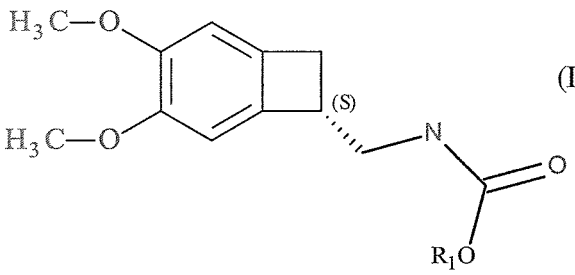
CLAIMS

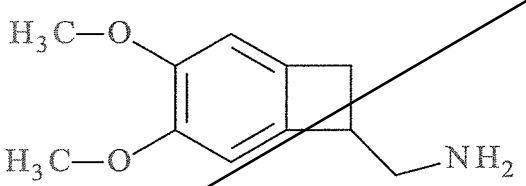
1. Process for the synthesis of the compound of formula (IX):



(IX),

wherein R_1 represents a linear or branched C_1-C_6alkyl, allyl or benzyl group,

by enantioselective enzymatic acylation of the racemic amine of formula (IV):



(IV)

using a lipase (EC 3.1.1.3 in the international classification of enzymes),

with a carbonate of formula R_1O-(CO)-OR_1, wherein R_1 is as defined hereinbefore,
in an amount ranging from 1 to 15 molar equivalents relative to the amine of formula (IV),
in an organic or aqueous solvent, a mixture of organic solvents or a mixture of organic and aqueous solvents,
at a concentration from 5 to 500 g/L of compound of formula (IV) per litre of solvent or mixture of solvents,
at an E/S ratio of from 10/1 to 1/100, at a temperature from 25°C to 40°C.

2. Synthesis process according to claim 1, wherein the lipase is selected from lipases of *Pseudomonas fluorescens*, of *Pseudomonas cepacia*, of porcine pancreas, and the lipases PS 'Amano' SD (*Burkholderia cepacia*) and IM (immobilised on Diatomite).

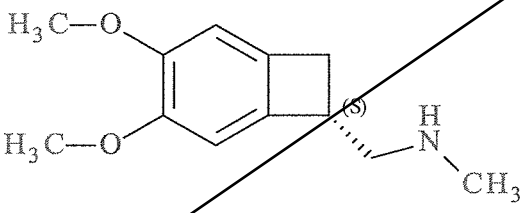
3. Synthesis process according to claim 2, wherein the lipase is a lipase of *Pseudomonas cepacia* or a lipase PS 'Amano' IM.

4. Synthesis process according to any one of claims 1 to 3, wherein the E/S ratio is from 1/1 to 1/10.

5. Synthesis process according to any one of claims 1 to 4, wherein the solvent is selected from TBME, THF, 2-MeTHF and 1,4-dioxane, on their own or in admixture with a buffer of pH=7.

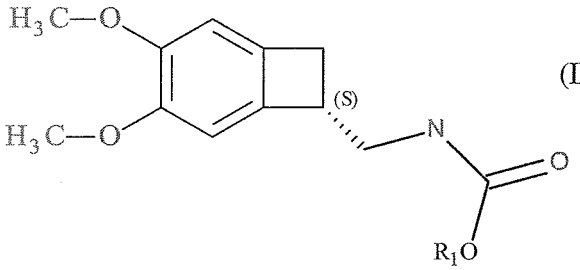
6. Synthesis process according to any one of claims 1 to 5, wherein R_1 is an ethyl, allyl or benzyl group.

7. Process for the synthesis of the compound of formula (I):



(I)

by enzymatic acylation of the racemic amine of formula (IV) in accordance with any one of claims 1 to 6 to yield the carbamate of formula (IX):

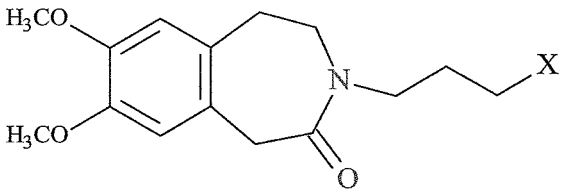


(IX),

wherein R_1 represents a linear or branched C_1-C_6alkyl, allyl or benzyl group,

which is then reduced using a reducing agent selected from $LiAlH_4$ and Red-Al to yield the compound of formula (I).

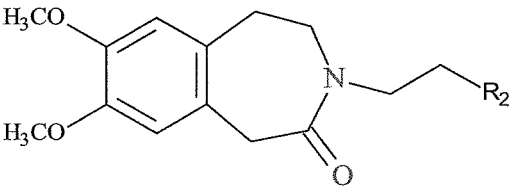
8. Synthesis process according to claim 7, wherein the compound of formula (I) subsequently is either coupled with a compound of formula (X):



(X),

wherein X represents a halogen atom,

or, in the presence of a reducing agent, subjected to a reductive amination reaction with a compound of formula (XI):



(XI),

wherein R_2 represents a group selected from CHO and CHR_3R_4,

wherein R_3 and R_4 each represent a linear or branched (C_1-C_6)alkoxy group or form, together with the carbon atom carrying them, a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring,

to yield ivabradine, which is then converted into an addition salt with a pharmaceutically acceptable acid, in anhydrous or hydrate form.

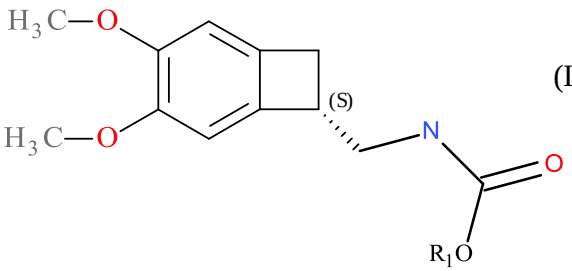
9. Synthesis process according to claim 8, wherein X is an iodine atom.

10. Synthesis process according to claim 8, wherein the compound of formula (I) used in the reductive amination reaction is in the form of its hydrochloride, to yield ivabradine in the form of the hydrochloride.

11. Synthesis process according to either claim 8 or claim 10, wherein the reductive amination reaction with a compound of formula (XI) is carried out in the presence of dihydrogen catalysed by palladium-on-carbon.

CLAIMS

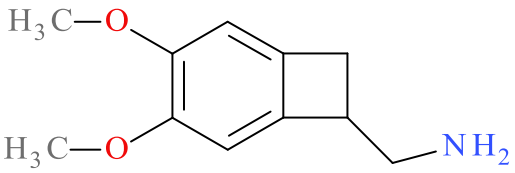
1. A process for the synthesis of a compound of formula (IX):



(IX) ,

wherein R_1 represents a linear or branched C_1-C_6alkyl, allyl or benzyl group,

by enantioselective enzymatic acylation of the racemic amine of formula (IV):



(IV)

using a lipase (EC 3.1.1.3 in the international classification of enzymes),

with a carbonate of formula R_1O-(CO)-OR_1, wherein R_1 is as defined hereinbefore,
in an amount ranging from 1 to 15 molar equivalents relative to the amine of formula (IV),
in an organic or aqueous solvent, a mixture of organic solvents or a mixture of organic and aqueous solvents,
at a concentration from 5 to 500 g/L of compound of formula (IV) per litre of solvent or mixture of solvents,
at an Enzyme/Substrate ratio (E/S) of from 10/1 to 1/100, at a temperature from 25°C to 40°C.

2. The process according to claim 1, wherein the lipase is selected from lipases of *Pseudomonas fluorescens*, of *Pseudomonas cepacia*, of porcine pancreas, and the lipases PS ‘Amano’ SD (*Burkholderia cepacia*) and IM (immobilised on Diatomite).

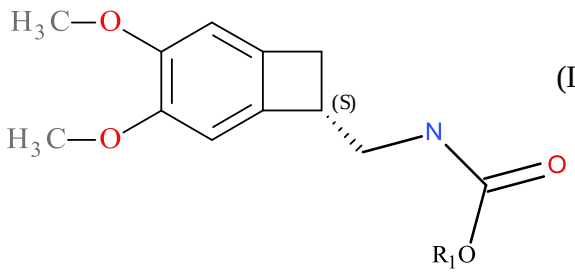
3. The process according to claim 2, wherein the lipase is a lipase of *Pseudomonas cepacia* or a lipase PS 'Amano' IM.

4. The process according claim 1, wherein the E/S ratio is from 1/1 to 1/10.

5. The process according to claim 1, wherein the solvent is selected from TBME, THF, 2-MeTHF and 1,4-dioxane, and mixtures thereof, with a buffer of pH=7.

6. The process according to claim 1, wherein R_1 is an ethyl, allyl or benzyl group.

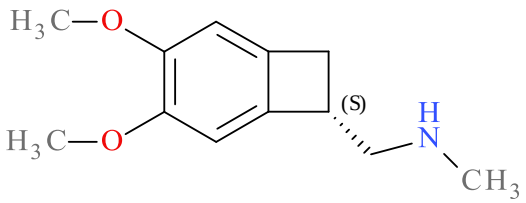
7. The process accordingly to claim 1, further comprising reduction of the compound of formula (IX):



(IX)

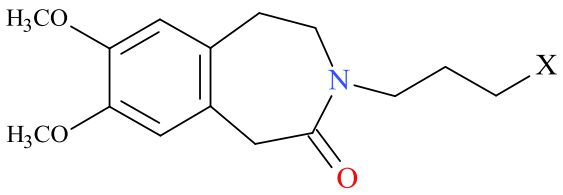
wherein R_1 represents a linear or branched C_1-C_6alkyl, allyl or benzyl group,

using a reducing agent selected from $LiAlH_4$ and Red-Al to yield the compound of formula (I):



(I)

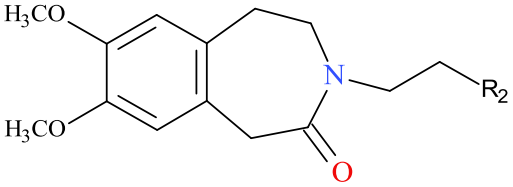
8. The process according to claim 7, wherein the compound of formula (I) subsequently is either coupled with a compound of formula (X):



(X),

wherein X represents a halogen atom,

or, in the presence of a reducing agent, subjected to a reductive amination reaction with a compound of formula (XI):



(XI),

wherein R_2 represents a group selected from CHO and CHR_3R_4,

wherein R_3 and R_4 each represent a linear or branched (C_1-C_6)alkoxy group or, together with the carbon atom carrying them, form a 1,3-dioxane, 1,3-dioxolane or 1,3-dioxepane ring,

to yield ivabradine, which is then converted into an addition salt with a pharmaceutically acceptable acid, in anhydrous or hydrate form.

9. The process according to claim 8, wherein X is an iodine atom.

10. The process according to claim 8, wherein the compound of formula (I) used in the reductive amination reaction is in the form of its hydrochloride salt, to yield ivabradine in the form of its hydrochloride salt.

11. The process according to claim 8, wherein the reductive amination reaction with a compound of formula (XI) is carried out in the presence of dihydrogen catalysed by palladium-on-carbon.

12. The process according to claim 10, wherein the reductive amination reaction with a compound of formula (XI) is carried out in the presence of dihydrogen catalysed by palladium-on-carbon.