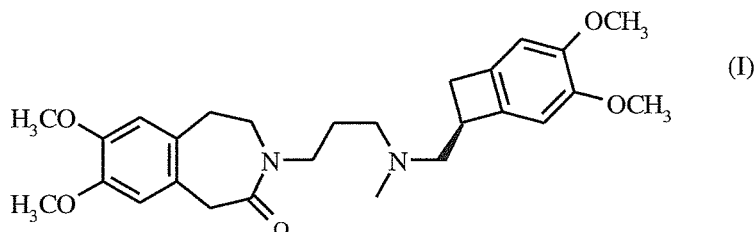
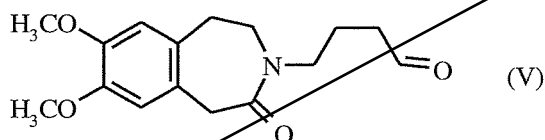


CLAIMS

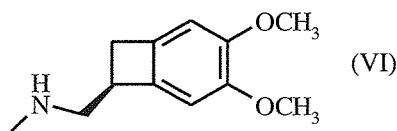
1. Process for the synthesis of ivabradine of formula (I):



characterised in that the compound of formula (V):



is subjected to a reductive amination reaction with the amine of formula (VI):



in the presence of an iron-based catalyst,

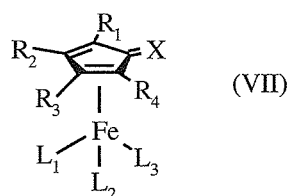
in the presence or not of trimethylamine *N*-oxide,

under dihydrogen pressure of from 1 to 20 bars,

in an organic solvent or mixture of organic solvents,

at a temperature from 25 to 100°C.

2. Synthesis process according to claim 1, characterised in that the iron-based catalyst has the following general formula:



wherein R₁, R₂, R₃ and R₄ independently represent:

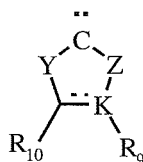
- a hydrogen atom, or
- a group –SiR₅R₆R₇, wherein R₅, R₆ and R₇ independently represent an optionally substituted, linear or branched (C₁-C₆)alkyl group or an optionally substituted aromatic or heteroaromatic group, or
- an optionally substituted aromatic or heteroaromatic group, or
- an optionally substituted, linear or branched (C₁-C₆)alkyl group, or
- an electron-attracting group, or
- an amine group that is aliphatic, aromatic, heteroaromatic or carrying an electron-attracting group, or
- an aliphatic, aromatic or heteroaromatic ether group,

or the pairs R₁ and R₂, or R₂ and R₃, or R₃ and R₄ form, together with the carbon atoms carrying them, a 3- to 7-membered carbocycle or heterocycle,

X represents:

- an oxygen atom, or
- a –NH group or a nitrogen atom substituted by an aliphatic, aromatic, heteroaromatic or electron-attracting group, or
- a –PH group or a phosphorus atom substituted by one or more aliphatic, aromatic or electron-attracting groups, or
- a sulphur atom,

L₁, L₂ and L₃ independently represent a carbonyl, nitrile, isonitrile, heteroaromatic, phosphine, phosphite, phosphonite, phosphoramidite, phosphinite, phospholane, phospholene, aliphatic amine, aromatic amine, heteroaromatic amine, electron-attracting-group-carrying amine, aliphatic ether, aromatic ether, heteroaromatic ether, sulphone, sulfoxide or sulfoximine group or an *N*-heterocyclic carbene group having one of the two following formulae:



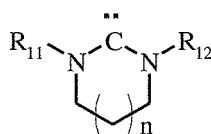
wherein Y and Z independently represent a sulphur or oxygen atom or a group NR₈ wherein R₈ represents an optionally substituted alkyl group or an optionally substituted aromatic or heteroaromatic group,

5 K represents a carbon or nitrogen atom,

R₉ and R₁₀ independently represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted aromatic or heteroaromatic group, a halogen atom, an aliphatic, aromatic or heteroaromatic ether group, an aliphatic, aromatic or heteroaromatic amine group, or the pair R₉ and R₁₀ form, together with the atoms carrying them, a 3- to 7-membered carbocycle or heterocycle,

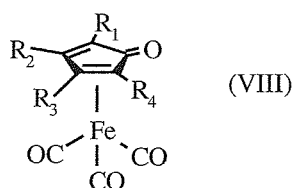
10

or



wherein R₁₁ and R₁₂ independently represent an optionally substituted alkyl group or an optionally substituted aromatic or heteroaromatic group.

