

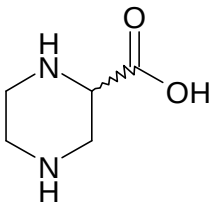
III

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

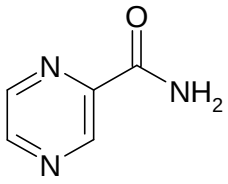
In one aspect, the present disclosure provides a process for the preparation of a chiral piperazine-2-carboxylic acid or of a salt thereof of the formula I



I

comprising the steps

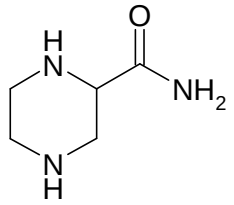
a) the catalytic hydrogenation of pyrazine-2-carboxamide of the formula II



II

to form the piperazine-2-carboxamide of formula III

2a

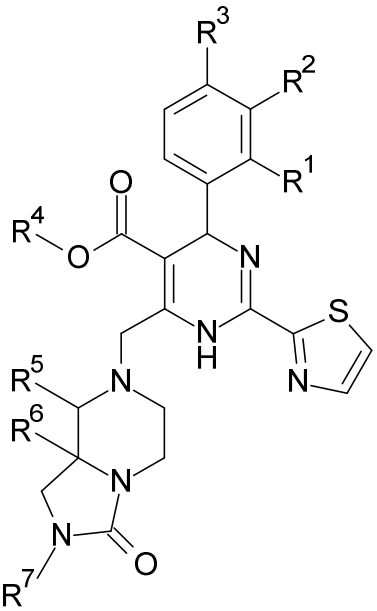


III

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.

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;

$R^4$ 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.

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "amino protecting group" refers to an acid or Lewis acid sensitive substituent conventionally used to hinder the reactivity of the amino group. Suitable acid or Lewis acid sensitive amino protecting groups are described in Green T., "Protective Groups in Organic Synthesis", 4th Ed. by Wiley Interscience, 2007, Chapter 7, 696 ff.. Suitable amino protecting groups for PG can therefore be selected from Boc (*tert*-butoxycarbonyl), benzyl, 4-methoxybenzyl, benzhydryl, Fmoc (fluorenylmethoxycarbonyl), Cbz (benzyloxycarbonyl), Moz (p-methoxybenzyl carbonyl), Troc (2,2,2-trichloroethoxycarbonyl), Teoc (2-(Trimethylsilyl)ethoxycarbonyl), Adoc (adamantoxycarbonyl), formyl, acetyl or from cyclobutoxycarbonyl. Preferred amino protecting group is Boc. .

The spiral bond

"  "

stands for "  " or for "  " thus indicating chirality of the molecule.

Whenever a chiral carbon is present in a chemical structure, it is intended that all stereoisomers associated with that chiral carbon are encompassed by the structure as pure stereoisomers as well as mixtures thereof.

Step a)

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