CLAIMS

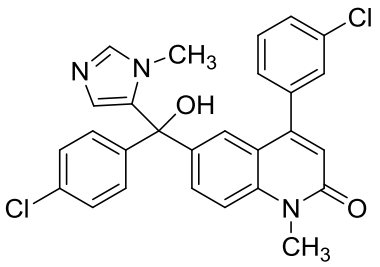
1. A method for preparing a desired enantiomer of tipifarnib comprising the steps of:

(i) obtaining a starting material comprising tipifarnib that is not enantiopure in the desired enantiomer;

(ii) transforming the starting material from step (i) to a racemic mixture of tipifarnib; wherein step (ii) comprises the steps of:

(ii)(a) reacting the starting material with sodium nitrite in a reaction solvent to give a product mixture;

(ii)(b) recovering a racemic alcohol of Formula (II) from the product mixture of step (ii)(a); and



Formula (II)

(ii)(c) transforming the racemic alcohol of step (ii)(b) to the racemic mixture of tipifarnib; and

(iii) recovering the desired enantiomer of tipifarnib from the racemic mixture of tipifarnib of step (ii).

2. The method of claim 1, wherein the desired enantiomer of tipifarnib is (R)-(+)-tipifarnib.

3. The method of claim 1, wherein the starting material of step (i) comprises a mother liquor from a crystallization process.

4. The method of claim 1, wherein the starting material of step (i) comprises an enantiomeric excess of an undesired enantiomer of tipifarnib.

5. The method of claim 4, wherein the undesired enantiomer of tipifarnib is (S)-(−)-tipifarnib.

6. The method of claim 1, wherein the starting material of step (i) comprises a salt of tipifarnib formed with an acid.

7. The method of claim 6, wherein the acid is an enantiopure chiral organic acid.

8. The method of claim 7, wherein the acid is a chiral resolving agent.

9. The method of claim 6, wherein the acid is (−)-dibenzoyl-L-tartaric acid.

10. The method of claim 1, wherein the reaction solvent of step (ii)(a) is an organic solvent, water, or a mixture thereof.

11. The method of claim 1, wherein reaction solvent of step (ii)(a) is a mixture of an organic solvent and water.

12. The method of claim 11, wherein the mixture has a volume ratio of organic solvent to water in a range from 20:1 to 3.5:1.

13. The method of claim 12, wherein the volume ratio of organic solvent to water is 4:1.

14. The method of any of claims 10-13, wherein the organic solvent is miscible with water.

15. The method of any of claims 10-13, wherein the organic solvent is acetone, acetonitrile, methanol, tert-amyl alcohol, or a mixture thereof.

16. The method of any of claims 10-13, wherein the organic solvent is acetone.

17. The method of any of claims 10-13, wherein the organic solvent is acetonitrile.

18. The method of claim 1, wherein step (ii)(a) takes place at a temperature ranging from about 20 °C to about 75 °C.

19. The method of claim 1, wherein step (ii)(a) takes place at a temperature of about 20 °C.

20. The method of claim 1, wherein step (ii)(a) takes place in the presence of an additive.

21. The method of claim 20, wherein the additive is an acid.

22. The method of claim 21, wherein the acid is sulfuric acid.

23. The method of claim 21, wherein the acid is hydrochloric acid.

24. The method of claim 1, wherein step (ii)(b) comprises:

adjusting the product mixture's pH with a base;

extracting the product mixture with an extraction solvent; and

crystallizing the racemic alcohol.

25. The method of claim 24, wherein the product mixture's pH is adjusted to a range from about 5 to about 10.

26. The method of claim 24, wherein the product mixture's pH is adjusted to about 10.

27. The method of claim 24, wherein the base is sodium hydroxide or ammonium hydroxide.

28. The method of claim 24, wherein the base is sodium hydroxide.

29. The method of claim 24, wherein the extraction solvent is isopropyl acetate or 2-methyltetrahydrofuran.

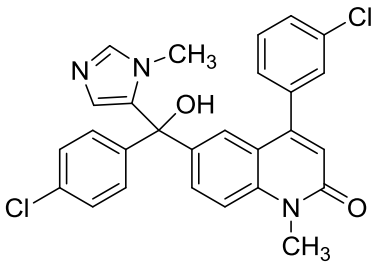
30. The method of claim 24, wherein the extraction solvent is isopropyl acetate.

