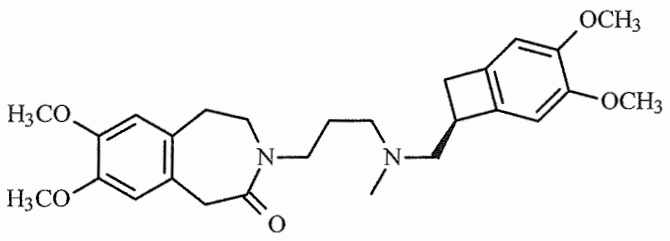
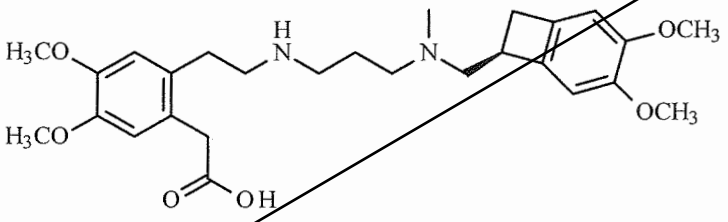
CLAIMS

1. Process for the synthesis of ivabradine of formula (I):



(I),

characterised in that the compound of formula (VI):



(VI)

is subjected to a lactamisation reaction,

in the presence of a coupling agent and a base,

in an organic solvent,

to yield ivabradine of formula (I), which may be converted into addition salts thereof with a pharmaceutically acceptable acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid and camphoric acid, and into hydrates thereof.

2. Synthesis process according to claim 1, characterised in that the coupling agent used to carry out the reaction for lactamisation of the compound of formula (VI) is selected from

oxalyl chloride, thionyl chloride, *N,N*-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), *N,N*-carbonyldiimidazole (CDI), 1-propanephosphonic acid cyclic anhydride (T3P) and 1-(methylsulphonyl)-1H-benzotriazole.

3. Synthesis process according to claim 2, characterised in that the coupling agent used to carry out the reaction for lactamisation of the compound of formula (VI) is thionyl chloride.

4. Synthesis process according to claim 3, characterised in that the amount of thionyl chloride used to carry out the reaction for lactamisation of the compound of formula (VI) is between 1 and 5 equivalents, inclusive.

5. Synthesis process according to any one of claims 1 to 4, characterised in that the base used to carry out the reaction for lactamisation of the compound of formula (VI) is selected from triethylamine, diisopropylethylamine and pyridine.

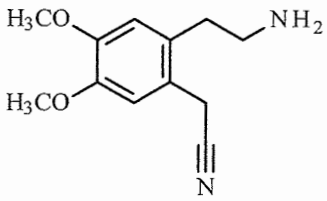
6. Synthesis process according to claim 5, characterised in that the base used to carry out the reaction for lactamisation of the compound of formula (VI) is triethylamine.

7. Synthesis process according to any one of claims 1 to 6, characterised in that the organic solvent used to carry out the reaction for lactamisation of the compound of formula (VI) is selected from dichloromethane, tetrahydrofuran, acetonitrile, acetone and toluene.

8. Synthesis process according to claim 7, characterised in that the organic solvent used to carry out the reaction for lactamisation of the compound of formula (VI) is dichloromethane.

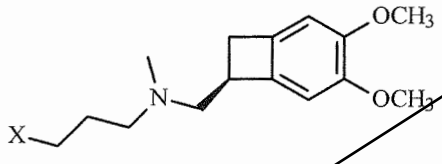
9. Synthesis process according to any one of claims 1 to 8, characterised in that the reaction for lactamisation of the compound of formula (VI) is carried out at a temperature between 0°C and 40°C, inclusive.

10. Synthesis process according to claim 1, characterised in that the compound of formula (VI) is prepared starting from the compound of formula (VII):



(VII),

which is reacted with the compound of formula (VIII):



