ENDOXIFEN COMPOSITIONS AND METHODS OF USE THEREOF AND SYNTHESIS THEREOF

CROSS-REFERENCE

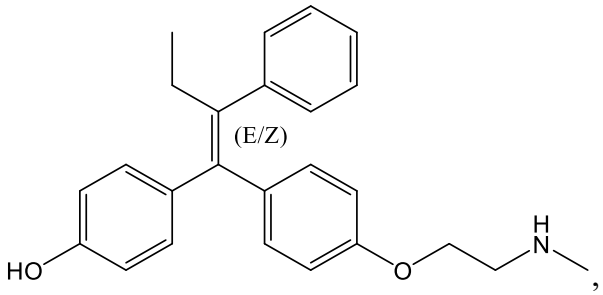
[0001] This application claims the benefit of U.S. Provisional Application No. 63/527,801, entitled "ENDOXIFEN COMPOSITIONS AND METHODS OF USE THEREOF AND SYNTHESIS THEREOF," filed July 19, 2023, which application is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Cancer is a group of diseases characterized by uncontrolled cell growth. Cancer can be deadly and while many treatment options exist, there is a need for continuous development of new treatment therapies and regimens. New pharmaceutical drugs can allow for treatment of wider ranges of cancers and be helpful for the treatment of current therapy resistant cancers and tumors. Hence, there remains a need for new active pharmaceutical ingredients (APIs) and compositions thereof that act as anti-tumor compounds and methods of making them.

SUMMARY

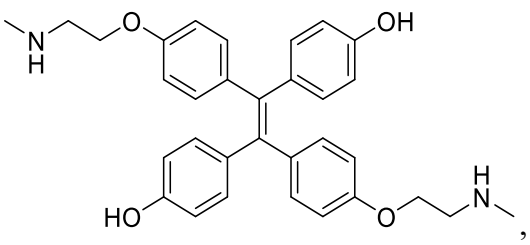
[0002a] In one aspect, the present disclosure refers to a composition comprising:
an endoxifen:

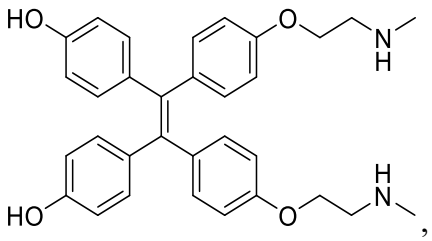


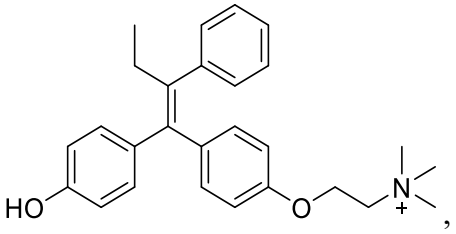
or a pharmaceutically acceptable salt or tautomer thereof; and

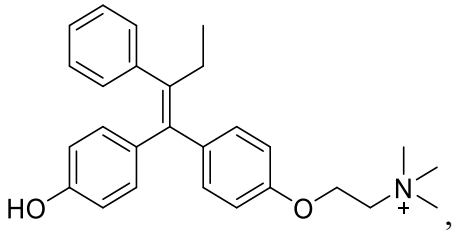
not less than 0.01 and not more than 1% w/w of a further component, wherein the further component comprises one or more of the following compounds, or a pharmaceutically acceptable salt or tautomer thereof:

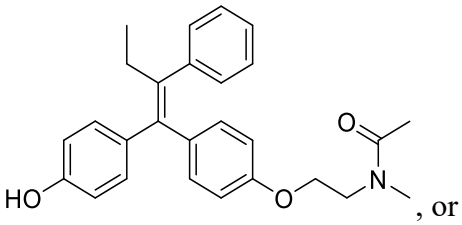
Compound 4a:

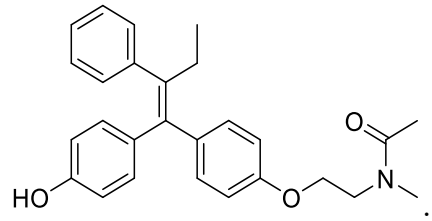


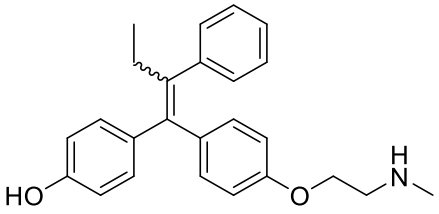
Compound 4b: ,

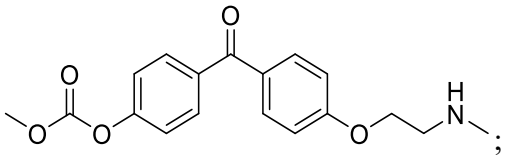
Compound 5a: ,

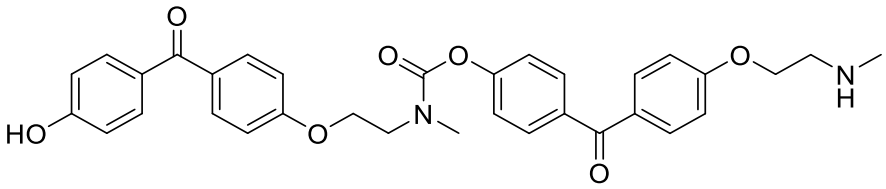
Compound 5b: ,

Compound 7a: , or

Compound 7b: .

