weighted syringe fitted with a 23G needle as applied to the shaved back of a guinea pig (*Cavia porcellus*) is assessed following subcutaneous administration of sufficient (50 µl, 10 mg/ml) solution in saline to raise a visible bleb on the skin. Each test is performed on the central area of the bleb and also on its periphery to check for diffusion of the test solution from the point of administration. If the test animal produces a flinch in response to the stimulus, this demonstrates the absence of blockade of pain sensation. Testing may be carried out at intervals for up to 8 hours or more post- administration. The sites of bleb formation are examined after 24 hours to check for skin abnormalities consequent to local administration of test substances or of the vehicle used for preparation of the test solutions.

The following examples are offered by way of illustration and not by way of limitation. In the Examples, and unless otherwise specified, starting materials were obtained from well-known commercial supply houses, *e.g.*, Aldrich Chemical Company (Milwaukee, WI), and were of standard grade and purity. "Ether" and "ethyl ether" each refers to diethyl ether; "h." refers to hours; "min." refers to minutes; "GC" refers to gas chromatography; "v/v" refers to volume per volume; and ratios are weight ratios unless otherwise indicated.

EXAMPLE 1

(1R,2R)-2-[(3R)-HYDROXYPYRROLIDINYL]-1-(3,4-DIMETHOXYPHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND 1).

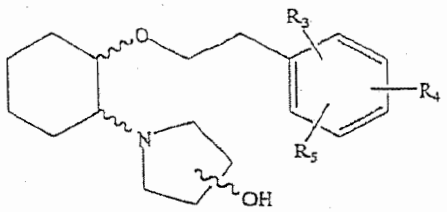
The reaction scheme for the preparation of compound 1 described herein is illustrated in Figure 1.

PREPARATION OF INTERMEDIATES

N-tert-Butoxycarbonyl-3*R*-pyrrolidinol (1R)

The present invention also provides any one of the embodiments disclosed below and indicated with the numbers 1 to 100.

1. A compound of formula (IA), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(IA)

wherein, R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

2. A compound of formula (IA) according to claim 1, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

3. A compound of formula (IA) according to claim 1, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

4. A compound of formula (IA) according to claim 1, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy.

5. A compound of formula (IA) according to claim 1, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

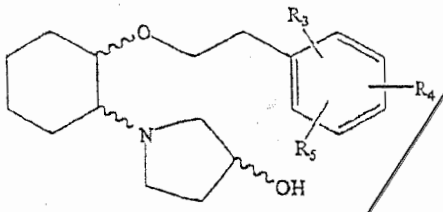
6. A compound of formula (IA) according to claim 1, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

7. A compound of formula (IA) according to claim 1, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or

amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

8. A compound of formula (IA) according to claim 1, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

9. A compound of formula (IB), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(IB)

wherein, R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

10. A compound of formula (IB) according to claim 9, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

11. A compound of formula (IB) according to claim 9, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

12. A compound of formula (IB) according to claim 9, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy.

13. A compound of formula (IB) according to claim 9, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric,

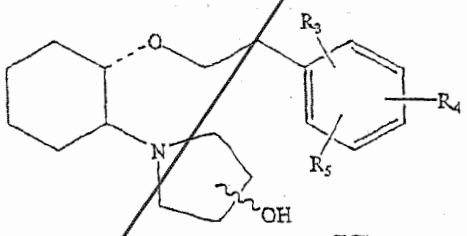
diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

14. A compound of formula (IB) according to claim 9, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

15. A compound of formula (IB) according to claim 9, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

16. A compound of formula (IB) according to claim 9, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1 alkoxy.

17. A compound of formula (IC), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(IC)

wherein, R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

18. A compound of formula (IC) according to claim 17, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

19. A compound of formula (IC) according to claim 17, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

20. A compound of formula (IC) according to claim 17, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy.

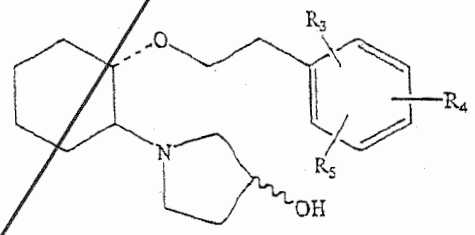
21. A compound of formula (IC) according to claim 17, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

22. A compound of formula (IC) according to claim 17, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

23. A compound of formula (IC) according to claim 17, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

24. A compound of formula (IC) according to claim 17, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1 alkoxy.

25. A compound of formula (ID), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(ID)

wherein, R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

26. A compound of formula (ID) according to claim 25, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

27. A compound of formula (ID) according to claim 25, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

28. A compound of formula (ID) according to claim 25, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy.

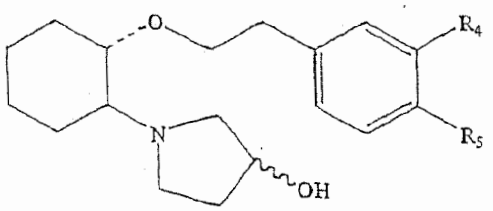
29. A compound of formula (ID) according to claim 25, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

30. A compound of formula (ID) according to claim 25, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

31. A compound of formula (ID) according to claim 25, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

32. A compound of formula (ID) according to claim 25, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

33. A compound of formula (IE), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(IE)

wherein, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_4 and R_5 cannot all be hydrogen.

34. A compound of formula (IE) according to claim 33, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

35. A compound of formula (IE) according to claim 33, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

36. A compound of formula (IE) according to claim 33, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_3alkoxy.

37. A compound of formula (IE) according to claim 33, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

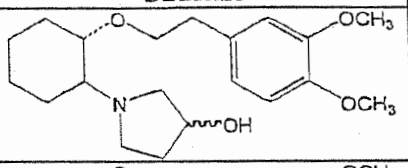
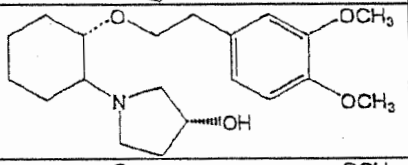
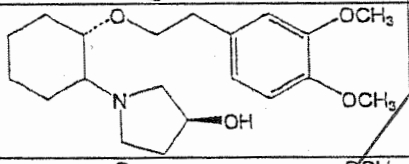
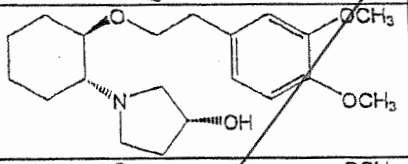
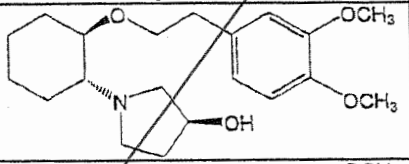
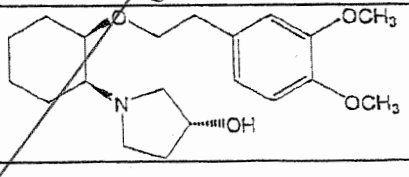
38. A compound of formula (IE) according to claim 33, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are independently selected from C_1-C_3alkoxy.

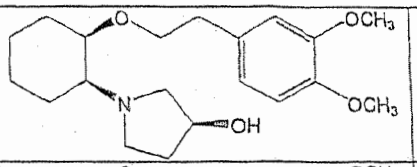
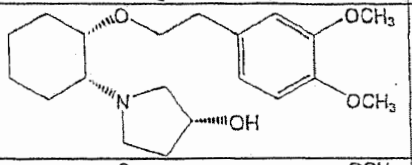
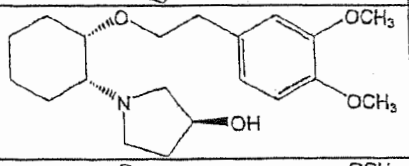
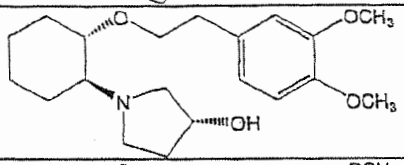
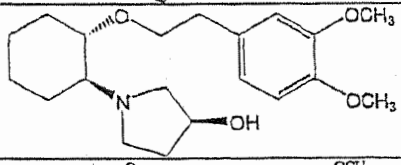
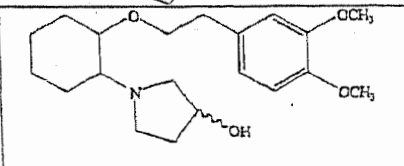
39. A compound of formula (IE) according to claim 33, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or

amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are C_1alkoxy.

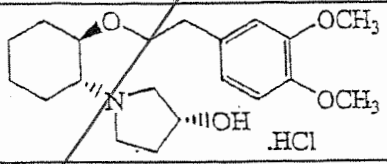
40. A compound of formula (IE) according to claim 33, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are C_1alkoxy.

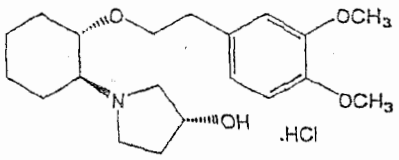
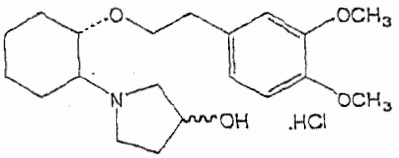
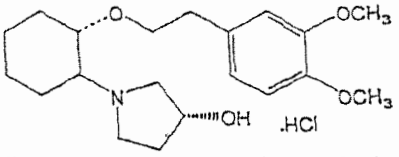
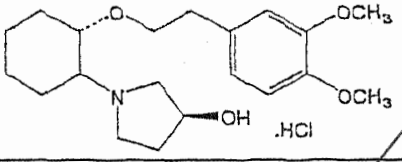
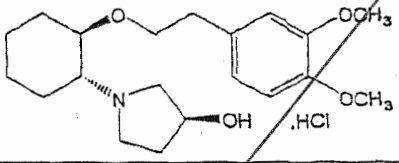
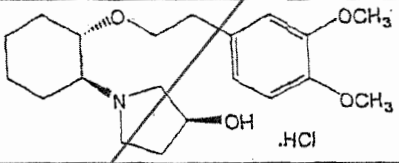
41. A compound, or mixture comprising compounds, or a solvate, or pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, selected from the group consisting of:

	Structure	Chemical name
		(1R,2R)/(1S,2S)-2-[(3R)/(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1R,2R)/(1S,2S)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1R,2R)/(1S,2S)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1R,2R)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1R,2R)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1R,2S)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane

		(1R,2S)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1S,2R)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1S,2R)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1S,2S)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1S,2S)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane
		(1R,2S)/(1S,2R)-2-[(3R)/(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane

42. A compound, or mixture comprising compounds, or a solvate thereof, selected from the group consisting of:

	Structure	**Chemical name**
		(1R,2R)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride

		(1S,2S)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride
		(1R,2R)/(1S,2S)-2-[(3R)/(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride
		(1R,2R)/(1S,2S)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride
		(1R,2R)/(1S,2S)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride
		(1R,2R)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride
		(1S,2S)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride

43. A compound which is (1R,2R)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

44. A compound which is (1R,2R)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

45. A compound which is (1S,2S)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

46. A compound which is (1S,2S)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane, or a pharmaceutically acceptable salt thereof, or a solvate thereof.

47. A compound which is (1R,2R)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride, or a solvate thereof.

48. A compound which is (1R,2R)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride, or a solvate thereof.

49. A compound which is (1S,2S)-2-[(3R)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride, or a solvate thereof.

50. A compound which is (1S,2S)-2-[(3S)-Hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy)-cyclohexane monohydrochloride, or a solvate thereof.

51. A composition comprising a compound according to any one of claims 1 to 50 in combination with a pharmaceutically acceptable carrier, excipient or diluent.

