

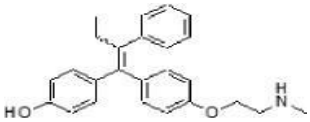
to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

b. subjecting the first mother liquor to recrystallization from a second solvent by concentrating the first mother liquor or by swapping out the first solvent from the first mother liquor with the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen Form I, 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; and

c. optionally, subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid.

[0044f] In one aspect, the present disclosure provides an industrially scalable process for manufacturing the crystalline form as described herein, comprising the steps of:

a. subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III) represented by



to fractional crystallization from ethyl acetate to form a first crystalline solid and first crystalline mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

b. subjecting the first mother liquor to recrystallization from isopropyl alcohol or isopropyl alcohol/process purified water by concentrating the first mother liquor, or by swapping out the ethyl acetate from the first mother liquor with isopropyl alcohol or isopropyl alcohol/process purified water one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and

c. optionally, subjecting the second crystalline solid to recrystallization from ethanol or column chromatographic treatment one or more times to form a third crystalline solid.

[0044g] In one aspect, the present disclosure provides an industrially scalable process for manufacturing the crystalline form as described herein, comprising: a. reacting to 6N HCL in ethyl acetate

a starting mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z-ratio ranging from 99:1 to 40:60; b. neutralizing with 8N NaOH ; c. washing one or more times with ethyl acetate; d. washing one or more times with a mixture of ethyl acetate and n-heptane; and e. recovering the crystalline form as described herein.

[0044h] In one aspect, the present disclosure provides an oral composition comprising the composition as described herein, for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject: a. a steady state plasma level of endoxifen within 7 to 21 days; b. a steady state plasma level of endoxifen ranging from 25 nM to 300 nM; c. a steady state plasma level of endoxifen greater than 30 nM; d. maximal plasma levels of endoxifen within 2 to 10 hours after administration; or e. any combination thereof.

[0044i] In one aspect, the present disclosure provides a use of the oral composition as described herein in the manufacture of a medicament for treating or preventing a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in a subject in need thereof, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

[0044j] In one aspect, the present disclosure provides a use of an oral composition comprising the composition as described herein in the manufacture of a medicament for treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder or both, wherein the medicament is to be administered orally, wherein administration of the medicament achieves: a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration; b. a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and c. a steady state plasma level of endoxifen greater than 30 nM.

INCORPORATION BY REFERENCE

[0045] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

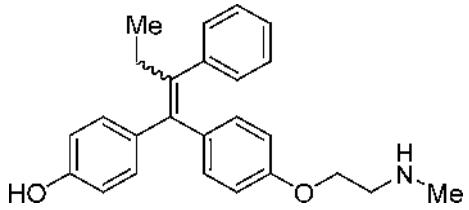
[0046] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0047] Fig. 1 is a scheme depicting the metabolic route of tamoxifen to endoxifen and other metabolites. The plasma concentrations of 4-hydroxytamoxifen are low relative to those of N-desmethyl tamoxifen, indicating that the primary route for metabolism of the parent drug is via

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising a crystalline form of a compound of Formula (III):



Formula (III),

wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer, and wherein the crystalline form of the (Z)-isomer is Form I, 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.

2. The composition of claim 1, wherein the composition is stable for at least 9 months at 5 °C and 60% relative humidity or at 25 °C and 60% relative humidity.

3. The composition of claim 1 or 2, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta.

4. The composition of any one of claims 1-3, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

5. The composition of any one of claims 1-4, wherein the x-ray powder diffraction pattern further comprises peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

6. The composition of any one of claims 1 to 5, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 9 or Fig. 10.

7. The composition of any one of claims 1 to 6, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form I.

8. The composition of any one of claims 1 to 8, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form I.

9. The composition of claim 8, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form I.

10. The composition of any one of claims 1 to 9, wherein the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) in an E/Z ratio between 0.9 and 1.3.

