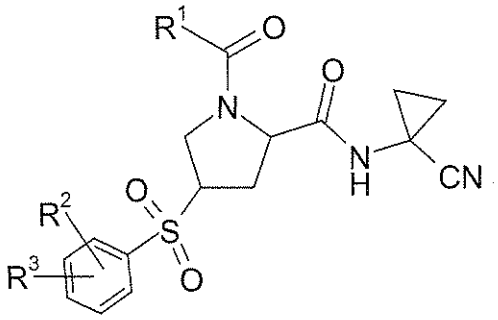
Process For The Preparation Of 1-Acyl-4-Phenylsulfonylprolinamide Derivatives And New Intermediates

The invention relates to a process for the preparation of proline derivatives of the formula



I

wherein,

R^1 is selected from C_{1-7}-alkyl or from

wherein R^4 is selected from C_{1-7}-alkyl, halogen-C_{1-7}-alkyl or from phenyl which is optionally substituted by halogen;

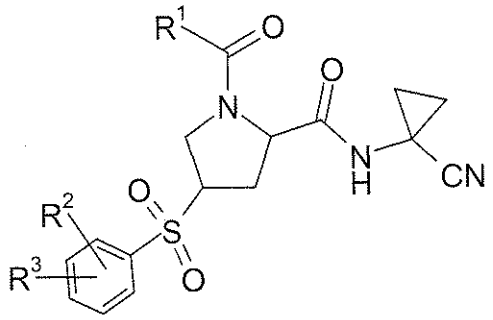
R^2 is selected from halogen or halogen-C_{1-7}-alkyl; and

R^3 is selected from hydrogen, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy or from a 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms, the ring which is optionally substituted by C_{1-7}-alkyl or halogen.

The proline derivatives of the formula I are preferential inhibitors of the cysteine protease Cathepsin S and are therefore useful to treat metabolic diseases like diabetes, atherosclerosis, abdominal aortic aneurysm, peripheral arterial disease and diabetic nephropathy (PCT Publ. WO 2010/121918).

Object of the ~~present invention~~ embodiments disclosed herein is to provide a scalable process for the manufacture of the compounds of formula I.

In a first aspect, there is provided a process for the preparation of proline derivatives of formula I~~The object could be achieved with the process of the present invention which comprises the steps:~~



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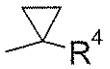


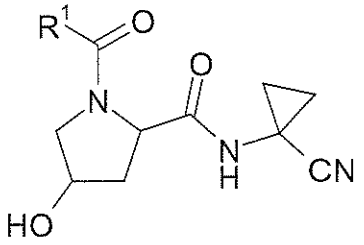
wherein R^4 is selected from C_{1-7}-alkyl, halogen-C_{1-7}-alkyl or from phenyl which is optionally substituted by halogen;

R^2 is selected from halogen or halogen-C_{1-7}-alkyl; and

R^3 is selected from hydrogen, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy or from a 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms, the ring which is optionally substituted by C_{1-7}-alkyl or halogen;

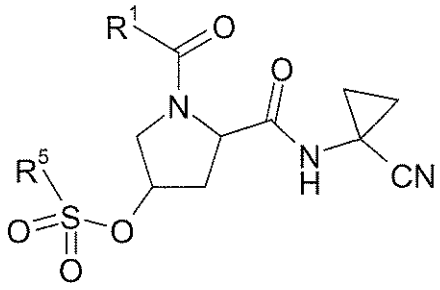
comprising the steps

a) transforming an alcohol of formula II



II

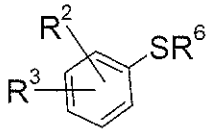
wherein R^1 has the meaning as above into the sulfonate of the formula III



III

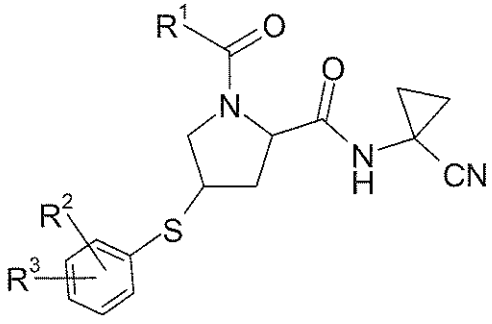
wherein R^1 has the meaning as above and R^5 is C_{1-7}-alkyl, halogen-C_{1-7}-alkyl or phenyl which is optionally substituted by C_{1-7}-alkyl, nitro or bromo;

b) reacting the sulfonate of formula III with a thio compound of formula IV



IV

wherein R^2 and R^3 are as outlined above and R^6 is hydrogen or a protecting group to form the thioether of the formula V

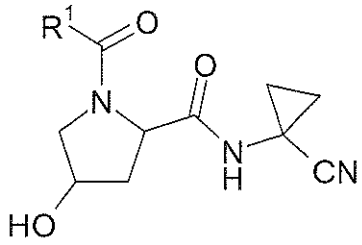


V

wherein R^1, R^2 and R^3 are as outlined above and

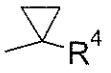
c) oxidizing the thioether of formula V to form the proline derivative of formula I, wherein R^1, R^2 and R^3 are as outlined above.

In a second aspect, there is provided an alcohol of formula II



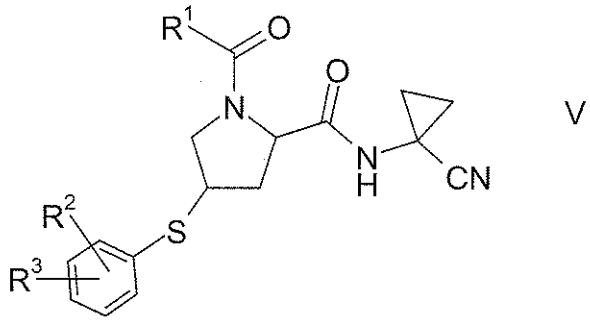
II

wherein R^1 is selected from C_{1-7}-alkyl or from



wherein R^4 has the meaning of methyl or trifluoromethyl.

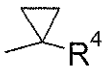
In a third aspect, there is provided a thioether of formula V



V

wherein

R^1 is selected from C_{1-7}-alkyl or from



wherein R^4 is selected from C_{1-7}-alkyl, halogen-C_{1-7}-alkyl or from phenyl which is optionally substituted by halogen;

R^2 is selected from halogen or halogen-C_{1-7}-alkyl; and

R^3 is selected from hydrogen, halogen, halogen-C_{1-7}-alkyl, C_{1-7}-alkoxy, halogen-C_{1-7}-alkoxy or from a 5- or 6-membered heterocyclic ring containing one or two nitrogen atoms, the ring which is optionally substituted by C_{1-7}-alkyl or halogen.