52. Use of a compound according to any one of claims 1 to 50 or a composition of claim 51 in the manufacture of a medicament.

53. A method for modulating ion channel activity in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

54. A method for modulating ion channel activity in an *in vitro* setting comprising administering *in vitro* an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

55. A method for blocking/inhibiting the activity/conductance of an ion channel in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

56. A method for blocking/inhibiting the activity/conductance of an ion channel in an *in vitro* setting

comprising administering *in vitro* an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

57. The method of claims 53, 54, 55 or 56, wherein said ion channel is a potassium channel.

58. The method of claim 57, wherein said potassium channel is a voltage-activated potassium channel.

59. A method for modulating cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

60. A method for blocking/inhibiting cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

61. A method for blocking/inhibiting the cardiac ion channels responsible for the cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

62. A method for blocking/inhibiting cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal under conditions where an arrhythmogenic substrate is present in the heart of said warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

63. A method for blocking/inhibiting the cardiac ion channels responsible for the cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal under conditions where an arrhythmogenic substrate is present in the heart of said warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

64. The method of claims 59 to 63, wherein said cardiac early repolarising currents comprise ionic currents which activate rapidly after depolarisation of membrane voltage and which effect repolarisation of the cell.

65. The method of claims 59 to 64, wherein said early repolarising currents comprise the cardiac

transient outward potassium current (I_{to}) and/or the ultrarapid delayed rectifier current (I_{Kur}).

66. The method of claim 65, wherein the cardiac transient outward potassium current (I_{to}) and/or the ultrarapid delayed rectifier current (I_{Kur}) comprise at least one of the Kv4.2, Kv4.3, Kv2.1, Kv1.4 and Kv1.5 currents.

67. A method for treating and/or preventing arrhythmia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

68. A pharmaceutical composition comprising an amount of a compound according to claims 1 to 50 effective to treat and/or prevent atrial arrhythmia in a warm-blooded animal in need of the treatment and/or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

69. A method for treating and/or preventing atrial arrhythmia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

70. A method for treating and/or preventing ventricular arrhythmia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

71. A pharmaceutical composition comprising an amount of a compound according to claims 1 to 50 effective to treat and/or prevent ventricular arrhythmia in a warm-blooded animal in need of the treatment and/or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

72. A method for treating and/or preventing atrial fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

73. A method for treating and/or preventing atrial flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

74. A method for treating and/or preventing ventricular fibrillation in a warm-blooded animal

comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

75. A method for treating and/or preventing ventricular flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

76. A method for treating atrial fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

77. A method for treating atrial flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

78. A method for treating ventricular fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

79. A method for treating ventricular flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

80. A method for preventing atrial fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

81. A method for preventing atrial flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

82. A method for preventing ventricular fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

83. A method for preventing ventricular flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 50, or a composition of claim 51, or a medicament manufactured according to claim 52.

84. A method for treating and/or preventing arrhythmia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof, an effective amount of a compound according to any one of claims 41 to 50.

85. A pharmaceutical composition comprising an amount of a compound according to claims 41 to 50 effective to treat and/or prevent atrial arrhythmia in a warm-blooded animal in need of the treatment and/or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

86. A method for treating and/or preventing atrial arrhythmia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

87. A method for treating and/or preventing ventricular arrhythmia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

88. A pharmaceutical composition comprising an amount of a compound according to claims 41 to 50 effective to treat and/or prevent ventricular arrhythmia in a warm-blooded animal in need of the treatment and/or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

89. A method for treating and/or preventing atrial fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

90. A method for treating and/or preventing atrial flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

91. A method for treating and/or preventing ventricular fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

92. A method for treating and/or preventing ventricular flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

93. A method for treating atrial fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

94. A method for treating atrial flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

95. A method for treating ventricular fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

96. A method for treating ventricular flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

97. A method for preventing atrial fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

98. A method for preventing atrial flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

99. A method for preventing ventricular fibrillation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

100. A method for preventing ventricular flutter in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 41 to 50.

The following examples are offered by way of illustration and not by way of limitation. In the Examples, and unless otherwise specified, starting materials were obtained from well-known commercial supply houses, *e.g.*, Aldrich Chemical Company (Milwaukee, WI), and were of standard grade and purity. "Ether" and "ethyl ether" each refers to diethyl ether; "h." refers to hours; "min." refers to minutes; "GC" refers to gas chromatography; "v/v" refers to volume per volume; and ratios are weight ratios unless otherwise indicated.

EXAMPLE 1

(1R,2R)-2-[(3R)-HYDROXYPYRROLIDINYL]-1-(3,4-DIMETHOXYPHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE (COMPOUND 1).

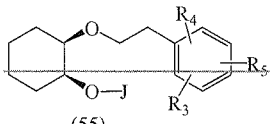
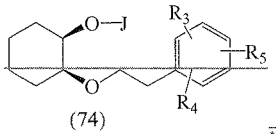
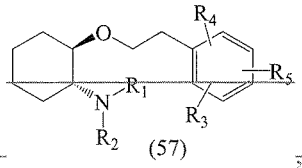
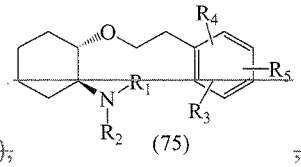
The reaction scheme for the preparation of compound 1 described herein is illustrated in Figure 1.

PREPARATION OF INTERMEDIATES

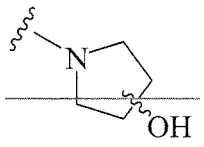
N-tert-Butoxycarbonyl-3*R*-pyrrolidinol (1R)

Claims

1. A method of stereoselectively making an aminocyclohexyl ether comprising:

reacting a compound of formula (55),  (55) , or a compound of formula (74),  (74) , with a compound of formula (56),  (56) , to form a compound of formula (57),  (57) , or a compound of formula (75),  (75) , respectively,

wherein R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (57) or (75), form a ring denoted by formula (II):



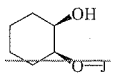
(II)

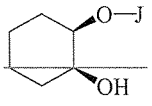
; and

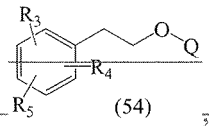
wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen; and

wherein O-J is a leaving group.

2. The method according to claim 1, wherein before said reacting step, the method further comprises:

alkylating a compound of formula (53),  (53) , or a compound of formula



(84), (84) , with a compound of formula (54),  (54) , to form the compound of formula (55) or the compound of formula (74), respectively;

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group; and

wherein O-Q is a leaving group that reacts with -OH in formula (53) or (84) to form the compound of formula (55) or the compound of formula (74), such that the stereochemical configuration of the compound of formula (53) or the compound of formula (84) is retained in the compound of formula (55) or the compound of formula (74), respectively; and

optionally protecting the compound of formula (53) or the compound of formula (84) before said alkylating step.

3. The method according to claim 2, wherein at least one of R_3, R_4 and R_5 is C_1-C_6alkoxy.

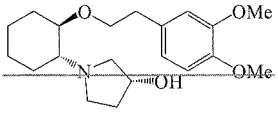
4. The method according to claim 3:



(65)

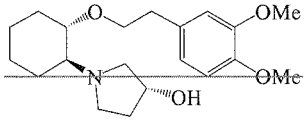
; and

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group; and



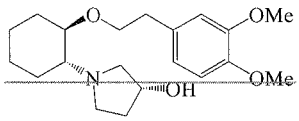
(66)

or



(79)

is formed.



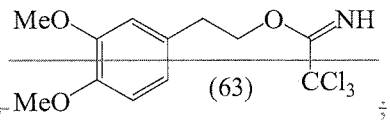
(66)

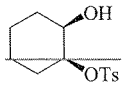
5. The method according to claim 4 wherein is formed.

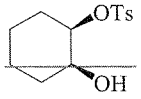
6. The method according to claim 2, wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group; and wherein at least one of R_3, R_4 and R_5 is C_1-C_6alkoxy; and

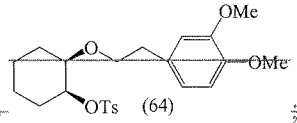
~~wherein O-Q is trichloroacetimidate.~~

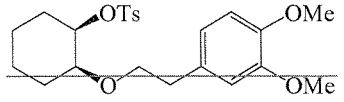
~~7. The method according to claim 6 wherein:~~

~~the compound of formula (54) is~~  (63) ~~;~~

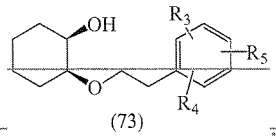
~~the compound of formula (53) is~~  (62) ~~;~~

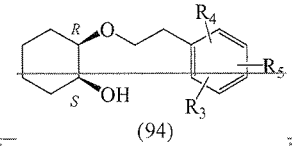
~~the compound of formula (84) is~~  (87) ~~;~~

~~the compound of formula (55) is~~  (64) ~~; and~~

~~the compound of formula (74) is~~  (78) ~~.~~

~~8. The method according to claim 1, wherein before said reacting step, the method further comprises:~~

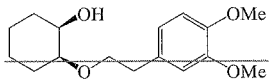
~~activating a compound of formula (73),~~  (73) ~~, or a compound of formula~~

~~(94),~~  (94) ~~, with a hydroxy activating reagent to form the compound of formula (74) or the compound of formula (55), respectively.~~

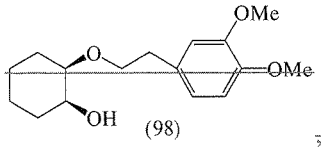
~~9. The method according to claim 8, wherein:~~

~~at least one of R_3, R_4 and R_5 is C_1-C_6alkoxy; and the hydroxy activating reagent is tosyl chloride.~~

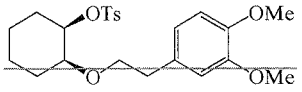
10. The method according to claim 9 wherein:



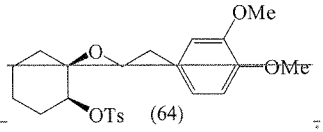
the compound of formula (73) or the compound of formula (94) is (77) or



(98) , respectively;

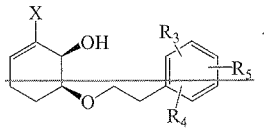


the compound of formula (74) is (78) ; and



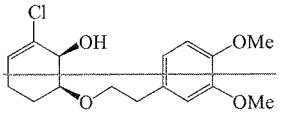
the compound of formula (55) is (64) .

11. The method according to claim 8, wherein before said activating step, the method further comprises;



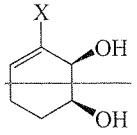
hydrogenating and hydrogenolyzing a compound of formula (72), (72) ; wherein X is a halide, to form the compound of formula (73).

12. The method according to claim 11, wherein the compound of formula (72) is

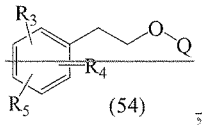


(76) .

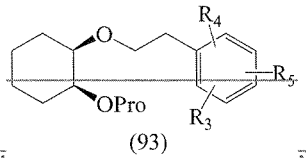
13. The method according to claim 11, further comprising before said hydrogenating and hydrogenolyzing step,



alkylating a compound of formula (51), (51) , with a compound of formula (54);

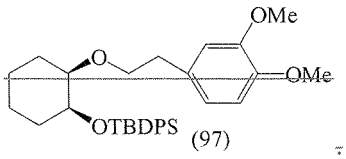

(54) , to form the compound of formula (72).

14. The method according to claim 8, wherein before said activating step, the method further comprises:

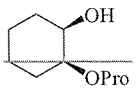

(93)

deprotecting a compound of formula (93), , wherein Pro is a protecting group, to form the compound of formula (94).

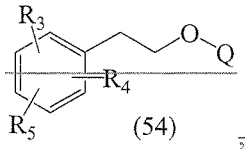
15. The method according to claim 14 wherein the compound of formula (93) is


(97) .