11. The composition of claim 10, wherein the E/Z ratio is about 1.1.

12. The composition of claim 10 or 11, further comprising a crystalline form of Form II of the compound of Formula (III), characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta.

13. The composition of claim 12, wherein the x-ray powder diffraction pattern of the crystalline form of Form II further comprises a peak at 22.0 ± 0.3° two theta.

14. The composition of claim 12 or 13, wherein the x-ray powder diffraction pattern of the crystalline form of Form II further comprises at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta.

15. The composition of any one of claims 12 to 14, wherein the x-ray powder diffraction pattern of the crystalline form of Form II further comprises peaks at 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta.

16. The composition of any one of claims 12 to 15, wherein the crystalline form of Form II is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 11 or Fig. 12.

17. The composition of any one of claims 12 to 16, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form II.

18. The composition of any one of claims 12 to 17, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form II.

19. The composition of claim 18, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form II.

20. The composition of claim 10 or 11, further comprising a crystalline form of Form III of the compound of Formula (III), characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta.

21. The composition of claim 20, wherein the x-ray powder diffraction pattern of the crystalline form of Form III further comprises a peak at 25.3 ± 0.3° two theta.

22. The composition of claim 20 or 21, wherein the x-ray powder diffraction pattern of the crystalline form of Form III further comprises at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta.

23. The composition of any one of claims 20 to 22, wherein the x-ray powder diffraction pattern of the crystalline form of Form III further comprises peaks at 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta.

24. The composition of any one of claims 20 to 23, wherein the crystalline form of Form III is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 13.

25. The composition of any one of claims 20 to 24, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form III.

26. The composition of any one of claims 20 to 25, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form III.

27. The composition of claim 26, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form III.

28. The composition of any one of claims 1 to 27, further comprising a pharmaceutically acceptable carrier or diluent.

29. The composition of any one of claims 1 to 28, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

30. The composition of any one of claims 1 to 29, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

31. The composition of any one of claims 1 to 30, wherein a mean half-life of endoxifen in a subject treated with the composition is between 30 hours to 60 hours.

32. The composition of any one of claims 1 to 31, wherein the composition is formulated for oral delivery as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

33. The composition of any one of claims 1 to 32, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines upon administration to a subject.

34. The composition of any one of claims 1 to 33, having a mean area under the curve extrapolated to time infinity (AUC0-inf) of endoxifen of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL upon administration to a subject.

35. The composition of any one of claims 1 to 34 for use in therapy.

36. Use of the composition of any one of claims 1 to 35 in the manufacture of a medicament for treating or preventing a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in a subject in need thereof, wherein the subject

has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

37. The use of claim 36, 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.

38. The use of claim 36 or 37, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

39. The use of any one of claims 36 to 38, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

40. The use of any one of claims 36 to 39, wherein the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

41. The use of any one of claims 36 to 40, wherein the composition comprises 0.01 mg to 200 mg of (Z)-endoxifen.

42. The use of any one of claims 36 to 41, wherein the subject is to be administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily.

43. The use of any one of claims 36 to 42, wherein a steady state plasma level of endoxifen in the subject is greater than 30 nM.

44. The use of any one of claims 36 to 43, wherein the steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the medicament.

45. The use of any one of claims 36 to 44, wherein time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administration of the medicament.

46. Use of the composition of any one of claims 1 to 35 in the manufacture of a medicament for treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the medicament is to be administered to the subject, wherein administration of the medicament achieves:

a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and a steady state plasma level of endoxifen greater than 30 nM.

47. The use of claim 46, wherein the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, 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, and vulvar cancer.

48. The use of claim 46 or 47, wherein the medicament comprises 0.01 mg to 200 mg of (Z)-endoxifen.

49. The use of claim 48, wherein the subject is to be administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen.

50. The use of any one of claims 36 to 49, wherein the mean area under the curve extrapolated to time infinity (AUC0-inf) of endoxifen is 200 hr*ng/mL to 10000 hr*ng/mL, 300 hr*ng/mL to 8000 hr*ng/mL, 400 hr*ng/mL to 6000 hr*ng/mL or 700 hr*ng/mL to 6000 hr*ng/mL.