31. The method of claim 24, wherein the racemic alcohol is crystallized as a hydrochloride salt.

32. The method of claim 1, wherein step (ii) comprises the steps of:

(ii)(a) heating the starting material in a reaction solvent to give a product mixture;

(ii)(b) recovering a racemic alcohol of Formula (II) from the product mixture of step (ii)(a); and



Formula (II)

(ii)(c) transforming the racemic alcohol of step (ii)(b) to the racemic mixture of tipifarnib.

33. The method of claim 32, wherein the reaction solvent of step (ii)(a) is an organic solvent, water, or a mixture thereof.

34. The method of claim 33, wherein reaction solvent of step (ii)(a) is a mixture of an organic solvent and water.

35. The method of claim 34, wherein the mixture has a volume ratio of organic solvent to water in a range from 6:1 to 2:1.

36. The method of claim 35, wherein the volume ratio of organic solvent to water is 2:1.

37. The method of any of claims 33-36, wherein the organic solvent is miscible with water.

38. The method of any of claims 33-36, wherein the organic solvent is acetonitrile, methylethylketone, acetone, DMF, or a mixture thereof.

39. The method of any of claims 33-36, wherein the organic solvent is methylethylketone.

40. The method of any of claims 33-36, wherein the organic solvent is acetonitrile.

41. The method of claim 32, wherein step (ii)(a) takes place at a temperature ranging from about 60 °C to about 80 °C.

42. The method of claim 41, wherein step (ii)(a) takes place at a temperature of about 80 °C.

43. The method of claim 41, wherein step (ii)(a) takes place at a temperature of about 76 °C.

44. The method of claim 32, wherein step (ii)(a) takes place in the presence of an additive.

45. The method of claim 44, wherein the additive is an acid.

46. The method of claim 45, wherein the acid is sulfuric acid.

47. The method of claim 32, wherein step (ii)(b) comprises:

adjusting the product mixture's pH with a base;

extracting the product mixture with an extraction solvent; and

crystallizing the racemic alcohol.

48. The method of claim 47, wherein the product mixture's pH is adjusted to about 8.

49. The method of claim 47, wherein the base is sodium hydroxide.

50. The method of claim 47, wherein the extraction solvent is isopropyl acetate.

51. The method of claim 47, wherein the racemic alcohol is crystallized as a hydrochloride salt.

52. The method of claim 1, wherein step (iii) comprises:

(iii)(a) crystallizing the desired enantiomer of tipifarnib from the racemic mixture of tipifarnib in the presence of a chiral resolving agent; and

(iii)(b) separating crystals of the desired enantiomer of tipifarnib from a mother liquor.

53. The method of claim 52, wherein the chiral resolving agent of step (iii)(a) is (−)-dibenzoyl-L-tartaric acid.

54. The method of claim 52, wherein the mother liquor of step (iii)(a) comprises an enantiomeric excess of an undesired enantiomer of tipifarnib.

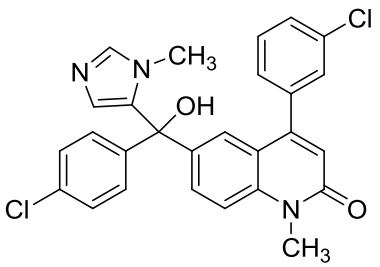
55. The method of claim 52, wherein the steps (i) to (iii) may be run in multiple cycles.