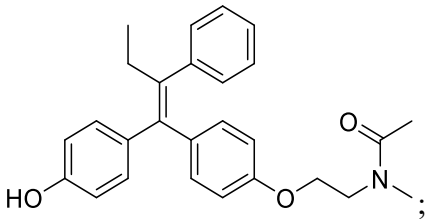
[0003] In various examples, the present disclosure provides a composition comprising: an endoxifen (i.e., ), or a pharmaceutically acceptable salt or tautomer thereof; and not less than 0.01 and not more than 10% w/w of a further component, wherein the further component comprises one or more of the following compounds, or a pharmaceutically acceptable salt or tautomer thereof:

Compound **1** ;

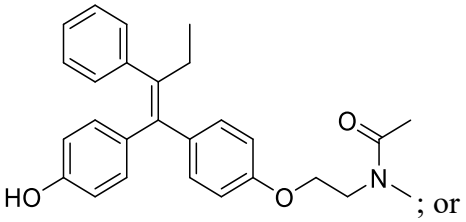
Compound **2** 

;

Compound **7a**

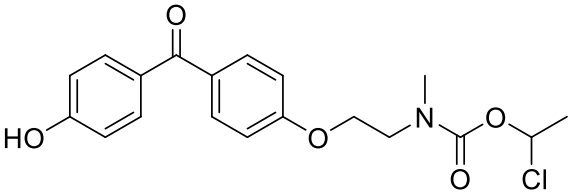


Compound **7b**

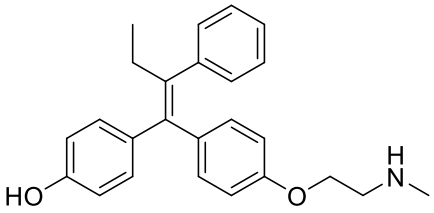


; or

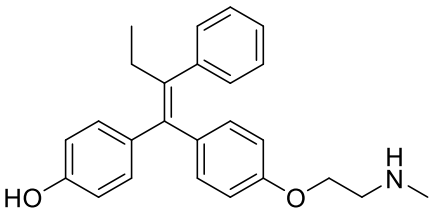
Compound **8**



[0004] In some examples, the endoxifen is not less than 90% (Z)-endoxifen:



. In some examples, the endoxifen is between 50% and 60%, between 50% and 70%, between 50% and 75%, between 50% and 80%, between 50% and 85%, between 50% and 90%, between 50% and 95%, between 50% and 97.5%, between 50% and 99%, between 50% and 99.5%, between 60% and 70%, between 60% and 75%, between 60% and 80%, between 60% and 85%, between 60% and 90%, between 60% and 95%, between 60% and 97.5%, between 60% and 99%, between 60% and 99.5%, between 70% and 75%, between 70% and 80%, between 70% and 85%, between 70% and 90%, between 70% and 95%, between 70% and 97.5%, between 70% and 99%, between 70% and 99.5%, between 75% and 80%, between 75% and 85%, between 75% and 90%, between 75% and 95%, between 75% and 97.5%, between 75% and 99%, between 75% and 99.5%, between 80% and 85%, between 80% and 90%, between 80% and 95%, between 80% and 97.5%, between 80% and 99%, between 80% and 99.5%, between 85% and 90%, between 85% and 95%, between 85% and 97.5%, between 85% and 99%, between 85% and 99.5%, between 90% and 95%, between 90% and 97.5%, between 90% and 99%, between 90% and 99.5%, between 95% and 97.5%, between 95% and 99%, between 95% and 99.5%, between 97.5% and 99.5%, not less than 95%, not less

than 96%, not less than 97%, not less than 98%, not less than 99%, or not less than 99.5% (Z)-endoxifen: 

.. In some examples, the composition comprises not less than 0.01% and not more than 0.1%, not less than 0.1% and not more than 1%, not less than 0.25% and not more than 1%, not less than 0.5% and not more than 1.5%, not less than 0.5% and not more than 2.5%, not less than 0.5% and not more than 5%, not less than 1% and not more than 2%, not less than 1% and not more than 2.25%, not less than 1% and not more than 2.5%, not less than 1% and not more than 3.75%, not less than 1% and not more than 4%, not less than 1% and not more than 4.25%, not less than 1% and not more than 4.5%, not less than 1% and not more than 4.75%, not less than 1% and not more than 5%, not less than 1% and not more than 5.5%, not less than 1% and not more than 6%, not less than 1% and not more than 6.5%, not less than 1% and not more than 7%, or not less than 1% and not more than 7.5% w/w of the further component.

[0005] In some examples, the composition comprises not less than 0.01% and not more than 0.1%, not less than 0.1% and not more than 1%, not less than 0.25% and not more than 1%, or not less than 0.5% and not more than 1.5% w/w of Compound **1**. In some examples, the composition comprises not less than 0.01% and not more than 0.1%, not less than 0.1% and not more than 1%, not less than 0.25% and not more than 1%, or not less than 0.5% and not more than 1.5% w/w of Compound **2**. In some examples, the composition comprises not less than 0.01% and not more than 0.1%, not less than 0.1% and not more than 1%, not less than 0.25% and not more than 1%, or not less than 0.5% and not more than 1.5% w/w of Compound **3**. In some examples, the composition comprises not less than 0.01% and not more than 0.1%, not less than 0.1% and not more than 1%, not less than 0.25% and not more than 1%, or not less than 0.5% and not more than 1.5% w/w of Compounds **4a** and **4b**. In some examples, the composition comprises not less than 0.01% and not more than 0.1%, not less than 0.1% and not more than 1%, not less than 0.25% and not more than 1%, or not less than 0.5% and not more than 1.5% w/w of Compounds **5a** and **5b**. In some examples, the composition comprises not less than 0.01% and not more than 0.1%, not less than 0.1% and not more than 1%, not less than 0.25% and not more than 1%, or not less than 0.5% and not more than 1.5% w/w of Compounds **6a** and **6b**. In some examples, the composition comprises not less than 0.01% and not more than 0.1%, not less than 0.1% and not

more than 1%, not less than 0.25% and not more than 1%, or not less than 0.5% and not more than 1.5% w/w of Compounds **7a** and **7b**.