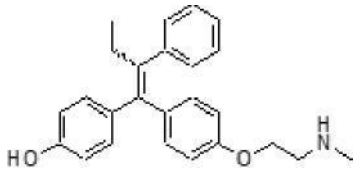
51. The use of any one of claims 36 to 50, wherein the medicament is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

52. The use of any one of claims 36 to 51, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the medicament is released in the intestines.

53. The use of any one of claims 36 to 52, wherein the medicament is to be administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

54. An industrially scalable process for manufacturing (Z)-endoxifen, comprising the steps of:

a. subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by

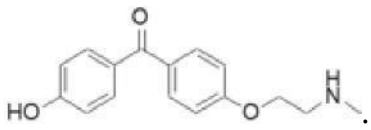


to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

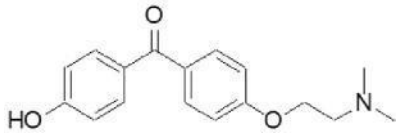
b. subjecting the first mother liquor to recrystallization from a second solvent by concentrating the first mother liquor or by swapping out the first solvent from the first mother liquor with the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen Form I, 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; and

c. optionally, subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid.

55. The process of claim 54, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is prepared by coupling a compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction via a titanium salt and a reducing agent in an inert organic solvent to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein the compound of Formula (II) has a structure represented by



56. The process of claim 55, further comprising preparing the compound of Formula (II) by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, a compound of Formula (I), wherein the compound of Formula (I) has the structure



with a demethylating agent and a proton acceptor in an inert organic solvent to form the compound of Formula (II).

57. The process of any one of claims 54 to 56, wherein the first solvent is ethyl acetate, isopropyl alcohol, isopropyl alcohol/process purified water, acetonitrile, acetonitrile/process purified water, or acetone.

58. The process of any one of claims 54 to 57, wherein the second solvent is isopropyl alcohol, isopropyl alcohol/process purified water, acetone, ethanol, ethyl acetate, or acetone/MTBE.

59. The process of claim 58, wherein the second solvent is isopropyl alcohol.

60. The process of any one of claims 54 to 59, wherein the third solvent is ethanol, methanol, ethyl acetate, isopropyl alcohol, isopropyl alcohol/process purified water, n-heptane, or acetone.

61. The process of any one of claims 54 to 60, further comprising pre-heating any one or more of the first solvent, the second solvent and the third solvent to a temperature ranging from 40 °C to 80 °C.

62. The process of any one of claims 54 to 61, wherein each fractional crystallization and recrystallization step independently comprises a step of distillation at 50 °C to 80 °C; and cooling the solution to a temperature ranging from 0 °C to not more than 35 °C.

63. The process of any one of claims 54 to 62, further comprising the steps of:

a. reacting the compound of Formula (II) with propiophenone in an inert organic solvent;

b. preparing a titanium salt and a reducing agent in an inert organic solvent; and

c. reacting the compound of Formula (II) of step (a) with the titanium salt and a reducing agent in an inert organic solvent of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen.

64. The process of any one of claims 54 to 63, further comprising the steps of:

a. reacting the compound of Formula (II) with propiophenone in an inert organic solvent;

b. preparing a titanium salt and a reducing agent in an inert organic solvent; and

c. reacting the compound of Formula (II) of step (a) with the titanium salt and a reducing agent in an inert organic solvent of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen.

65. The process of claim 64, wherein the inert organic solvent is at a concentration of 1:1 to 1:20 (wt/wt) with respect to the compound of Formula (II), the propiophenone is at a concentration of 1:0.01 to 1:5 (wt/wt) with respect to the compound of Formula (II), the titanium

salt is at a concentration of 1:0.1 to 1:12 (wt/wt) with respect to the compound of Formula (II), and the reducing agent is at a concentration of 1:0.01 to 1:10 wt/wt) with respect to the compound of Formula (II).