15 3. Synthesis process according to claim 2, characterised in that the iron-based catalyst has the following general formula:

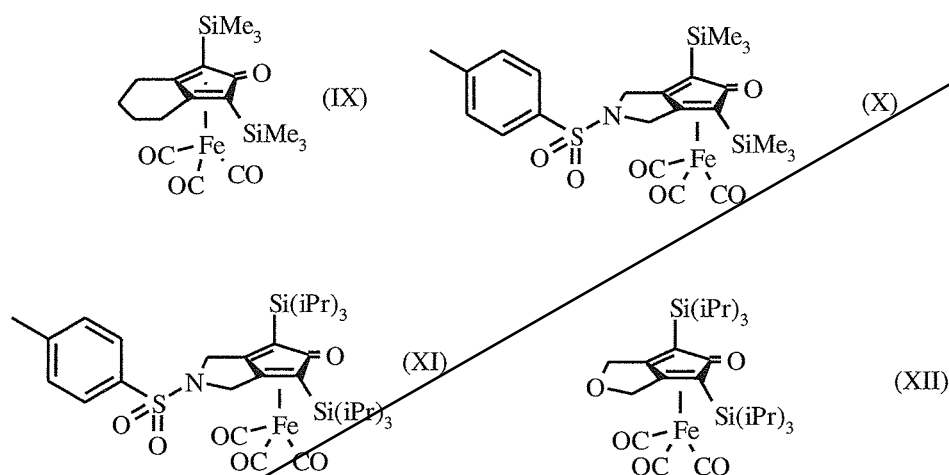


wherein R₂ and R₃ each represent a hydrogen atom or form, together with the carbon atoms carrying them, a 3- to 7-membered carbocycle or heterocycle,

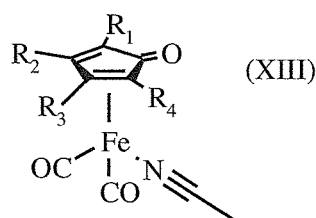
20 and R₁ and R₄ independently represent:

- either a group $-\text{SiR}_5\text{R}_6\text{R}_7$, wherein R_5 , R_6 and R_7 independently represent an optionally substituted, linear or branched $(\text{C}_1\text{-C}_6)$ alkyl group or an optionally substituted aryl group,
- or an optionally substituted aromatic or heteroaromatic group,
- or an optionally substituted, linear or branched $(\text{C}_1\text{-C}_6)$ alkyl group.

4. Synthesis process according to claim 3, characterised in that the iron-based catalyst is selected from:



5. Synthesis process according to claim 2, characterised in that the iron-based catalyst has the following general formula:

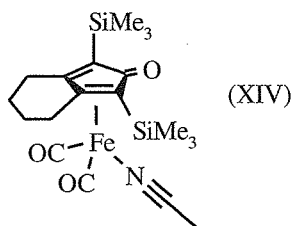
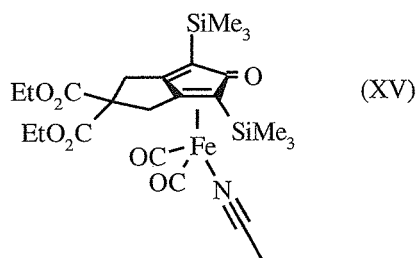


wherein R_2 and R_3 each represent a hydrogen atom or form, together with the carbon atoms carrying them, a 3- to 7-membered carbocycle or heterocycle,

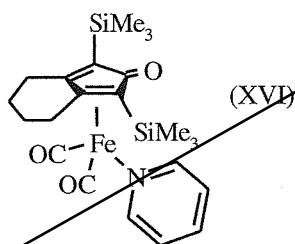
and R_1 and R_4 independently represent:

- either a group $-\text{SiR}_5\text{R}_6\text{R}_7$, wherein R_5 , R_6 and R_7 independently represent an optionally substituted, linear or branched $(\text{C}_1\text{-C}_6)$ alkyl group or an optionally substituted aromatic or heteroaromatic group,
- or an optionally substituted aromatic or heteroaromatic group,
- or an optionally substituted, linear or branched $(\text{C}_1\text{-C}_6)$ alkyl group.

