Claims:

1. A pharmaceutical composition comprising:

1. (a) at least 9498% enantiomeric excess (*ee*) of N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate:.

(b) about 1.0% to about 1.9% or less N-{[(2*S*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide, or pharmaceutically acceptable salt thereof; and

(c) about 0.05% to about 0.1% methyl (Z)-N-(2-hydroxy-3-(piperidin-1-yl)propoxy)nicotinimidate 1-oxide, or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition according to claim 1, wherein the *ee* of N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate is at least 95%.

3. The pharmaceutical composition according to any one of the preceding claims, wherein the *ee* of N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate is at least 96%.

4. The pharmaceutical composition according to any one of the preceding claims, wherein the *ee* of N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate is at least 97%.

5. The pharmaceutical composition according to any one of the preceding claims, wherein the *ee* of N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate is at least 98%.

6. 2. The pharmaceutical composition of claim 1according to any one of the preceding claims, wherein the composition comprises:

a) at least 94% *ee* of N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate, such as at least 95% *ee*, such as at least 96% *ee*, such as at least 97% *ee*, such as at least 98% *ee*; and

b) 0.1% or less methyl (Z)-N-(2-hydroxy-3-(piperidin-1-yl)propoxy)nicotinimidate 1-oxide, or a pharmaceutically acceptable salt thereofis a pharmaceutical composition.

7. 3. The pharmaceutical composition according to any one of the preceding claim 2ms, wherein the composition further comprises:

a) at least 94% *ee* of N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate, such as at least 95% *ee*, such as at least 96% *ee*, such as at least 97% *ee*, such as at least 98% *ee*;

b) 0.1% or less methyl (Z)-N-(2-hydroxy-3-(piperidin-1-yl)propoxy)nicotinimidate 1-oxide, or a pharmaceutically acceptable salt thereof; and

c) less than 2 ppm N-nitrosopiperidine.

4. The pharmaceutical composition according to claim 3, wherein the composition comprises: about 0.8 ppm to about 2 ppm N-nitrosopiperidine.

8. The pharmaceutical composition according to any one of the preceding claims, wherein the purity of the composition is greater than or equal to 99.0% N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate as determined by HPLC.

9. The pharmaceutical composition according to any one of the preceding claims, comprising N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate particles having a D10 particle size determined using Malvern Mastersizer 3000 of from about 2.0 µm to about 20.0 µm.

10. The pharmaceutical composition according to any one of the preceding claims, comprising N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate particles having a D50 particle size determined using Malvern Mastersizer 3000 of from about 5.0 µm to about 60.0 µm.

11. The pharmaceutical composition according to any one of the preceding claims, comprising N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl

chloride 1-oxide citrate particles having a D90 particle size determined using Malvern Mastersizer 3000 of from about 30.0 µm to about 130.0 µm.

12. The pharmaceutical composition according to any one of the preceding claims, wherein the composition comprises:

a) at least 98.0% N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate; and

b) 1.9% or less N-{[(2*S*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide, or pharmaceutically acceptable salt thereof; and

c) 0.1% or less methyl (Z)-N-(2-hydroxy-3-(piperidin-1-yl)propoxy)nicotinimidate 1-oxide, or a pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition according to any one of the preceding claims, wherein the composition comprises:

a) at least 98.0% N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate; and

b) 1.9% or less N-{[(2*S*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide, or pharmaceutically acceptable salt thereof;

c) 0.1% or less methyl (Z)-N-(2-hydroxy-3-(piperidin-1-yl)propoxy)nicotinimidate 1-oxide, or a pharmaceutically acceptable salt thereof; and

d) less than 2 ppm N-nitrosopiperidine.

14. 5. An oral formulation comprising the pharmaceutical composition as defined in any one of the preceding claims 1-13 of claim 1, and at least one pharmaceutically acceptable excipient.

15. The oral formulation according to claim 14, wherein the oral formulation comprises a capsule.

~~16. The oral formulation according to any one of claims 14-15, wherein the oral formulation comprises a filler.~~

~~17. The oral formulation according to any one of claims 14-16, wherein the oral formulation comprises a lubricant.~~

~~18. The oral formulation according to any one of claims 15-17, wherein the capsule comprises hydroxypropyl methylcellulose (HPMC), titanium dioxide, and optionally one or more colorant.~~

~~19. The oral formulation according to any one of claims 16-18, wherein the filler is microcrystalline cellulose (MCC).~~

~~20. The oral formulation according to any one of claims 17-19, wherein the lubricant is magnesium stearate.~~

~~21.~~ 6. The oral formulation according to ~~any one of claims 14-20~~claim 5, wherein the N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate is present at a dosage from about 50 mg to about 500 mg.

~~22. The oral formulation according to any one of claims 14-21, wherein the N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate is present at a dosage of about 75 mg, about 100 mg, about 150 mg, about 200 mg, or about 400 mg.~~

7. The oral formulation ~~according to~~of ~~any one of claims 14-22~~claim 5, wherein the oral formulation comprises from about 20% to about 60% w/w of N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate.

~~23.~~

8. The oral formulation of claim 5, comprising N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate at a dosage of about 47 mg, about 62 mg, about 93 mg, or about 124 mg.

24. The oral formulation according to any one of claims 14-23, wherein the oral formulation comprises about 26.3% or about 52.6% w/w of N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate.

25. The oral formulation according to any one of claims 14-24, wherein the oral formulation comprises from about 40% to about 80% w/w of microcrystalline cellulose.

26. The oral formulation according to any one of claims 14-25, wherein the oral formulation comprises about 73.2% or about 46.9% w/w of microcrystalline cellulose.