16. The method according to claim 14 wherein before said deprotecting step, the method further comprises:

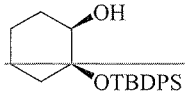

(92)

alkylating a compound of formula (92), , with a compound of formula (54),

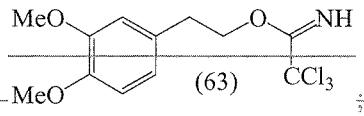

(54)

, to form the compound of formula (93).

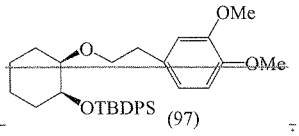
17. The method according to claim 16 wherein:

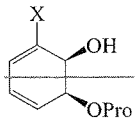

(96)

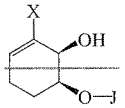
the compound of formula (92) is ;

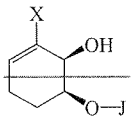
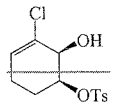

(63)

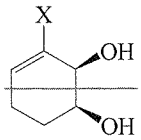
the compound of formula (54) is ; and

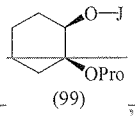
the compound of formula (93) is  (97) .

18. The method according to claim 16, further comprising before said alkylating step,  (91) , to form the compound of formula (92).

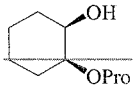
19. The method according to claim 2, further comprising before the alkylating step:  (52) , wherein X is a halide, to form the compound of formula (53).

20. The method according to claim 19, wherein  (52) is  (61) .

21. The method according to claim19, further comprising before said hydrogenating and hydrogenolyzing step:  (51) , with a hydroxy activating reagent to form the compound of formula (52).

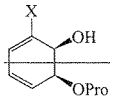
22. The method according to claim 2, further comprising before said alkylating step:  (99) , wherein Pro is a protecting group, to form the compound of formula (84).

23. The method according to claim 22, further comprising before said deprotecting step:



activating a compound of formula (92), (92) , wherein Pro is a protecting group, with a hydroxy activating reagent to form the compound of formula (99).

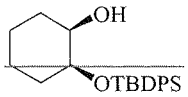
24. The method according to claim 23, further comprising before said activating step,



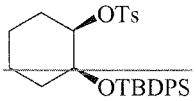
hydrogenating and hydrogenolyzing a compound of formula (91), (91) , to form the compound of formula (92).

25. The method according to claim 23 wherein:

the hydroxy activating reagent is tosyl halide;

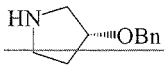


the compound of formula (92) is (96) ; and

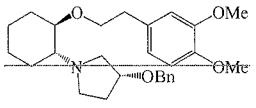


the compound of formula (99) is (100) .

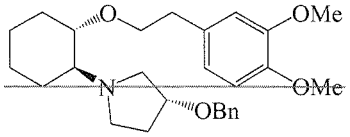
26. The method according to claim 1, wherein:



the compound of formula (56) is (65A) ; and

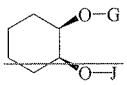
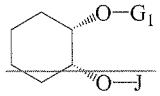
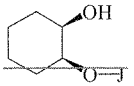
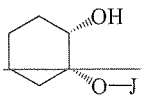


wherein (67) or



(80) is formed.

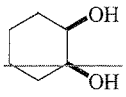
27. The method according to claim 2, further comprising before said alkylating step:

removing a functional group G or G_1 from a compound of formula (85),  (85) , or a compound of formula (86),  (86) , respectively, to form  (53) or  (84) , respectively.

28. The method according to claim 2, further comprising, before said alkylating step:
separating a racemic mixture of the compound of formula (53) and the compound of formula (84).

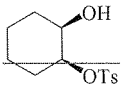
29. The method according to claim 28, wherein said separation step further comprises:
functionalizing one or both of the compound of formula (53) and the compound of formula (84) such that the compounds are capable of resolution;
performing resolution to separate the compounds; and
optionally removing the functional group on said one or both functionalized compounds.

30. The method according to claim 28, wherein before said separating step the method further comprises:

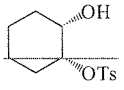


activating a compound of formula (83), (83) , with a hydroxy activating reagent to form the racemic mixture of the compound of formula (53) and the compound of formula (84).

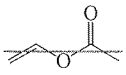
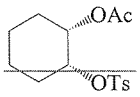
31. The method according to claim 29:

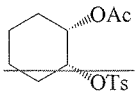


wherein the compound of formula (53) is (62) ;

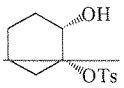


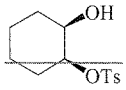
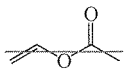
wherein the compound of formula (84) is (87) and is enzymatically functionalized with

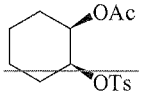

(88) to form 
(89) ; and

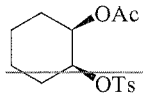
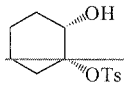

performing resolution to separate the compound of formula (62) from (89) .

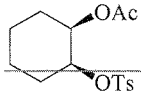
32. The method according to claim 29:


wherein the compound of formula (84) is (87) ; and

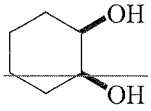

wherein the compound of formula (53) is (62) and is functionalized with 
(88) to


form (90) ; and further comprising:

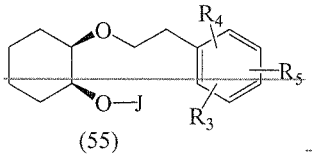

performing resolution to separate (90) from 
(87) ; and


removing the functional group from (90) to form (62) .

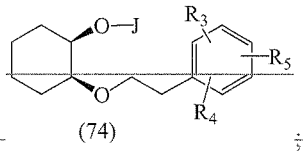
33. The method according to claim 28 further comprising before said separating step: activating


(83) with a hydroxy activating reagent to form a racemic mixture.

34. A method of making a compound of formula (55) or formula (74):

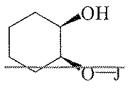

(55)

~~or~~

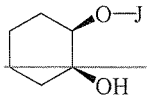

(74)

~~;~~

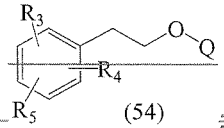
~~wherein the method comprises:~~



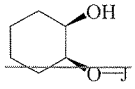
~~alkylating a compound of formula (53),~~ (53) ~~, or a compound of formula (84),~~


(84)

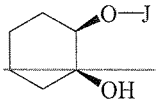
~~, with a compound of formula (54),~~


(54)

~~; to form the compound of formula (55) or the compound of formula (74); respectively; and~~



~~optionally protecting a compound of formula (53),~~ (53) ~~, or a compound of formula~~


(84)

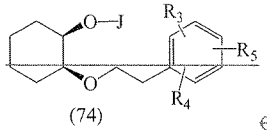
~~(84),~~ ~~, before said alkylating step;~~

~~wherein O-Q is a leaving group that reacts with -OH in formula (53) or (84) to form the compound of formula (55) or the compound of formula (74), such that the stereochemical configuration of the compound of formula (53) or the compound of formula (84) is retained in the compound of formula (55) or the compound of formula (74), respectively;~~

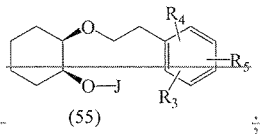
~~wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen; and~~

~~wherein O-J is a leaving group.~~

~~35. A method of making a compound of formula (74) or formula (55):~~

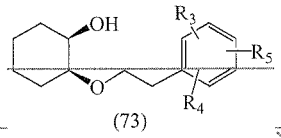
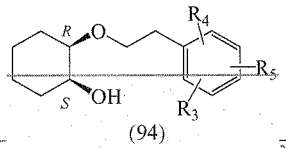

(74)

~~or~~


(55)

~~;~~

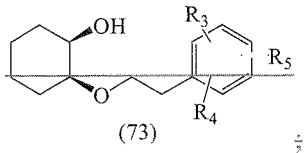
~~wherein the method comprises:~~

activating a compound of formula (73),  (73) , or a compound of formula (94),  (94) , with a hydroxy activating reagent to form the compound of formula (74) or the compound of formula (55), respectively;

wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen; and

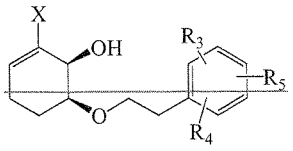
wherein O-J is a leaving group.

36. A method of making a compound of formula (73):


(73)

;

wherein the method comprises:

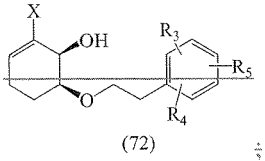

(72)

hydrogenating and hydrogenolyzing a compound of formula (72), ; to form the compound of formula (73);

wherein X is a halide; and

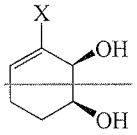
wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

37. A method of making a compound of formula (72):

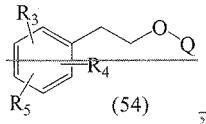

(72)

;

wherein the method comprises:

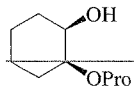


(51)



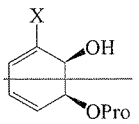
(54)

~~39. A method of making a compound of formula (92):~~



~~(92) ;~~

~~wherein the method comprises:~~

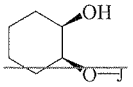


~~hydrogenating and hydrogenolyzing a compound of formula (91),~~ (91) ~~, to form the compound of formula (92);~~

~~wherein Pro is a protecting group; and~~

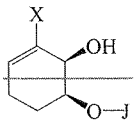
~~wherein X is a halide.~~

~~40. A method of making a compound of formula (53):~~



~~(53) ;~~

~~wherein the method comprises:~~

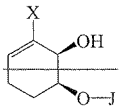


~~hydrogenating and hydrogenolyzing a compound of formula (52),~~ (52) ~~, to form the compound of formula (53);~~

~~wherein X is a halide; and~~

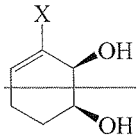
~~wherein O-J is a leaving group.~~

~~41. A method of making a compound of formula (52):~~



~~(52) ;~~

~~wherein the method comprises:~~

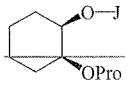


activating a compound of formula (51), (51) , with a hydroxy activating reagent to form the compound of formula (52);

wherein X is a halide; and

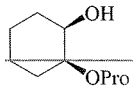
wherein O-J is a leaving group.

42. A method of making a compound of formula (99):



(99) ;

wherein the method comprises:

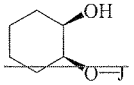


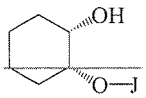
activating a compound of formula (92), (92) , with a hydroxy activating reagent to form the compound of formula (99);

wherein Pro is a protecting group; and

wherein O-J is a leaving group.

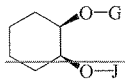
43. A method of making a compound of formula (53) or a compound of formula (84):



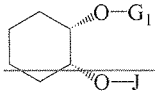
(53) or 

(84) ;

wherein the method comprises:

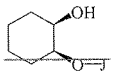


removing a functional group G or G_1 from a compound of formula (85), (85) , or a

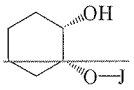


compound of formula (86), (86) , respectively, to form the compound of formula (53) or the compound of formula (84), respectively;

wherein O-J is a leaving group.



44. A method comprising separating a racemic mixture of a compound of formula (53), (53)



and a compound of formula (84), (84) .

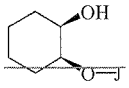
45. The method according to claim 44 wherein said separation step further comprises:

functionalizing one or both of the compound of formula (52) and the compound of formula (84) such that the compounds are capable of resolution;

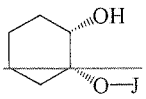
performing resolution to separate the compounds; and

optionally removing the functional group on said one or both functionalized compounds.