[0006] In some examples, the composition has aromatase inhibition activity. In some examples, the composition has an affinity to an estrogen receptor.

[0007] In some examples, the pharmaceutically acceptable salt of the endoxifen is selected from the group consisting of an: arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc salt. In some examples, the pharmaceutically acceptable salt of the endoxifen is endoxifen gluconate. In some examples, the pharmaceutically acceptable salt of the endoxifen is endoxifen citrate. In some examples, the pharmaceutically acceptable salt of the endoxifen is endoxifen hydrochloride.

[0008] In some examples, the composition is formulated as a suspension, a tablet, a capsule, a caplet, a liquid, or a gel. In some examples, the composition comprises an alcohol, a plant oil, a mineral oil, a glycol, an agar, or a mixture thereof. In some examples, the composition is formulated as an enteric formulation. In some examples, the composition comprises hydroxypropyl methyl cellulose. In some examples, the composition is formulated as a delayed release composition.

[0009] In some examples, the composition comprises from 0.01 mg to 200 mg, from 0.1 mg to 100 mg, from 0.1 mg to 50 mg, from 0.1 mg to 20 mg, or from 1 mg to 20 mg of the endoxifen. In some examples, the composition comprises a 0.05 mg/kg unit dose, a 0.1 mg/kg unit dose, a 0.5 mg/kg unit dose, a 1 mg/kg unit dose, or a 1.5 mg/kg unit dose of the endoxifen.

[0010] In certain examples, the composition comprises less than 2.5%, less than 2%, less than 1.5%, less than 1%, less than 0.75%, less than 0.5%, less than 0.25%, less than 0.2%, less than 0.15%, less than 0.1%, or less than 0.05% water content. In additional examples, the composition comprises less than 1%, less than 0.8%, less than 0.6%, less than 0.4%, less than 0.2%, less than 0.1%, or less than 0.05% sulphated ash. In further examples, the composition comprises less than 6000 ppm methanol, less than 5000 ppm methanol, less than

4000 ppm methanol, less than 3000 ppm methanol, less than 2000 ppm methanol, less than 1000 ppm methanol, less than 500 ppm

methanol, less than 250 ppm methanol, less than 200 ppm methanol, less than 150 ppm methanol, less than 100 ppm methanol, less than 75 ppm methanol, less than 50 ppm methanol, less than 25 ppm methanol, or less than 10 ppm methanol. In another aspect, the composition comprises less than 9000 ppm ethanol, less than 6000 ppm ethanol, less than 5000 ppm ethanol, less than 4000 ppm ethanol, less than 3000 ppm ethanol, less than 2000 ppm ethanol, less than 1000 ppm ethanol, less than 500 ppm ethanol, less than 250 ppm ethanol, less than 200 ppm ethanol, less than 150 ppm ethanol, less than 100 ppm ethanol, less than 75 ppm ethanol, less than 50 ppm ethanol, less than 25 ppm ethanol, or less than 10 ppm ethanol. In a particular aspect, the composition comprises less than 9000 ppm acetone, less than 6000 ppm acetone, less than 5000 ppm acetone, less than 4000 ppm acetone, less than 3000 ppm acetone, less than 2000 ppm acetone, less than 1000 ppm acetone, less than 500 ppm acetone, less than 250 ppm acetone, less than 200 ppm acetone, less than 150 ppm acetone, less than 100 ppm acetone, less than 75 ppm acetone, less than 50 ppm acetone, less than 25 ppm acetone, or less than 10 ppm acetone. In a specific example, the composition comprises less than 9000 ppm isopropyl alcohol, less than 6000 ppm isopropyl alcohol, less than 5000 ppm isopropyl alcohol, less than 4000 ppm isopropyl alcohol, less than 3000 ppm isopropyl alcohol, less than 2000 ppm isopropyl alcohol, less than 1000 ppm isopropyl alcohol, less than 500 ppm isopropyl alcohol, less than 250 ppm isopropyl alcohol, less than 200 ppm isopropyl alcohol, less than 150 ppm isopropyl alcohol, less than 100 ppm isopropyl alcohol, less than 75 ppm isopropyl alcohol, less than 50 ppm isopropyl alcohol, less than 25 ppm isopropyl alcohol, or less than 10 ppm isopropyl alcohol. In a further aspect, the composition comprises less than 1000 ppm acetonitrile, less than 500 ppm acetonitrile, less than 250 ppm acetonitrile, less than 200 ppm acetonitrile, less than 150 ppm acetonitrile, less than 100 ppm acetonitrile, less than 75 ppm acetonitrile, less than 50 ppm acetonitrile, less than 25 ppm acetonitrile, less than 10 ppm acetonitrile, or less than 5 ppm acetonitrile. In another example, the composition comprises less than 9000 ppm ethyl acetate, less than 6000 ppm ethyl acetate, less than 5000 ppm ethyl acetate, less than 4000 ppm ethyl acetate, less than 3000 ppm ethyl acetate, less than 2000 ppm ethyl acetate, less than 1000 ppm ethyl acetate, less than 500 ppm ethyl acetate, less than 250 ppm ethyl acetate, less than 200 ppm ethyl acetate, less than 150 ppm ethyl acetate, less than 100 ppm ethyl acetate, less than 75 ppm ethyl acetate, less than 50 ppm ethyl acetate, less than 25 ppm ethyl acetate, or less than 10 ppm ethyl acetate. In an additional example, the composition comprises less than 1500 ppm tetrahydrofuran, 1000 ppm tetrahydrofuran, less than 500 ppm tetrahydrofuran, less than 250 ppm tetrahydrofuran, less than 200 ppm tetrahydrofuran, less than 150 ppm tetrahydrofuran, less