27. The oral formulation according to any one of claims 14-26, wherein the oral formulation comprises from about 0.0% to about 1.0% magnesium stearate.

28. The oral formulation according to any one of claims 14-27, wherein the oral formulation comprises about 0.5% magnesium stearate.

29. 9. A unit dosage form of the pharmaceutical composition as defined in any one of the preceding claims 1-13, of claim 1 and a pharmaceutically acceptable carrier or excipient.

30. 10. The unit dosage form according to claim 29, comprising N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide, or a pharmaceutically acceptable salt thereof at a dosage from about 50 mg to about 500 mg.

31. 11. The unit dosage form according to any one of claims 29-30, or the oral formulation according to any one of claims 14-28, comprising N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate at a dosage of about 47 mg, about 62 mg, about 93 mg, or about 124 mg.

32. A kit comprising a unit dosage form according to any one of claims 29-31, and instructions for administration.

~~33. The kit of according to claim 32, wherein the kit further comprises prescribing information and/or multiple unit doses.~~

~~34. A method of treating or preventing Niemann Pick disease, type C in a subject in need thereof, wherein the subject is administered a therapeutically effective amount of the pharmaceutical composition, oral formulation, or unit dosage as defined in any one of claims 1-31.~~

~~35. A pharmaceutical composition an oral formulation, or unit dosage as defined in any one of claims 1-31 for use in treating or preventing Niemann Pick disease, type C in a subject in need thereof.~~

~~36.~~ 12. ~~A~~Use of a pharmaceutical composition according to claim 2, ~~an oral formulation, or unit dosage as defined in any one of claims 1-31, for use~~ in the manufacture of a medicament for the treatment ~~or prevention~~ of Niemann Pick disease, type C in a subject in need thereof.

~~37.~~ 13. Use of ~~a pharmaceutical composition,~~ an oral formulation according to claim 5, ~~or unit dosage as defined in any one of claims 1-31~~ in the manufacture of a medicament ~~,~~ for the treatment ~~or prevention~~ of Niemann Pick disease, type C in a subject in need thereof.

14. Use of a unit dosage form according to claim 9, in the manufacture of a medicament for the treatment of Niemann Pick disease, type C in a subject in need thereof.

~~38. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-37, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered three times daily.~~

15. A composition comprising:

(a) at least 98% N-{[(2*R*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate:

(b) about 1.0% to about 1.9% or less N-{[(2*S*)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide, or pharmaceutically acceptable salt thereof; and

(c) about 0.8 ppm to about 2 ppm N-nitrosopiperidine.

16. The composition of claim 15, wherein the composition is a pharmaceutical composition.

17. The pharmaceutical composition according to claim 16, wherein the composition comprises less than about 0.1% methyl (Z)-N-(2-hydroxy-3-(piperidin-1-yl)propoxy)nicotinimidate 1-oxide, or a pharmaceutically acceptable salt thereof.

18. The pharmaceutical composition according to claim 17, wherein the composition comprises about 0.05% to about 0.1% methyl (Z)-N-(2-hydroxy-3-(piperidin-1-yl)propoxy)nicotinimidate 1-oxide, or a pharmaceutically acceptable salt thereof.

19. An oral formulation comprising the composition of claim 15, and at least one pharmaceutically acceptable excipient.

20. The oral formulation according to claim 19, wherein the N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate is present at a dosage from about 50 mg to about 500 mg.

21. The oral formulation of claim 22, wherein the oral formulation comprises from about 20% to about 60% w/w of N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate.

22. The oral formulation of claim 22, comprising N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate at a dosage of about 47 mg, about 62 mg, about 93 mg, or about 124 mg.

23. A unit dosage form of the composition of claim 15 and a pharmaceutically acceptable carrier or excipient.

24. The unit dosage form according to claim 20, comprising N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide, or a pharmaceutically acceptable salt thereof at a dosage from about 50 mg to about 500 mg.

25. The unit dosage form of claim 23, comprising N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate at a dosage of about 47 mg, about 62 mg, about 93 mg, or about 124 mg.

26. Use of a pharmaceutical composition according to claim 15, in the manufacture of a medicament for the treatment of Niemann Pick disease, type C in a subject in need thereof.

27. Use of an oral formulation according to claim 19, in the manufacture of a medicament for the treatment of Niemann Pick disease, type C in a subject in need thereof.

28. Use of a unit dosage form according to claim 23, in the manufacture of a medicament for the treatment of Niemann Pick disease, type C in a subject in need thereof.

~~39. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered to a pediatric subject having a body weight of about 8 kg to about 15 kg.~~

~~40. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to claim 39, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered at a dosage of 47 mg.~~

~~41. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage~~

according to claim 39, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered at a dosage of 75 mg.

42. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered to a subject having a body weight of greater than about 15 kg to about 30 kg.

43. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to claim 42, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered at a dosage of 62 mg.

44. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to claim 42, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered at a dosage of 100 mg.

45. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered to a subject having a body weight of greater than about 30 kg to about 55 kg.

46. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to claim 45, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered at a dosage of 93 mg.

47. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage

according to claim 45, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered at a dosage of 150 mg.

48. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered to a subject having a body weight of greater than about 55 kg.

49. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to claim 48, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered at a dosage of 124 mg.

50. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to claim 48, wherein the oral formulation, pharmaceutical composition, or unit dosage is administered at a dosage of 200 mg.

51. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-50, wherein not less than about 85% of the N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide, or pharmaceutically acceptable salt thereof is dissolved into solution in about 15 minutes.

52. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-51, wherein the capsule ingredients are mixed with a liquid for oral administration as a liquid.

53. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-52, wherein the geometric mean C_{max} of the

composition is within about 80.00% to about 125.00% of a C_{max} of 1749 (CV 49%) ng/mL, after administration of a single dose.

54. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-52, wherein the $AUC_{0\text{-}8\ hrs}$ of the composition is within about 80.00% to about 125.00% of a $AUC_{0\text{-}8\ hrs}$ of 5317 (CV 17%) h·ng/mL, after administration of a single dose.

55. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-52, wherein the $AUC_{0\text{-}infinity}$ of the composition is within about 80.00% to about 125.00% of a $AUC_{0\text{-}infinity}$ of 6331 (CV 17%) h·ng/mL, after administration of a single dose.

56. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-52, wherein the geometric mean $C_{max,steady\ state}$ of the composition at steady state is within about 80.00% to about 125.00% of a $C_{max,steady\ state}$ of 2090 (CV 23%) ng/mL, after administration.

57. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-52, wherein the $AUC_{0\text{-}8\ hrs,\ steady\ state}$ of the composition is within about 80.00% to about 125.00% of a $AUC_{0\text{-}8\ hrs,\ steady\ state}$ of 7207 (CV 19%) h·ng/mL, after administration.

58. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 54-57, wherein the N-[(2R, Z)-2-hydroxy-3-(1-piperidyl)propoxy]pyridine-3-carboximidoyl chloride, 1-oxide citrate is measured in plasma.

59. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the geometric mean $C_{max,steady\ state}$ of the composition at steady state is within about 80.00% to about 125.00% of a $C_{max,steady\ state}$ of 533 ng/mL (368-770 ng/mL 5th and 95th percentiles), after administration of said composition in a human weighing from about 8 kg to about 15 kg.

60. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the $AUC_{0-8\ hrs,\ steady\ state}$ of the composition is within about 80.00% to about 125.00% of a $AUC_{0-8\ hrs,\ steady\ state}$ of 2916 h·ng/mL (1924-4436 h·ng/mL 5th and 95th percentiles), after administration of said composition in a human weighing from about 8 kg to about 15 kg.

61. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the geometric mean $C_{max,steady\ state}$ of the composition at steady state is within about 80.00% to about 125.00% of a $C_{max,steady\ state}$ of 593 ng/mL (395-878 ng/mL 5th and 95th percentiles), after administration of said composition in a human weighing from greater than about 15kg to about 30 kg.

62. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the $AUC_{0-8\ hrs,\ steady\ state}$ of the composition is within about 80.00% to about 125.00% of a $AUC_{0-8\ hrs,\ steady\ state}$ of 3043 h·ng/mL (1938-4763 h·ng/mL 5th and 95th percentiles), after administration of said composition in a human weighing from greater than about 15 kg to about 30 kg.

63. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the geometric mean $C_{max,steady\ state}$ of the composition at steady state is within about 80.00% to about 125.00% of a $C_{max,steady\ state}$ of

679 ng/mL (450-1024 ng/mL 5th and 95th percentiles), after administration of said composition in a human weighing from greater than about 30 to about 55 kg.

64. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the $AUC_{0\text{-}8\ hrs,\ steady\ state}$ of the composition is within about 80.00% to about 125.00% of a $AUC_{0\text{-}8\ hrs,\ steady\ state}$ of 3149 h·ng/mL (2010-4855 h·ng/mL 5th and 95th percentiles), after administration of said composition in a human weighing from great than about 30 kg to about 55 kg.

65. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the geometric mean $C_{max,steady\ state}$ of the composition at steady state is within about 80.00% to about 125.00% of a $C_{max,steady\ state}$ of 743 ng/mL (479-743 ng/mL 5th and 95th percentiles), after administration of said composition in a human weighing greater than about 55 kg.

66. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the $AUC_{0\text{-}8\ hrs,\ steady\ state}$ of the composition is within about 80.00% to about 125.00% of a $AUC_{0\text{-}8\ hrs,\ steady\ state}$ of 3182 h·ng/mL (2057-4921 h·ng/mL 5th and 95th percentiles), after administration of said composition in a human weighing greater than about 55 kg.

67. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate exposure increases dose-proportionally following a single oral dosage from about 31 mg to about 496 mg, wherein the estimates of the proportionality coefficient (90% CI) for C_{max} is 1,149 (1,07 – 1,20) and for $AUC_{0\text{-}inf}$ is 1,027 (0,98 – 1,08).

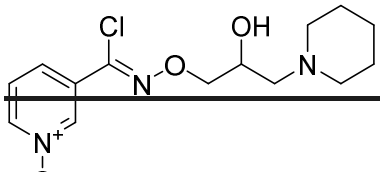
68. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the overall median t_{max} after administration is 0.25 to 3.0 hours.

69. The method, the oral formulation, pharmaceutical composition, or unit dosage for use, or use of the oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 34-38, wherein the median t_{max} after administration is about 0.5 hours.

70. The oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 1-31, wherein the oral formulation, pharmaceutical composition, or unit dosage has a shelf-life of at least 24 months from about 20 °C to about 25 °C.

71. The oral formulation, pharmaceutical composition, or unit dosage according to any one of claims 1-31, wherein the oral formulation, pharmaceutical composition, or unit dosage comprises N-{[(2R)-2-hydroxy-3-piperidin-1-ylpropyl]oxy}pyridine-3-carboximidoyl chloride 1-oxide citrate having a purity greater than or equal to 98.0% as determined by HPLC.