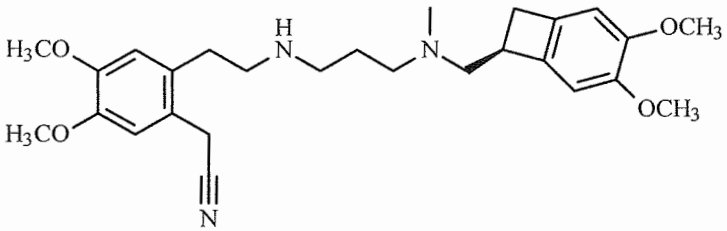
(VIII),

wherein X represents a halogen atom, a mesylate group or a tosylate group,

in the presence of a base,

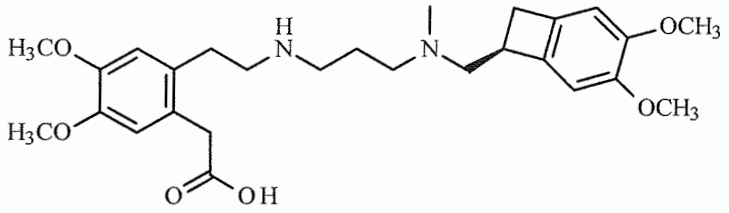
in an organic solvent,

to yield the compound of formula (IX):



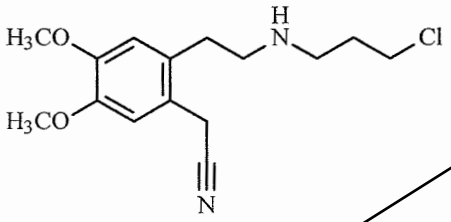
(IX),

which is hydrolysed, by the action of a base in a mixture of organic solvent and water, to form the compound of formula (VI):



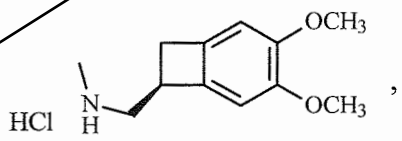
(VI).

11. Synthesis process according to claim 1, characterised in that the compound of formula (VI) is prepared starting from the compound of formula (X):



(X),

which is reacted with the hydrochloride of the compound of formula (III):

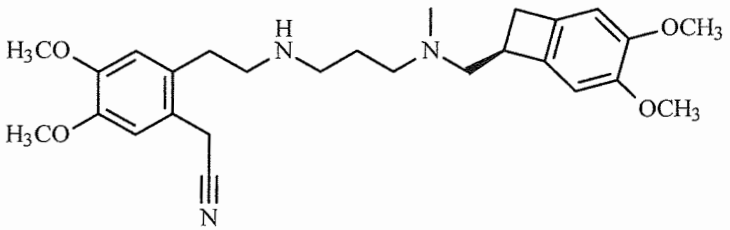


,

in the presence of a base,

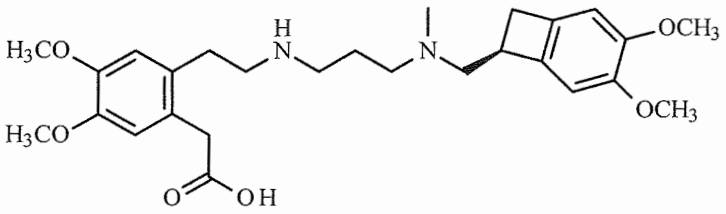
in an organic solvent,

to yield the compound of formula (IX):



(IX),

which is hydrolysed, by the action of a base in a mixture of organic solvent and water, to form the compound of formula (VI):



(VI).

12. Synthesis process according to either claim 10 or claim 11, characterised in that the base used to carry out the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) or the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is selected from potassium carbonate, sodium carbonate, caesium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, triethylamine, diisopropylethylamine and pyridine.

13. Synthesis process according to claim 12, characterised in that the base used to carry out the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) or the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is triethylamine.

14. Synthesis process according to any one of claims 10 to 13, characterised in that the organic solvent used to carry out the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) or the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is selected from acetonitrile, acetone, methyl ethyl ketone (MEK), dimethylformamide (DMF), *N*-methylpyrrolidone (NMP) and dimethyl sulphoxide (DMSO).

15. Synthesis process according to claim 14, characterised in that the organic solvent used to carry out the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) or the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is acetonitrile.

16. Synthesis process according to any one of claims 10 to 15, characterised in that the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) or the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is carried out at a temperature between 20°C and 100°C, inclusive.

17. Synthesis process according to any one of claims 10 to 16, characterised in that the base used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is selected from potassium hydroxide, sodium hydroxide, lithium hydroxide and barium hydroxide.

18. Synthesis process according to claim 17, characterised in that the base used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is sodium hydroxide.