than 100 ppm tetrahydrofuran, less than 75 ppm tetrahydrofuran, less than 50 ppm tetrahydrofuran, less than 25 ppm tetrahydrofuran, less than 10 ppm tetrahydrofuran, or less than 5 ppm tetrahydrofuran. In a certain example, the composition comprises less than 1500 ppm 2-methyltetrahydrofuran, 1000 ppm 2-methyltetrahydrofuran, less than 500 ppm 2-methyltetrahydrofuran, less than 250 ppm 2-methyltetrahydrofuran, less than 200 ppm 2-methyltetrahydrofuran, less than 150 ppm 2-methyltetrahydrofuran, less than 100 ppm 2-methyltetrahydrofuran, less than 75 ppm 2-methyltetrahydrofuran, less than 50 ppm 2-methyltetrahydrofuran, less than 25 ppm 2-methyltetrahydrofuran, less than 10 ppm 2-methyltetrahydrofuran, or less than 5 ppm 2-methyltetrahydrofuran. In some examples, the composition comprises less than 250 ppm benzene, less than 200 ppm benzene, less than 150 ppm benzene, less than 100 ppm benzene, less than 75 ppm benzene, less than 50 ppm benzene, less than 25 ppm benzene, less than 10 ppm benzene, less than 5 ppm benzene, less than 2.5 ppm benzene, less than 2 ppm benzene, less than 1.5 ppm benzene, less than 1 ppm benzene, or less than 0.5 ppm benzene. In further examples, the composition comprises less than 250 ppm mesityl oxide, less than 200 ppm mesityl oxide, less than 150 ppm mesityl oxide, less than 100 ppm mesityl oxide, less than 75 ppm mesityl oxide, less than 50 ppm mesityl oxide, less than 25 ppm mesityl oxide, less than 10 ppm mesityl oxide, less than 5 ppm mesityl oxide, less than 2.5 ppm mesityl oxide, less than 2 ppm mesityl oxide, less than 1.5 ppm mesityl oxide, less than 1 ppm mesityl oxide, or less than 0.5 ppm mesityl oxide. In additional examples, the composition comprises less than 500 ppm zinc, less than 250 ppm zinc, less than 200 ppm zinc, less than 150 ppm zinc, less than 100 ppm zinc, less than 75 ppm zinc, less than 50 ppm zinc, less than 25 ppm zinc, less than 10 ppm zinc, less than 5 ppm zinc, less than 2.5 ppm zinc, less than 2 ppm zinc, less than 1.5 ppm zinc, less than 1 ppm zinc. In specific examples, the composition comprises less than 500 ppm titanium, less than 250 ppm titanium, less than 200 ppm titanium, less than 150 ppm titanium, less than 100 ppm titanium, less than 75 ppm titanium, less than 50 ppm titanium, less than 25 ppm titanium, less than 10 ppm titanium, less than 5 ppm titanium, less than 2.5 ppm titanium, less than 2 ppm benzene, less than 1.5 ppm titanium, less than 1 ppm titanium.

[0011] In various aspects, the present disclosure provides a pharmaceutical composition comprising the composition as described herein and a pharmaceutically acceptable excipient or diluent.

[0011a] In another aspect, there is provided the use of a composition as described above or a pharmaceutical composition as described above in the manufacture of a medicament for the treatment of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, a depression, or any combinations thereof in a subject in need thereof.

[0012] In some examples, the composition as described herein is present in between 40-60%, 50-70%, 60-80%, 70-90%, 80-90%, 85-95%, 90-95%, or 95-99% w/w.

[0013] In various examples, the present disclosure provides a method comprising administering the composition as described herein or the pharmaceutical composition as described herein to a subject.

[0014] In some examples, the method further comprises treating a condition in a subject in need thereof. In some examples, the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both. In some examples, the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer. In some examples, the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia. In some examples, the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder. In some examples, the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone. In some examples, the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg, or 20 mg of the endoxifen daily.

[0015] In various examples, the present disclosure provides a method of producing the composition as described herein, the method comprising purifying a composition of Compound **S3** to comprise >90% of Compound **E1**.

[0016] In some examples, the method is performed in an organic solvent. In some examples, the organic solvent comprises an aprotic solvent. In some aspects, the organic solvent comprises ethyl acetate. In some examples, the method further comprises the addition of an acid. In some examples, the acid comprises between about 2 to 12 N of the acid. In some examples, the acid comprises HCl. In some aspects, the method comprises maintaining the coupling at a temperature of between 0 to 20°C, between -5 to 10°C, or between -10 to 10°C during the addition of the acid.

