-0225130 A1<br>US 6723738 B2<br>US 6723738 D<br>US 6875775 B2                                                                                                                                                                         | 04.12.2003<br>20.04.2004<br>20.04.2004<br>05.04.2005                                                                                                                 |
| US 2005-0096384 A1                        | 05.05.2005          | US 2009-0176305 A1<br>US 7531578 B2                                                                                                                                                                                                          | 09.07.2009<br>12.05.2009                                                                                                                                             |
| US 7812197 B2                             | 12.10.2010          | AU 2008-214530 A1<br>CA 2677861 A1<br>CN 101636372 A<br>EP 2121553 A1<br>JP 2010-518150 A<br>JP 2010-518150 T<br>KR 10-2009-0110862 A<br>MX 2009008660 A<br>RU 2009134131 A<br>US 2008-0207956 A1<br>US 2011-0015448 A1<br>WO 2008-099059 A1 | 21.08.2008<br>21.08.2008<br>27.01.2010<br>25.11.2009<br>27.05.2010<br>27.05.2010<br>22.10.2009<br>13.10.2009<br>20.03.2011<br>28.08.2008<br>20.01.2011<br>21.08.2008 |