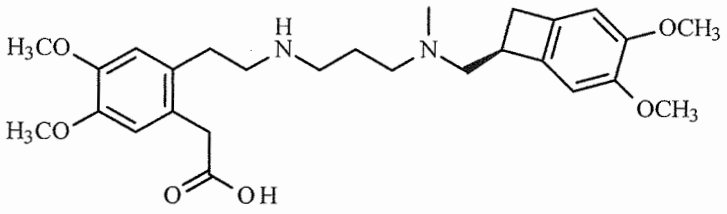
19. Synthesis process according to any one of claims 10 to 18, characterised in that the organic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is an alcoholic solvent.

20. Synthesis process according to claim 19, characterised in that the alcoholic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is selected from methanol, ethanol, isopropanol and butanol.

21. Synthesis process according to claim 20, characterised in that the alcoholic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is ethanol.

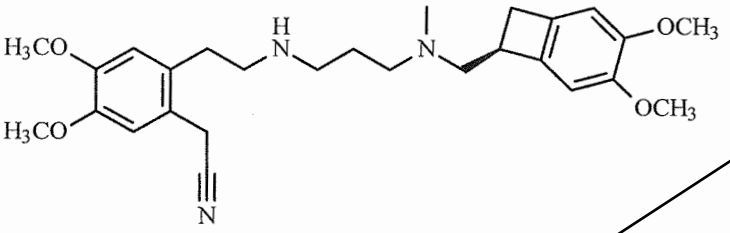
22. Synthesis process according to any one of claims 10 to 21, characterised in that the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is carried out at a temperature between 0°C and 110°C, inclusive.

23. Compound of formula (VI):



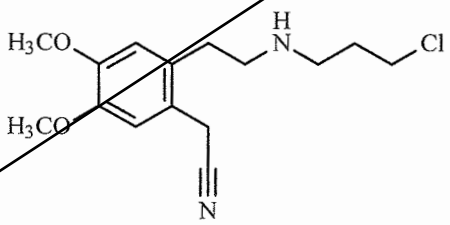
(VI).

24. Compound of formula (IX):



(IX).

25. Compound of formula (X):



(X).

26. 3-[{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]-1-propanol.

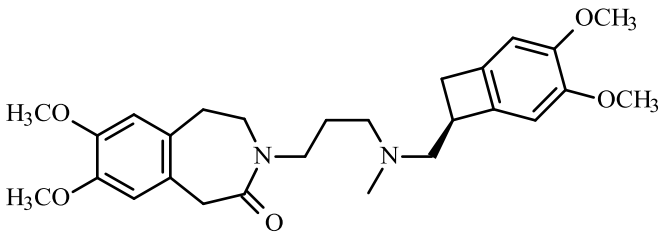
27. Ethyl *N*-{2-[2-(cyanomethyl)-4,5-dimethoxyphenyl]ethyl}-β-alaninate oxalate.

28. (2-{2-[(3-hydroxypropyl)amino]ethyl}-4,5-dimethoxyphenyl)acetonitrile.

The invention claimed is:

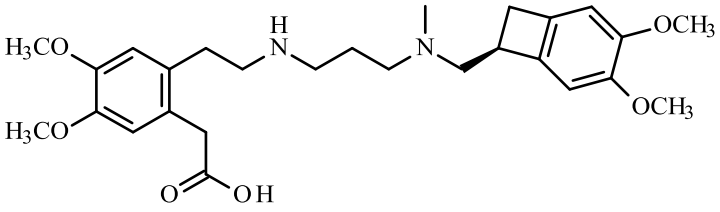
1. A process for the synthesis of ivabradine of formula (I):

(I)



wherein a compound of formula (VI):

(VI)



is subjected to a lactamisation reaction,

in the presence of a coupling agent and a base,

in an organic solvent,

to yield ivabradine of formula (I), which may be converted into an addition salt thereof with a pharmaceutically acceptable acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid and camphoric acid, and into hydrates thereof.

2. The process according to claim 1, wherein the coupling agent used to carry out the reaction for lactamisation of the compound of formula (VI) is selected from oxalyl chloride, thionyl chloride, N,N-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), N,N-carbonyldiimidazole (CDI), 1-

propanephosphonic acid cyclic anhydride (T3P) and 1-(methylsulphonyl)-1H-benzotriazole.