46. A method of forming a racemic mixture of a compound of formula (53) and a compound of formula (84):

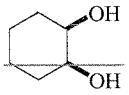


(53) and



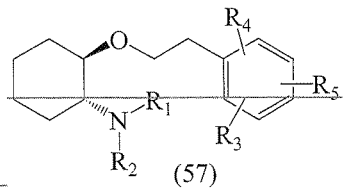
(84)

wherein the method comprises:



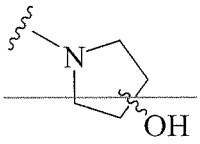
activating a compound of formula (83), (83) , with a hydroxy activating reagent to form the racemic mixture of the compound of formula (53) and the compound of formula (84); wherein O-J is a leaving group.

47. A method for stereoselectively making an aminocyclohexyl ether of formula (57):



(57)

wherein R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (57), form a ring denoted by formula (II):

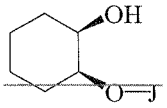


(II)

; and

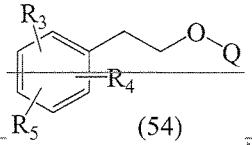
wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen;

wherein the method comprises:



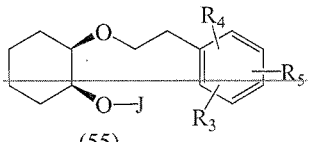
(53)

(a) reacting a compound of formula (53), , wherein O-J is a leaving group,



(54)

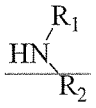
with a compound of formula (54), , wherein R_3, R_4 and R_5 are as defined above and O-Q is a leaving group that reacts with the hydroxy group (-OH) in formula (53) to form a compound of formula (55),



(55)

, such that the stereochemical configuration of the compound of formula (53) is retained in the compound of formula (55);

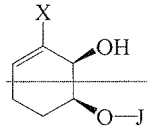
(b) optionally protecting the compound of formula (53) before the first reaction; and



(56)

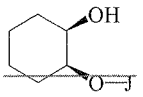
(c) reacting the compound of formula (55) with a compound of formula (56), , wherein R_1 and R_2 are as defined above, to form the aminocyclohexyl ether of formula (57).

48. The method according to claim 47, further comprising before said first reaction step (a):



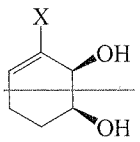
(52)

hydrogenating and hydrogenolyzing a compound of formula (52), wherein X is a

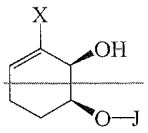


halide, to form a compound of formula (53), (53) .

49. The method according to claim 48, further comprising before said hydrogenating and hydrogenolyzing reaction:

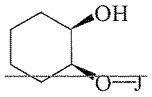


activating a compound of formula (51), (51) , with a hydroxy activating reagent to

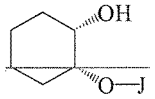


form a compound of formula (52), (52) .

50. The method according to claim 47, further comprising before said first reaction step (a):



separating a racemic mixture of a compound of formula (53), (53) and a compound of



formula (84), (84) , to obtain (53), wherein said separation step further comprises optionally functionalizing one or both of the compound of formula (53) and the compound of formula (84) such that the compounds are amenable to resolution;

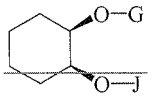
performing resolution to separate the compounds; and

optionally removing the functional group on said one or both functionalized compounds.

51. The method according to claim 50, wherein said separation step comprises enzymatic resolution, crystallization and/or chromatographic resolution.

52. The method according to claim 50, wherein said resolution is lipase mediated.

53. The method according to claim 47, further comprising before reaction step (a):



removing a functional group G from a compound of formula (85), (85) to form the compound of formula (53).

54. The method according to any one of claims 47, 48, 49, 50, 51, and 52 wherein:

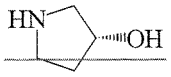
wherein at least one of R_3, R_4 and R_5 is C_1-C_6alkoxy;

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate; and

wherein, if present, X is Cl.

55. The method according to any one of claims 47, 48, 49, 50, 51, and 52 wherein:



(65)

or



(65A) ; and

wherein the compound of formula (56) is

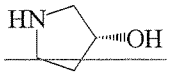
wherein R_3 is hydrogen, and R_4 and R_5 are C_1-C_6alkoxy.

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate; and

wherein, if present, X is Cl.

56. The method according to any one of claims 47, 48, 49, 50, 51, and52:



(65) ;

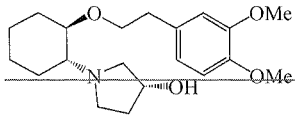
wherein the compound of formula (56) is

wherein R_3 is hydrogen, R_4 is methoxy at C_3 of the phenyl group and R_5 is methoxy at C_4 of the phenyl group;

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate; and

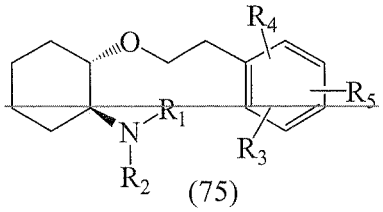
wherein, if present, X is Cl;



(66)

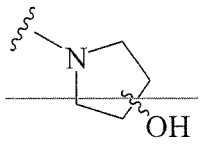
such that the aminocyclohexyl ether of formula (57) is .

57. A method for stereoselectively making an aminocyclohexyl ether of formula (75):



(75)

wherein R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (57) or (75), form a ring denoted by formula (II):

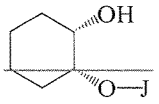


(II)

; and

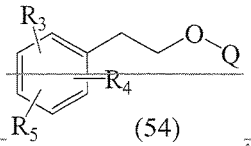
wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen;

wherein the method comprises:



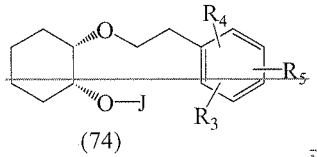
(84)

(a) reacting a compound of formula (84), , wherein O-J is a leaving group,



(54)

with a compound of formula (54), , wherein R_3, R_4 and R_5 are as defined above and O-Q is a leaving group that reacts with the hydroxy group (-OH) in the compound of formula (84) to form a compound of formula (74),

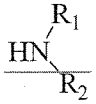


(74)

, such that the stereochemical configuration of the compound of formula (84) is retained in the compound of formula (74);

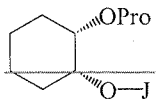
(b) optionally protecting the compound of formula (84) before the first reaction step (a);

and



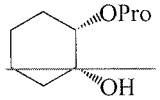
(c) reacting the compound of formula (74) with a compound of formula (56), (56) , wherein R_1 and R_2 are as defined above, to form the aminocyclohexyl ether of formula (75).

58. The method according to claim 57, further comprising before said first reaction step(a):

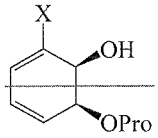


deprotecting a compound of formula (99), (99) wherein Pro is a protecting group, to form the compound of formula (84).

59. The method according to claim 58, further comprising before said deprotecting reaction step:

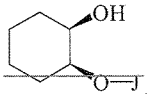


activating a compound of formula (92), (92) , with a hydroxy activating reagent to form the compound of formula (99), and optionally further comprising before said activating



reaction, hydrogenating and hydrogenolyzing a compound of formula (91), (91) wherein X is a halide, to form the compound of formula (92).

60. The method according to claim 57, further comprising before said first reaction step (a):



separating a racemic mixture of a compound of formula (53), (53) , and the compound of formula (84) to obtain the compound of formula (84);

wherein said separation step further comprises optionally functionalizing one or both of the compound of formula (53) and the compound of formula (84) such that the compounds are amenable to resolution;

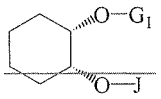
performing resolution to separate the compounds; and

optionally removing the functional group on said one or both functionalized compounds.

61. The method according to claim 60, wherein said separation step comprises enzymatic resolution, crystallization and/or chromatographic resolution.

62. The method according to claim 60, wherein said resolution is lipase mediated.

63. The method according to claim 57, further comprising before said first reaction step (a):



(86)

removing a functional group G_1 from a compound of formula (86), to form the compound of formula (84).

64. The method according to any one of claims 57, 58, 59, 60, 61, and62:

wherein at least one of R_3, R_4 and R_5 is C_1-C_6alkoxy;

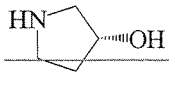
wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate;

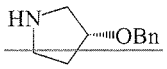
wherein, if present, Pro is TBDPS; and

wherein, if present, X is Cl.

65. The method according to any one of claims 57, 58, 59, 60, 61, and62:



(65)



(65A)

wherein the compound of formula (56) is or ; and

wherein R_3 is hydrogen, and R_4 and R_5 are C_1-C_6alkoxy.

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate;

wherein, if present, Pro is TBDPS; and

wherein, if present, X is Cl.

66. The method according to any one of claims 57, 58, 59, 60, 61, and62:



(65) ;

wherein the compound of formula (56) is

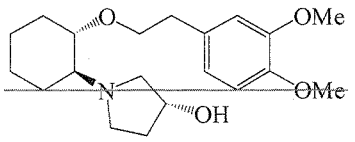
wherein R_3 is hydrogen, R_4 is methoxy at C_3 of the phenyl group and R_5 is methoxy at C_4 of the phenyl group;

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate;

wherein, if present, Pro is TBDPS; and

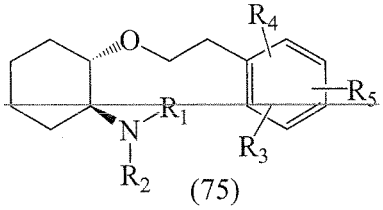
wherein, if present, X is Cl;



(79) ;

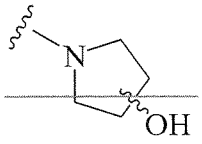
such that the aminocyclohexyl ether of formula (75) is

67. A method for stereoselectively making an aminocyclohexyl ether of formula (75):



(75)

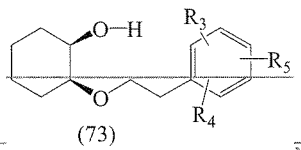
wherein R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (57) or (75), form a ring denoted by formula (II):



(II) ; and

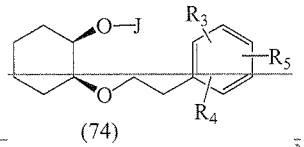
wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen;

wherein the method comprises:



(73)

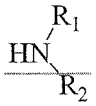
(a) reacting a compound of formula (73), , with a hydroxy



(74)

activating reagent to form a compound of formula (74), wherein O-J is a leaving group, R_3, R_4 and R_5 are as defined above; and

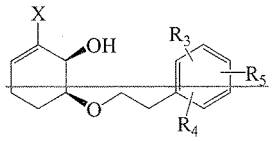
(b) reacting the product of the first reaction, compound of formula (74) with a compound



(56)

of formula (56), , wherein R_1 and R_2 are as defined above, to form the aminocyclohexyl ether of formula (75).

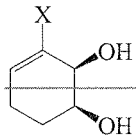
68. The method according to claim67, further comprising before reaction step (a):



(72)

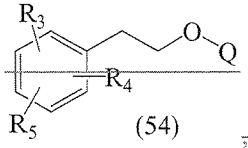
hydrogenating and hydrogenolyzing a compound of formula (72), wherein X is a halide, to form the compound of formula (73).

69. The method according to claim68, further comprising before said hydrogenating and hydrogenolyzing reaction:



(51)

reacting a compound of formula (51), , with a compound of formula (54),



(54)

, wherein O-Q is a leaving group that reacts preferentially with one of the hydroxy groups (-OH) in the compound of formula (51) to form a compound of formula (72), such that the stereochemical configuration of the compound of formula (51) is retained in the compound of formula (72).