[0017] In some examples, the method further comprises heating the coupling to between 50 to 60°C, between 55 to 65°C, or between 60 to 70°C. In some examples, the method further comprises stirring the solution for between 5 to 15 hours, between 8 to 12 hours, or between 9 to 11 hours. In some examples, the method further comprises washing, purifying, or separating Compound **S3** using a base, an aqueous solution, an alcohol, an organic solvent, or a combination thereof. In some examples, the base is sodium hydroxide. In some examples, the

aqueous solution is a sodium chloride solution. In some examples, the sodium chloride solution is between 5 to 25% NaCl, between 10 to 30% NaCl, or between 15 to 25% NaCl. In some examples, the alcohol is ethanol, 2-propanol, or isopropyl alcohol. In some examples, the organic solvent is ethyl acetate or acetone. In some examples, the method further comprises adding a base to the purification increasing the pH to a basic pH. In some examples, the base comprises about 2N to 12N of the base. In some examples, the base is sodium hydroxide. In some examples, the basic pH is between about 10 to 12. In some examples, the purification comprises separation, filtration, distillation, isolation, drying, and slurry formation. In some examples, the slurry formation uses an organic solvent. In some examples of the slurry formation, the organic solvent is ethyl acetate.

[0018] In some exampels, the method further comprises: producing Compound **S3** by coupling Compound **S2** with propiophenone. In some examples, the coupling comprises an olefination reaction. In some examples, the coupling comprises a McMurry reaction. In some examples, the method comprises activating Compound **S2** and propiophenone with a metal catalyst. In some examples, the method comprising generating the metal catalyst by combining a metal salt with a reducing agent. In some examples, the metal catalyst comprises titanium, zirconium, vanadium, niobium, molybdenum, tungsten, aluminum, or zinc. In some examples, the metal catalyst comprises titanium. In some examples, the metal salt comprises a titanium halide. In some aspects, the titanium halide comprises $TiCl_3$ or $TiCl_4$. In certain examples, the method comprises between 1 and 1.5, 1 and 2, 1 and 2.5, 1 and 3, 1 and 4, 1 and 5, 1 and 6, 1.5 and 2, 1.5 and 2.5, 1.5 and 3, 1.5 and 4, 1.5 and 5, 1.5 and 6, 2 and 2.5, 2 and 3, 2 and 4, 2 and 5, 2 and 6, 2.5 and 3, 2.5 and 4, 2.5 and 5, 2.5 and 6, 3 and 4, 3 and 5, 3 and 6, 4 and 5, 4 and 6, or 5 and 6 equivalents of the metal catalyst relative to the Compound **S2**.

[0019] In some examples, the reducing agent comprises zinc, zirconium, vanadium, niobium, molybdenum, tungsten, aluminum, magnesium, potassium, zinc-copper couple, alkali and alkali earth metals, butylium, lithium, or lithium aluminum hydride. In some examples, the zinc comprises zinc powder. In particular aspects, the method comprises between 2 and 3, 2 and 4, 2 and 5, 2 and 6, 2 and 8, 2 and 10, 3 and 4, 3 and 5, 3 and 6, 3 and 8, 3 and 10, 4 and 5, 4 and 6, 4 and 8, 4 and 10, 5 and 6, 5 and 8, 5 and 10, 6 and 8, 6 and 10, or 8 and 10 equivalents of the reducing agent relative to the Compound **S2**.

[0020] In some examples, the method further comprises a first solution made by combining the reducing agent and an organic solvent under an inert atmosphere at a temperature between 15° to 30°C. In some examples, the organic solvent is THF. In some

examples, the inert atmosphere is a N_2 atmosphere. In some examples, the method further comprises cooling the first solution to a

temperature between -10° to 5°C and adding the metal catalyst. In some examples, the method further comprises maintaining the first solution at a temperature less than 20°C during the addition of the metal catalyst. In some examples, the method further comprises heating the first solution to a temperature between 50° to 70°C for 1 hour, 1.5 hours, 2 hours, 2.5 hours, or 3 hours.

[0021] In some examples, the method further comprises a second solution made by adding Compound **S2** and propiophenone to an organic solvent. In some examples, the organic solvent is THF. In some examples, the method further comprises heating the second solution to between 50° to 70°C.

[0022] In some examples, the method further comprises a third solution made by adding the second solution to the first solution over 1 hour, 1.5 hours, or 2 hours. In some examples, the method further comprises stirring the third solution at between 50° to 70°C for 7 hours, 8 hours, 9 hours, or 10 hours.

[0023] In some examples, the method further comprises distilling, washing, filtering, separating, extracting, precipitating, collecting, or a combination thereof, Compound **S3** with an organic solvent, an acid, or an aqueous solution. In some examples, the organic solvent is MeTHF. In some aspects, the washing comprises an organic solvent, an acid, a base, a solvent mixture, or a combination thereof. In some examples, the organic solvent is MeTHF, acetonitrile, acetone, or a combination thereof. In some examples, the acid is between 2N to 12 N HCl. In some examples, the aqueous solution is 30-35% HCl, between 10% to 60% NaCl, or between 10% to 60% K_2CO_3.