3. The process according to claim 2, wherein the coupling agent used to carry out the reaction for lactamisation of the compound of formula (VI) is thionyl chloride.

4. The process according to claim 3, wherein the amount of thionyl chloride used to carry out the reaction for lactamisation of the compound of formula (VI) is between 1 and 5 equivalents.

5. The process according to claim 1, wherein the base used to carry out the reaction for lactamisation of the compound of formula (VI) is selected from triethylamine, diisopropylethylamine and pyridine.

6. The process according to claim 5, wherein the base used to carry out the reaction for lactamisation of the compound of formula (VI) is triethylamine.

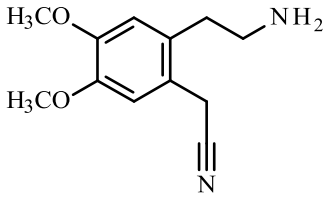
7. The process according to claim 1, wherein the organic solvent used to carry out the reaction for lactamisation of the compound of formula (VI) is selected from dichloromethane, tetrahydrofuran, acetonitrile, acetone and toluene.

8. The process according to claim 7, wherein the organic solvent used to carry out the reaction for lactamisation of the compound of formula (VI) is dichloromethane.

9. The process according to claim 1, wherein the reaction for lactamisation of the compound of formula (VI) is carried out at a temperature between 0°C and 40°C.

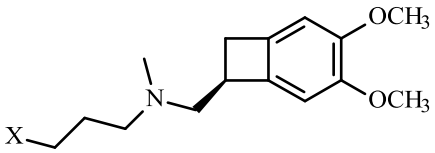
10. The process according to claim 1, wherein the compound of formula (VI) is prepared starting from the compound of formula (VII):

(VII)



which is reacted with a compound of formula (VIII):

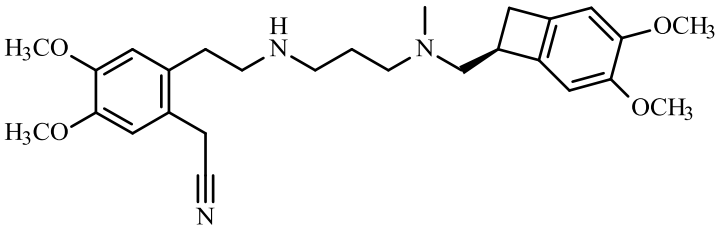
(VIII)



wherein X represents a halogen atom, a mesylate group or a tosylate group,

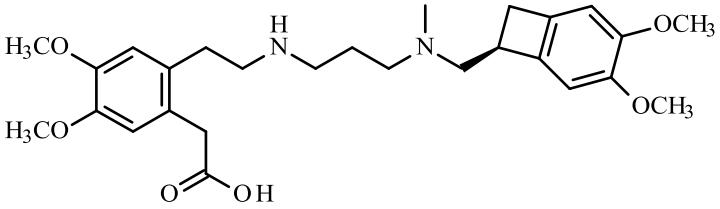
in the presence of a base,
in an organic solvent,
to yield the compound of formula (IX):

(IX)



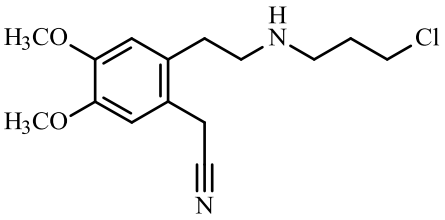
which is hydrolysed, by the action of a base in a mixture of organic solvent and water, to form the compound of formula (VI)

(VI)

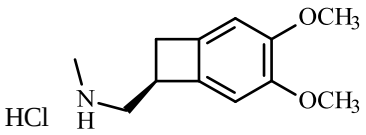


11. The process according to claim 1, wherein the compound of formula (VI) is prepared starting from a compound of formula (X):

(X)

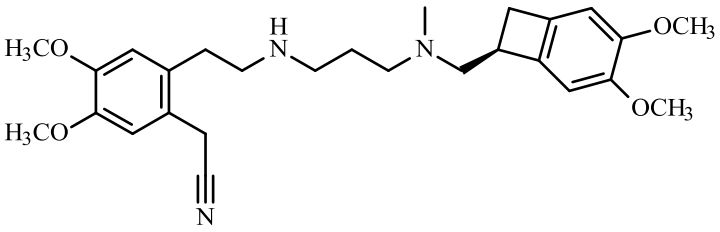


which is reacted with the hydrochloride of the compound of formula (III):