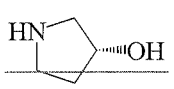
70. The method according to any one of claims 67, 68 and 69, wherein at least one of R_3, R_4 and R_5 is C_1-C_6alkoxy;

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate; and

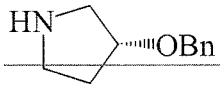
wherein, if present, X is Cl.

71. The method according to any one of claims 67, 68 and 69:



(65)

or



(65A)

; and

wherein the compound of formula (56) is

wherein R_3 is hydrogen, and R_4 and R_5 are C_1-C_6alkoxy.

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate; and

wherein, if present, X is Cl.

72. The method according to any one of claims 67, 68 and 69:



(65)

;

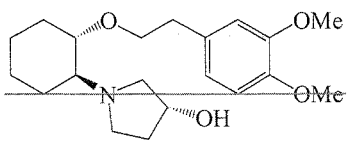
wherein the compound of formula (56) is

wherein R_3 is hydrogen, R_4 is methoxy at C_3 of the phenyl group and R_5 is methoxy at C_4 of the phenyl group;

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate; and

wherein, if present, X is Cl;

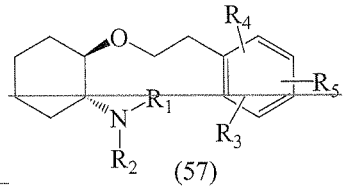


(79)

;

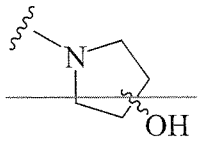
such that the aminocyclohexyl ether of formula (75) is

73. A method for stereoselectively making an aminocyclohexyl ether of formula (57):



(57)

wherein R_1 and R_2, when taken together with the nitrogen atom to which they are directly attached in formula (57) or (75), form a ring denoted by formula (II):

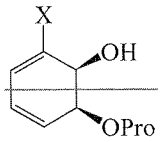


(II)

; and

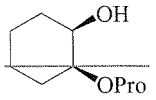
wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen;

wherein the method comprises:



(91)

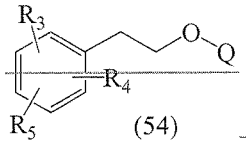
(a) hydrogenating and hydrogenolyzing a compound of formula (91), to



(92)

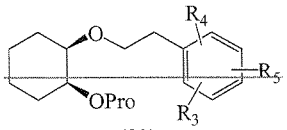
form a compound of formula (92), wherein Pro is a protecting group, X is a halide;

(b) alkylating the compound of formula (92) with a compound of formula (54),



(54)

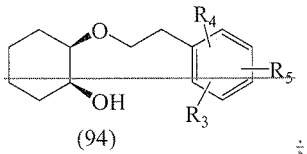
, wherein R_3, R_4 and R_5 are as defined above and O-Q is a leaving group that reacts with the hydroxy group (-OH) in formula (92) to form a



(93)

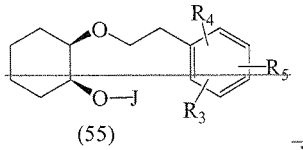
compound of formula (93), , such that the stereochemical configuration of the compound of formula (92) is retained in the compound of formula (93);

(c) deprotecting the compound of formula (93) to form a compound of formula (94),

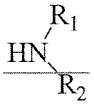


(94) ;

(d) activating the compound of formula (94) to form a compound of formula (55),



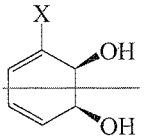
(55) , wherein O-J is a leaving group; and



(56) ,

(e) reacting the compound of formula (55) with a compound of formula (56), wherein R_1 and R_2 are as defined above, to form the aminocyclohexyl ether of formula (57).

74. A method according to claim 73, further comprising before reaction step (a):



(50) to form the compound of formula (91).

75. The method according to any one of claims 73 and 74:

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate;

wherein, if present, Pro is TBDPS; and

wherein, if present, X is Cl.

76. The method according to any one of claims 73 and 74:

wherein at least one of R_3, R_4 and R_5 is C_1-C_6alkoxy;

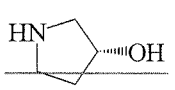
wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate;

wherein, if present, Pro is TBDPS; and

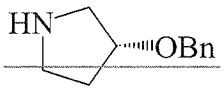
wherein, if present, X is Cl.

77. The method according to any one of claims 73 and 74:



(65)

or



(65A)

; and

wherein the compound of formula (56) is

wherein R_3 is hydrogen, and R_4 and R_5 are C_1-C_6alkoxy;

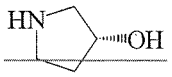
wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate;

wherein, if present, Pro is TBDPS; and

wherein, if present, X is Cl.

78. The method according to any one of claims 73 and 74:



(65)

;

wherein the compound of formula (56) is

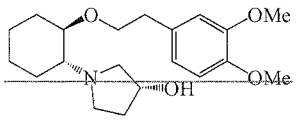
wherein R_3 is hydrogen, R_4 is methoxy at C_3 of the phenyl group and R_5 is methoxy at C_4 of the phenyl group;

wherein O-J is a mesylate group, a tosylate group, a nosylate group, a 2-bromophenylsulfonate group or a 4-bromophenylsulfonate group;

wherein O-Q is trichloroacetimidate;

wherein, if present, Pro is TBDPS; and

wherein, if present, X is Cl;

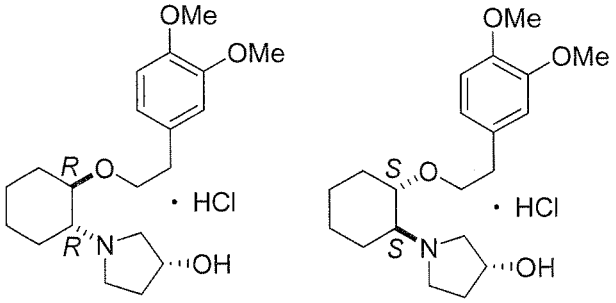


(66)

such that the aminocyclohexyl ether of formula (57) is

;

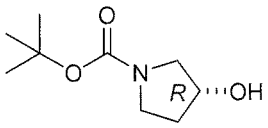
791. A method of making compound (1) or compound (2):



(1) or **(2)** ;

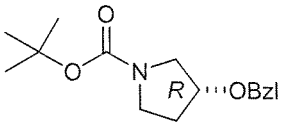
wherein the method comprises:

a) reacting  with $(Boc)_2O$ under suitable conditions to form compound (1R):



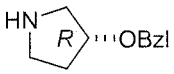
1R ;

b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):

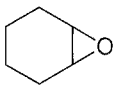


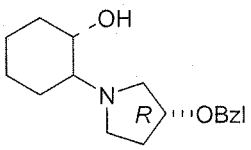
2R ;

c) hydrolyzing compound (2R) under suitable conditions to form compound (3R):

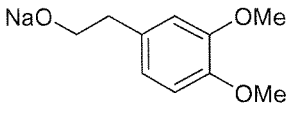


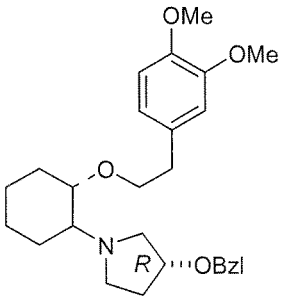
3R ;

d) reacting compound (3R) with  under suitable conditions to form compound (4R):



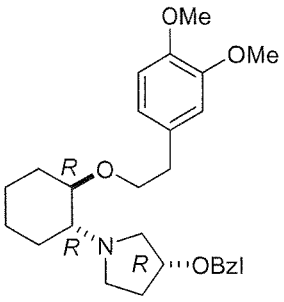
4R ;

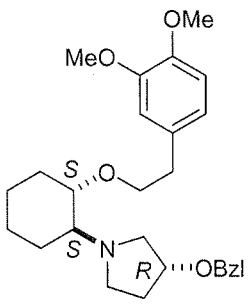
e) reacting compound (4R) with  under suitable conditions to form compound (5R);



5R ;

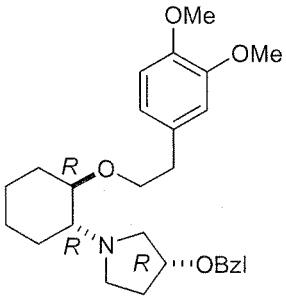
f) resolving compound (5R) under suitable conditions to form compound (5RRR) and compound (5SSR):

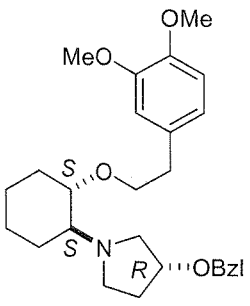


5RRR and  **5SSR** ; and

g) hydrogenolyzing compound (5RRR) under suitable conditions to form compound (1), as described above, and hydrogenolyzing compound (5SSR) under suitable conditions to form compound (2), as described above.

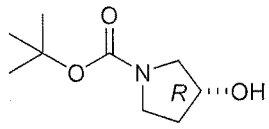
802. A method of making compound (5RRR) or compound (5SSR):



5RRR and  **5SSR** ;

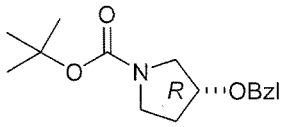
wherein the method comprises:

a) reacting  with $(Boc)_2O$ under suitable conditions to form compound (1R):



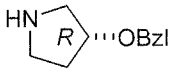
1R ;

b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):

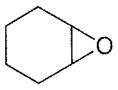


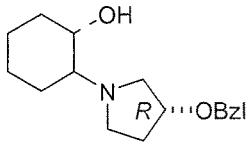
2R ;

c) hydrolyzing compound (2R) under suitable conditions to form compound (3R):

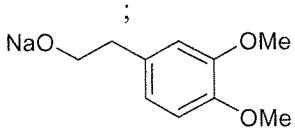


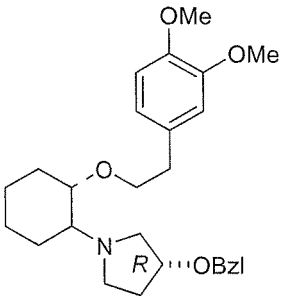
3R ;

d) reacting compound (3R) with  under suitable conditions to form compound (4R):



4R ;

e) reacting compound (4R) with  under suitable conditions to form compound (5R);

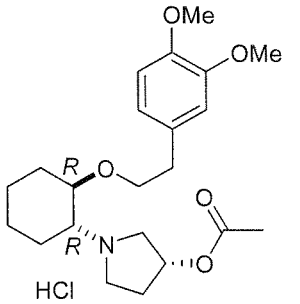


5R ; and

f) resolving compound (5R) under suitable conditions to form compound (5RRR) and compound (5SSR), as described above.

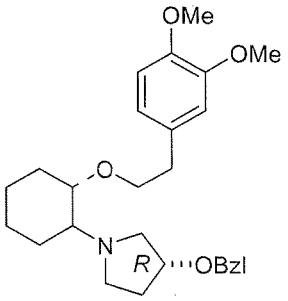
813. The method according to Claim 802 further comprising:

reacting compound (5RRR) under suitable conditions to form compound (17):



(17)

824. A method of making compound (5R):

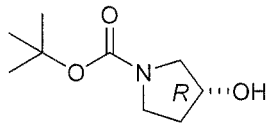


5R ;

wherein the method comprises:

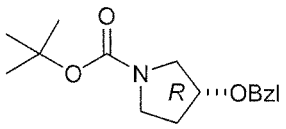
a) reacting 

with $(Boc)_2O$ under suitable conditions to form compound (1R):



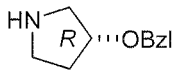
1R ;

b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):

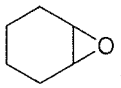


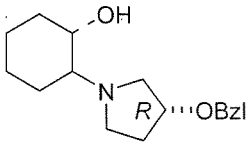
2R ;

c) hydrolyzing compound (2R) under suitable conditions to form compound (3R):

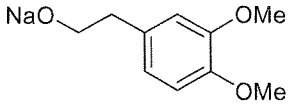


3R ;

d) reacting compound (3R) with  under suitable conditions to form compound (4R):

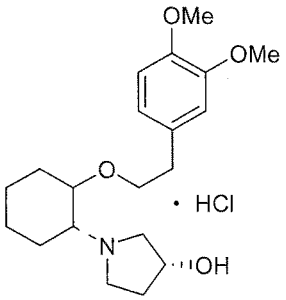


4R ; and

e) reacting compound (4R) with  under suitable conditions to form compound (5R), as described above.

