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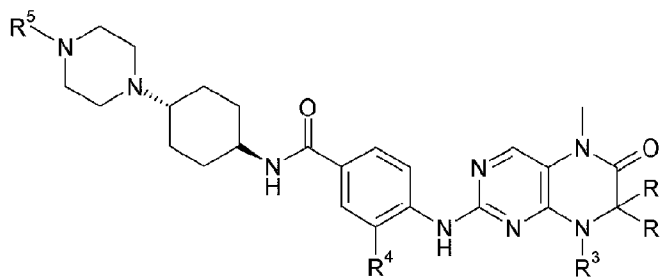
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(54) Title: PROCESS FOR MANUFACTURING DIHYDROPTERIDINONES AND INTERMEDIATES THEREOF



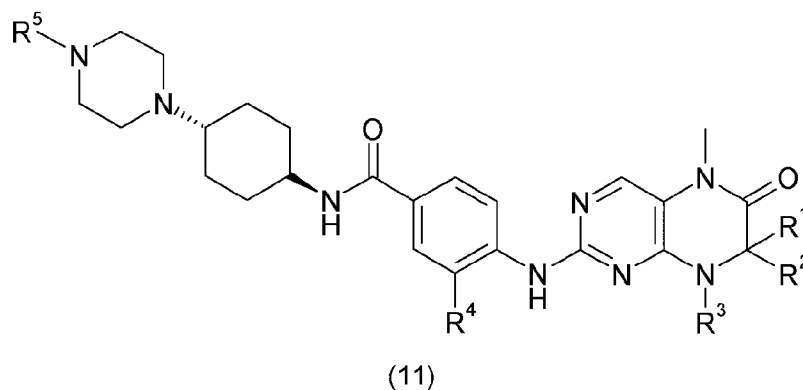
(11)

(57) Abstract: The present invention relates to an improved process for manufacturing dihydropteridinones of general formula (12) as well as intermediates thereof, wherein the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> have the meanings given in the claims and specification.

WO 2012/049153 A1

**Process for manufacturing dihydropteridinones and intermediates thereof**

The present invention relates to a process for manufacturing dihydropteridinones of general formula (11)



10 wherein the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> have the meanings given in the claims and specification, as well as related intermediates thereof, optionally in form of the tautomers, racemates, enantiomers, diastereomers and the mixtures thereof and optionally the salts thereof.

**Background of the invention**

15 Pteridinone and pteridinone derivatives are known in prior art as active substances with an antiproliferative activity, particularly for the treatment of diseases comprising an abnormal cell proliferation by inhibition of polo-like kinases as mitotic regulators, especially in case the polo-like kinase is PLK-1, preferably for the treatment and/or  
20 prevention of cancer, infections, inflammatory and autoimmune diseases.

For example, WO 01/019825 A1 discloses specific pteridinones which are described to be potent inhibitors of cyclin-dependent kinases (cdks) and growth-factor-mediated kinases and are used for the treatment of cell proliferative diseases and disorders,  
25 particularly tumour and viral diseases. Also WO 03/020711 discloses the use of dihydropteridinone derivatives for the treatment of tumoral diseases. Further, WO 2006/018185 A2 is related to the use of dihydropteridinones in the cancer therapy.

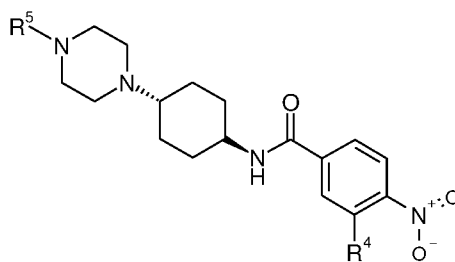
Also a number of manufacturing processes of pteridones is described in prior art:

For example, WO 2004/076454 A1 and WO 2006/018220 disclose specific dihydropteridinones, methods for the production and use thereof.

Nevertheless, there exists a need for an improved method of manufacturing  
 5 dihydropteridinones which overcomes the above described deficiencies. The object of the present invention is therefore to provide a method according to which dihydropteridinones may be provided in a high yield with improved high purities which may be readily conducted in large-scale.

### Summary of the invention

10 A first aspect of the invention provides for a process for manufacturing a compound of formula (8)



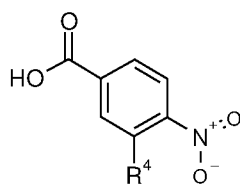
(8)

wherein

15 R<sup>5</sup> denotes C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyl-C<sub>3</sub>-C<sub>10</sub>-cycloalkyl or C<sub>3</sub>-C<sub>10</sub>-cycloalkyl,  
 R<sup>4</sup> denotes hydrogen or a group selected from among -CN, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>5</sub>-alkyloxy and C<sub>1</sub>-C<sub>6</sub>-alkylthio,

wherein

a compound of general formula (7)



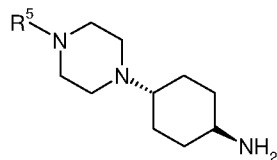
(7)

20

2a

wherein

$R^4$  is as hereinbefore defined, optionally converted into an acyl halide compound, is reacted with the amine compound of formula (6)



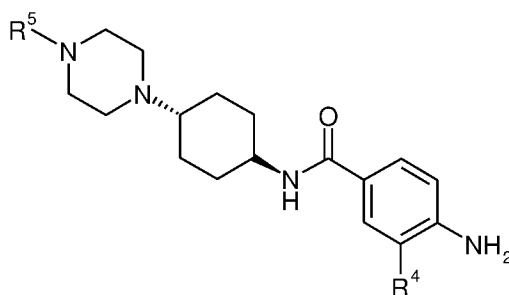
(6)

wherein

$R^5$  is as hereinbefore defined,

using an alkali or alkaline earth hydroxide as base and a protic solvent.

A second aspect of the invention provides for a process for manufacturing a compound of formula (9)



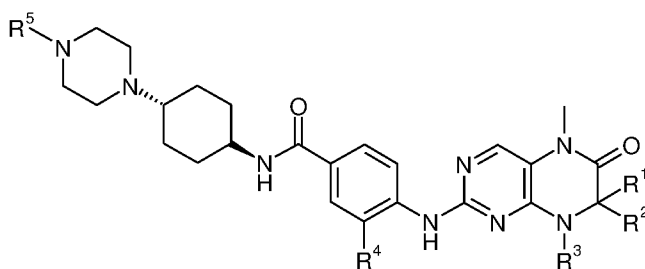
(9)

wherein

$R^4$  and  $R^5$  are as hereinbefore defined,

using the first aspect of the invention.

A third aspect of the invention provides for a process for manufacturing a compound of formula (11)



2b

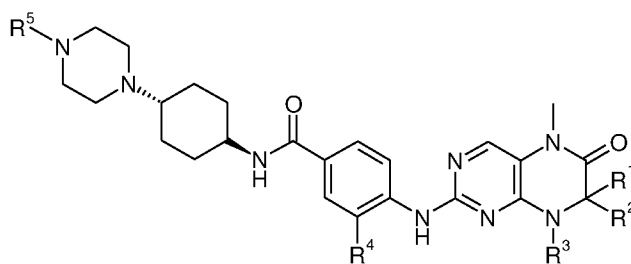
(11)

wherein

$R^1$  to  $R^5$  are as hereinbefore defined,

using the first aspect of the invention.

- 5 A fourth aspect of the invention provides for a process for manufacturing a compound of formula (11)

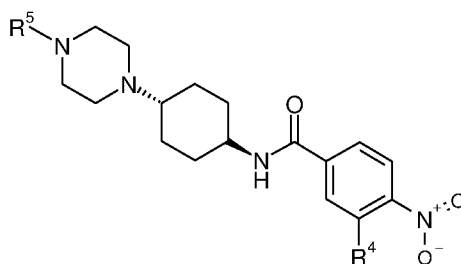


(11)

wherein

- 10  $R^1$  to  $R^5$  are as hereinbefore defined,

using a compound of formula (8)



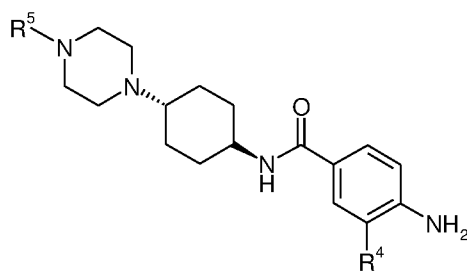
(8)

obtained using the process of the first aspect of the invention;

- 15 or

using a compound of formula (9)

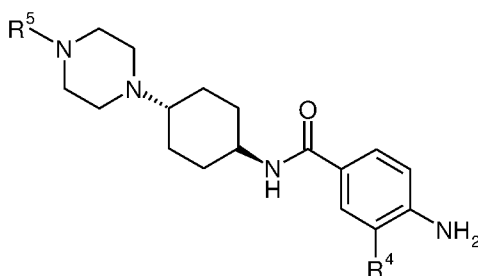
2c



(9)

using the process of the second aspect of the invention.

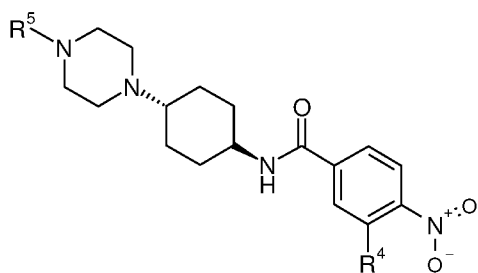
A fifth aspect of the invention provides for a process for manufacturing a compound of  
5 formula (9)



(9)

wherein

a compound of general formula (8)



(8)

wherein

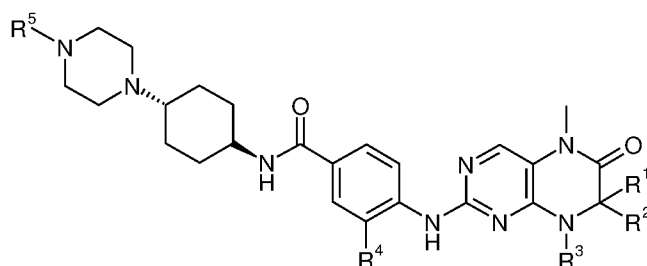
$R^4$  and  $R^5$  are as hereinbefore defined,

is hydrogenated,

15 wherein the compound of formula (8) is obtained using the process according to the first aspect of the invention.

2d

A sixth aspect of the invention provides for a process for manufacturing a compound of formula (11)

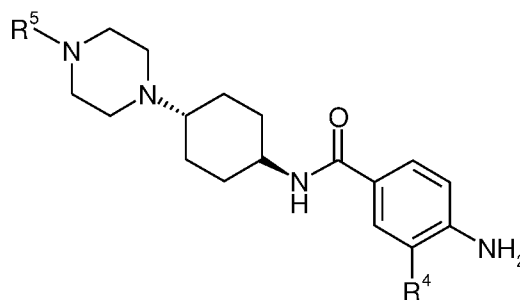


(11)

5 wherein

R<sup>1</sup> to R<sup>5</sup> are as hereinbefore defined,

wherein a compound of formula (9)

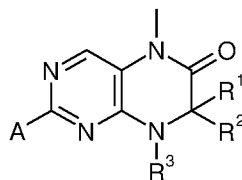


(9)

10 wherein

R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined,

is reacted with a compound of formula (10)



(10)

15 wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as hereinbefore defined and A is a leaving group,

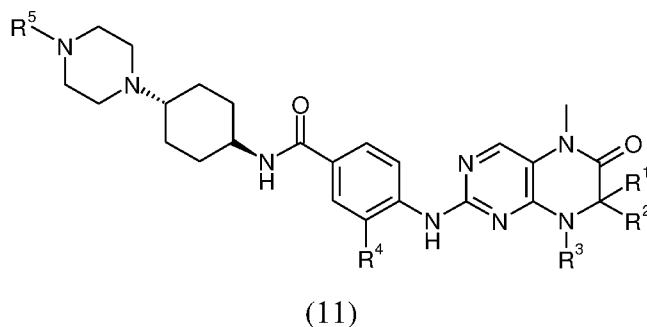
wherein the compound of formula (9) is obtained using the process according to the fifth aspect of the invention.

A seventh aspect of the invention provides for a process for manufacturing a compound



2e

of formula (11)

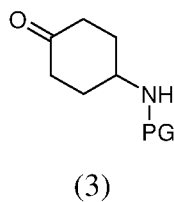


wherein

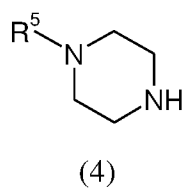
5  $R^1$  to  $R^5$  are as hereinbefore defined,

comprising the following steps:

step 1: a compound of formula (3)



10 wherein PG is a protecting group  
is reacted with a compound of general formula (4)



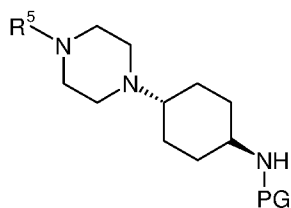
wherein

15  $R^5$  is as hereinbefore defined,

via an enamine intermediate which is hydrogenated in the presence of a metal catalyst and a solvent or a mixture of solvents

to obtain a compound of formula (5)

2f



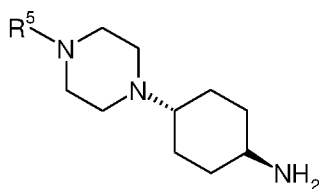
(5)

wherein R<sup>5</sup> and PG are as hereinbefore and hereinafter defined;

step 2: in a compound of formula (5) as hereinbefore defined,

- 5 the protecting group PG is removed by acidic hydrolysis using p-toluenesulfonic acid (TsOH),

to obtain a compound of formula (6)

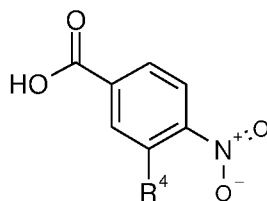


(6)

- 10 wherein

R<sup>5</sup> is as hereinbefore defined;

step 3: a compound of general formula (7)

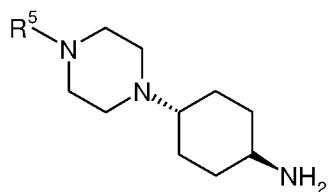


(7)

- 15 wherein

2g

$R^4$  is as hereinbefore defined, optionally converted into an acyl halide compound, is reacted with the amine compound of formula (6)



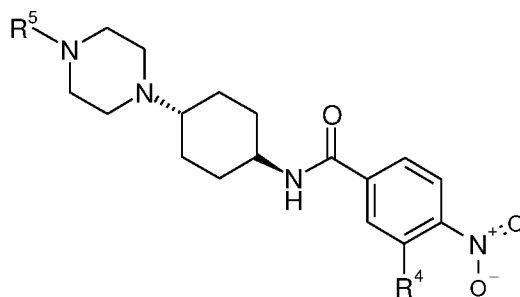
(6)

5 wherein

$R^5$  is as hereinbefore defined,

using an alkali or alkaline earth hydroxide as base and a protic solvent,

to obtain a compound of formula (8)



(8)

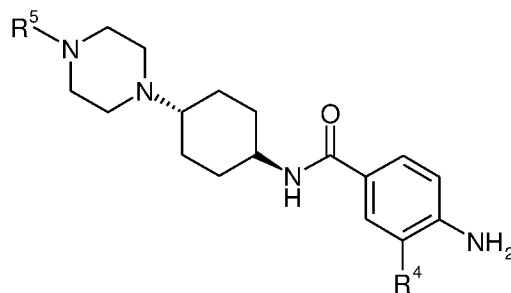
10

wherein

$R^4$  and  $R^5$  are as hereinbefore defined;

step 4: a compound of general formula (8) as hereinbefore defined

is hydrogenated to obtain a compound of formula (9)



(9)

15

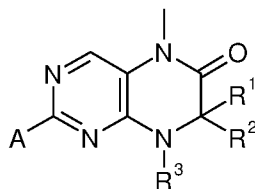
2h

wherein

$R^4$  and  $R^5$  are as hereinbefore defined;

step 5: a compound of formula (9) as hereinbefore defined,

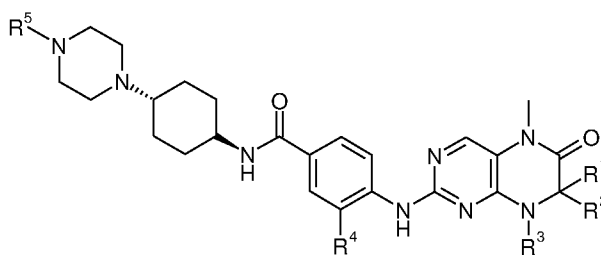
is reacted with a compound of formula (10)



(10)

wherein  $R^1$ ,  $R^2$  and  $R^3$  are as hereinbefore defined and A is a leaving group,

to obtain a compound of formula (11)



(11)

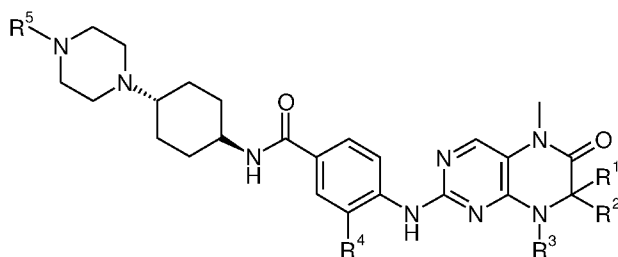
wherein

$R^1$  to  $R^5$  are as hereinbefore defined.

### **Detailed description of the invention**

The present invention relates to a process of manufacturing dihydropteridinones and related intermediates thereof.

According to the present invention the produced compounds of general formula (11) are as follows:



(11)

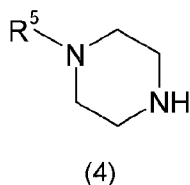
wherein

- 5 R<sup>1</sup> and R<sup>2</sup> denote independently from each other a hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl,
- R<sup>3</sup> denotes hydrogen or a group selected from C<sub>1</sub>-C<sub>6</sub>-alkyl and C<sub>3</sub>-C<sub>8</sub>-cycloalkyl,
- R<sup>4</sup> denotes hydrogen or a group selected from among -CN, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkyl,



- 4 -

is reacted with a compound of general formula (4)



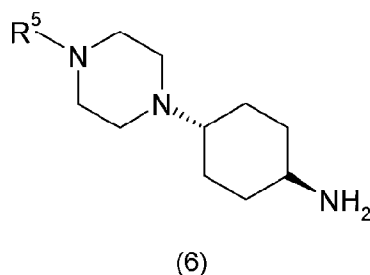
5 wherein

R<sup>5</sup> is as hereinbefore defined,

via an enamine intermediate which is hydrogenated in the presence of a metal catalyst like Ni, Pd, Pt and a solvent or a mixture of solvents. Preferred catalysts are Pt/C and platinum-IV-oxide (PtO<sub>2</sub>). Most preferred is platinum-IV-oxide (PtO<sub>2</sub>). The solvent is

10 preferably an aprotic organic solvent or an alcohol or a mixture of an aprotic solvent and an alcohol. Particularly use is made of a toluene/ethanol mixture.

The present invention relates also to a process (step 2) for manufacturing a compound of formula (6)

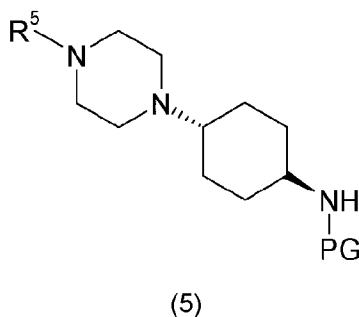


15

wherein

R<sup>5</sup> is as hereinbefore defined, characterised in that

the protecting group PG in a compound of general formula (5)



20

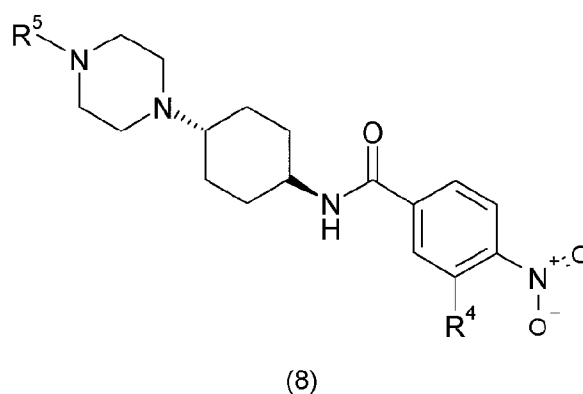
wherein

R<sup>5</sup> and PG are as hereinbefore and hereinafter defined,

- 5 -

is removed by acidic hydrolysis using p-toluenesulfonic acid (TsOH) as non-nucleophilic acidic reagent for cleavage of the protecting group.

The present invention also relates to a process (step 3) for manufacturing a compound of formula (8)



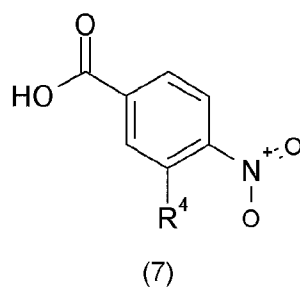
wherein

$R^5$  is as hereinbefore defined,

$R^4$  denotes hydrogen or a group selected from among -CN, hydroxy,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_5$ -alkyloxy and  $C_1$ - $C_6$ -alkylthio,

characterised in that

a compound of general formula (7)

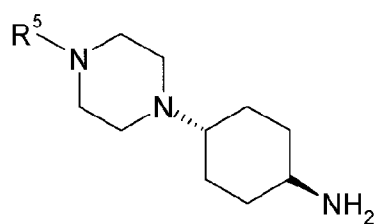


wherein

$R^4$  is as hereinbefore defined, optionally converted into an acyl halide compound, is reacted with the amine compound of formula (6)



- 6 -



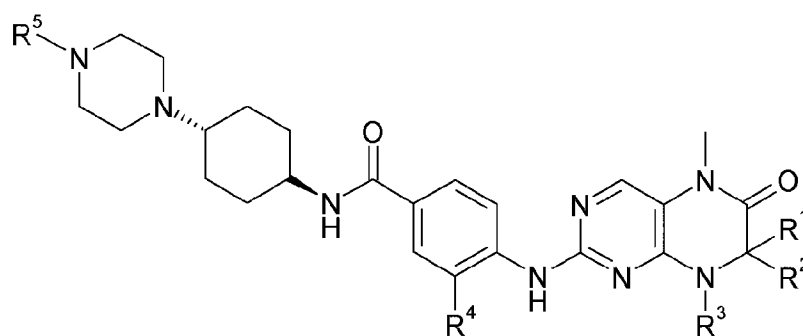
(6)

wherein

$R^5$  is as hereinbefore defined,

- 5 using an alkali or alkaline earth hydroxide, preferably NaOH or KOH, as base and a protic solvent, preferably water.

The present invention also relates to a process (step 1 to step 5) for manufacturing a compound of formula (11)



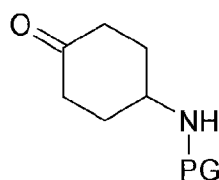
(11)

wherein

$R^1$  to  $R^5$  are as hereinbefore defined,

- 15 comprising the following steps:

step 1: a compound of formula (3)

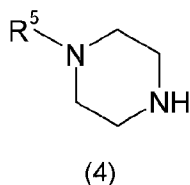


(3)

- 20 wherein PG is a protecting group

- 7 -

is reacted with a compound of general formula (4)

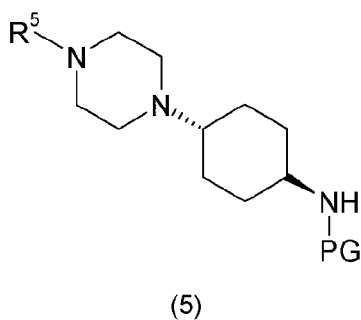


5 wherein

R<sup>5</sup> is as hereinbefore defined,

via an enamine intermediate which is hydrogenated in the presence of a metal catalyst, preferably, a Pt catalyst and a solvent or a mixture of solvents;

10 to obtain a compound of formula (5)

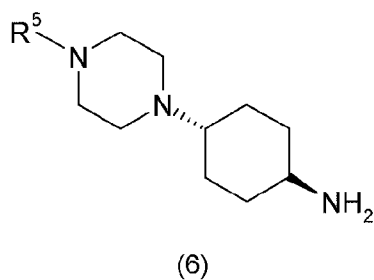


wherein R<sup>5</sup> and PG are as hereinbefore and hereinafter defined;

15 step 2: in a compound of formula (5) as hereinbefore defined,

the protecting group PG is removed by acidic hydrolysis using p-toluenesulfonic acid (TsOH) as non-nucleophilic acidic reagent for cleavage of the protecting group

20 to obtain a compound of formula (6)

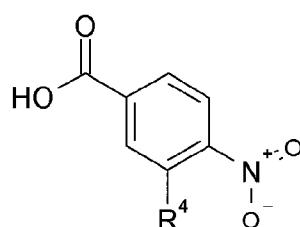


wherein

- 8 -

R<sup>5</sup> is as hereinbefore defined;

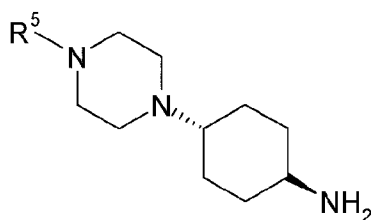
step 3: a compound of general formula (7)



(7)

wherein

R<sup>4</sup> is as hereinbefore defined, optionally converted into an acyl halide compound, is reacted with the amine compound of formula (6)



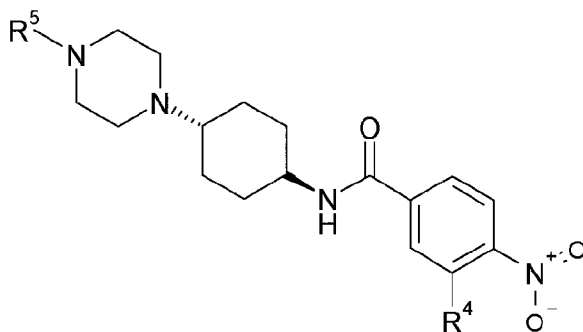
(6)

wherein

R<sup>5</sup> is as hereinbefore defined,

using an alkali or alkaline earth hydroxide, preferably NaOH or KOH, as base and a protic solvent, preferably water,

to obtain a compound of formula (8)



(8)

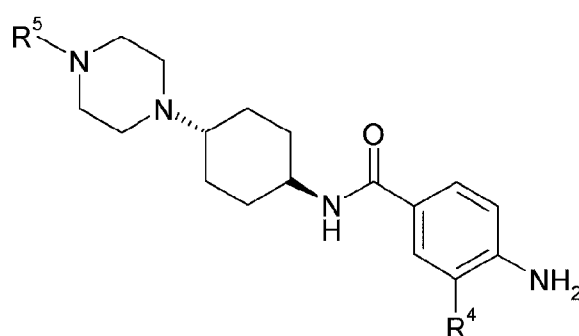
- 9 -

wherein

$R^4$  and  $R^5$  are as hereinbefore defined;

5 step 4: a compound of general formula (8) as hereinbefore defined

is hydrogenated to obtain a compound of formula (9)



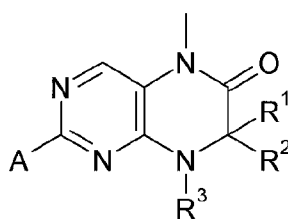
(9)

wherein

$R^4$  and  $R^5$  are as hereinbefore defined;

step 5: a compound of formula (9) as hereinbefore defined,

is reacted with a compound of formula (10)

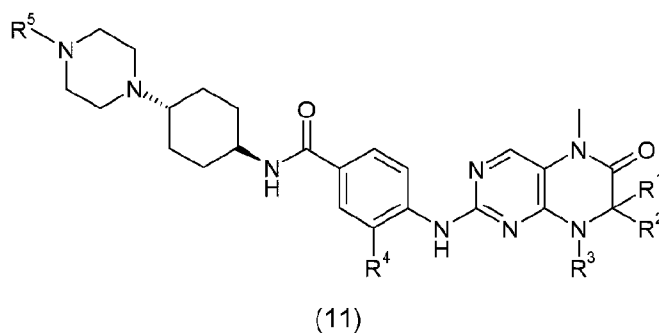


(10)

wherein  $R^1$ ,  $R^2$  and  $R^3$  are as hereinbefore defined and  $A$  is a leaving group,

to obtain a compound of formula (11)

- 10 -

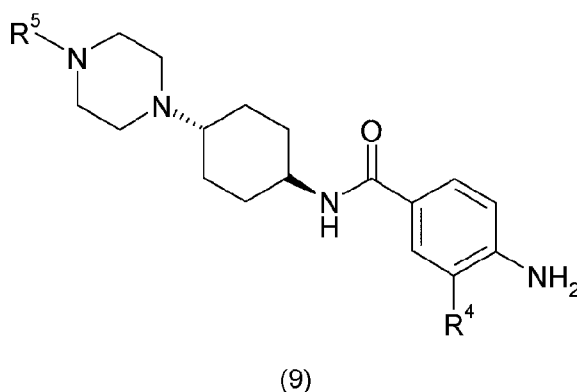


wherein

R<sup>1</sup> to R<sup>5</sup> are as hereinbefore defined.

5

The present invention also relates to a process for manufacturing a compound of formula (9)



10

wherein

R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined,

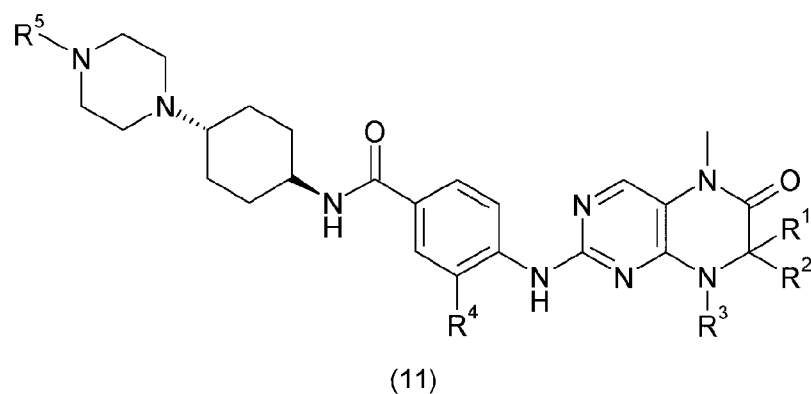
using process step 1 and/or process step 2 and/or process step 3 as hereinbefore

15

defined.

The present invention also relates to a process for manufacturing a compound of formula (11)

- 11 -



wherein

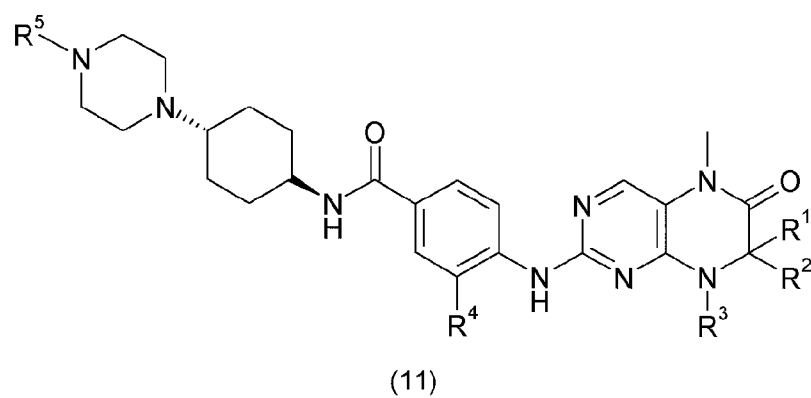
R<sup>1</sup> to R<sup>5</sup> are as hereinbefore defined,

5

using process step 1 and/or process step 2 and/or process step 3 as hereinbefore defined.

The present invention also relates to a process for manufacturing a compound of

10 formula (11)



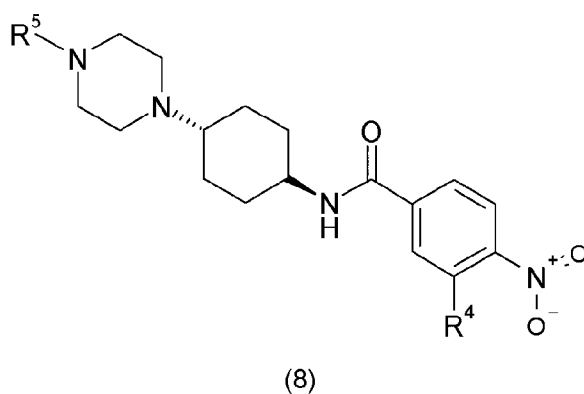
wherein

R<sup>1</sup> to R<sup>5</sup> are as hereinbefore defined

15

using a compound of formula (8)

- 12 -



wherein

R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined,

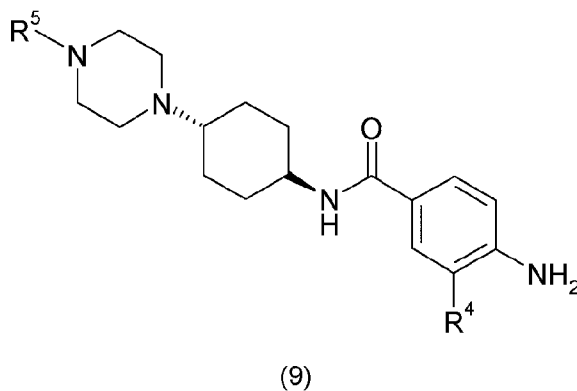
5

wherein the compound of formula (8) is obtained using process step 1 and/or process step 2 and/or process step 3 as hereinbefore defined;

or

10

using a compound of formula (9)



wherein

15

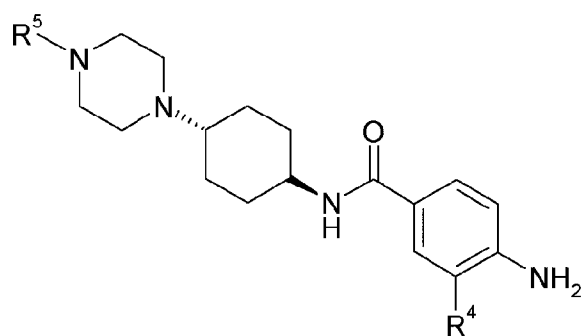
R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined,

wherein the compound of formula (9) is obtained using process step 1 and/or process step 2 and/or process step 3 as hereinbefore defined.

The present invention also relates to a process (step 4) for manufacturing a compound of formula (9)

20

- 13 -



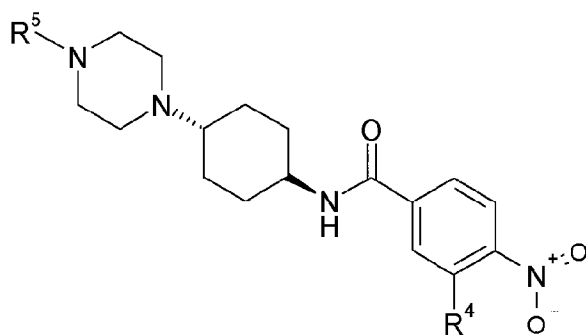
(9)

wherein

R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined, characterised in that

5

a compound of general formula (8)



(8)

wherein

10 R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined,  
is hydrogenated,

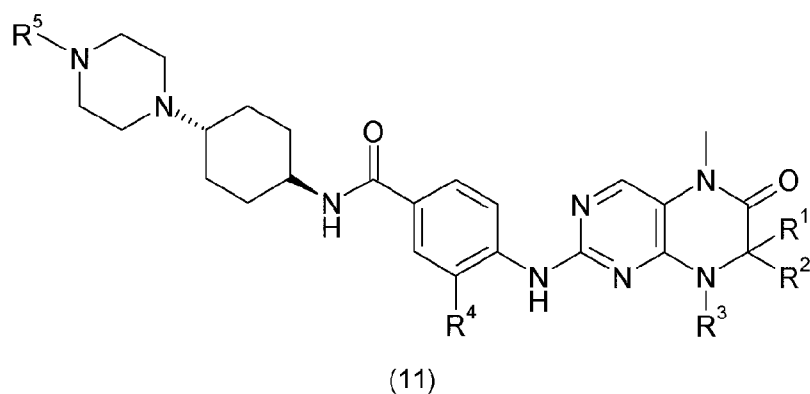
wherein the compound of formula (8) is obtained using process step 1 and/or process step 2 and/or process step 3 as hereinbefore defined.

15

The present invention also relates to a process (step 5) for manufacturing a compound of formula (11)



- 14 -

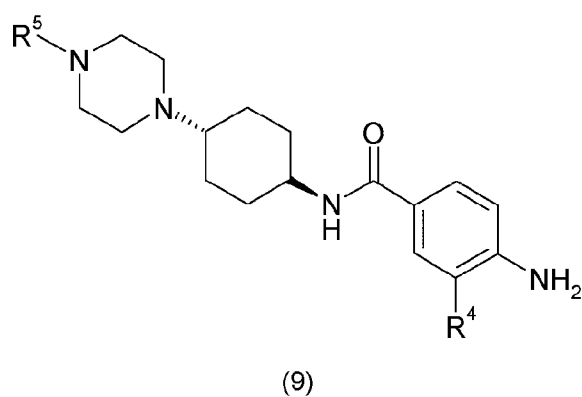


wherein

R<sup>1</sup> to R<sup>5</sup> are as hereinbefore defined,

5

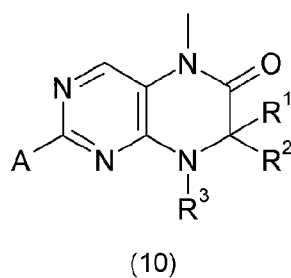
wherein a compound of formula (9)



wherein

10 R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined,

is reacted with a compound of formula (10)

15 wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as hereinbefore defined and A is a leaving group,

wherein the compound of formula (9) is obtained using process step 1 and/or process

step 2 and/or process step 3 as hereinbefore defined.

#### Definition of terms used

- 5 The term "alkyl groups", including alkyl groups which are a part of other groups, denotes branched and unbranched alkyl groups with 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms, most preferably 1 to 4 carbon atoms, such as, for example methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and dodecyl. Unless otherwise stated, the abovementioned terms propyl, butyl, pentyl, hexyl, 10 heptyl, octyl, nonyl, decyl and dodecyl include all the possible isomeric forms. For example, the term propyl includes the two isomeric groups n-propyl and isopropyl, the term butyl includes n-butyl, iso-butyl, sec-butyl and tert.-butyl, the term pentyl includes iso-pentyl, neopentyl, etc.
- 15 In the above-mentioned alkyl groups one or more hydrogen atoms may optionally be replaced by other groups. For example these alkyl groups may be substituted by halogen, preferably fluorine, chlorine and bromine. All the hydrogen atoms of the alkyl group may optionally be replaced.
- 20 Examples of "cycloalkyl groups" are cycloalkyl groups with 3 to 8 carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, preferably cyclopropyl, cyclopentyl or cyclohexyl, while each of the above-mentioned cycloalkyl groups may optionally also carry one or more substituents, for example OH, NO<sub>2</sub>, CN, OMe, -OCHF<sub>2</sub>, -OCF<sub>3</sub>, -NH<sub>2</sub> or halogen, preferably fluorine or chlorine, C<sub>1</sub>- 25 C<sub>10</sub>-alkyl, preferably C<sub>1</sub>-C<sub>5</sub>-alkyl, preferably C<sub>1</sub>-C<sub>3</sub>-alkyl, more preferably methyl or ethyl, -O-C<sub>1</sub>-C<sub>3</sub>-alkyl, preferably -O-methyl or -O-ethyl, -COOH, -COO-C<sub>1</sub>-C<sub>4</sub>-alkyl, preferably -COO-methyl or -COO-ethyl or -CONH<sub>2</sub>. Particularly preferred substituents of the cycloalkyl groups are =O, OH, NH<sub>2</sub>, methyl or F.
- 30 Generally, the term "halogen" denotes fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, most preferably chlorine.

The "leaving group A" denotes a leaving group such as for example -O-methyl, -SCN, fluorine, chlorine, bromine, iodine, methanesulphonyl, ethanesulphonyl,

trifluoromethanesulphonyl or p-toluenesulphonyl, preferably chlorine.

The protective group "PG" denotes a protective group such as for example methyl carbamate, ethyl carbamate, 2,2,2-trichloroethyl carbamate, 2-trimethylsilylethyl carbamate, 2-chloroethyl carbamate, t-butyl carbamate, vinyl carbamate, allyl carbamate, benzyl carbamate, p-methoxybenzyl carbamate, N-formyl amide, N-acetyl amide, N-trifluoroacetyl amide, N-phenylacetyl amide, N-benzoyl amide, and benzyloxycarbonyl amide,

Further usable protective groups usable to protect the amino group of the compound of formula (5) are described in: *Protective Groups in Organic Synthesis, Third Edition. Theodora W. Greene, Peter G.M. Wuts, 1999 John Wiley & Sons, Inc., Chapter 7 p494-653*;

#### Preferred embodiments of the present invention

##### Preferred compounds produced

According to a preferred embodiment  $R^3$  to  $R^5$  are as hereinbefore defined, and  $R^1$  and  $R^2$  denote independently from each other a hydrogen or  $C_1$ - $C_3$ -alkyl. More preferred  $R^1$  and  $R^2$  denote independently from each other a hydrogen, methyl, or ethyl. Most preferably,  $R^1$  denotes hydrogen and  $R^2$  denotes ethyl.

According to a preferred embodiment  $R^1$ ,  $R^2$ ,  $R^4$  and  $R^5$  are as hereinbefore defined, and  $R^3$  preferably denotes hydrogen or a group selected from  $C_1$ - $C_3$ -alkyl and  $C_3$ - $C_6$ -cycloalkyl. More preferred  $R^3$  denotes methyl, ethyl, propyl or isopropyl. Most preferably, the substituent of  $R^3$  denotes isopropyl.

According to a preferred embodiment  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^5$  are as hereinbefore defined, and  $R^4$  preferably denotes hydrogen or a group selected from among -CN, hydroxy,  $C_1$ - $C_3$ -alkyl,  $C_1$ - $C_3$ -alkyloxy and  $C_1$ - $C_3$ -alkylthio. More preferred  $R^4$  denotes, methoxy, ethoxy, methylthio and ethylthio. Most preferably, the substituent of  $R^4$  denotes methoxy.

According to a preferred embodiment  $R^1$  to  $R^4$  are as hereinbefore defined, and

R<sup>5</sup> preferably denotes C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>2</sub>-alkyl-C<sub>3</sub>-C<sub>6</sub>-cycloalkyl or C<sub>3</sub>-C<sub>6</sub>-cycloalkyl.

More preferred R<sup>5</sup> denotes methyl, ethyl, propyl or -CH<sub>2</sub>-cyclopropyl.

Most preferably, the substituent of R<sup>5</sup> denotes -CH<sub>2</sub>-cyclopropyl.

5 Particularly preferred compounds of formula (11) which may be manufactured according to the process of the present invention with regard to especially preferred groups of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are disclosed in prior art documents WO 2006/018220 A2 and WO 2004/076454 A1, the whole disclosure of both documents is incorporated by reference, respectively, in the content of the present description.

10

All the groups mentioned in the definition of R<sup>1</sup> to R<sup>5</sup> may optionally be branched and/or substituted.

Within the meaning of the present invention, the compounds of general formula (5), (6),  
15 (8), (9) or (11) produced according to the processes of the present invention may be optionally in form of its tautomers, racemates, enantiomers, diastereomers and the mixtures thereof and optionally in form of the salts. The compounds of general formula (11) also embrace the physiologically acceptable or pharmacologically acceptable salts, solvates, hydrates or polymorphs thereof. The compounds of formula (5), (6), (8)  
20 and (9) represent important intermediate products for preparing the compounds of formula (11).

The compounds produced according to the invention may be prepared by synthesis methods described hereinafter, while the substituents of general formulae (3) to (11)  
25 have the meanings given hereinbefore. In case a number of steps, for example 2 steps, are combined, the product of every step may be purified according to known processes, preferably recrystallisation, respectively, or the obtained product may be used as such in the subsequent step.

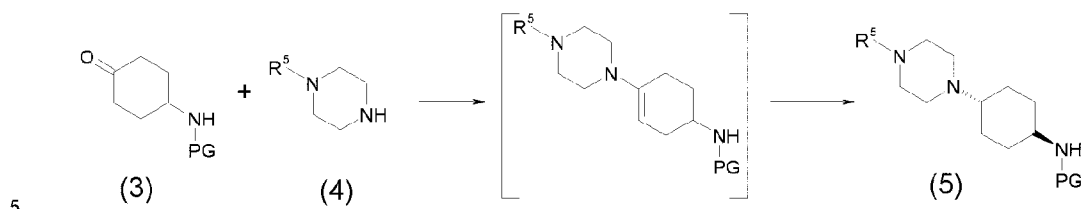
### 30 Preferred methods of production

#### Step 1

According to Step 1, a compound of formula (3) is reacted with a compound of formula (4) to obtain a compound of formula (5) (see Diagram 1). Compound (3) and compound

(4) are either commercially available or may be prepared by procedures known from the chemical literature.

**Diagram 1**



In Step 1, the compound (3), an aminocyclohexanone wherein the nitrogen atom is protected by a protecting group PG, is reacted with the heterocyclic compound of general formula (4) in a suitable solvent or mixture of solvents. The reaction is preferably conducted under reflux. The resulting enamine is then hydrogenated with a metal catalyst, preferably, Pt catalyst, preferably selected from Pt/C and platinum-IV-oxide (PtO<sub>2</sub>), most preferably platinum-IV-oxide (PtO<sub>2</sub>), in an appropriate solvent, like THF, toluene, ethanol, methanol, ethylacetate and mixtures thereof under a suitable hydrogen pressure, e.g. between 30 and 60 psi. The reaction is usually performed at a temperature above room temperature, for example, in the range of 35°C to 65°C. Then the catalyst is removed. The reaction product in form of a mixture of the cis- and trans-form (free base) is obtained and may be worked up as usual (e.g. addition of water and subsequently diluted acid such as aqueous hydrochloric acid). The cis- and trans-compounds are separated by crystallisation out of water. For example, the crude product may be recrystallised from a suitable solvent in order to obtain the pure trans-product.

10  
15  
20

In the process as known from prior art, for example WO 2006/018220, the reductive amination of the enamine is performed with NaBH<sub>4</sub> as source of hydrogen and subsequently hydrochloric acid is added. However, the use of the sodium borohydride reagent leads to potential disadvantages, which might result in an inhomogeneous reaction process, with decreased yield and side-products.

25

In the present step 1 according to the invention and in contrast to the prior art process a heterogeneous catalytical method with hydrogen is performed. It has been found that a suitable catalyst is a metal catalyst, preferably a Pt catalyst. Preferable

30

catalysts are Pt/C and platinum-IV-oxide (PtO<sub>2</sub>). Most preferred is platinum-IV-oxide (PtO<sub>2</sub>). The solvent is preferably an aprotic organic solvent, for example, dichloromethane, acetone, ethylene glycol dimethyl ether, diglyme, toluene, tetrahydrofuran (THF), preferably toluene or THF, most preferably toluene. A preferred solvent is also an alcohol such as ethanol, methanol, isopropanol, n-propanol, n-butanol and/or tert.-butanol, most preferably ethanol or methanol. More preferably the solvent is a mixture of an aprotic solvent and an alcohol. Preferably the solvent is a mixture of toluene and an alcohol. Particularly use is made of a toluene/ethanol mixture. The ratio of the mixture of toluene/alcohol, preferably toluene/ethanol is preferably adjusted in the range from about 4 - 5 : 1. Present step 1 allows for a significantly improved ratio of trans-compound : cis-compound which is about 3 : 1. Therefore, a stereoselective reductive amination is achieved. The best results are obtained with platinum-IV-oxide as catalyst in a mixture of toluene/ethanol, preferably in the range from about 4 - 5 : 1. Thus an isolated yield of >50% (trans-isomer) can be achieved. Other catalysts like Pd/C or Raney-Ni hydrogenate the enamine as well, with trans/cis ratios as shown in the following table:

Table:

Catalyst	Pt/C 5%	Pt/C 5%	Pd/C 5%	Ra.-Ni	PtO <sub>2</sub> 1%	PtO <sub>2</sub> 1%	Pt/C 5%
Solvent	THF	Ethanol	Ethanol	Ethanol	Ethanol	THF	Toluene/ Ethanol (4:1)
trans : cis ratio	45:55	44:56	36:64	19:81	60:40	60:40	48:52
isolated yield (trans)	33%	23%	23%	--	--	--	--

20

Step 2

According to Step 2, in compound (5) obtained in Step 1 the protecting group is removed to obtain compound (6) (see Diagram 2).

25

**Diagram 2**

- 20 -



The cleavage of a protecting group PG is a procedure well known in the prior art.

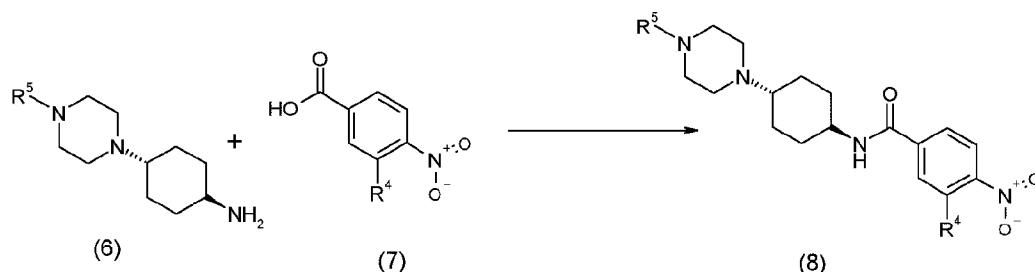
5 Usually, the amino-protecting group PG can be any suitable amino-protecting group that is known in the art. Typical examples of protecting groups have already been described above such as tert-butyloxycarbonyl (Boc), acetyl and formyl. The step of cleaving the nitrogen protecting group is generally accomplished by well known techniques in prior art. Usually an acidic hydrolysis with an organic or inorganic acid is  
10 used such as HCl, H<sub>2</sub>SO<sub>4</sub>, TFA, AcOH, MeSO<sub>3</sub>H or TsOH in a variety of protic or polar nonprotic solvents such as alcohols, ethers or dichloromethane (DCM). However, in the process of prior art the removal of the protecting group is usually accomplished with hydrochloric acid under reflux for several hours. The resulting amine is isolated as its HCl salt. The problem of this process is the potential formation of impurities  
15 because the hydrochloric acid can react with substituents present at the heteroatom.

In the process step 2 according to the present invention the formation of this impurity is circumvented. The acidic hydrolysis is performed using p- toluenesulfonic acid (tosic  
20 acid, TsOH) as non-nucleophilic acidic reagent for cleavage of the protecting group. This kind of non-nucleophilic acidic reagent does not react with any substituent under decomposition of the compound in an undesired side-reaction. Preferably protecting groups used in step 2 according to the present invention are acetyl, formyl, trifluoroacetyl, ethoxycarbonyl, tert.-butoxycarbonyl, benzyloxycarbonyl, benzyl,  
25 methoxybenzyl or 2,4-dimethoxybenzyl group. The product in step 2 is therefore a crystalline tritosylate salt which is usually obtained in good yield.

### Step 3

According to Step 3, the compound of formula (6) obtained in Step 2 is reacted with a  
30 compound of general formula (7) to obtain a compound of general formula (8) (see Diagram 3).

Diagram 3



- 5 In Step 3, the benzoic acid compound (7), optionally at first converted into an acyl halide compound, is reacted with the amine compound of formula (6) using a base and a solvent. The reaction is usually performed at a temperature which is above room temperature, preferably in the range of 35°C to 75°C. The reaction product (compound (8)) precipitates and is then worked up as usual. The obtained compound (6) may be
- 10 purified by chromatography or by crystallisation or used as the crude product in the subsequent Step 4 of the synthesis.

In the process according to prior art the base commonly used is N-ethyldiisopropylamine (Hunigsbase) and the solvent commonly used is THF. It has been found that the

15 use of an alkali or alkaline earth hydroxide as base such as NaOH or KOH instead of N-ethyldiisopropylamine as base and a protic solvent such as water instead of the aprotic solvent THF is advantageous. Surprisingly the yield can be significantly increased from 83 to 97%.

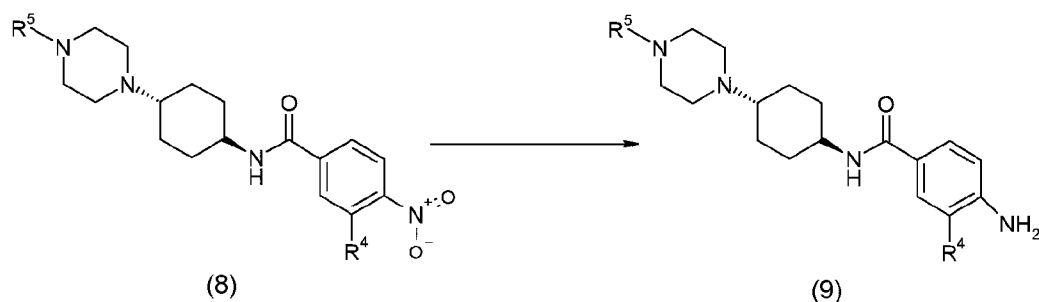
#### 20 Step 4

According to Step 4, the compound of formula (8) obtained in Step 3 is hydrogenated to form the compound of formula (9) (see Diagram 4). This step may be carried out using methods known from the chemical literature.

#### 25 Diagram 4



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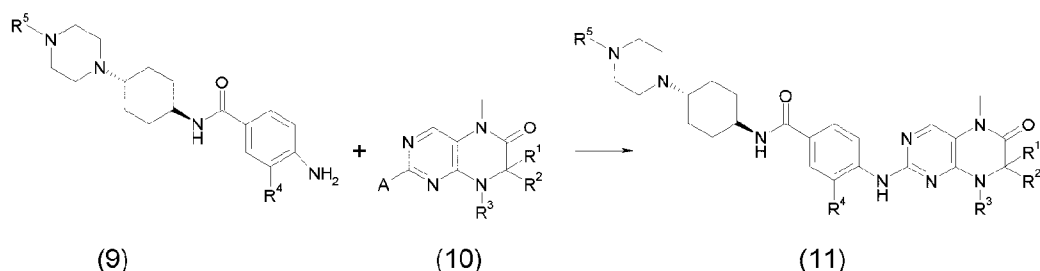


In Step 4, the compound of formula (8) is hydrogenated using a catalyst in a solvent under a suitable hydrogen pressure (20-100 psi), preferably in the range of 30 to 60 psi. The hydrogenation reaction is usually performed at a temperature which exceeds room temperature, for example in the range of 40 to 70°C. The catalyst may be any catalyst known from prior art, particularly preferred is Raney-Nickel. After completion of the reaction the catalyst is removed. The obtained compound of formula (9) may be purified or used as such in the next step without further purification.

#### Step 5

According to Step 5, the reaction of the compound of formula (9) obtained in Step 4 to yield the compound of formula (11) (Diagram 5) may be carried out using methods known from the chemical literature, for e.g. in WO 2009/019205; WO 2007/090844, WO 2006/021378, WO 2006/018220 and 2004/076454.

#### Diagram 5



For example, in step 5, compound of formula (10) and compound of formula (9) are stirred with acid, for example hydrochloric acid or tosic acid, in a solvent, for example ethanol, propanol, butanol, pentanol, 4-methyl-2-pentanol at reflux temperature for several hours. The precipitated product (11) is separated and worked up as usual,

optionally washed with water, and dried. The obtained compound (11) may be purified by chromatography or by crystallisation.

As a matter of course any of the above-described steps may be used isolated or two or several steps may be combined to obtain the desired reaction products.

5

Optimum reaction conditions and reaction times for each individual step may vary depending on the particular reactants employed. Unless otherwise specified, solvents, temperatures and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthesis Example section.

10 Typically, reaction progress may be monitored by high pressure liquid chromatography (HPLC) if desired. Intermediates and products may be purified by crystallization.

Unless otherwise described, the starting materials and reagents are either commercially available or may be prepared by one skilled in the art from commercially available materials using methods described in the chemical literature.

15

### Synthesis Example

#### Abbreviations:

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EtOH	ethanol
MeOH	methanol
THF	tetrahydrofuran
p-TsOH	p-toluenesulfonic acid

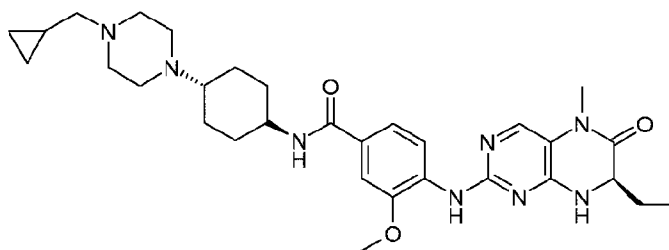
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### Synthesis of Compound (11a)

For the sake of completeness, a process for the manufacture of the compound of general formula (11a) is described hereinafter in detail.

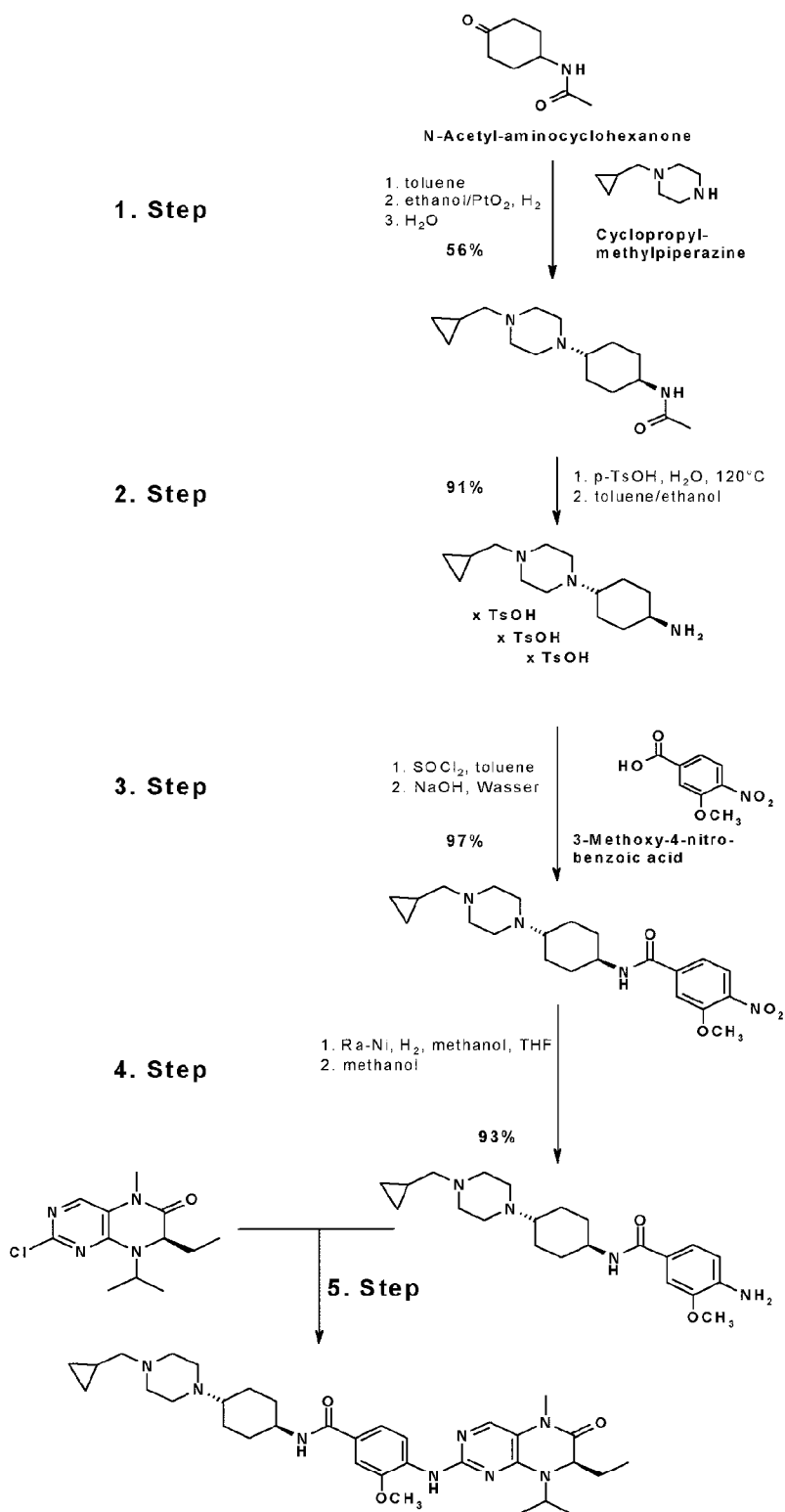
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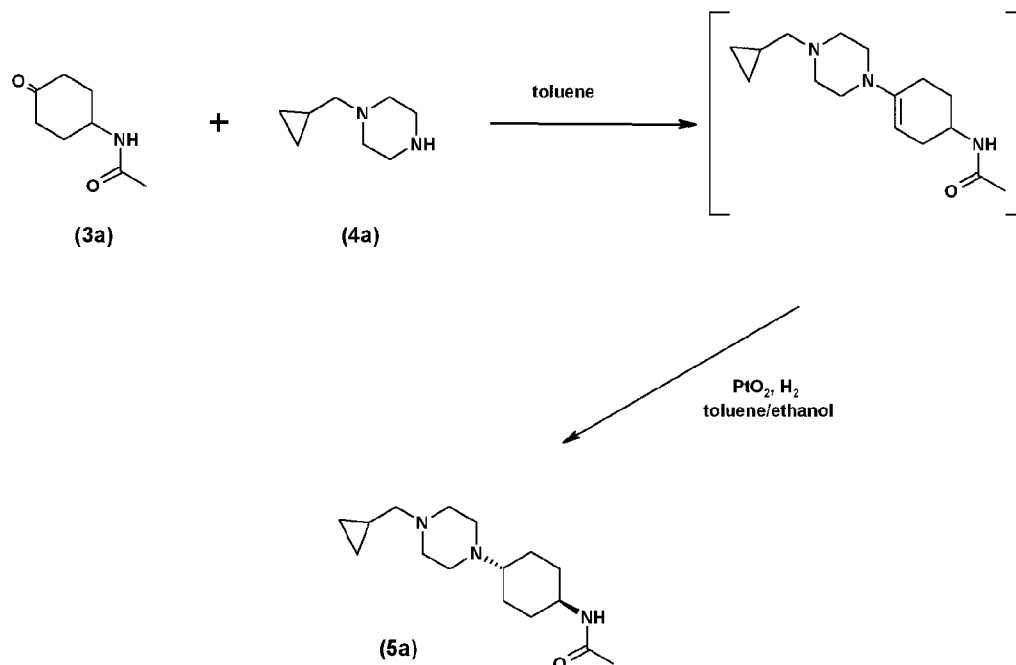
- 24 -



(11a)

- 5 The following method is to be understood as an illustration of the invention without restricting it to the subject matter thereof. In the following scheme 1 the reaction step 1 to step 5 are shown in detail.

**Scheme 1a**

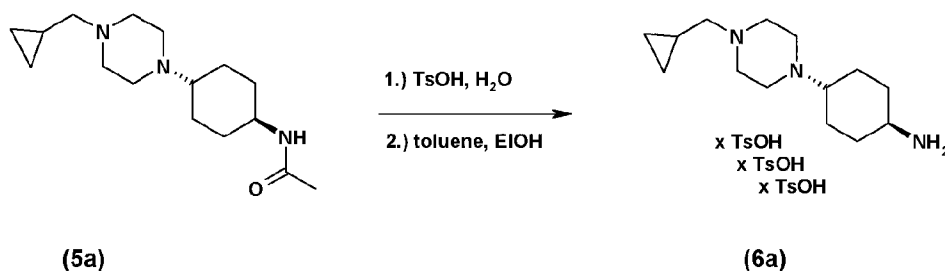
**Step 1**

- 5 A mixture of 100.0 g (644.4 mmol) of compound (3a), namely N-acetyl-aminocyclohexanone, 1.0 L toluene, and 99.4 g (708.8 mmol) cyclopropylmethyl-piperazine compound (4a) was heated to reflux. Under reflux water was removed by a water separator, and additional 35 mL of toluene were distilled off. After completion of the reaction, the reaction mixture was cooled to 70°C, and 200 mL of ethanol were
- 10 added. The solution containing the enamine was hydrogenated at 50 psi in presence of 1.00 g PtO<sub>2</sub> at 50°C. After complete conversion, the catalyst was filtered off, and the cake was rinsed with 275 ml toluene. The toluene was partly removed by distillation. To the residue 600 ml water were added at 50°C followed by the addition of 83.0 g (68.31 mmol) aqueous HCl. To the separated aqueous layer 59.3 g (74.10 mmol) aqueous
- 15 NaOH (50%) dissolved in 60 ml water were added. After addition crystallisation occurred. The suspension was cooled to 20°C within 1.5 hours. The product was collected by filtration, washed twice with 75 ml water each, and dried under vacuum at 50°C.
- 20 Yield: 101.0 g (56,1%) of piperazin compound (5a).