[0024] In some examples, the method further comprises producing Compound **S2** by demethylating Compound **S1**. In some examples, Compound **S1** is demethylated by a demethylating agent. In some examples, the demethylating agent is 1-chloroethyl chloroformate. In some examples, the demethylating comprises 1 to 1.5, 1 to 2, 1 to 2.5, 1 to 3, 1 to 4, 1 to 5, 1.5 to 2, 1.5 to 2.5, 1.5 to 3, 1.5 to 4, 1.5 to 5, 2 to 2.5, 2 to 3, 2 to 4, 2 to 5, 2.5 to 3, 2.5 to 4, 2.5 to 5, 3 to 4, 3 to 5, or 4 to 5 equivalents of the demethylating agent relative to the Compound **S1**. In some examples, the demethylation comprises an organic solvent. In some examples, the organic solvent comprises a solvent mixture. In some examples, the solvent mixture comprises tetrahydrofuran and N-ethyldiisopropylamine. In some examples, the organic solvent comprises a base. In certain examples, the base is a tertiary amine. In particular examples, the base is ehtyldiisopropylamine. In particular examples, the demethylating comprises between 1 and 2, 1 and 3, 1 and 4, 1 and 5, 1 and 6, 1 and 8, 2 and 3, 2 and 4, 2 and 5, 2 and 6, 2 and 8, 3 and 4, 3 and 5, 3 and 6, 3 and 8, 4 and 5, 4 and 6, 4 and 8, 5 and 6, 5 and 8, or 6 and 8 equivalents of the

base relative to the Compound **S1**. In some examples, the method further comprises incubating the demethylation under an inert atmosphere. In some examples, the inert atmosphere is a N_2 atmosphere. In some examples, the method further comprises heating the demethylation to between 30 to 70°C, between 40 to 70°C, between 50 to 70°C, or between 55 to 65°. In some examples, the method further comprises heating the demethylation to an elevated temperature for between 8 to 16 hours, between 10 to 14 hours, or between 9 to 11 hours. In some examples, the elevated temperature is a boiling point of the organic solvent.

[0025] In some examples, the method further comprises adding an alcohol to the demethylation. In some examples, the alcohol is methanol. In some examples, the method further comprises heating the demethylation to between 30 to 70°C, between 40 to 70°C, between 50 to 70°C, or between 55 to 65°C and distilling the coupling to a reduced volume. In some aspects, the reduced volume to total volume ratio is 1:3, 1:5, or 1:10. In some examples, the method further comprises adding an acid. In some aspects, the acid comprises 2N to 12N of the acid. In some examples, the acid is hydrochloric acid.

[0026] In some examples, the separating comprises phase separation. In some examples, the separating comprises distillation. In particular examples, the distillation comprises vacuum distillation. In further examples, the distillation is performed at atmospheric pressure. In additional examples, the distillation is performed at a temperature of between 5 °C and 10 °C, 5 °C and 15 °C, 5 °C and 20 °C, 5 °C and 25 °C, 5 °C and 30 °C, 5 °C and 40 °C, 5 °C and 50 °C, 10 °C and 15 °C, 10 °C and 20 °C, 10 °C and 25 °C, 10 °C and 30 °C, 10 °C and 40 °C, 10 °C and 50 °C, 15 °C and 20 °C, 15 °C and 25 °C, 15 °C and 30 °C, 15 °C and 40 °C, 15 °C and 50 °C, 20 °C and 25 °C, 20 °C and 30 °C, 20 °C and 35 °C, 20 °C and 40 °C, 20 °C and 50 °C, 25 °C and 30 °C, 25 °C and 40 °C, 25 °C and 50 °C, 30 °C and 40 °C, 30 °C and 50 °C, or 40 °C and 50 °C.

[0027] In one example, the separating uses between 1 and 2, 1 and 3, 1 and 4, 1 and 5, 1 and 6, 1 and 8, 1 and 10, 1 and 12, 1.5 and 3, 1.5 and 4, 1.5 and 5, 1.5 and 6, 1.5 and 8, 1.5 and 10, 1.5 and 12, 2 and 3, 2 and 4, 2 and 5, 2 and 6, 2 and 8, 2 and 10, 2 and 12, 3 and 4, 3 and 5, 3 and 6, 3 and 8, 3 and 10, 3 and 12, 4 and 5, 4 and 6, 4 and 8, 4 and 10, 4 and 12, 5 and 6, 5 and 8, 5 and 10, 5 and 12, 6 and 8, 6 and 10, 6 and 12, 8 and 10, 8 and 12, or 10 and 12 equivalents of the acid (weight/weight). In another example, the separating uses between 3.2 and 4.8 equivalents of the acid (weight/weight). In a further example, the Compound **S2** comprises less than 5%, less than 4%,

less than 3%, less than 2.5%, less than 2%, less than 1.5%, less than 1%, less than 0.75%, less than 0.5%, less than 0.25%, or less than 0.1% Compound **8**. In particular examples, the Compound **S2** exhibits less than 10%, less than 8%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1.5%, or less than 1% weight loss upon drying. In further aspects, the Compound **S2** comprises less than 5000 ppm, less than 4000 ppm, less than 3000 ppm, less than 2500 ppm, less than 2000 ppm, less than 1500 ppm, less than 1000 ppm, less than 500 ppm, less than 200 ppm, or less than 100 ppm DIPEA.

[0028] In some examples, the method further comprises heating the demethylation to between 30 to 70°C, between 40 to 70°C, between 50 to 70°C, or between 55 to 65°C for between 2 to 20 hours, between 6 to 18 hours, or between 8 to 16 hours.