835. The method according to Claim ~~82~~ 4 further comprising:

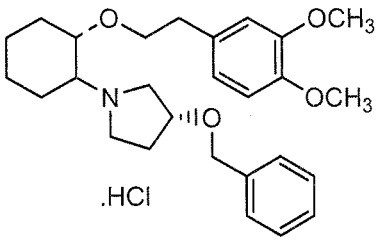
reducing compound (5R) under suitable conditions to form compound (4):



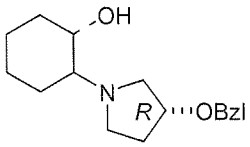
(4)

846. The method according to Claim 82-4 further comprising:

reacting compound (5R) under suitable conditions to form compound (12):



857. A method of making compound (4R):

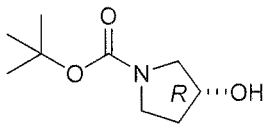


4R ;

wherein the method comprises:

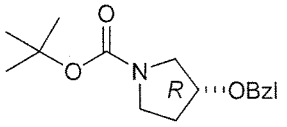
a) reacting 

with $(Boc)_2O$ under suitable conditions to form compound (1R):



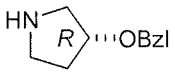
1R ;

b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):

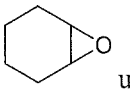


2R ;

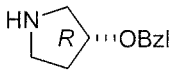
c) hydrolyzing compound (2R) under suitable conditions to form compound (3R):



3R ; and

d) reacting compound (3R) with  under suitable conditions to form compound (4R), as described above.

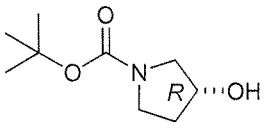
~~868~~. A method of making compound (3R):



3R ;

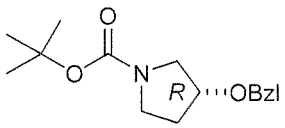
wherein the method comprises:

a) reacting  with $(Boc)_2O$ under suitable conditions to form compound (1R):



1R ;

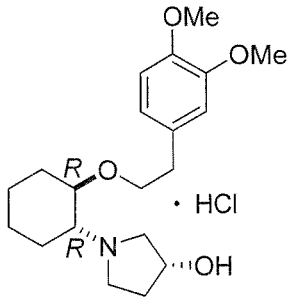
b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):



2R ; and

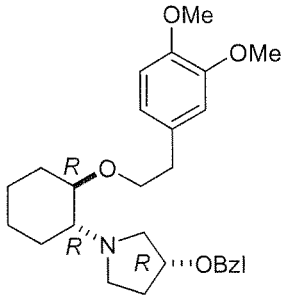
c) hydrolyzing compound (2R) under suitable conditions to form compound (3R), as described above.

~~879~~. A method of making compound (1):



(1) ;

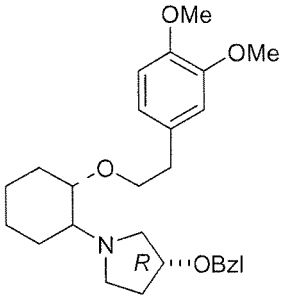
wherein the method comprises hydrogenolyzing compound (5RRR):



5RRR

under suitable conditions to form compound (1), as described above.

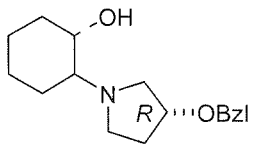
~~8810~~. The method according to claim ~~879~~ further comprising, prior to the hydrogenolyzing step, resolving compound (5R):



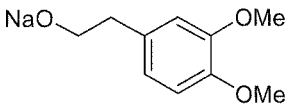
5R

under suitable conditions to form compound (5RRR), as described above.

8911. The method according to claim 88-10 further comprising, prior to the resolving step, reacting compound (4R):

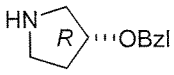


4R

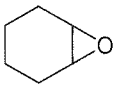


with under suitable conditions to form compound (5R), as described above.

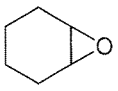
9012. The method according to claim 89-11 further comprising, prior to the reacting step, reacting compound (3R):



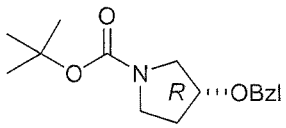
3R



with under suitable conditions to form compound (4R), as described above.

9113. The method according to claim 90-12 further comprising, prior to the reaction of compound (3R) with 

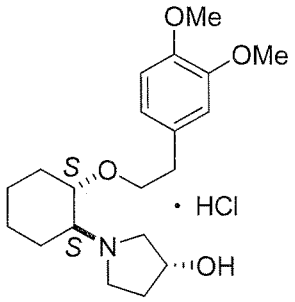
, hydrolyzing compound (2R):



2R

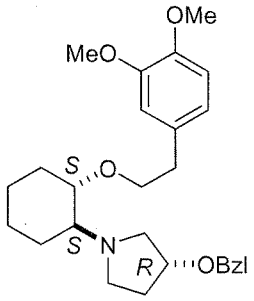
under suitable conditions to form compound (3R), as described above.

~~92~~14. A method of making compound (2):



(2) ;

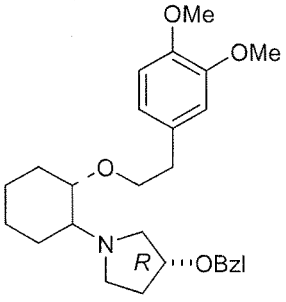
wherein the method comprises hydrogenolyzing compound (5SSR):



5SSR

under suitable conditions to form compound (2), as described above.

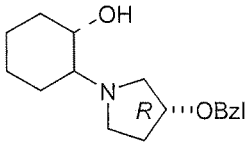
~~93~~15. The method according to claim ~~92~~14 further comprising, prior to the hydrogenolyzing step, resolving compound (5R):



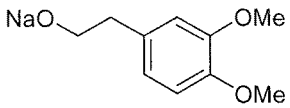
5R

under suitable conditions to form compound (5SSR), as described above.

9416. The method according to claim 93-15 further comprising, prior to the resolving step, reacting compound (4R):

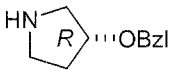


4R

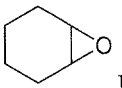


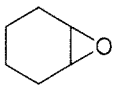
with under suitable conditions to form compound (5R), as described above.

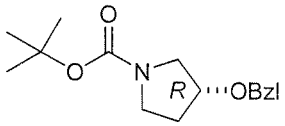
9517. The method according to claim 94-16 further comprising, prior to the reacting step, reacting compound (3R):



3R

with  under suitable conditions to form compound (4R), as described above.

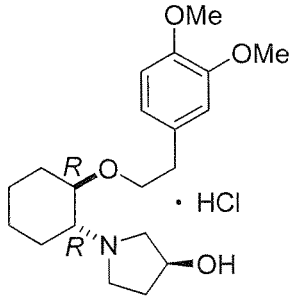
9618. The method according to claim 95-17 further comprising, prior to the reaction of compound (3R) with  , hydrolyzing compound (2R):



2R

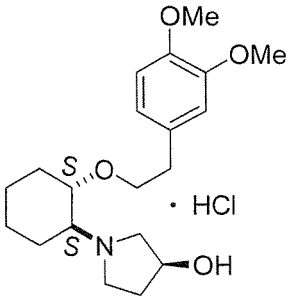
under suitable conditions to form compound (3R), as described above.

~~9719~~. A method of making compound (6) or compound (7):



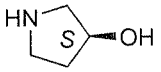
(6)

or

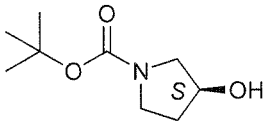


(7) ;

wherein the method comprises:

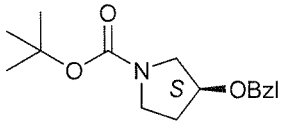
a) reacting 

with $(Boc)_2O$ under suitable conditions to form the following compound:



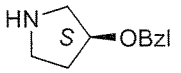
;

b) reacting the compound formed in step a) with benzyl bromide under suitable conditions to form the following compound:

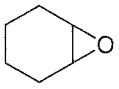


;

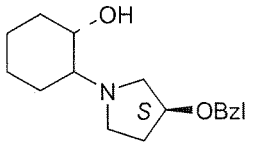
c) hydrolyzing the compound formed in step b) under suitable conditions to form the following compound:



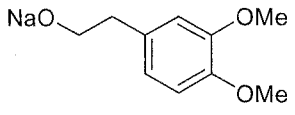
;

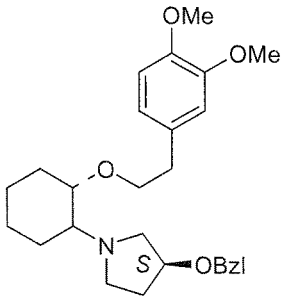
d) reacting the compound formed in step c) with 

under suitable conditions to form the following compound:



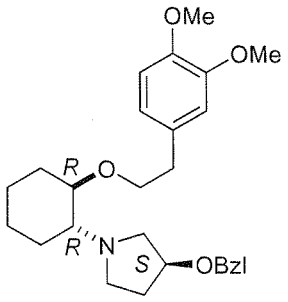
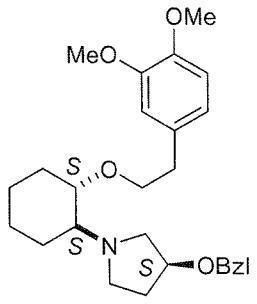
;

e) reacting the compound formed in step d) with  under suitable conditions to form the following compound:

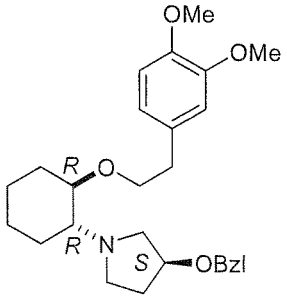


;

f) resolving the compound formed in step e) under suitable conditions to form the following compounds:

 and  ; and

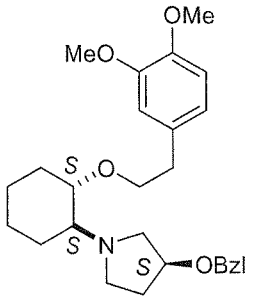
g) hydrogenolyzing the following compound formed in step f):



,

under suitable conditions to form compound (6), as described above;

and hydrogenolyzing the following compound formed in step f):

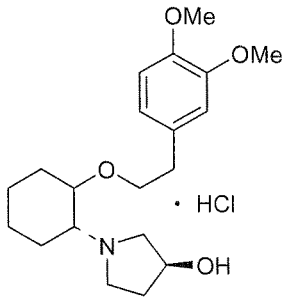


,

under suitable conditions to form compound (7), as described above.

