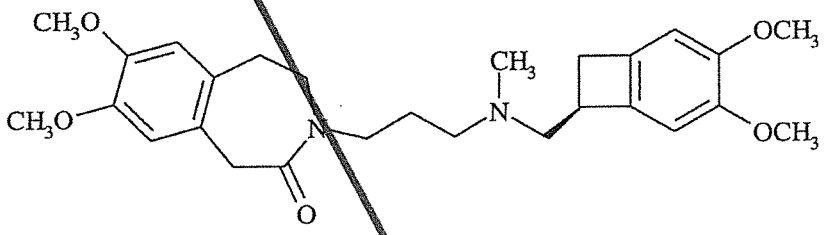
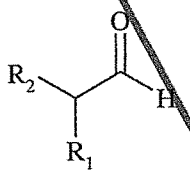
CLAIMS

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



(I),

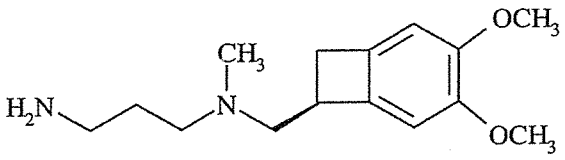
characterised in that the compound of formula (VI):



(VI),

wherein R_1 and R_2, which are the same or different, represent linear or branched $(C_1\text{-}C_6)$alkoxy groups or together with the carbon atom carrying them form a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring,

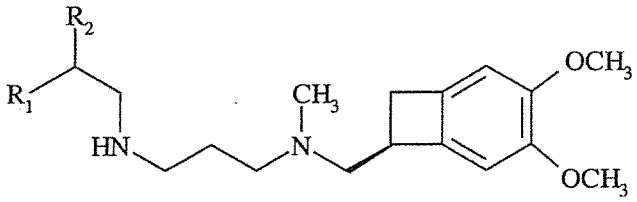
is subjected to a reductive amination reaction with the compound of formula (VII):



(VII)

in the presence of a reducing agent,
in an organic solvent, a mixture of organic solvents or a mixture of organic solvent(s) and water,

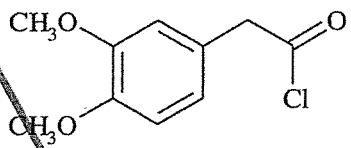
to yield the compound of formula (VIII):



(VIII),

wherein R_1 and R_2 are as defined hereinbefore,

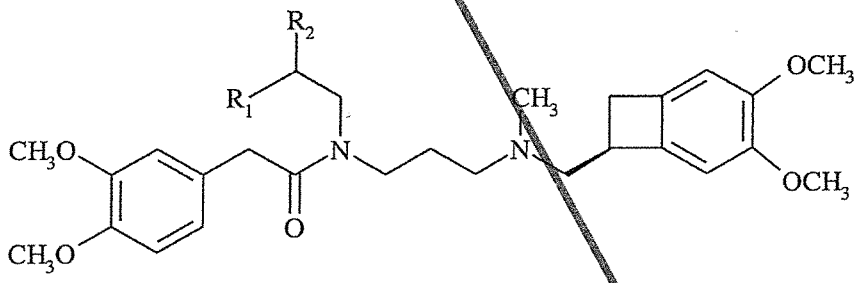
which is subjected to a condensation reaction with the compound of formula (IX):



(IX),

in the presence of a base in an organic solvent,

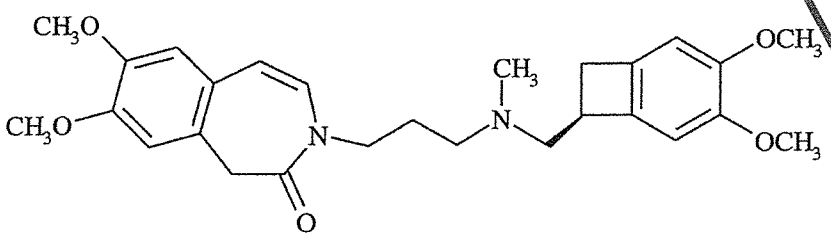
to yield the compound of formula (X):



(X),

wherein R_1 and R_2 are as defined hereinbefore,

which is subjected to a cyclisation reaction in an acid medium to yield the compound of formula (V):



(V),

which is subjected to a hydrogenation reaction to yield ivabradine of formula (I), which may optionally 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 reducing agent used to carry out the reductive amination reaction of the compound of formula (VI) with the compound of formula (VII) is selected from sodium triacetoxyborohydride, sodium cyanoborohydride, and dihydrogen in the presence of a catalyst such as palladium, platinum, nickel, ruthenium, rhodium, and compounds thereof, especially on a support or in the form of oxides.