[0029] In some examples, the method further comprises distilling, washing, purifying, or separating Compound **S2** using an acid, a base, an aqueous solution, an alcohol, or an organic solvent. In some examples, the aqueous solution is water. In some examples, the base comprises 2N to 12N of the base. In some examples, the base is sodium hydroxide. In some examples, the organic solvent is ethyl acetate. In some aspects, the acid comprises 2N to 12N of the acid. In some aspects, the acid is hydrochloric acid.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee. The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0031] **FIG. 1** illustrates a UV chromatogram of Compound **1**.

[0032] **FIG. 2** illustrates a TIC chromatogram of Compound **1**.

[0033] **FIG. 3** illustrates a mass spectrum of Compound **1**.

[0034] **FIG. 4** illustrates a proton NMR spectrum of Compound **1**.

[0035] **FIG. 5** illustrates a carbon NMR spectrum of Compound **1**.

[0036] **FIG. 6** illustrates a proton NMR spectrum of Compound **2**.

[0037] **FIG. 7** illustrates a carbon NMR spectrum of Compound **2**.

[0038] **FIG. 8** illustrates a COSY NMR 2D spectrum of Compound **2**.

[0039] **FIG. 9** illustrates a UV chromatogram of Compound **2**.

[0040] **FIG. 10** illustrates a TIC chromatogram of Compound **2**.

[0041] **FIG. 11** illustrates a mass spectrum of Compound **2**.

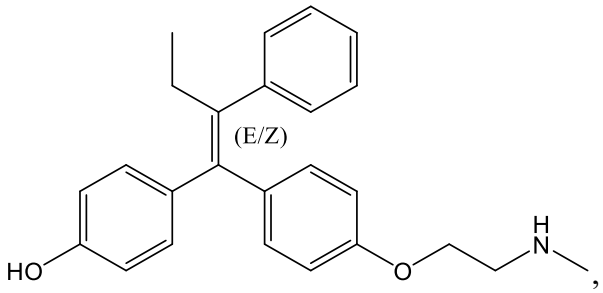
[0042] **FIG. 12** illustrates a proton NMR spectrum of Compound **3**.

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising:

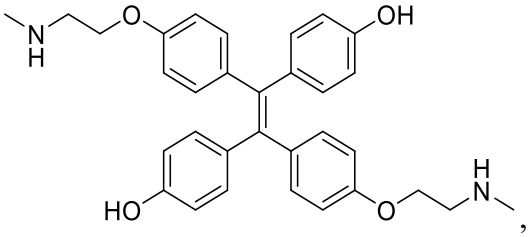
an endoxifen:



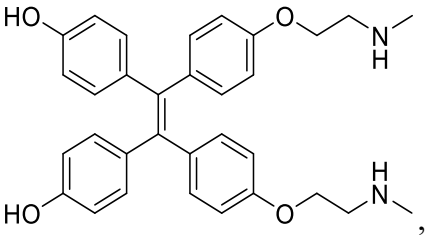
or a pharmaceutically acceptable salt or tautomer thereof; and

not less than 0.01 and not more than 1% w/w of a further component, wherein the further component comprises one or more of the following compounds, or a pharmaceutically acceptable salt or tautomer thereof:

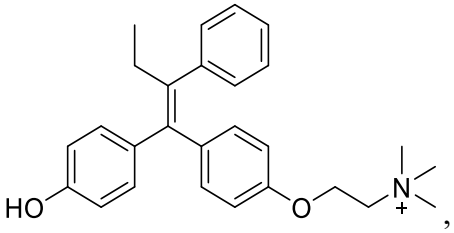
Compound 4a:

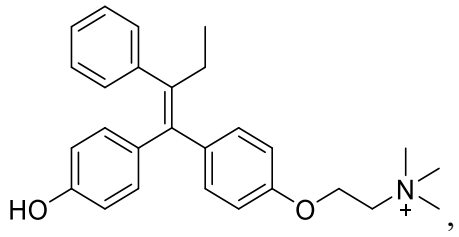


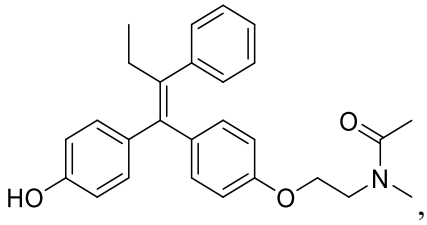
Compound 4b:

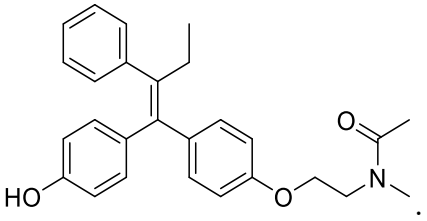


Compound 5a:

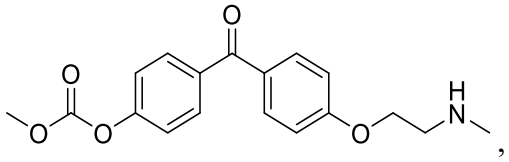


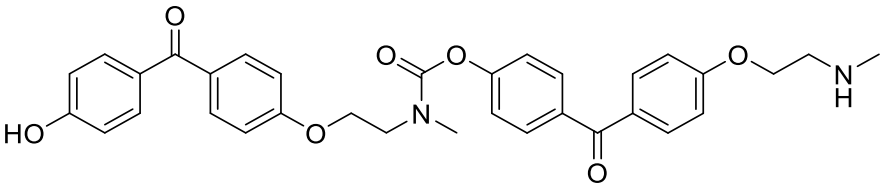
Compound 5b: ,

Compound 7a: , or

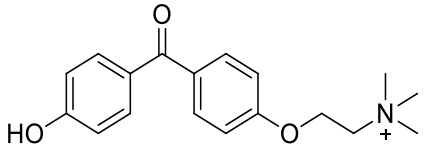
Compound 7b: .