66. The process of any one of claims 54 to 65, wherein the titanium salt is selected from the group consisting of titanium halides, titanium(IV) trichloride isopropoxide, and titanium isopropoxide.

67. The process of any one of claims 54 to 66, wherein the reducing agent is selected from the group consisting of zinc, zirconium, vanadium, niobium, molybdenum, tungsten, aluminum, magnesium, potassium, zinc-copper couple, alkali and alkali earth metals, butylium, lithium, and lithium aluminum hydride.

68. The process of any one of claims 56 to 67, wherein the inert organic solvent is selected from the group consisting of dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene, diethyl ether, 1,4-dioxane, tert-butyl methyl ether, tetrahydrofuran, N,N-dimethylformamide, N-methylpyrrolidone, diglyme, nitromethane, 1,2-dimethoxyethane, pyridine, acetone, acetonitrile, benzene, o-xylene, m-xylene, p-xylene, xylenes, hexanes, cyclohexane, heptane, octane, nonane, and decane, or a combination thereof.

69. The process of any one of claims 56 to 68, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises maintaining the temperature of the reaction at a temperature of not more than 75 °C, not more than 65 °C, not more than 55 °C, not more than 50 °C, not more than 45 °C, not more than 40 °C, not more than 35 °C, not more than 30 °C, not more than 25 °C, not more than 20 °C, or not more than 15 °C when the titanium salt is added to the reducing agent and the inert organic solvent.

70. The process of any one of claims 56 to 69, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent further comprising maintaining the temperature of the reaction at a temperature not more than 75 °C, not more than 70 °C, not more than 65 °C, not more than 60 °C, not more than 55 °C, not more than 50 °C, or not more than 45 °C when the titanium salt is added to the reducing agent and the inert organic solvent.

71. The process of any one of claims 56 to 70, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises heating the titanium salt and the reducing agent in the inert organic solvent to a temperature ranging from 20 °C to 250 °C, from 40 °C to 70 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, or from 150 °C to 200 °C.

72. The process of any one of claims 56 to 71, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises heating the titanium salt and the reducing agent in the inert organic solvent under reflux for not less than 30 min, not less than 1 hour, not less than 2 hours, not less than 4 hours, not less than 6 hours, or not less than 8 hours under N_2 or argon.

73. The process of any one of claims 54 to 72, wherein the compound of Formula (II) of step (a) is reacted with titanium salt and a reducing agent in an inert organic solvent of step (b) under reflux to form the mixture of (E)-endoxifen and (Z)-endoxifen.

74. The process of any one of claims 54 to 73, wherein the compound of Formula (II) of step (a) is reacted with titanium salt and a reducing agent in an inert organic solvent of step (b) at a temperature ranging from 40 °C to 80 °C to form the mixture of (E)-endoxifen and (Z)-endoxifen for not less than 4 hours, not less than 6 hours, not less than 8 hours, not less than 12 hours, not less than 24 hours, or not less than 48 hours.

75. The process of any one of claims 54 to 74, further comprising a step of cooling the mixture of (E)-endoxifen and (Z)-endoxifen to a temperature ranging from 0 °C to 30 °C.

76. The process of any one of claims 54 to 75, further comprising one or more steps of:

a. extraction of the mixture of (E)-endoxifen and (Z)-endoxifen;

b. washing the mixture of (E)-endoxifen and (Z)-endoxifen;

c. distillation of the mixture of (E)-endoxifen and (Z)-endoxifen; and

d. crystallization to afford a crystalline solid mixture of (E)-endoxifen and (Z)-endoxifen.

77. The process of claim 76, wherein the extraction is carried out one or more times in MeTHF or THF.

78. The process of any one of claims 56 to 77, further comprising generating the compound of Formula (II) by demethylating the compound of Formula (I) with a demethylating agent and a proton acceptor in an inert organic solvent to form the compound of Formula (II).

