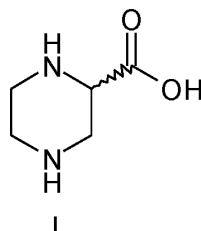


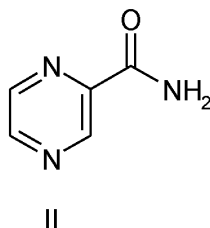
Claims

1. Process for the preparation of a chiral piperazine-2-carboxylic acid or of a salt thereof of the formula I

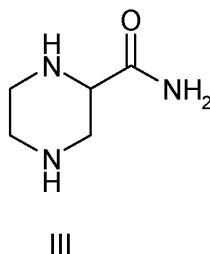


5 comprising the steps

a) the catalytic hydrogenation of pyrazine-2-carboxamide of the formula II



to form the piperazine-2-carboxamide of formula III



10 and

b) the enzymatic conversion of the piperazine-2-carboxamide of formula III with a hydrolase to form the chiral piperazine-2-carboxylic acid or a salt thereof of the formula I.

2. Process of claim 1, wherein the bond

15 “  ” stands for “  ” or for “  ”.

3. Process of claim 1 or 2, wherein the catalytic hydrogenation is performed with hydrogen in the presence of a metal hydrogenation catalyst and a solvent

4. Process of claim 3, wherein the metal hydrogenation catalyst is Pd or Pt, preferably Pd, with a metal loading on support of 0.5% w/w to 20% w/w, preferably 3% w/w to 15%, more preferably 8 to 12% w/w and an inert support selected from carbon or aluminum oxide, more preferably from carbon.

5. Process of claim 3 or 4, wherein the solvent is an organic solvent selected from aliphatic alcohols such as methanol or ethanol or water or mixtures thereof, but preferably water.

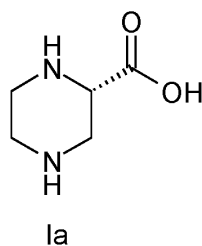
6. Process of any one of claim 3 to 5, wherein the catalytic hydrogenation is performed at a reaction temperature of 20 °C to the boiling temperature of the solvent, preferably from 30 °C to 60 °C at a hydrogen pressure from 5 bar to 50 bar, preferably from 15 bar to 25 bar.

7. Process of any one of claims 1 to 6, wherein the piperazine-2-carboxamide of formula III obtained in step a) is not isolated and in situ further processed in step b).

8. Process of any one of claims 1 to 7, wherein the hydrogenation catalyst is re-used.

9. Process of claim 1, wherein the hydrolase used in the enzymatic conversion of step b) is a peptidase or an amidase or mixtures thereof.

10. Process of claim 9, wherein the hydrolase has the potential to form the (*S*)-piperazine-2- carboxylic acid of the formula Ia



with an enantiomeric excess of at least 90% .

11. Process of claim 9 or 10, wherein the hydrolase has an amino acid sequence, which is at least 80%, at least 85%, at least 90%. or at least 95% identical to the amino acid sequence of SEQ ID NO 1.

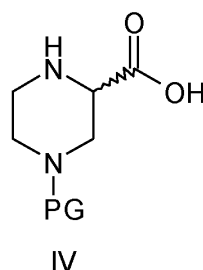
12. Process of claim 9 or 10, wherein the hydrolase is the enzyme mixture Flavourzyme® or an enzyme preparation containing the hydrolase of SEQ ID NO 1.

13. Process of any one of claims 9 to 12, wherein the enzymatic conversion is performed at a reaction temperature of 10 °C to 50 °C, preferably 20 °C to 30 °C, in the solvent used in the hydrogenation step a), preferably in water.

14. Process of any one of claims 9 to 13, wherein subsequent to the enzymatic conversion the chiral piperazine-2-carboxylic acid of formula I is converted into its hydrochloride salt by adding an aqueous hydrochloric acid to the reaction mixture in a manner that the reaction temperature is maintained in the range of -15 °C to 30 °C.

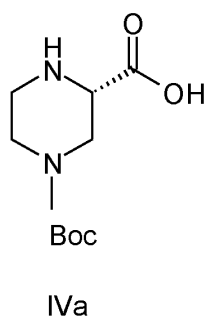
15. Process of claim 1, wherein the process further contains the step

c) the introduction of an amino protecting group PG to form the chiral piperazine-2-carboxylic acid of formula IV

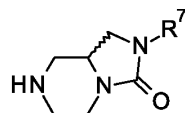


wherein PG stands for an amino protecting group.

16. Process of claim 15, wherein PG is Boc (*tert*-butoxycarbonyl) and the chiral piperazine-2-carboxylic acid of formula IV is the (2*S*)-4-*tert*-butoxycarbonylpiperazine-2-carboxylic acid of formula IVa



17. Process of claim 15 or 16, wherein the process further comprises the formation of a compound of formula IX or its enantiomers or stereoisomers thereof,



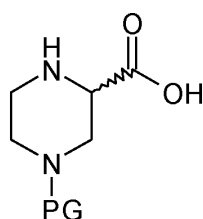
IX

5 wherein

R^7 is C_{1-6} -alkyl, C_{3-7} -cycloalkyl, $-C_mH_{2m}-COOH$, $-C_mH_{2m}-C_{3-7}$ -cycloalkyl- $COOH$ or carboxyphenyl;

comprising the steps

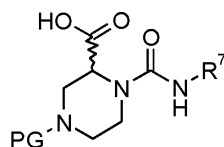
10 d) the conversion of the chiral piperazine-2-carboxylic acid of formula IV, or of a salt thereof,



IV

wherein PG is an amino protecting group, with an amine R^7-NH_2 , wherein R^7 is as above, in the presence of a coupling agent and a base to form the mixed urea of formula V or of a salt thereof,

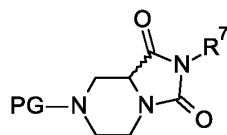
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V

wherein PG and R^7 are as above;

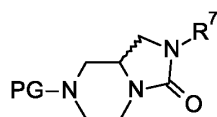
e) the cyclisation of the mixed urea of formula V to form the hydantoin of formula VI



VI

wherein PG and R⁷ are as above;

5 f) the reduction of the hydantoin of formula VI to form the cyclic urea of formula VII

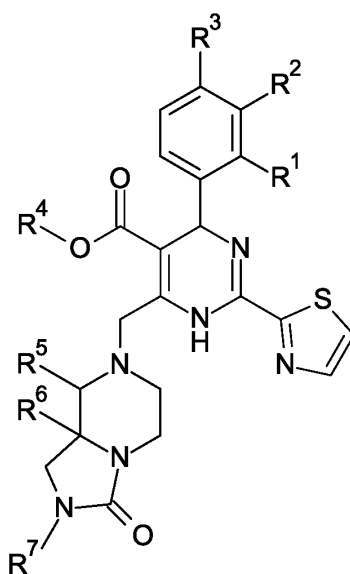


VII

wherein PG and R⁷ are as above; and

g) the deprotection and formation of the compound of formula IX.

18. Use of the process of claims 1 to 17 for the preparation of compounds of the formula X



X

wherein

- R¹ is halogen or C₁₋₆-alkyl;
R² is hydrogen or halogen;
R³ is hydrogen or halogen;
5 R⁴ is C₁₋₆-alkyl;
R⁵ is hydrogen or carboxy;
R⁶ is hydrogen;
R⁷ is C₁₋₆-alkyl, C₃₋₇-cycloalkyl, -C_mH_{2m}-COOH, -C_mH_{2m}-C₃₋₇-cycloalkyl-COOH or
carboxyphenyl;
10 m is 1-6;
or pharmaceutically acceptable salts, or enantiomers or diastereomers thereof