3. Synthesis process according to claim 2, characterised in that the reducing agent used to carry out the reductive amination reaction of the compound of formula (VI) with the compound of formula (VII) is dihydrogen in the presence of palladium-on-carbon.

4. Synthesis process according to claim 3, characterised in that the reductive amination reaction between the compound of formula (VI) and the compound of formula (VII) is carried out at a dihydrogen pressure of from 0.5 to 1.5 bar.

5. Synthesis process according to any one of claims 1 to 4, characterised in that the solvent used to carry out the reductive amination reaction of the compound of formula (VI) with the compound of formula (VII) is selected from tetrahydrofuran, dichloromethane, 1,2-dichloroethane, acetates and alcohols, preferably ethanol, methanol or isopropanol, toluene and xylene.

6. Synthesis process according to claim 5, characterised in that the solvent used to carry out the reductive amination reaction of the compound of formula (VI) with the compound of formula (VII) comprises a mixture of ethanol and water.

7. Synthesis process according to any one of claims 1 to 6, characterised in that the reductive amination reaction between the compound of formula (VI) and the compound of formula (VII) is carried out at a temperature of from 0 to 40°C.

8. Synthesis process according to any one of claims 1 to 7, characterised in that the organic solvent used in the reaction between the compounds of formulae (VIII) and (IX) is selected from toluene, dichloromethane, 2-methyltetrahydrofuran, chlorobenzene, 1,2-dichloroethane, chloroform and dioxane.

9. Synthesis process according to claim 8, characterised in that the organic solvent used in the reaction between the compounds of formulae (VIII) and (IX) is dichloromethane.

10. Synthesis process according to any one of claims 1 to 9, characterised in that the reaction between the compounds of formulae (VIII) and (IX) is carried out at a temperature of from 0 to 40°C.

11. Synthesis process according to any one of claims 1 to 10, characterised in that the base used in the reaction between the compounds of formulae (VIII) and (IX) is selected from pyridine, 4-dimethylaminopyridine (DMAP) and a tertiary amine.

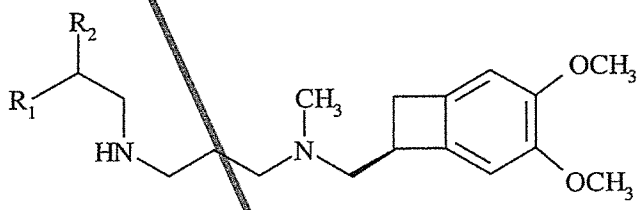
12. Synthesis process according to claim 11, characterised in that the base used in the reaction between the compounds of formulae (VIII) and (IX) is triethylamine.

13. Synthesis process according to any one of claims 1 to 12, characterised in that the acid used to carry out cyclisation of the compound of formula (X) to form the compound of formula (V) is selected from concentrated sulphuric acid, polyphosphoric acid, concentrated hydrochloric acid in aqueous solution, concentrated hydrochloric acid in solution in acetic acid, concentrated hydrobromic acid in solution in acetic acid, and methanesulphonic acid.

14. Synthesis process according to claim 13, characterised in that the acid used to carry out cyclisation of the compound of formula (X) to form the compound of formula (V) is concentrated hydrochloric acid in solution in acetic acid.

15. Synthesis process according to any one of claims 1 to 14, characterised in that cyclisation of the compound of formula (X) to form the compound of formula (V) is carried out at a temperature of from 0 to 40°C.

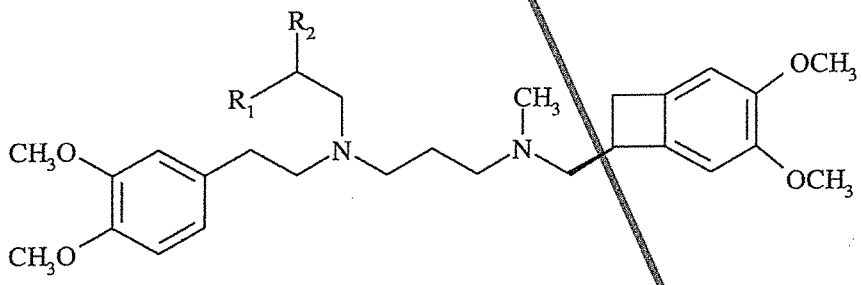
16. Compound of formula (VIII):



(VIII)

wherein R_1 and R_2, which are the same or different, represent linear or branched (C_1-C_6)alkoxy groups or together with the carbon atom carrying them form a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring.