56. A method for preparing a desired enantiomer of tipifarnib comprising the steps of:

(i) obtaining a starting material comprising tipifarnib that is not enantiopure in the desired enantiomer;

(ii)(a) reacting the starting material with sodium nitrite to give a product mixture;

(ii)(b) recovering a racemic alcohol of Formula (II) from the product mixture of step (ii)(a);



Formula (II)

(ii)(c) transforming the racemic alcohol of step (ii)(b) to a racemic mixture of tipifarnib;

(iii)(a) crystallizing the desired enantiomer of tipifarnib from the racemic mixture of tipifarnib of step (ii)(c) in the presence of a chiral resolving agent;

(iii)(b) separating crystals of the desired enantiomer of tipifarnib from the mother liquor of step (iii)(a); and

(iv) recycling the mother liquor of step (iii)(b) to be used as the starting material in step (i).

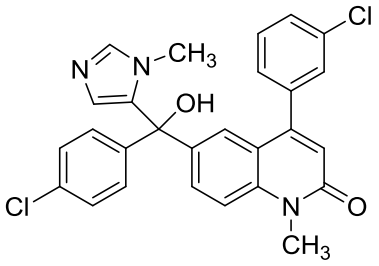
57. A method for preparing a desired enantiomer of tipifarnib comprising the steps of:

(i) preparing a racemic mixture of tipifarnib;

(ii) crystallizing the desired enantiomer of tipifarnib from the racemic mixture of tipifarnib of step (i) in the presence of a chiral resolving agent;

(iii) separating crystals of the desired enantiomer of tipifarnib from a mother liquor;

(iv) transforming any remaining tipifarnib in the mother liquor from step (iii) to a racemic alcohol of Formula (II);



Formula (II)

(v) transforming the racemic alcohol of step (iv) to a racemic mixture of tipifarnib; and

(vi) recycling the racemic mixture of tipifarnib of step (v) back to step (i).

58. A method for transforming an enantiomerically enriched amine of Formula (IV) comprising:

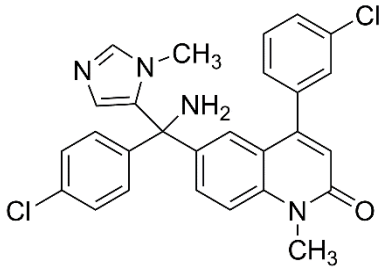
(i) reacting the enantiomerically enriched amine of Formula (IV) or its salt with sodium nitrite in a 4:1 mixture of acetone and water at 20 °C to afford a product mixture;

(ii) adjusting the product mixture's pH to about 10 with sodium hydroxide;

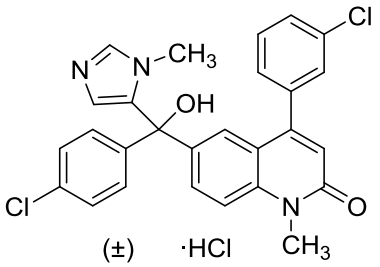
(iii) extracting the product mixture with isopropyl acetate;

(iv) adding 1.5 equivalents of concentrated hydrochloric acid; and

(v) recovering a racemic alcohol of Formula (IIa) by crystallization.



Formula (IV)



Formula (IIa)

59. A method for transforming an enantiomerically enriched amine of Formula (IV) comprising:

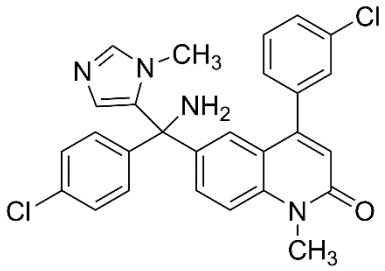
(i) heating the enantiomerically enriched amine of Formula (IV) or its salt in a 2:1 mixture of methylethylketone and water at 76 °C to afford a product mixture;

(ii) adjusting the product mixture's pH to about 8 with sodium hydroxide;

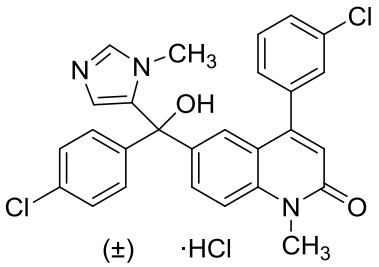
(iii) extracting the product mixture with isopropyl acetate;

(iv) adding concentrated hydrochloric acid; and

(v) recovering a racemic alcohol of Formula (IIa) by crystallization.



Formula (IV)



Formula (IIa)