79. The process of any one of claims 57 to 78, wherein the proton acceptor is selected from the group consisting of carbonates, such as sodium carbonate and potassium carbonate, and bicarbonates, such as sodium bicarbonate and potassium bicarbonate, proton sponge, and DIPEA.

80. The process of any one of claims 57 to 79, wherein the demethylating agent is selected from the group consisting of N-iodosuccinamide, ethyl chloroformates, vinyl chloroformate, cynogen bromide, diethyl azodicarboxylate, and pyridinium chloride.

81. The process of any one of claims 57 to 80, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor at a temperature ranging from 20 °C to 250 °C, from 40 °C to 80 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, and from 150 °C to 200 °C.

82. The process of any one of claims 57 to 81, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor under reflux.

83. The process of any one of claims 57 to 82, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor for not less than 5 hours, not less than 8 hours, not less than 12 hours, not less than 24 hours, not less than 36 hours, not less than 48 hour or not less than 72 hours.

84. The process of any one of claims 54 to 83, further comprising one or more steps of:

a. distillation;

b. reaction with solvent/acid mixture;

c. neutralization with a neutralizing agent; and

d. drying under reduced pressure.

85. The process of claim 84, wherein the distillation step comprises one or more solvent swaps with an organic distillation solvent selected from the group consisting of ethyl acetate, alcohols, such as methanol, ethanol, n-propanol, and isopropanol, benzene, acetone, acetonitrile, toluene, dichloromethane, 1,2-dichloroethane, and chloroform.

86. The process of claim 84 or 85, wherein the solvent/acid mixture is selected from the group consisting of methanol/HCl, ethanol/HCl, propanol/HCl, isopropanol/HCl, methanol/sulfuric acid, methanol/phosphoric acid, ethanol/sulfuric acid, ethanol/phosphoric acid, propanol/sulfuric acid, propanol/phosphoric acid, isopropanol/sulfuric acid, isopropanol/phosphoric acid, methanol/acetic acid, ethanol/acetic acid, propanol/acetic acid, isopropanol/acetic acid, methanol/formic acid, ethanol/formic acid, propanol/formic acid, and isopropanol/formic acid.

87. The process of any one of claims 84 to 86, wherein neutralizing agent is sodium hydroxide, ammonium hydroxide, potassium hydroxide, or aminomethylpropanol.

88. The process of any one of claims 54 to 87, further comprising converting (E)-endoxifen to (Z)-endoxifen by reacting a mixture of (E)-endoxifen and (Z)-endoxifen to an acid in a solvent.

89. The process of claim 88, wherein the acid is at a concentration of 1:1 to 1:5 (wt/wt) with respect to the compound of Formula (III), and the solvent is at a concentration of 1:1 to 1:20 (wt/wt) with respect to the compound of Formula (III).

90. The process of claim 89, wherein the acid is HCl, TCA, or TFA.

91. The process of claim 54 to 90, wherein the solvent is acetonitrile, acetonitrile/process purified water, isopropyl alcohol, isopropyl alcohol/process purified water, dichloromethane, or ethyl acetate.

92. The process of any one of claims 54 to 91, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is heated with the acid in the solvent under reflux and stirred for not less than 4 hours, not less than 6 hours, not less than 12 hours, not less than 24 hours, or not less than 48 hours.

93. The process of any one of claims 54 to 92, further comprising one or more steps of:

a. neutralization with a neutralizing agent;

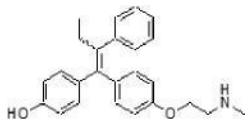
b. extraction;

c. one or more washes; and

d. treatment with activated carbon.

94. An industrially scalable process for manufacturing the crystalline form of any one of claims 1 to 11, comprising the steps of:

a. subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III) represented by



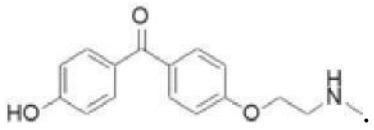
to fractional crystallization from ethyl acetate to form a first crystalline solid and first crystalline mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

b. subjecting the first mother liquor to recrystallization from isopropyl alcohol or isopropyl alcohol/process purified water by concentrating the first mother liquor, or by swapping out the ethyl acetate from the first mother liquor with isopropyl alcohol or isopropyl alcohol/process purified water one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and

c. optionally, subjecting the second crystalline solid to recrystallization from ethanol or column chromatographic treatment one or more times to form a third crystalline solid.

95. The process of claim 94, wherein the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), in step a is pretreated with 6N HCl and neutralized with 8N NaOH.

96. The process of claim 94 or 95, wherein the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), is prepared by coupling a compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone catalyzed in a McMurry reaction via $TiCl_4$ and Zn in THF to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein the compound of Formula (II) has a structure represented by



97. The process of claim 96, further comprising the steps of:

a. reacting the compound of Formula (II) with propiophenone in THF;

b. preparing $TiCl_4$ and Zn in THF; and

c. reacting the compound of Formula (II) of step (a) with the $TiCl_4$ and Zn in THF of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen.

98. The process of claim 96 or 97, comprising the steps of:

reacting the compound of Formula (II) with propiophenone in THFa. ;

b. preparing a $TiCl_4$ and Zn in THF; and

c. reacting the compound of Formula (II) of step (a) with the $TiCl_4$ and Zn in THF of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen.

99. The process of any one of claims 96 to 98, wherein preparation of $TiCl_4$ and Zn in THF further comprises heating under reflux for not less than 2 hours under N_2.

100. The process of any one of claims 96 to 99, further comprising the steps of extractive purification, distillation, and crystallization.

101. The process of any one of claims 96 to 100, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising a step of:

a. extraction one or more times with ammonium chloride, silicon dioxide, 40% K_2CO_3, and THF;

b. extraction one or more times with K_2CO_3 and MeTHF;

c. extraction one or more times with NaOH, NaCl, and MeTHF;

d. extraction one or more times with MeTHF or THF;

e. extraction one or more times with 20% NaCl; or

f. a combination thereof.

102. The process of any one of claims 96 to 101, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising the steps of:

a. extraction one or more times with 40% K_2CO_3 and MeTHF;

b. extraction one or more times with 1N NaOH, NaCl and MeTHF;

c. extraction one or more times with MeTHF; and

d. extraction with 20% NaCl.

103. The process of any one of claims 96 to 102, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising the steps of:

a. extraction with 25% ammonium chloride, silicon dioxide and THF;

b. one or more washes with THF; and

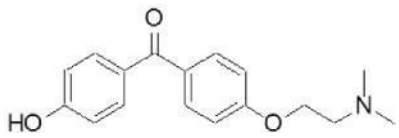
c. one or more washes with 40%K_2CO_3

104. The process of claim 100 to 103, wherein the step of distillation is performed 1 to 5 times with EtOAc or isopropyl alcohol.

105. The process of any one of claims 100 to 104, wherein the step of distillation is performed at a temperature ranging from 30 °C to 90 °C.

106. The process of any one of claims 100 to 105, wherein the distillation is performed at not more than 75 °C.

107. The process of any one of claims 96 to 106, wherein the compound of Formula (II) is prepared by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, a compound of Formula (I), wherein the compound of Formula (I) has the structure



with 1-chloroethyl chloroformate and DIPEA in THF to form the compound of Formula (II).

108. The process of claim 107, comprising the steps of:

a. reacting the compound of Formula (I) with DIPEA in tetrahydrofuran;

b. adding 1-chloroethyl chloroformate;

c. distilling with methanol;

d. reacting with methanol/6N HCl; and

e. neutralizing with 8N NaOH.

109. The process of claim 107 or 108, comprising the steps of:

a. reacting the compound of Formula (I) with DIPEA in THF;

b. adding 1-chloroethyl chloroformate;

c. distilling with methanol one or more times;

d. reacting with methanol /6N HCl; and

e. neutralizing with 8N NaOH.