17. Compound of formula (X):

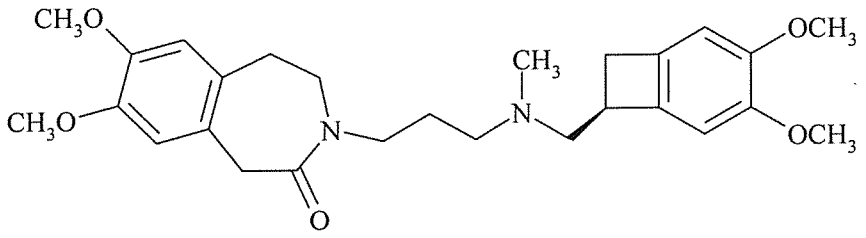


(X)

wherein R_1 and R_2 are as defined in claim 16.

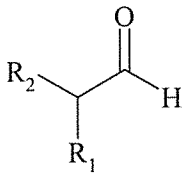
CLAIMS

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



(I),

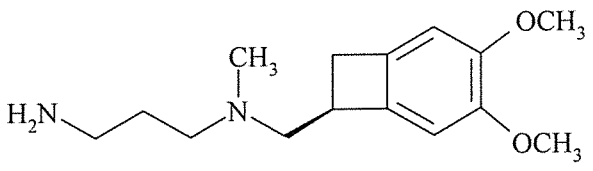
characterised in that the compound of formula (VI):



(VI),

wherein R_1 and R_2, which are the same or different, represent linear or branched (C_1-C_6)alkoxy groups or together with the carbon atom carrying them form a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring,

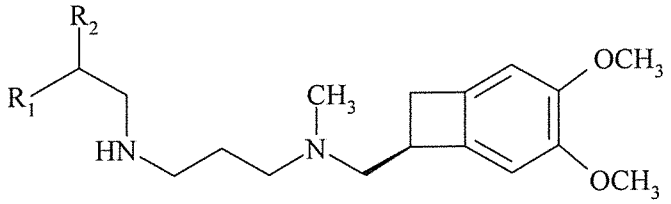
is subjected to a reductive amination reaction with the compound of formula (VII):



(VII)

in the presence of a reducing agent,
in an organic solvent, a mixture of organic solvents or a mixture of organic solvent(s) and water,

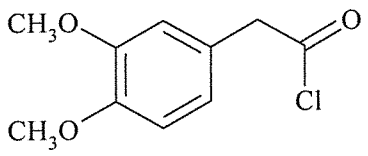
to yield the compound of formula (VIII):



(VIII),

wherein R_1 and R_2 are as defined hereinbefore,

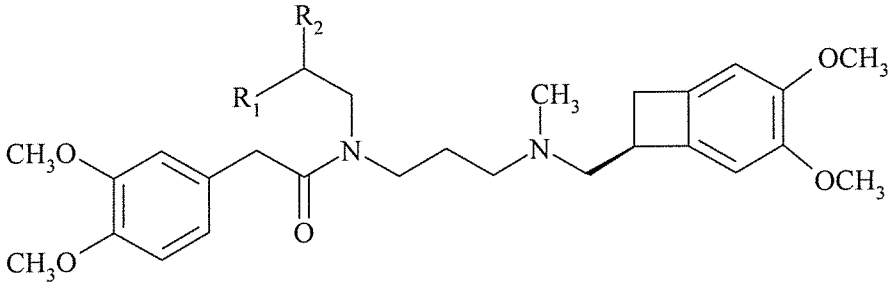
which is subjected to a condensation reaction with the compound of formula (IX):



(IX),

in the presence of a base in an organic solvent,

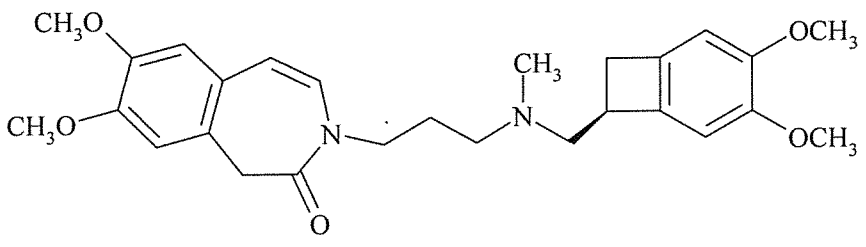
to yield the compound of formula (X):



(X),

wherein R_1 and R_2 are as defined hereinbefore,

which is subjected to a cyclisation reaction in an acid medium to yield the compound of formula (V):



(V),

which is subjected to a hydrogenation reaction to yield ivabradine of formula (I), which may optionally 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. The process according to claim 1, wherein the reducing agent used to carry out the reductive amination reaction of the compound of formula (VI) with the compound of formula (VII) is selected from sodium triacetoxyborohydride, sodium cyanoborohydride, and dihydrogen in the presence of a catalyst.