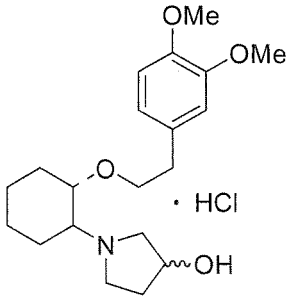
9820. The method according to claim 97-19 further comprising:

reducing the compound formed in step e) under suitable conditions to form compound (5):



(5)

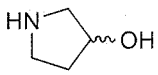
9921. A method of making compound (3):



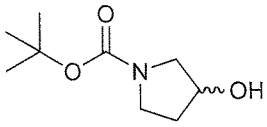
(3)

;

wherein the method comprises:

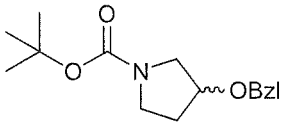
a) reacting 

with $(Boc)_2O$ under suitable conditions to form the following compound:



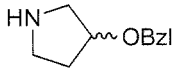
;

b) reacting the compound formed in step a) with benzyl bromide under suitable conditions to form the following compound:

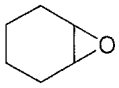


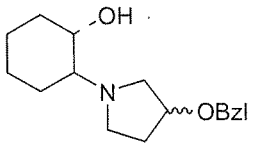
;

c) hydrolyzing the compound formed in step b) under suitable conditions to form the following compound:

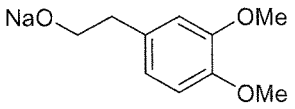


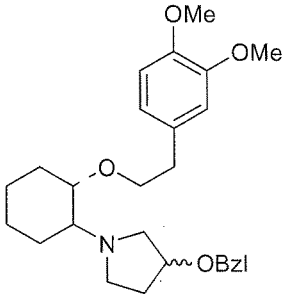
;

d) reacting the compound formed in step c) with  under suitable conditions to form the following compound:



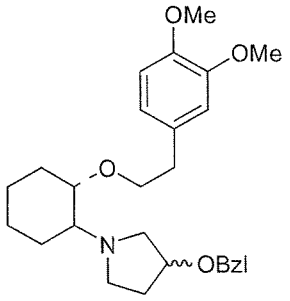
;

e) reacting the compound formed in step d) with  under suitable conditions to form the following compound:



;

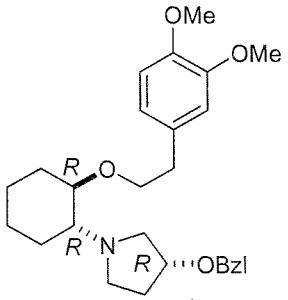
f) hydrogenolyzing the following compound formed in step e):



,

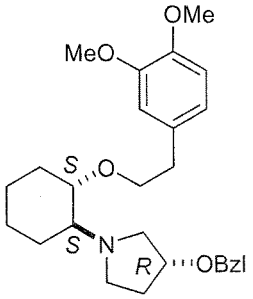
under suitable conditions to form compound (3), as described above.

~~10022~~. The compound (5RRR):



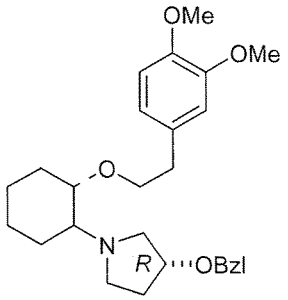
5RRR

~~10123~~. The compound (5SSR):



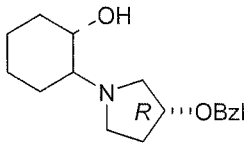
5SSR

~~10224~~. The compound (5R):



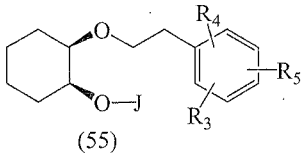
5R

~~10325~~. The compound (4R):



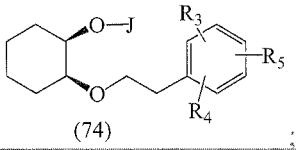
4R

26. A method of making a compound of formula (55) or formula (74):



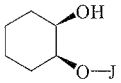
(55)

or

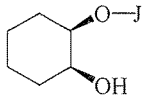


(74) ;

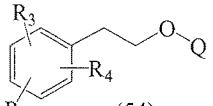
wherein the method comprises:



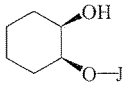
alkylating a compound of formula (53), (53) , or a compound of formula (84),



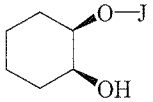
(84) , with a compound of formula (54),



(54) ; to form the compound of formula (55) or the compound of formula (74); respectively; and



optionally protecting a compound of formula (53), (53) , or a compound of formula



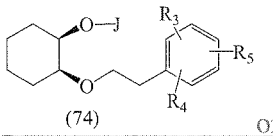
(84), (84) , before said alkylating step;

wherein O-Q is a leaving group that reacts with -OH in formula (53) or (84) to form the compound of formula (55) or the compound of formula (74), such that the stereochemical configuration of the compound of formula (53) or the compound of formula (84) is retained in the compound of formula (55) or the compound of formula (74), respectively;

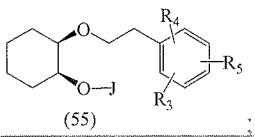
wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen; and

wherein O-J is a leaving group.

27. A method of making a compound of formula (74) or formula (55):


(74)

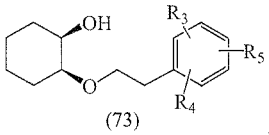
or


(55)

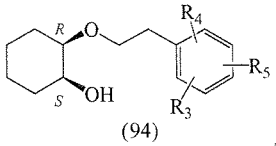
;

wherein the method comprises:

activating a compound of formula (73),


(73)

, or a compound of formula (94),

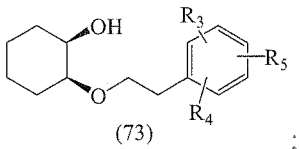

(94)

, with a hydroxy activating reagent to form the compound of formula (74) or the compound of formula (55), respectively;

wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen; and

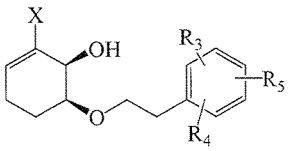
wherein O-J is a leaving group.

28. A method of making a compound of formula (73):


(73)

;

wherein the method comprises:

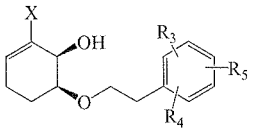


hydrogenating and hydrogenolyzing a compound of formula (72), (72), to form the compound of formula (73);

wherein X is a halide; and

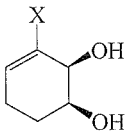
wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

29. A method of making a compound of formula (72):

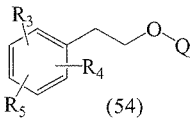


(72);

wherein the method comprises:



alkylating a compound of formula (51), (51), with a compound of formula (54),



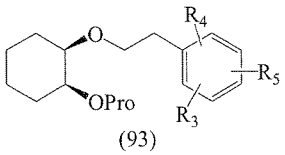
(54), to form the compound of formula (72);

wherein X is a halide

wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen; and

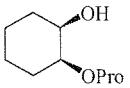
wherein O-Q is a leaving group that reacts with -OH in the compound of formula (51) to form the compound of formula (72), such that the stereochemical configuration of the compound of formula (51) is retained in the compound of formula (72).

30. A method of making a compound of formula (93):

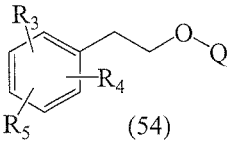


(93) ;

wherein the method comprises:



alkylating a compound of formula (92), (92) , with a compound of formula (54),



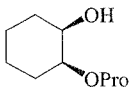
(54) , to form the compound of formula (93);

wherein Pro is a protecting group;

wherein R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1-C_6alkoxy, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen; and

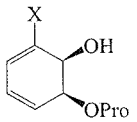
wherein O-Q is a leaving group that reacts with -OH in the compound of formula (92) to form the compound of formula (93), such that the stereochemical configuration of the compound of formula (92) is retained in the compound of formula (93).

31. A method of making a compound of formula (92):



(92) ;

wherein the method comprises:

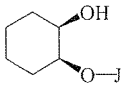


hydrogenating and hydrogenolyzing a compound of formula (91), (91) , to form the compound of formula (92);

wherein Pro is a protecting group; and

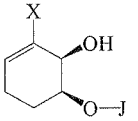
wherein X is a halide.

32. A method of making a compound of formula (53):



(53) ;

wherein the method comprises:

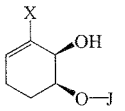


hydrogenating and hydrogenolyzing a compound of formula (52), (52) , to form the compound of formula (53);

wherein X is a halide; and

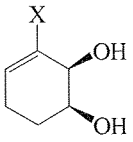
wherein O-J is a leaving group.

33. A method of making a compound of formula (52):



(52) ;

wherein the method comprises:

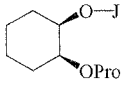


activating a compound of formula (51), (51) , with a hydroxy activating reagent to form the compound of formula (52);

wherein X is a halide; and

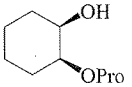
wherein O-J is a leaving group.

34. A method of making a compound of formula (99):



(99) ;

wherein the method comprises:



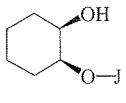
activating a compound of formula (92), (92) , with a hydroxy activating reagent to form

the compound of formula (99);

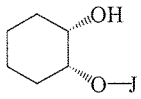
wherein Pro is a protecting group; and

wherein O-J is a leaving group.

35. A method of making a compound of formula (53) or a compound of formula (84):

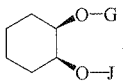


(53)



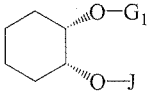
(84) ;

wherein the method comprises:



(85)

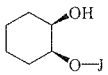
removing a functional group G or G_1 from a compound of formula (85), , or a



(86)

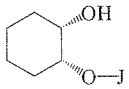
compound of formula (86), , respectively, to form the compound of formula (53) or the compound of formula (84), respectively;

wherein O-J is a leaving group.



(53)

36. A method comprising separating a racemic mixture of a compound of formula (53), ,



(84)

and a compound of formula (84), .

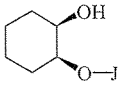
37. The method according to claim 36 wherein said separation step further comprises:

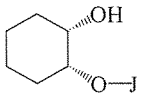
functionalizing one or both of the compound of formula (52) and the compound of formula (84) such that the compounds are capable of resolution;

performing resolution to separate the compounds; and

optionally removing the functional group on said one or both functionalized compounds.

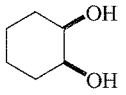
38. A method of forming a racemic mixture of a compound of formula (53) and a compound of formula (84):



(53) and 

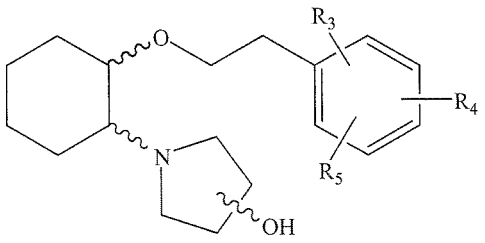
(84)

wherein the method comprises:



activating a compound of formula (83), (83) , with a hydroxy activating reagent to form the racemic mixture of the compound of formula (53) and the compound of formula (84); wherein O-J is a leaving group.

~~104~~39. A compound of formula (IA), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(IA)

wherein, R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

~~105~~40. A compound of formula (IA) according to claim ~~104~~39, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~106~~41. A compound of formula (IA) according to claim ~~104~~39, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~107~~42. A compound of formula (IA) according to claim ~~104~~39, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy.