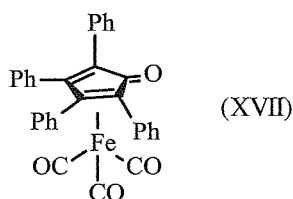
6. Synthesis process according to claim 5, characterised in that the iron-based catalyst is selected from:



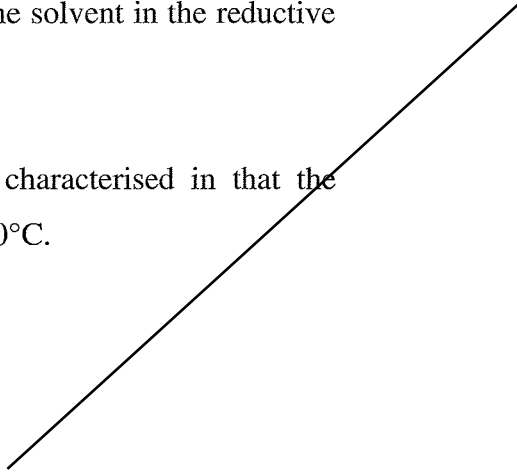
7. Process according to claim 2, characterised in that the iron-based catalyst has the following formula:



8. Process according to claim 2, characterised in that the iron-based catalyst has the following formula:



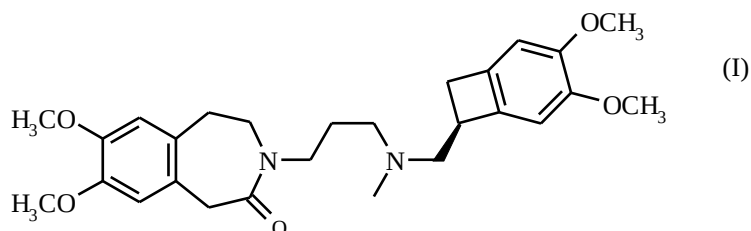
9. Synthesis process according to any one of claims 1 to 8, characterised in that the amount of catalyst used in the reductive amination reaction is from 1 mol% to 10 mol% relative to the aldehyde.
10. Synthesis process according to any one of claims 1 to 9, characterised in that the amount of trimethylamine *N*-oxide used in the reductive amination reaction is from 0 to 3 equivalents relative to the catalyst.

11. Synthesis process according to claim 10, characterised in that the amount of trimethylamine *N*-oxide used in the reductive amination reaction is from 0.5 to 1.5 equivalents relative to the catalyst.
12. Synthesis process according to any one of claims 1 to 11, characterised in that the
5 dihydrogen pressure in the reductive amination reaction is from 1 to 10 bars.
13. Synthesis process according to any one of claims 1 to 12, characterised in that the solvent in the reductive amination reaction is an alcohol.
14. Synthesis process according to claim 13, characterised in that the solvent in the reductive amination reaction is ethanol.
- 10 15. Synthesis process according to any one of claims 1 to 14, characterised in that the temperature of the reductive amination reaction is from 50 to 100°C.
- 

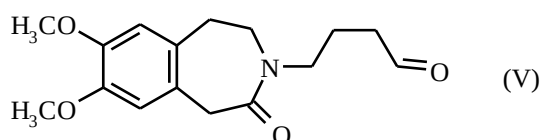
CLAIMS

The invention claimed is:

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

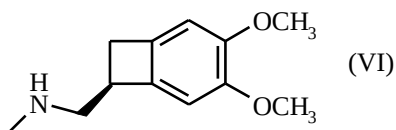


wherein a compound of formula (V):



5

is subjected to a reductive amination reaction with an amine of formula (VI):



in the presence of an iron-based catalyst,

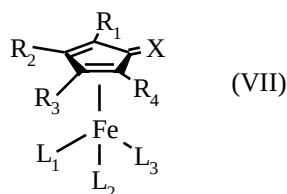
optionally in the presence of trimethylamine *N*-oxide,

10 under dihydrogen pressure of from 1 to 20 bars,

in an organic solvent or mixture of organic solvents,

at a temperature from 25 to 100°C.