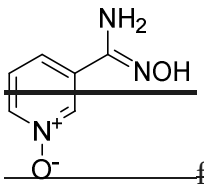
72. A process for preparing ORZY-01,



(ORZY-01);

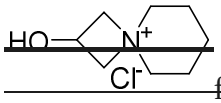
wherein the process comprises

step 1A) mixing a compound of formula (I);



formula (I);

with a compound of formula (II) in a container;



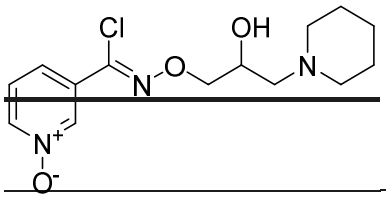
formula (II);

in a first solvent at a first temperature for more than 2 hours to provide an intermediate; followed by

step 1B) wherein the intermediate is reacted with $NaNO_2$ at a second temperature in a second solvent to provide ORZY-01,

thereby providing ORZY-01.

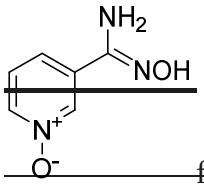
73. A process for preparing ORZY-01,



(ORZY-01);

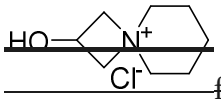
wherein the process comprises

step 1A) mixing a compound of formula (I);



formula (I);

with a compound of formula (II) in a container;



formula (II);

in a first solvent at a first temperature to provide an intermediate; followed by step 1B) wherein the intermediate is reacted with $NaNO_2$ at a second temperature in a second solvent to provide ORZY-01,

thereby providing ORZY-01.

74. The process according to any one of claims 72-73, wherein the intermediate is isolated, optionally purified, prior to step 1B).

75. The process according to any one of claims 72-74, wherein the first solvent is a polar protic solvent or a mixture of polar protic solvents.

76. The process according to any one of claims 72-75, wherein the first solvent is selected from the group consisting of ethanol, water, methanol, 2-propanol, and any mixture thereof.

77. The process according to any one of claims 72-76, wherein the first solvent is a mixture of ethanol and water.

78. The process according to any one of claims 72-77, wherein step 1A is performed under basic conditions, such as by the addition of a hydroxide, such as NaOH or KOH.

79. The process according to any one of claims 72-78, wherein the second solvent is a chlorinated hydrocarbon or a mixture containing a chlorinated hydrocarbon.

80. The process according to any one of claims 72-79, wherein the second solvent is a mixture of dichloromethane and water.

81. The process according to any one of claims 72-80, wherein the first solvent is different from the second solvent.

82. The process according to any one of claims 72-81, wherein the first temperature is at the boiling point of the solvent.

83. The process according to any one of claims 72-82, wherein the first temperature is higher than the second temperature.

84. The process according to any one of claims 72-83, wherein the first temperature is from 70 °C to 90 °C, such as from 72 °C to 88 °C, such as from 74 °C to 86°C, such as from 76 °C to 84 °C, such as from 78 °C to 82 °C, for example 80 °C.

85. The process according to any one of claims 72-84, wherein the second temperature is from 0 °C to 15 °C, such as from 0 °C to 1°C, such as from 1°C to 2 °C, such as from 2 °C to 3 °C, such as from 3 °C to 4 °C, such as from 5 °C to 6 °C, such as from 6 °C to 7 °C, such as from 7 °C to 8 °C, such as from 8 °C to 9 °C, such as from 9 °C to 10 °C, such as from 10 °C to 11 °C, such as from 11 °C to 12 °C, such as from 12 °C to 13 °C, such as from 13 °C to 14 °C, such as from 14 °C to 15 °C.

86. The process according to any one of claims 72-85, wherein the second temperature is maintained for 1 hour.

87. The process according to any one of claims 72-86, wherein the compound of formula (II) is mixed in a molar ratio of 1.3 : 1.0 with the compound of formula (I).

88. The process according to any one of claims 72-87, wherein the intermediate is not isolated prior to the reaction with $NaNO_2$.

89. The process according to any one of claims 72-88, wherein the intermediate is reacted with at least 1.2 equivalents $NaNO_2$.

90. The process according to any one of claims 72-89, wherein the intermediate is reacted with from 1.2 to 1.6 equivalents $NaNO_2$.

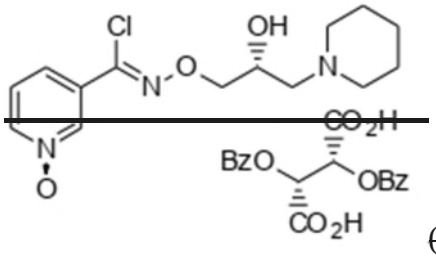
91. The process according to any one of claims 72-90, wherein the first solvent is heated under reflux for at least 2.5 hours, such as 3 hours or more, such as 4 hours or more, such as 5 hours or more, such as 6 hours or more.

92. The process according to any one of claims 72-91, wherein the first solvent is heated at from 75 °C to 85 °C, such as 80 °C for at least 3.5 hours.

93. The process according to any one of claims 72-92, wherein the first solvent is a mixture of ethanol, optionally denatured; and water, and the first solvent is maintained at 80 °C for at least 3 hours.

94. The process according to any one of claims 72-93, wherein the first solvent is a mixture of ethanol, optionally denatured; and water, and the first solvent is maintained at 80 °C for at least 3 hours; and wherein the second solvent is a mixture of dichloromethane and water.

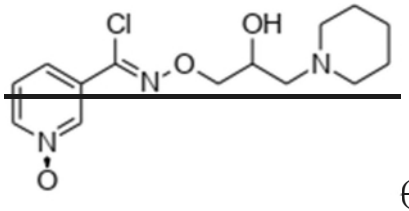
95. A process for preparing ORZY-03,



(ORZY-03),

wherein the process comprises the consecutive steps of:

a) mixing ORZY-01,



(ORZY-01),

with dibenzoyl *L*-tartaric acid (L-DBTA) in a container in a first step 2 solvent and heating the first step 2 solvent to a first step 2 temperature, optionally agitating the first step 2 solvent;

b) cooling the first step 2 solvent to a second step 2 temperature at a cooling rate of 15 K/h or higher to provide a solid composition comprising ORZY-03; wherein the first step 2 temperature is higher than the second step 2 temperature; and

c) separation the first step 2 solvent and the solid composition comprising ORZY-03, optionally the separation is by filtration;

thereby providing ORZY-03.

96. The process according to claim 95, further comprising step:

d) washing the solid composition comprising ORZY-03 one or more times with a first predefined volume of the first step 2 solvent.

97. The process according to any one of claims 95-96, further comprising step:

e) drying the solid composition comprising ORZY-03 at reduced pressure.

98. The process according to any one of claims 95-97, further comprising step a1) prior to step b), wherein the first step 2 solvent is cooled to a third step 2 temperature; wherein the third step 2 temperature is higher than the second step 2 temperature.

99. The process according to any one of claims 95-98, wherein the cooling rate is selected from the group consisting of: 15 K/h; 16 K/h; 17 K/h; 18 K/h; 19 K/h; 20 K/h; 21 K/h; 22 K/h; 23 K/h; 24 K/h; 25 K/h; 26 K/h; 27 K/h; 28 K/h; 29 K/h; 30 K/h; 31 K/h; 32 K/h; 33 K/h; 34 K/h; 35 K/h; 36 K/h; 37 K/h; 38 K/h; 39 K/h; 40 K/h; 41 K/h; 42 K/h; 43 K/h; 44 K/h; 45 K/h; 46 K/h; 47 K/h; 48 K/h; 49 K/h; and 50 K/h.

100. The process according to any one of claims 95-99, wherein the cooling rate is from 15 K/h to 50 K/h, such as from 15 K/h to 16 K/h; such as from 16 K/h to 17 K/h; such as from 17 K/h to 18 K/h; such as from 18 K/h to 19 K/h; such as from 19 K/h to 20 K/h; such as from 20 K/h to 21 K/h; such as from 21 K/h to 22 K/h; such as from 22 K/h to 23 K/h; such as from 23 K/h to 24 K/h; such as from 24 K/h to 25 K/h; such as from 25 K/h to 26 K/h; such as from 26 K/h to 27 K/h; such as from 27 K/h to 28 K/h; such as from 28 K/h to 29 K/h; such as from 29 K/h to 30 K/h; such as from 30 K/h to 31 K/h; such as from 31 K/h to 32 K/h; such as from 32 K/h to 33 K/h; such as from 33 K/h to 34 K/h; such as from 34 K/h to 35 K/h; such as from 35 K/h to 36 K/h; such as from 36 K/h to 37 K/h; such as from 37 K/h to 38 K/h; such as from 38 K/h to 39 K/h; such as from 39 K/h to 40 K/h; such as from 40 K/h to 41 K/h; such as from 41 K/h to 42 K/h; such as from 42 K/h to 43 K/h; such as from 43 K/h to 44 K/h; such as from 44 K/h to 45 K/h; such as from 45 K/h to 46 K/h; such as from 46 K/h to 47 K/h; such as from 47 K/h to 48 K/h; such as from 48 K/h to 49 K/h; such as from 49 K/h to 50 K/h.

101. The process according to any one of claims 95-100, wherein the cooling rate is from 15 K/h to 50 K/h.

102. The process according to any one of claims 95-101, wherein the cooling rate is from 15 K/h to 40 K/h.

103. The process according to any one of claims 95-102, wherein the cooling rate is from 15 K/h to 30 K/h.

104. The process according to any one of claims 95-103, wherein the cooling rate is from 17 K/h to 30 K/h.

105. The process according to any one of claims 95-104, wherein the first step 2 solvent is a polar protic solvent or a mixture of polar protic solvents.

106. The process according to any one of claims 95-105, wherein the first step 2 solvent is selected from the group consisting of ethanol, water, methanol, 2-propanol, and any mixture thereof.

107. The process according to any one of claims 95-106, wherein the first step 2 solvent is a mixture of ethanol and water.

108. The process according to any one of claims 95-107, wherein the first step 2 solvent is from 20.5 to 23.5 kg water per 55 kg ORZY-01; and from 200 to 240 kg EtOH per 55 kg ORZY-01.

109. The process according to any one of claims 95-108, wherein the first step 2 solvent is 22 kg water per 55 kg ORZY-01; and 220 kg EtOH per 55 kg ORZY-01.

110. The process according to any one of claims 95-109, wherein the first step 2 temperature is from 60 to 75 °C, such as from 61 to 74 °C, such as from 62 to 73 °C, such as from 63 to 72 °C, such as from 64 to 71 °C, such as from 65 to 70 °C, for example 65 °C.

111. The process according to any one of claims 95-110, wherein the second step 2 temperature is from 10 to 30 °C, such as from 11 to 29 °C, such as from 12 to 28 °C, such as from 13 to 27 °C, such as from 14 to 26 °C, such as from 15 to 25 °C, for example 20 °C.

112. The process according to any one of claims 95-111, wherein the third step 2 temperature is from 45 to 65 °C, such as from 46 to 64 °C, such as from 47 to 63 °C, such as from 48 to 62 °C, such as from 49 to 61 °C, such as from 50 to 60 °C, such as from 51 to 59 °C, such as from 52 to 58 °C, such as from 53 to 57 °C, such as from 54 to 56 °C, such as 55 °C.

113. The process according to any one of claims 95-112, wherein the third step 2 temperature is maintained for at least 30 minutes, such as at least 60 minutes.

114. The process according to any one of claims 95-113, wherein one or more seed crystals of ORZY-03 is added to the container prior to step b.

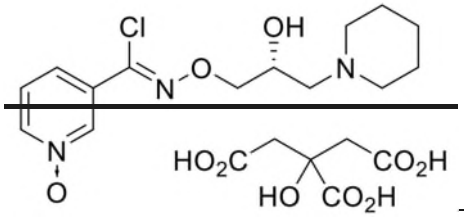
115. The process according to any one of claims 95-114, wherein the one or more seed crystals of ORZY-03 has a chiral purity of at least 95%.

116. The process according to any one of claims 95-115, wherein the mass of the one or more seed crystals of ORZY-03 is from 0.2 to 0.8 kg per 55 kg ORZY-03, for example 0.55 kg per 55 kg ORZY-03.

117. The process according to any one of claims 95-116, wherein the first predefined volume of the first step 2 solvent is from 35 to 55 kg per 55 kg ORZY-03.

118. The process according to any one of claims 95-117, wherein the first predefined volume of the first step 2 solvent is from 41 to 45 kg per 55 kg ORZY-03.

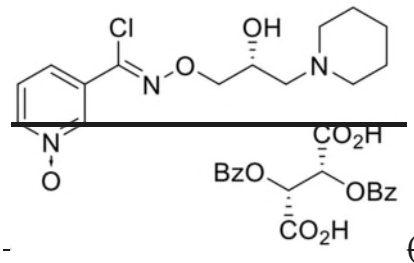
119. A process for preparing ORZY-05,



(ORZY-05);

wherein the process comprises the steps of:

a) adding a catalytic amount of citric acid to a solution of ORZY-03 in a container in a first step 3 solvent;



- (ORZY-03)

b) exchanging the solvent of the mixture of step a) from the first step 3 solvent to a second step 3 solvent; wherein the first step 3 solvent is different from the second step 3 solvent;

c) adding about a stoichiometric amount of citric acid to the mixture obtained in step b) to form a suspension;

d) filtering the suspension provided in step c) to obtain ORZY-04, which is a crude of ORZY-05; and

e) purifying the ORZY-04 of step d) to obtain ORZY-05.

120. The process according to claim 119, wherein the process further comprises the steps of:

f) mixing the compound ORZY-03 with an aqueous solution of a first step 3 base; and

g) extracting the mixture obtained in step a) with the first step 3 solvent to afford a solution of ORZY-03 in the first step 3 solvent;

before adding the catalytic amount of citric acid according to step a) of claim 119 to the solution of ORZY-03 in the first step 3 solvent.

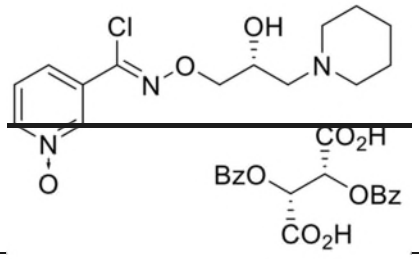
121. The process according to any one of claims 119 to 120, wherein the process further comprises washing the first step 3 solvent one or more times with water whereby one or more by-products from the first step 3 solvent are removed.

122. The process according to any one of claims 119 to 121, wherein the process further comprises washing the first step 3 solvent one or more times with water

subsequent to the addition of the first step 3 base, whereby one or more by-products from the first step 3 solvent are removed.

123. The process according to any one of claims 119 to 122, wherein the process comprises the steps of:

a) mixing the compound ORZY-03 with an aqueous solution of the first step 3 base;



(ORZY-03)

b) extracting the mixture obtained in step a) with the first step 3 solvent;

c) adding a catalytic amount of citric acid to the organic phase(s) of step b);

d) exchanging the solvent of the mixture of step c) from the first step 3 solvent to the second step 3 solvent;

e) adding about a stoichiometric amount of citric acid to the mixture obtained in step d) to form a suspension; and

f) filtering the suspension provided in step e) to obtain crude ORZY-05 (ORZY-04).

124. The process according to any one of claims 119 to 123, wherein the first step 3 solvent is a chlorinated hydrocarbon or a mixture containing a chlorinated hydrocarbon.

125. The process according to any one of claims 119 to 124, wherein the first step 3 solvent is dichloromethane or dichloroethane, preferably dichloromethane.

126. The process according to any one of claims 119 to 125, wherein the second step 3 solvent is a polar protic solvent or a mixture of polar protic solvents.

127. The process according to any one of claims 119 to 126, wherein the second step 3 solvent is selected from the group consisting of methanol, water, ethanol, 2-propanol, and any mixture thereof.

128. The process according to any one of claims 119 to 127, wherein the second step 3 solvent is methanol.

129. The process according to any one of claims 119 to 128, wherein the first step 3 base is a carbonate.

130. The process according to any one of claims 119 to 129, wherein the first step 3 base is a carbonate selected from the group consisting of: K_2CO_3 and Cs_2CO_3.

131. The process according to any one of claims 119 to 130, wherein the first step 3 base is K_2CO_3.

132. The process according to any one of claims 119 to 131, wherein the aqueous solution of K_2CO_3 comprises 16.8 % K_2CO_3.

133. The process according to any one of claims 119 to 132, wherein the mixture of ORZY-03 and K_2CO_3 is extracted three times with CH_2Cl_2.

134. The process according to any one of claims 119 to 133, wherein exchanging the solvent from CH_2Cl_2 to CH_3OH comprises the steps of:

a. partly distilling the CH_2Cl_2 solution;

b. adding CH_3OH to the distilled solution provided in step a);

c. partly distilling the solution provided in step b); and

d. adding CH_3OH to the solution provided in step c).

135. The process according to claim 134, wherein the amount distilled of in steps a) and c) at least corresponds to the amount of CH_2Cl_2 that ORZY-03 was dissolved in prior to the solvent exchange step.

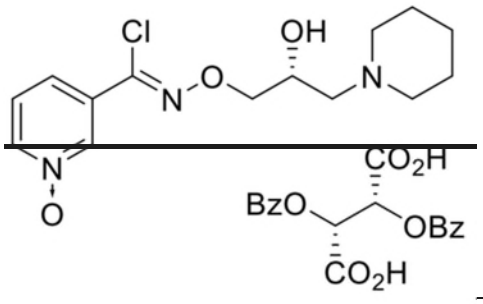
136. The process according to any one of claims 134 to 135, wherein the process further comprises the step of passing the solution obtained after exchanging the solvent from CH_2Cl_2 to CH_3OH through activated charcoal filter.

137. The process according to any one of claims 119 to 136, further comprising the step of drying ORZY-04.

138. The process according to claim 137, wherein the drying step includes drying the ORZY-04 at 45 °C in vacuum for at least 12 h.

139. The process according to claim 119, wherein the process comprises the consecutive steps of:

a) mixing the compound ORZY-03 with an 16.8% aqueous solution of K_2CO_3;



(ORZY-03)

b) extracting the mixture obtained in step a) with CH_2Cl_2 one or more times, such as three times; followed by one or more aqueous washes of the combined organic phases;

c) adding a catalytic amount of citric acid to the organic phase(s) of step b);

d) exchanging the solvent of the mixture of step c) from CH_2Cl_2 to CH_3OH by

e) partly distilling the CH_2Cl_2 solution of step c);

f) adding CH_3OH to the distilled solution provided in step i);

g) partly distilling the solution provided in step ii); and

h) adding CH_3OH to the solution provided in step iii)

i) passing the solution obtained in step d) through an activated charcoal filter;

j) adding about a stoichiometric amount of citric acid to the mixture obtained in step c) to form a suspension;

k) filtering the suspension provided in step c) to obtain ORZY-04;

l) drying ORZY-04 obtained in step g) at 45 °C in vacuum for at least 12 h, and

m) purifying the ORZY-04 of step h) to obtain ORZY-05.

140. The process according to any one of claims 119 to 139, wherein the step of purifying the ORZY-04 to obtain ORZY-05 comprises recrystallization of ORZY-04.

141. The process according to claim 140, wherein the solvent used in the recrystallization is acetone.

142. The process according to any one of claims 140 to 141, wherein the recrystallization comprises the steps of:

a. mixing ORZY-04 with H_2O and heating the mixture to 70 ± 5 °C until a clear solution is observed;

b. cooling the solution formed in step a) to 30 ± 5 °C;

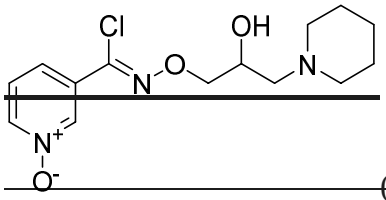
c. adding acetone to the solution of step b);

d. cooling the mixture of step c) to 0 ± 5 °C;

e. agitating the mixture of step d) for 12 h at 0 ± 10 °C to generate a suspension;

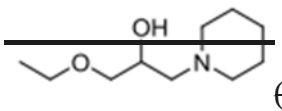
f. isolating ORZY-05 from the suspension of step e) by filtering said suspension; and drying the ORZY-05 obtained in step e) at 45 °C in vacuum for at least 12 h.

143. A composition comprising ORZY-01,

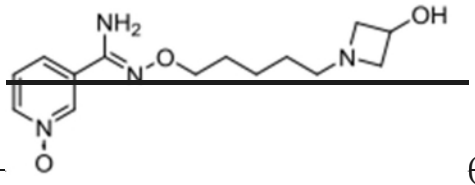


(ORZY-01), and

one or more impurities selected from the group consisting of:



(A), and



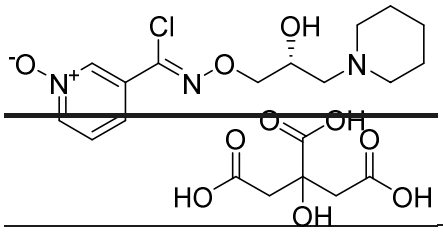
(B).

144. The composition according to claim 143, wherein (A) is present by weight in from 0.1% to 0.5% and/or (B) in from 0.1% to 0.5%.

145. The composition according to any one of claims 143 to 144, wherein (A) is present by weight in from 0.1% to 0.5%, such as from 0.1% to 0.2%, such as from 0.2% to 0.3%, such as from 0.3% to 0.4%, such as 0.4% to 0.5%.

146. The composition according to any one of claims 143 to 145, wherein (B) is present by weight in from 0.1% to 0.5%, such as from 0.1% to 0.2%, such as from 0.2% to 0.3%, such as from 0.3% to 0.4%, such as 0.4% to 0.5%.

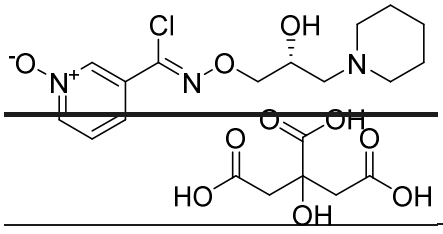
147. A process for preparing arimoclomol citrate (ORZY-05),



(arimoclomol citrate),

comprising one or more of the processes defined in any one of claims 72-142 to provide ORZY-01; ORZY-03; or OZY-04.

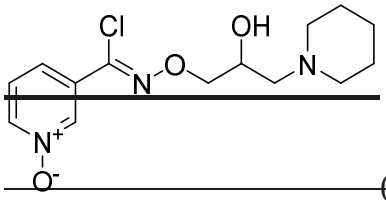
148. A process for preparing arimoclomol citrate (ORZY-05),



(arimoclomol citrate),

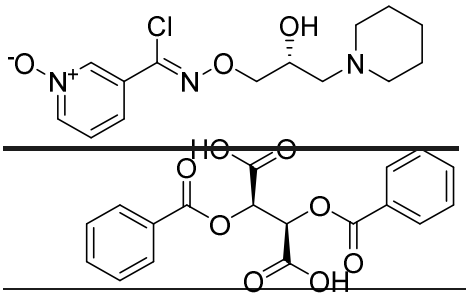
comprising the consecutive steps of:

a. the process as defined in any one of claims 72 to 94 to provide ORZY-01,



(ORZY-01),

b. precipitating ORZY-01 with dibenzoyl L-tartaric acid to provide ORZY-03,

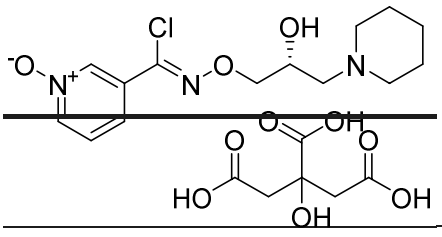


(ORZY-03), and

c. reacting ORZY-03 with a base and subsequently precipitating the resulting free base of ORZY-03 with citric acid to provide arimoclomol citrate,

thereby providing arimoclomol citrate.

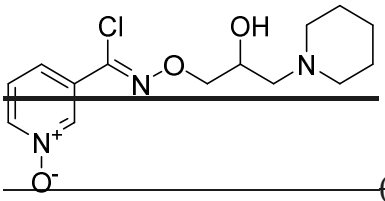
149. A process for preparing arimoclomol citrate,



(arimoclomol citrate),

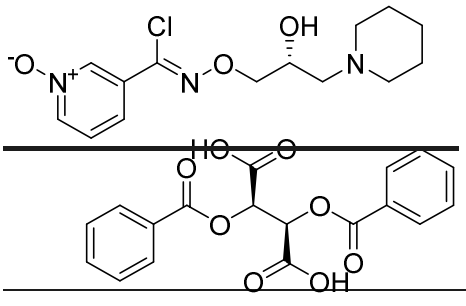
comprising the consecutive steps of:

a. providing ORZY-01,



(ORZY-01),

b. the process as defined in any one of claims 95 to 118 to provide ORZY-03,

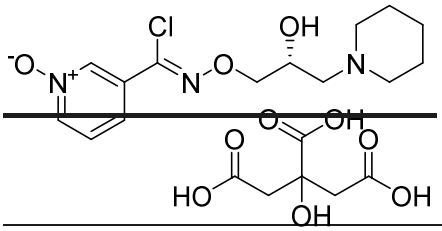


(ORZY-03), and

c. reacting ORZY-03 with a base and subsequently precipitating the resulting free base of ORZY-03 with citric acid to provide arimoclomol citrate,

thereby providing arimoclomol citrate.

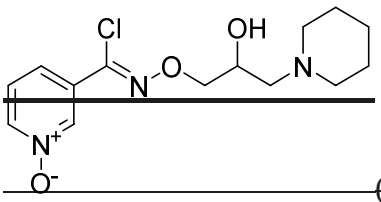
150. A process for preparing arimoclomol citrate,



(arimoclomol citrate),

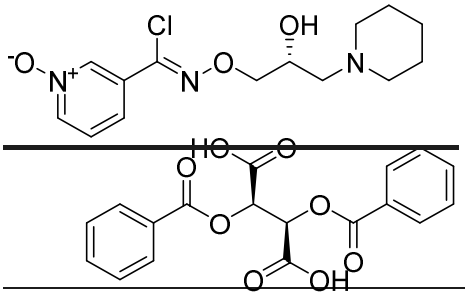
comprising the consecutive steps of:

a. providing ORZY-01,



(ORZY-01),

b. precipitating ORZY-01 with dibenzoyl L-tartaric acid to provide ORZY-03,



(ORZY-03), and

c. the process as defined in any one of claims 119 to 142 to provide ORZY-05; thereby providing arimoclomol citrate.

151. The process according to any one of claims 72-142, further comprising adding one or more seed crystals of ORZY-01 to the container.

152. The process according to any one claims 72-142, further comprising adding one or more seed crystals of ORZY-03 to the container.

153. The process according to any one of claims 72-142, further comprising adding one or more seed crystals of ORZY-05 to the container.

~~154. The process according to any one of claims 72-142, as the first step, adding one or more seed crystals of ORZY-01 to the container.~~

~~155. The process according to any one of claims 72-142, as the first step, adding one or more seed crystals of ORZY-03 to the container.~~

~~156. The process according to any one of claims 72-142, as the first step, adding one or more seed crystals of ORZY-05 to the container.~~

~~157. A pharmaceutical composition comprising ORZY-05 obtainable by the process as defined in any one of claims 119-142.~~