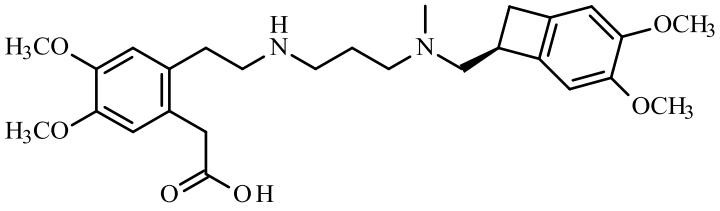
in the presence of a base,
in an organic solvent,
to yield the compound of formula (IX):

(IX)



which is hydrolysed, by the action of a base in a mixture of organic solvent and water, to form the compound of formula (VI):

(VI)



12. The process according to claim 10, wherein the base used to carry out the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) is selected from potassium carbonate, sodium carbonate, caesium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, triethylamine, diisopropylethylamine and pyridine.

13. The process according to claim 12, wherein the base used to carry out the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) is triethylamine.

14. The process according to claim 10, wherein the organic solvent used to carry out the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) is selected from acetonitrile, acetone, methyl ethyl ketone (MEK), dimethylformamide (DMF), N-methylpyrrolidone (NMP) and dimethyl sulphoxide (DMSO).

15. The process according to claim 14, wherein the organic solvent used to carry out the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) is acetonitrile.

16. The process according to claim 10, wherein the alkylation reaction between the compound of formula (VII) and the compound of formula (VIII) is carried out at a temperature between 20°C and 100°C.

17. The process according to claim 10, wherein the base used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is selected from potassium hydroxide, sodium hydroxide, lithium hydroxide and barium hydroxide.

18. The process according to claim 17, wherein the base used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is sodium hydroxide.

19. The process according to claim 10, wherein the organic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is an alcoholic solvent.

20. The process according to claim 19, wherein the alcoholic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is selected from methanol, ethanol, isopropanol and butanol.

21. The process according to claim 20, wherein the alcoholic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is ethanol.

22. The process according to claim 10, wherein the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is carried out at a temperature between 0°C and 110°C.

23. The process according to claim 11, wherein the based used to carry out the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is selected from potassium carbonate, sodium carbonate, caesium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, triethylamine, diisopropylethylamine and pyridine.

24. The process according to claim 23, wherein the based used to carry out the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is triethylamine.

25. The process according to claim 11, wherein the organic solvent used to carry out the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is selected from acetonitrile, acetone, methyl ethyl ketone (MEK), dimethylformamide (DMF), N-methylpyrrolidone (NMP) and dimethyl sulphoxide (DMSO).

26. The process according to claim 25, wherein the organic solvent used to carry out the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is acetonitrile.

27. The process according to claim 11, wherein the alkylation reaction between the compound of formula (X) and the hydrochloride of the compound of formula (III) is carried out at a temperature between 20°C and 100°C.

28. The process according to claim 11, wherein the base used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is selected from potassium hydroxide, sodium hydroxide, lithium hydroxide and barium hydroxide.

29. The process according to claim 28, wherein the base used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is sodium hydroxide.

30. The process according to claim 11, wherein the organic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is an alcoholic solvent.

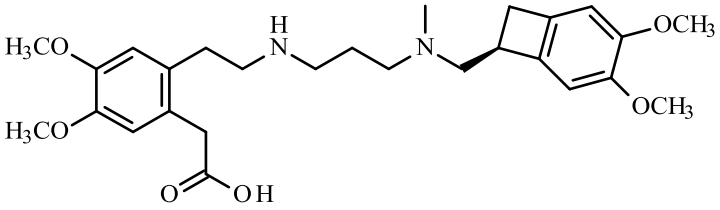
31. The process according to claim 30, wherein the alcoholic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is selected from methanol, ethanol, isopropanol and butanol.

32. The process according to claim 31, wherein the alcoholic solvent used to carry out the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is ethanol.

33. The process according to claim 11, wherein the hydrolysis of the compound of formula (IX) to form the compound of formula (VI) is carried out at a temperature between 0°C and 110°C.

34. A compound of formula (VI):

(VI)



35. A compound of formula (IX):

(IX)