2. The process according to claim 1, wherein the iron-based catalyst has the following general formula:



wherein R₁, R₂, R₃ and R₄ independently represent:

a hydrogen atom,

an-SiR₅R₆R₇ group, wherein R₅, R₆ and R₇ independently represent an optionally

5 substituted, linear or branched (C₁-C₆)alkyl group or an optionally substituted aromatic or heteroaromatic group, or

an optionally substituted aromatic or heteroaromatic group,

an optionally substituted, linear or branched (C₁-C₆)alkyl group,

an electron-attracting group,

10 an amine group that is aliphatic, aromatic, heteroaromatic or carrying an electron-attracting group, or

an aliphatic, aromatic or heteroaromatic ether group,

or the pairs R₁ and R₂, or R₂ and R₃, or R₃ and R₄ form, together with the carbon atoms carrying them, a 3- to 7-membered carbocycle or heterocycle,

15 X represents:

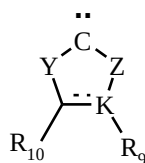
an oxygen atom, or

an -NH group or a nitrogen atom substituted by an aliphatic, aromatic, heteroaromatic or electron-attracting group, or

20 a -PH group or a phosphorus atom substituted by one or more aliphatic, aromatic or electron-attracting groups, or

a sulphur atom,

L₁, L₂ and L₃ independently represent a carbonyl, nitrile, isonitrile, heteroaromatic, phosphine, phosphite, phosphonite, phosphoramidite, phosphinite, phospholane, phospholene, aliphatic amine, aromatic amine, heteroaromatic amine, electron-attracting-group-carrying
25 amine, aliphatic ether, aromatic ether, heteroaromatic ether, sulphone, sulfoxide or sulfoximine group or an N-heterocyclic carbene group having one of the two following formulae:



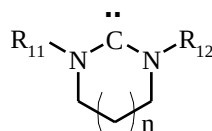
wherein Y and Z independently represent a sulphur or oxygen atom or a group NR₈ group wherein R₈ represents an optionally substituted alkyl group or an optionally substituted aromatic or heteroaromatic group,

5 K represents a carbon or nitrogen atom,

R₉ and R₁₀ independently represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted aromatic or heteroaromatic group, a halogen atom, an aliphatic, aromatic or heteroaromatic ether group, an aliphatic, aromatic or heteroaromatic amine group,

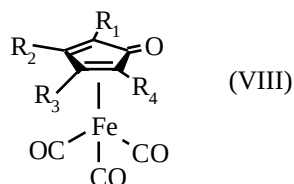
10 or the pair R₉ and R₁₀, together with the atoms to which they are attached, form a 3- to 7-membered carbocycle or heterocycle,

or



wherein R₁₁ and R₁₂ independently represent an optionally substituted alkyl group or an optionally substituted aromatic or heteroaromatic group and n is 1 or 2.

15 3. The process according to claim 2, wherein the iron-based catalyst has the following general formula:



wherein R₂ and R₃ each represent a hydrogen atom or, together with the carbon atoms to which they are attached, form a 3- to 7-membered carbocycle or heterocycle,

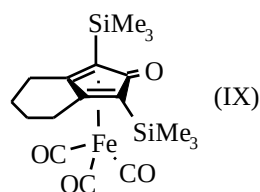
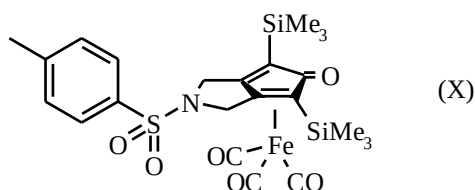
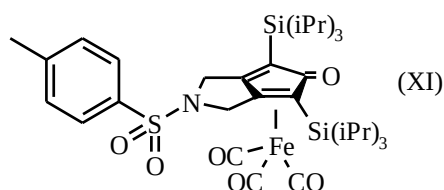
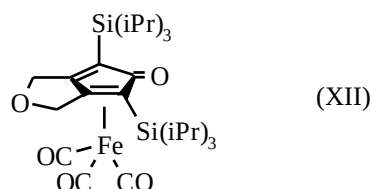
20 and R₁ and R₄ independently represent:

an $-\text{SiR}_5\text{R}_6\text{R}_7$ group, wherein R_5 , R_6 and R_7 independently represent an optionally substituted, linear or branched ($\text{C}_1\text{-C}_6$)alkyl group or an optionally substituted aryl group,

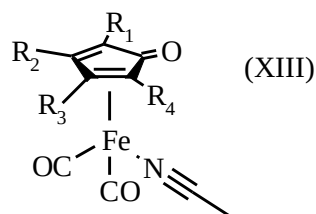
an optionally substituted aromatic or heteroaromatic group, or

5 an optionally substituted, linear or branched ($\text{C}_1\text{-C}_6$)alkyl group.

4. The process according to claim 3, wherein the iron-based catalyst is selected from:



5. The process according to claim 2, wherein the iron-based catalyst has the following general formula:



10

wherein R_2 and R_3 each represent a hydrogen atom or, together with the carbon atoms to which they are attached, form a 3- to 7-membered carbocycle or heterocycle,

and R_1 and R_4 independently represent:

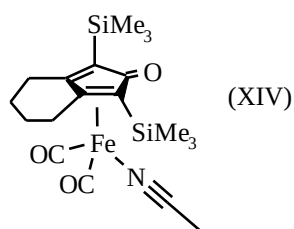
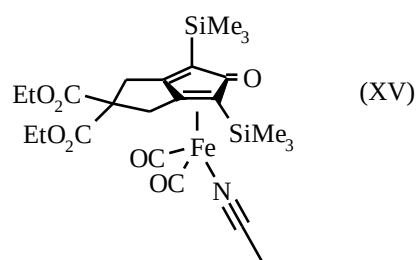
an $-\text{SiR}_5\text{R}_6\text{R}_7$, wherein R_5 , R_6 and R_7 independently represent an optionally substituted, linear or branched ($\text{C}_1\text{-C}_6$)alkyl group or an optionally substituted aromatic or heteroaromatic group,

15

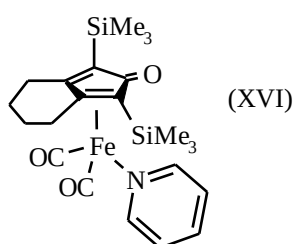
an optionally substituted aromatic or heteroaromatic group, or

an optionally substituted, linear or branched ($\text{C}_1\text{-C}_6$)alkyl group.

6. The process according to claim 5, wherein the iron-based catalyst is selected from:

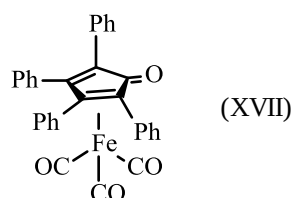


7. The process according to claim 2, wherein the iron-based catalyst has the following formula:



5

8. The process according to claim 2, wherein the iron-based catalyst has the following formula:



9. The process according to claim 1, wherein that the amount of catalyst used in the reductive amination reaction is from 1 mol% to 10 mol% relative to the aldehyde.
10. The process according to claim 1, wherein the amount of trimethylamine N-oxide used in the reductive amination reaction is from 0 to 3 equivalents relative to the catalyst.
11. The process according to claim 10, wherein the amount of trimethylamine N-oxide used in the reductive amination reaction is from 0.5 to 1.5 equivalents relative to the catalyst.

15

12. The process according to claim 1, wherein the dihydrogen pressure in the reductive amination reaction is from 1 to 10 bars.
13. The process according to claim 1, wherein the solvent in the reductive amination reaction is an alcohol.
- 5 14. The process according to claim 13, wherein the solvent in the reductive amination reaction is ethanol.
15. The process according to claim 1, wherein the temperature of the reductive amination reaction is from 50 to 100°C.