3. The process according to claim 2, wherein the catalyst is selected from palladium, platinum, nickel, ruthenium, rhodium, and compounds thereof, optionally on a support or in the form of oxides.

4. The process according to claim 2, wherein the reducing agent used to carry out the reductive amination reaction of the compound of formula (VI) and the compound of formula (VII) is dihydrogen in the presence of palladium-on-carbon.

5. The process according to claim 4, wherein the reductive amination reaction between the compound of formula (VI) and the compound of formula (VII) is carried out at a dihydrogen pressure of from 0.5 to 10.5 bar.

6. The process according to claim 1, wherein the solvent used to carry out the reductive amination reaction of the compound of formula (VI) with the compound of formula (VII) is selected from tetrahydrofuran, dichloromethane, 1,2-dichloroethane, acetates and alcohols, toluene and xylene.

7. The process according to claim 6, wherein the solvent used to carry out the reductive amination reaction of the compound of formula (VI) with the compound of formula (VII) is selected from ethanol, methanola and isopropanol.

8. The process according to claim 6, wherein the solvent used to carry out reductive amination reaction of the compound of formulae (VII) with the compound of formula (VII) comprises a mixture of ethanol and water.

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

10. The process of claim 1, wherein the organic solvent used in the reaction between the compounds of formulae (VII) and (IX) is selected from toluene, dichloromethane, 2-methyltetrahydrofuran, chlorobenzene, 1,2-dichloroethane, chloroform and dioxane.

11. The process according to claim 10, wherein the organic solvent used in the reaction between the compounds of formulae (VIII) and (IX) is dichloromethane.

12. The process according to claim 1, wherein the reaction between the compounds of formulae (VIII) and (IX) is carried out at a temperature of from 0 to 40°C.

13. The process of claim 1, wherein the base used in the reaction between the compounds of formulae (VIII) and (IX) is selected from pyridine, 4-dimethylami-nopyridine (DMAP) and a tertiary amine.

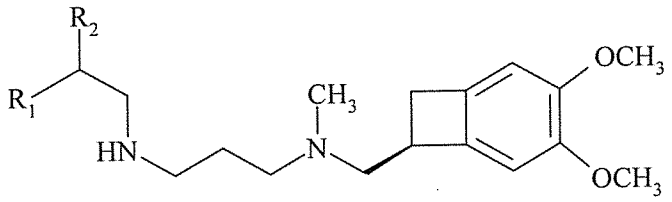
14. The process according to claim 13, wherein the base used in the reaction between the compounds of formulae (VII) and (IX) is triethylamine.

15. The process according to claim 1, wherein the acid used to carry out cyclisation of compound of formula (X) to form the compound of formula (V) is selected from concentrated sulphuric acid, polyphosphoric acid, concentrated hydrochloric acid in aqueous solution, concentrated hydrochloric acid in solution in acetic acid, concentrated hydrobromic acid in solution in acetic acid, and methanesulphonic acid.

16. The process according to claim 15, wherein the acid used to carry out cyclisation of the compound of formula (X) to form the compound of formula (V) is concentrated hydrochloric acid in solution in acetic acid.

17. The process according to claim 1, wherein cyclisation of the compound of formula (X) to form the compound of formula (V) is carried out at a temperature of from 0 to 40°C.

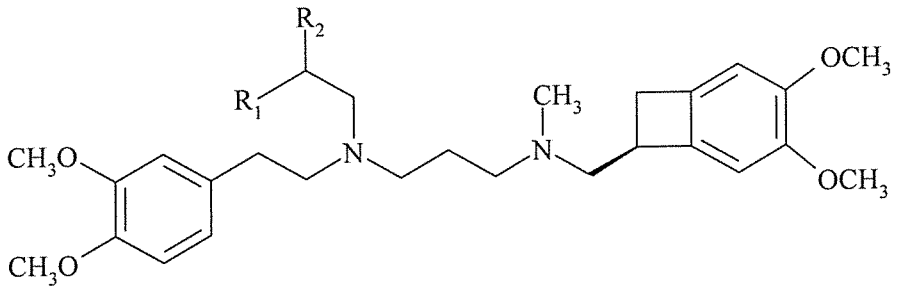
18. A compound selected from those of formula (VIII);



(VIII)

wherein R_1 and R_2, which are the same or different, represent linear or branched (C_1-C_6)alkoxy groups or together with the carbon atom carrying them form a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring.

19. Compound of formula (X):



(X)

wherein R_1 and R_2 which are the same or different, represent linear or branched (C_1-C_6)alkoxy groups or together with the carbon atom carrying them form a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring.