

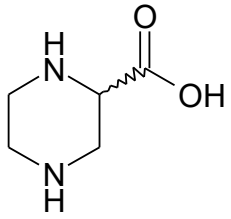
III

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

SUMMARY

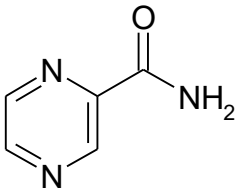
In one aspect, the present disclosure provides a process for the preparation of a chiral piperazine-2-carboxylic acid or of a salt thereof of the formula I



I

comprising the steps

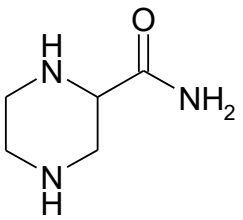
a) the catalytic hydrogenation of pyrazine-2-carboxamide of the formula II



II

with hydrogen in the presence of a metal hydrogenation catalyst and water

to form the piperazine-2-carboxamide of formula III

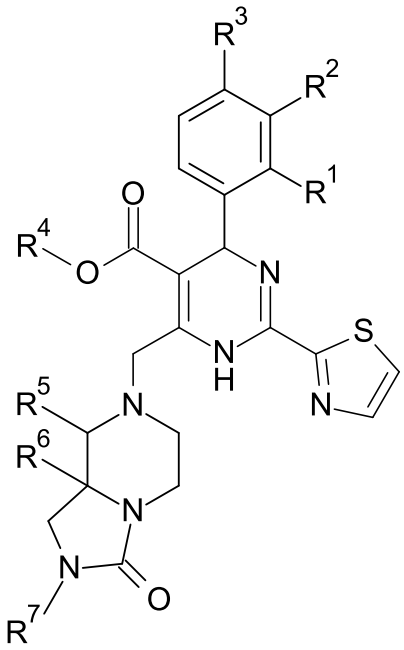


III

and

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

In another aspect, the present disclosure provides use of the process as described herein for the preparation of compounds of the formula X



X

wherein

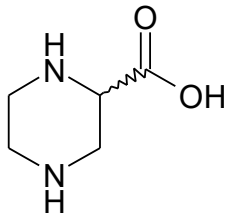
R^1 is halogen or C_{1-6}-alkyl;

R^2 is hydrogen or halogen;

R^3 is hydrogen or halogen;

Claims

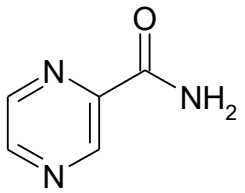
1. Process for the preparation of a chiral piperazine-2-carboxylic acid or of a salt thereof of the formula I



I

comprising the steps

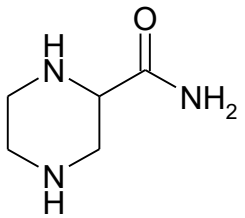
a) the catalytic hydrogenation of pyrazine-2-carboxamide of the formula II



II

with hydrogen in the presence of a metal hydrogenation catalyst and water

to form the piperazine-2-carboxamide of formula III



III

and

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

2. Process of claim 1, wherein the bond

“  ” stands for “  ” or for “  ”.

3. Process of claim 1 or 2, 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.

4. Process of claim 3, 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.

5. Process of any one of claims 1 to 4, wherein the piperazine-2-carboxamide of formula III obtained in step a) is not isolated and in situ further processed in step b).

6. Process of any one of claims 1 to 5, wherein the hydrogenation catalyst is re-used.

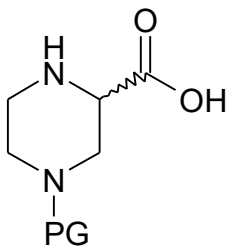
7. Process of claim 1, wherein the hydrolase is the enzyme mixture Flavourzyme®, or an enzyme preparation containing the hydrolase of SEQ ID NO 1.

8. Process of claim 1 or 7, wherein the enzymatic conversion is performed at a reaction temperature of 10 °C to 50 °C, preferably 20 °C to 30 °C.

9. Process of any one of claims 1, 7 or 8, 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.

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

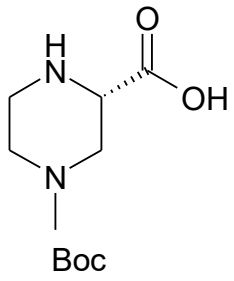
c) the introduction of an amino protecting group PG to form the chiral piperazine-2-carboxylic acid of formula IV



IV

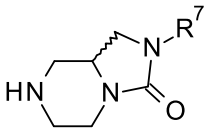
wherein PG stands for an amino protecting group.

11. Process of claim 10, 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



IVa .

12. Process of claim 10 or 11, wherein the process further comprises the formation of a compound of formula IX or its enantiomers or stereoisomers thereof,



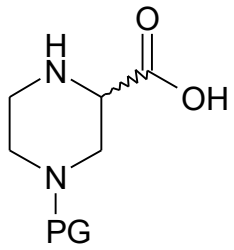
IX

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;

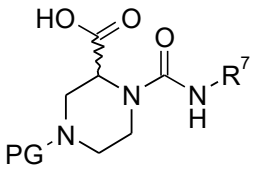
comprising the steps

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



IV

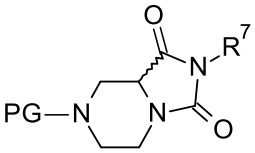
wherein PG is an amino protecting group, with an amine R^7-NH_2, wherein R^7 is as above, in the presence of a coupling agent and a base to form the mixed urea of formula V or of a salt thereof,



V

wherein PG and R^7 are as above;

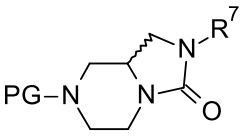
e) the cyclisation of the mixed urea of formula V to form the hydantoin of formula VI



VI

wherein PG and R^7 are as above;

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

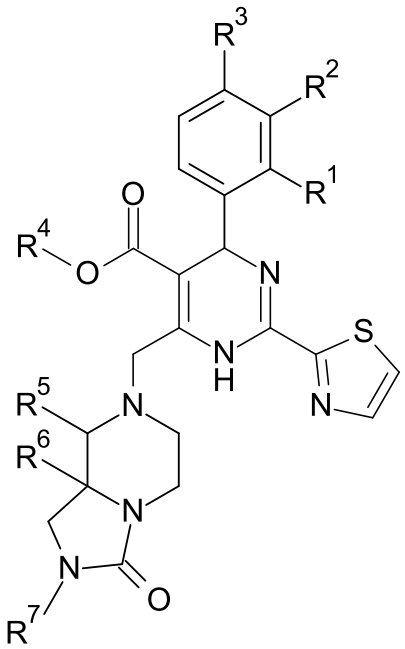


VII

wherein PG and R^7 are as above; and

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

13. Use of the process of claims 1 to 12 for the preparation of compounds of the formula X



X

wherein

R^1 is halogen or C_{1-6}-alkyl;

R^2 is hydrogen or halogen;

R^3 is hydrogen or halogen;

R^4 is C_{1-6}-alkyl;

R^5 is hydrogen or carboxy;

R^6 is hydrogen;

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;

m is 1-6;

or pharmaceutically acceptable salts, or enantiomers or diastereomers thereof.