110. The process of any one of claims 107 to 109, further comprising one or more steps of:

a. washing the compound of Formula (II) with purified water;

b. washing the compound of formula (II) with ethyl acetate; and

c. drying the compound of Formula (II) under reduced pressure at not more than 50°C.

111. The process of any one of claims 54 to 110, further comprising converting (E)-endoxifen to (Z)-endoxifen by reacting a mixture of (E)-endoxifen and (Z)-endoxifen to 6N HCl in EtOAc.

112. The process of claim 111, further comprising the steps of:

a. neutralizing with 8N NaOH;

b. extraction with ethyl acetate;

c. one or more washes with 20% NaCl; and

d. treatment with activated carbon.

113. An industrially scalable process for manufacturing the crystalline form of any one of claims 12 to 27, comprising:

a. reacting to 6N HCL in ethyl acetate a starting mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z-ratio ranging from 99:1 to 40:60;

b. neutralizing with 8N NaOH;

c. washing one or more times with ethyl acetate;

d. washing one or more times with a mixture of ethyl acetate and n-heptane; and

e. recovering the crystalline form of any one of claims 12 to 27.

114. The process of any one of claims 54 to 113, wherein the (Z)-endoxifen is reacted with D-gluconate or L-Gluconate to form (Z)-endoxifen L-gluconate or (Z)-endoxifen D-gluconate.

115. The process of any one of claims 54 to 114, wherein the (Z)-endoxifen free base has < 1% impurity.

116. The process of any one of claims 54 to 115, wherein the (Z)-endoxifen free base is stable at ambient temperature for at least 9 months at 5 °C and 60% relative humidity or at 25 °C and 60% relative humidity.

117. An oral composition comprising the composition of any one of claims 1 to 35, for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject:

a. a steady state plasma level of endoxifen within 7 to 21 days;

b. a steady state plasma level of endoxifen ranging from 25 nM to 300 nM;

c. a steady state plasma level of endoxifen greater than 30 nM;

d. maximal plasma levels of endoxifen within 2 to 10 hours after administration; or

e. any combination thereof.

118. The oral composition of claim 117, having a mean half-life of endoxifen in a subject ranging from 40 hours to 55 hours after administration.

119. The oral composition of claim 117 or 118, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

120. The oral composition of any one of claims 117 to 119, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen is released in the intestines of the subject.

121. The oral composition of any one of claims 117 to 120, having a mean area under the curve extrapolated to time infinity (AUC0-inf) of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL upon administration to the subject.

122. Use of the oral composition of any one of claims 117 to 121 in the manufacture of a medicament for treating or preventing a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in a subject in need thereof, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

123. The use of claim 122, 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.

124. The use of claim 122 or 123, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

125. The use of any one of claims 122 to 124, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

126. The use of any one of claims 122 to 125, wherein the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

127. The use of any one of claims 122 to 126, wherein the subject is to be administered 0.01 mg to 200 mg of (Z)-endoxifen.

128. The use of any one of claims 122 to 127, wherein the subject is to be administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily.

129. The use of any one of claims 122 to 128, wherein a steady state plasma level of endoxifen in the subject is greater than 30 nM.

130. The use of any one of claims 122 to 129, wherein the steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the medicament.

131. The use of any one of claims 122 to 130, wherein time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administration of the medicament.

132. Use of an oral composition comprising the composition of any one of claims 1 to 35 in the manufacture of a medicament for treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder or both, wherein the medicament is to be administered orally, wherein administration of the medicament achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

b. a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and

c. a steady state plasma level of endoxifen greater than 30 nM.

133. The use of claim 132, wherein the subject is to be administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen.

134. The use of claim 132 or 133, wherein the mean area under the curve extrapolated to time infinity (AUC0-inf) is 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

135. The use of any one of claims 132 to 134, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

136. The use of any one of claims 132 to 135, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the endoxifen is released in the intestines.

137. The use of claim 132 to 136, wherein the medicament is to be administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

138. The use of any one of claims 132 to 137, wherein the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, 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, and vulvar cancer.