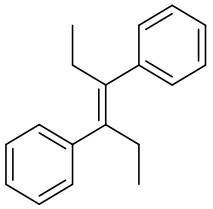
2. The composition of claim 1, wherein the further component comprises one or more of the following compounds, or a pharmaceutically acceptable salt of any one thereof:

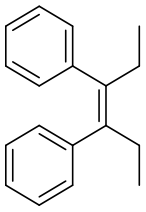
Compound 1: ,

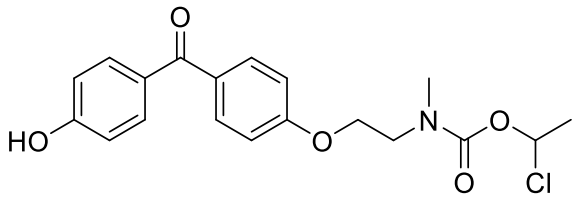
Compound 2: 

,

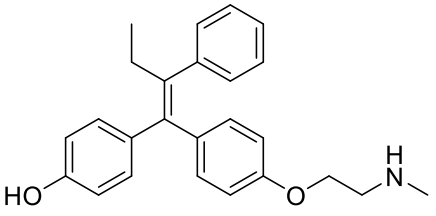
Compound 3: ,

Compound 6a: ,

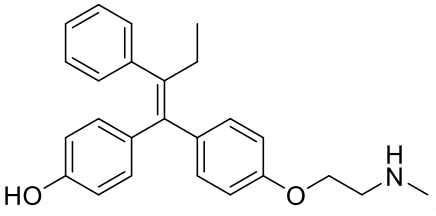
Compound 6b: , or

Compound 8: .

3. The composition of claim 1 or claim 2, wherein the endoxifen is not less than 95% (Z)-

endoxifen: .

4. The composition of any one of claims 1 to 3, the endoxifen is not more than 3% (E)-

endoxifen: .

5. The composition of any one of claims 1 to 4, wherein the composition comprises:
not less than 0.1% and not more than 1% w/w o**f Compound 4a** and **Compound 4b**,
not less than 0.01% and not more than 0.1% w/w of **Compound 5a** and **Compound 5b**,
not less than 0.01% and not more than 0.1% w/w of **Compound 7a** and **Compound 7b**, or
any combinations thereof.

6. The composition of any one of claims 1 to 4, wherein the composition comprises:
not less than 0.1% and not more than 1% w/w o**f Compound 4a** and **Compound 4b**,
not less than 0.01% and not more than 0.1% w/w of **Compound 5a** and **Compound 5b**, and
not less than 0.01% and not more than 0.1% w/w of **Compound 7a** and **Compound 7b**.

7. The composition of any one of claims 2 to 6, wherein the composition comprises:

not less than 0.1% and not more than 1% w/w o**f Compound 1**,
not less than 0.1% and not more than 1% w/w of **Compound 2**,
not less than 0.1% and not more than 1% w/w of **Compound 3**, or
any combinations thereof.

8. The composition of any one of claims 1 to 7, the total % w/w of the further component is less than or equal to 2% w/w of the composition.

9. The composition of any one of claims 1 to 8, wherein the pharmaceutically acceptable salt of the endoxifen is selected from the group consisting of an: arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc salt.

10. The composition of any one of claims 1 to 9, wherein the pharmaceutically acceptable salt of the endoxifen is endoxifen gluconate, endoxifen citrate, or endoxifen hydrochloride.

11. The composition of any one of claims 1 to 8, the (Z)-endoxifen is polymorphic Form I of (Z)-endoxifen that is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3°, and 21.8 ± 0.3° two theta.

12. The composition of any one of claims 1 to 11, the composition comprises from 0.01 mg to 200 mg of the endoxifen.

13. The composition of any one of claims 1 to 12, the composition comprises less than 0.25% water content.

14. The composition of any one of claims 1 to 13, the composition comprises less than:
6000 ppm methanol;
9000 ppm ethanol;
9000 ppm acetone;
9000 ppm isopropyl alcohol;
1000 ppm acetonitrile;

9000 ppm ethyl acetate;
1500 ppm tetrahydrofuran;
1500 ppm 2-methyltetrahydrofuran;
250 ppm benzene;
250 ppm mesityl oxide;
any combinations thereof.

15. The composition of any one of claims 1 to 14, the composition comprises less than:
500 ppm zinc;
500 ppm titanium; or
a combination thereof.

16. The composition of any one of claims 1 to 15, the composition is formulated as an enteric formulation or a delayed-release formulation.

17. A pharmaceutical composition comprising the composition of any one of claims 1 to 16 and a pharmaceutically acceptable excipient or diluent.

18. The composition of any one of claims 1 to 16 or the pharmaceutical composition of claim 17 for use in therapy.

19. Use of a composition of any one of claims 1 to 16 or a pharmaceutical composition of claim 17 in the manufacture of a medicament for the treatment of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, a depression, or any combinations thereof in a subject in need thereof.

20. The use of claim 19, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

21. The use of claim 19 or claim 20, wherein the subject in need thereof is tamoxifen-refractory or tamoxifen resistant, or is or will be treated with an SSRI drug selected from citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.