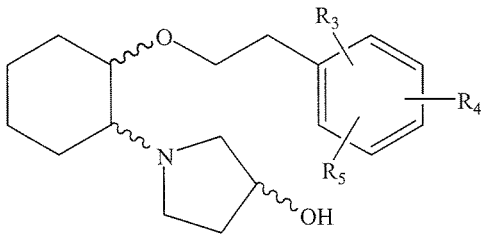
~~108~~43. A compound of formula (IA) according to claim ~~104~~39, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, include.ing isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~109~~44. A compound of formula (IA) according to claim ~~104~~39, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~110~~45. A compound of formula (IA) according to claim ~~104~~39, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

~~111~~46. A compound of formula (IA) according to claim ~~104~~39, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

~~112~~47. A compound of formula (IB), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(IB)

wherein, R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

~~113~~48. A compound of formula (IB) according to claim ~~112~~47, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~114~~49. A compound of formula (IB) according to claim ~~112~~47, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~115~~50. A compound of formula (IB) according to claim ~~112~~47, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy.

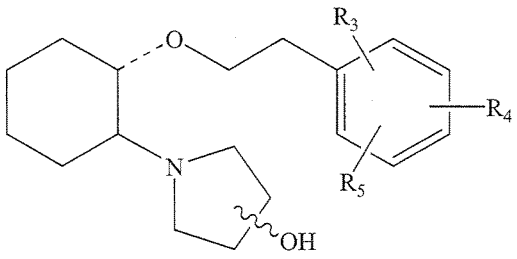
~~116~~51. A compound of formula (IB) according to claim ~~112~~47, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~117~~52. A compound of formula (IB) according to claim ~~112~~47, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~118~~53. A compound of formula (IB) according to claim ~~112~~47, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

~~119~~54. A compound of formula (IB) according to claim ~~112~~47, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

~~120~~55. A compound of formula (IC), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(IC)

wherein, R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

~~121~~56. A compound of formula (IC) according to claim ~~120~~55, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~122~~57. A compound of formula (IC) according to claim ~~120~~55, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~123~~58. A compound of formula (IC) according to claim ~~120~~55, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy.

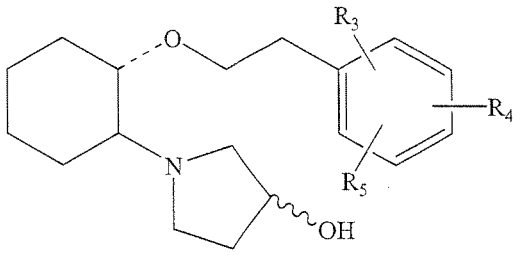
~~124~~59. A compound of formula (IC) according to claim ~~120~~55, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~125~~60. A compound of formula (IC) according to claim ~~120~~55, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~126~~61. A compound of formula (IC) according to claim ~~120~~55, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

~~127~~62. A compound of formula (IC) according to claim ~~120~~55, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

~~128~~63. A compound of formula (ID), or a solvate, pharmaceutically acceptable salt, ester, amide,3 complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(ID)

wherein, R_3, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_3, R_4 and R_5 cannot all be hydrogen.

~~129~~64. A compound of formula (ID) according to claim ~~128~~63, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~130~~65. A compound of formula (ID) according to claim ~~128~~63, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~131~~66. A compound of formula (ID) according to claim ~~128~~63, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy.

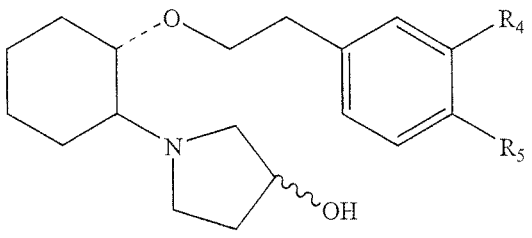
~~132~~67. A compound of formula (ID) according to claim ~~128~~63, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~133~~68. A compound of formula (ID) according to claim ~~128~~63, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~134~~69. A compound of formula (ID) according to claim ~~128~~63, or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

~~135~~70. A compound of formula (ID) according to claim ~~128~~63, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_3 is hydrogen, R_4 and R_5 are C_1alkoxy.

~~136~~71. A compound of formula (IE), or a solvate, pharmaceutically acceptable salt, ester, amide, complex, chelate, stereoisomer, stereoisomeric mixture, geometric isomer, crystalline or amorphous form, metabolite, metabolic precursor or prodrug thereof:



(IE)

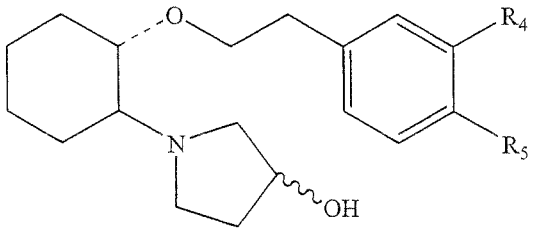
wherein, R_4 and R_5 are independently selected from hydrogen and hydroxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_4 and R_5 cannot all be hydrogen.

~~137~~72. A compound of formula (IE) according to claim ~~136~~71, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~138~~73. A compound of formula (IE) according to claim ~~136~~71, or a solvate, pharmaceutically acceptable salt thereof, wherein, R_4 and R_5 are independently hydroxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~139~~74. A compound of formula (IE) according to claim ~~136~~71, or a solvate, pharmaceutically acceptable salt thereof, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are independently hydroxy.

~~140~~75. A metabolite, metabolic precursor or prodrug of a compound of formula (IE):



(IE)

wherein, R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, with the proviso that R_4 and R_5 cannot all be hydrogen.

~~141~~76. A metabolite, metabolic precursor or prodrug according to claim ~~140~~75, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~142~~77. A metabolite, metabolic precursor or prodrug according to claim ~~140~~75, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_6alkoxy, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

~~143~~78. A metabolite, metabolic precursor or prodrug according to claim ~~140~~75, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are independently selected from hydroxy and C_1-C_3alkoxy.

~~144~~79. A metabolite, metabolic precursor or prodrug according to claim ~~140~~75, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are independently selected from C_1-C_6alkoxy.

~~145~~80. A metabolite, metabolic precursor or prodrug according to claim ~~140~~75, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are independently selected from C_1-C_3alkoxy.

~~146~~81. A metabolite, metabolic precursor or prodrug according to claim ~~140~~75, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are C_1alkoxy.

~~147~~82. A metabolite, metabolic precursor or prodrug according to claim ~~140~~75, including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof, wherein, R_4 and R_5 are C_1alkoxy.

~~148~~83. A composition comprising: a compound according to any one of claims ~~104~~39 to ~~139~~74 or a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~75 to ~~147~~82, in combination with a pharmaceutically acceptable carrier, excipient or diluent.

~~149~~84. Use of a compound according to any one of claims ~~104~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament.

~~150~~85. Use of a compound according to any one of claims ~~104~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~149~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for modulating ion channel activity in a warm-blooded animal.

~~151~~86. A method for modulating ion channel activity in an *in vitro* setting comprising administering *in vitro* an effective amount of a compound according to any one of claims ~~104~~ 39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims 75~~140~~ to ~~147~~82, a composition according to claim ~~148~~83, or a medicament manufactured according to claim ~~149~~84.

~~152~~87. Use of a compound according to any one of claims ~~104~~ 39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims 75~~140~~ to 82~~147~~, or a composition according to claim ~~148~~83, in the manufacture of a medicament for blocking/inhibiting the activity/conductance of an ion channel in a warm-blooded animal.

~~153~~88. A method for blocking/inhibiting the activity/conductance of an ion channel in an *in vitro* setting comprising administering *in vitro* an effective amount of a compound according to any one of claims ~~104~~ 39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~ 75 to ~~147~~82, or a composition according to claim ~~148~~83, or a medicament manufactured according to claim ~~149~~84.

~~154~~89. The use according to claim ~~150~~ 85 or ~~152~~87, wherein said ion channel is a potassium channel.

~~155~~90. The use according to claim ~~154~~89, wherein said potassium channel is a voltage-activated potassium channel.

~~156~~91. The method according to claim ~~151~~ 86 or ~~153~~88, wherein said ion channel is a potassium channel.

~~157~~92. The method according to claim ~~156~~91, wherein said potassium channel is a voltage-activated potassium channel.

~~158~~93. Use of a compound according to any one of claims ~~104~~ 39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~ 75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for modulating cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal.

~~159~~94. Use of a compound according to any one of claims ~~104-~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140-~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for blocking/inhibiting cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal.

~~160~~95. Use of a compound according to any one of claims ~~104-~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140-~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for blocking/inhibiting the cardiac ion channels responsible for the cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal.

~~161~~96. Use of a compound according to any one of claims ~~104-~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140-~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for blocking/inhibiting cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal under conditions where an arrhythmogenic substrate is present in the heart of said warm-blooded animal.

~~162~~97. Use of a compound according to any one of claims ~~104-~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140-~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for blocking/inhibiting the cardiac ion channels responsible for the cardiac early repolarising currents and cardiac sodium currents in a warm-blooded animal under conditions where an arrhythmogenic substrate is present in the heart of said warm-blooded animal.

~~163~~98. The use according to any one of claims ~~158-~~93 to ~~162~~97, wherein said cardiac early repolarising currents comprise ionic currents which activate rapidly after depolarisation of membrane voltage and which effect repolarisation of the cell.

~~164~~99. The use according to any one of claims ~~158-~~93 to ~~162~~97, wherein said early repolarising currents comprise the cardiac transient outward potassium current (I_{to}) and/or the ultrarapid delayed rectifier current (I_{Kur}).

~~165~~100.The use according to claim ~~164~~99, wherein the cardiac transient outward potassium current (I_{to}) and/or the ultrarapid delayed rectifier current (I_{Kur}) comprise at least one of the Kv4.2, Kv4.3, Kv2.1, Kv1.4 and Kv1.5 currents.

~~166~~101.Use of a compound according to any one of claims ~~104~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating and/or preventing arrhythmia in a warm-blooded animal.

~~167~~102.A pharmaceutical composition comprising an amount of a compound according to any one of claims ~~104~~39 to ~~139~~74, or a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~75 to ~~147~~82, effective to treat and/or prevent atrial arrhythmia in a warm-blooded animal in need of the treatment and/or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

~~168~~103.Use of a compound according to any one of claims ~~104~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating and/or preventing atrial arrhythmia in a warm-blooded animal.

~~169~~104.Use of a compound according to any one of claims ~~104~~39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating and/or preventing ventricular arrhythmia in a warm-blooded animal.

~~170~~105.A pharmaceutical composition comprising an amount of a compound according to any one of claims ~~104~~39 to ~~139~~74, or a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~75 to ~~147~~82, effective to treat and/or prevent ventricular arrhythmia in a warm-blooded animal in need of the treatment and/or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

~~171~~106.Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating and/or preventing atrial fibrillation in a warm-blooded animal.

~~172~~107.Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating and/or preventing atrial flutter in a warm-blooded animal.

~~173~~108. Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating and/or preventing ventricular fibrillation in a warm-blooded animal.

~~174~~109.Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating and/or preventing ventricular flutter in a warm-blooded animal.

~~175~~110. Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating atrial fibrillation in a warm-blooded animal.

~~176~~111.Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating atrial flutter in a warm-blooded animal.

~~177~~112. Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating ventricular fibrillation in a warm-blooded animal.

~~178~~113.Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for treating ventricular flutter in a warm-blooded animal.

~~179~~114. Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for preventing atrial fibrillation in a warm-blooded animal.

~~180~~115.Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for preventing atrial flutter in a warm-blooded animal.

~~181~~116. Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for preventing ventricular fibrillation in a warm-blooded animal.

~~182~~117. Use of a compound according to any one of claims ~~104~~-39 to ~~139~~74, a metabolite, metabolic precursor or prodrug according to any one of claims ~~140~~-75 to ~~147~~82, or a composition according to claim ~~148~~83, in the manufacture of a medicament for preventing ventricular flutter in a warm-blooded animal.