## Recrystallisation:

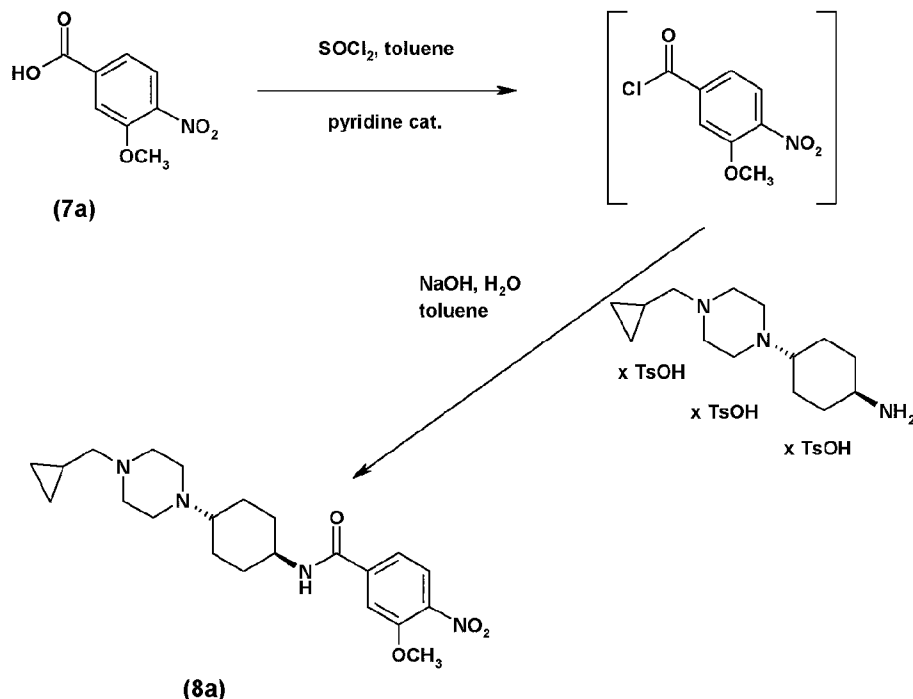
A mixture of 100.0 g piperazin compound (5a) (357.9 mmol) and 800 ml water was heated to reflux. The resulting solution was cooled to 20°C within 2.5 hours. The suspension was stirred for additional 30 minutes at 20°C. The product was collected by filtration, washed twice with 100 ml water each, and dried under vacuum at 50°C.

Yield: 79,0 g (79,0%) of piperazin compound (5a).

**Step 2**

A slurry of 20.0 g (71.57 mmol) piperazin compound (5a), 68.08 g (357.8 mmol) tosic acid, and 25 ml water was heated up to 120°C in a sealed reactor for 6 hours. After complete conversion, 120 ml toluene were added, and the biphasic mixture heated up to reflux. 29 ml of water were removed by azeotropic distillation. To the biphasic mixture 150 ml ethanol were added, and 100 ml of solvent were distilled off. The resulting suspension was cooled to 0°C and stirred for an additional hour at 0°C. The product was collected by filtration, washed twice with 40 ml toluene/ethanol mixture each, and dried under vacuum at 50°C.

Yield: 49.15 g (91,0%) of amine compound (6a).

**Step 3**

To a suspension of 11.5 g (58.36 mmol) 3-methoxy-4-nitrobenzoic acid (compound  
 5 (**7a**)) in 82 ml toluene 116  $\mu\text{L}$  pyridine were added, and heated up to reflux. Upon reflux  
 7.60 g (63.88 mmol) thionyl chloride dissolved in 38 ml toluene were added within 30  
 minutes. The mixture was stirred for an additional hour at reflux. After completion of the  
 reaction, the resulting solution was added to a mixture of 40.0 g of amine compound  
 (**6a**) (53.05 mmol), 74 ml water and 247 mmol  $\text{NaOH}$  at  $60^\circ\text{C}$ . The product precipitated  
 10 immediately during addition. The suspension was cooled to  $20^\circ\text{C}$  within one hour and  
 stirred for an additional hour at  $20^\circ\text{C}$ . The product was collected by filtration, and  
 washed twice with 100 ml water each. The product was dried at  $45^\circ\text{C}$  to constant  
 weight.

15 Yield: 21.49 g (97%) of amide compound (**8a**).

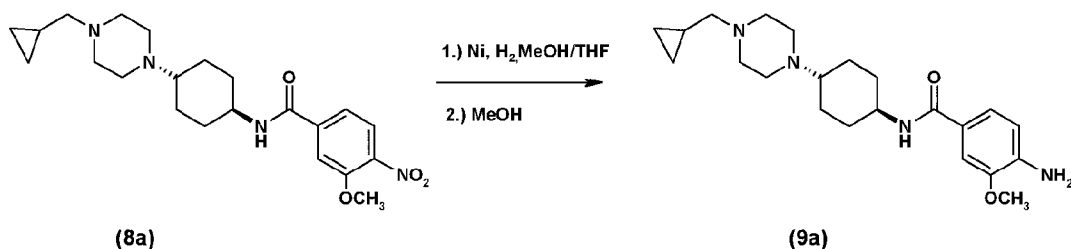
**Recrystallisation:**

10.0 g (24.0 mmol) of amide compound (**8a**) were dissolved in 60 ml ethanol under  
 reflux. The solution was cooled to  $20^\circ\text{C}$ . The suspension was stirred for an additional  
 20 hour at  $20^\circ\text{C}$ . The product was collected by filtration, and washed with 15 ml ethanol.

The product was dried at 45°C to constant weight.

Yield: 9.09 g (91%) of amide compound (8a).

5 **Step 4** (according to prior art)

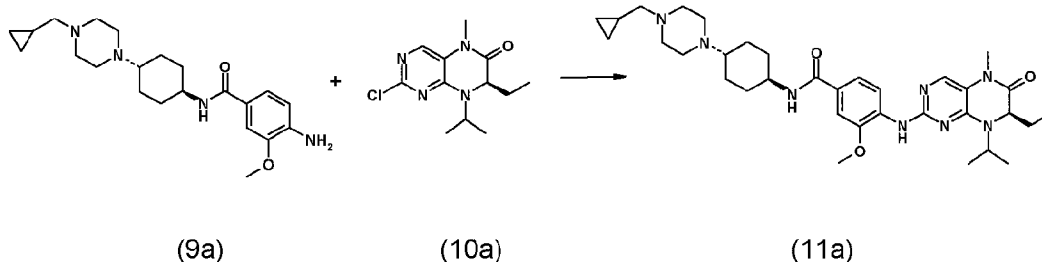


20.0 g (48.02 mol) of amide compound (8a) were dissolved in a mixture of 80 ml methanol and 100 ml tetrahydrofuran. After addition of 20 g Raney-Nickel, the mixture  
 10 was hydrogenated at 50 psi and 60°C. After complete conversion, the catalyst was filtered off, and the cake was rinsed with 40 ml methanol. 140 ml of solvent were removed in vacuo. To the residue 140 ml methanol were added. The suspension was refluxed until a clear solution was obtained. The solution was cooled to 2°C. The resulting suspension was stirred for an additional hour. The product was collected by  
 15 filtration, and washed with 60 ml methanol. The product was dried at 60°C to constant weight.

Yield: 17.30 g (93.0%) of aniline compound (9a).

**Step 5** (according to WO 2006/018220)

20



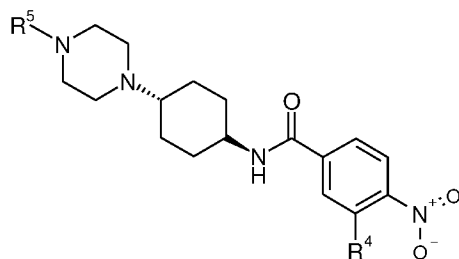
25 A solution of 23g (59.5 mmol) (9a), 16.8g (62.5 mmol) (10a) and 28.3g (149 mmol) para-toluenesulphonic acid hydrate in 350 mL 2-methyl-4-pentanol is refluxed for 22 hours using the water separator. After the addition of 1g of (10a) the mixture is refluxed



for a further 2 hours. 300 mL solvent are distilled off and the viscous oil is allowed to cool to 60°C. 300 mL methylene chloride and 300 mL demineralised water are added and the pH is raised by adding approx. 20 mL of 10 normal sodium hydroxide solution to pH = 9. The organic phase is washed twice with demineralised water and dried over sodium sulphate. The solvent is evaporated off under reduced pressure and the residue is dissolved at 65°C in 200 mL ethyl acetate. The mixture is left to cool slowly to 20°C, the precipitate is suction filtered and washed with cold ethyl acetate. After drying at 60°C in the vacuum drying cupboard 24.4g product (11a) is obtained (m.p. = 182°C, DSC: 10 K/min, additional endothermic effects in the DSC diagram before melting).

**Claims:**

1. A process for manufacturing a compound of formula (8)



(8)

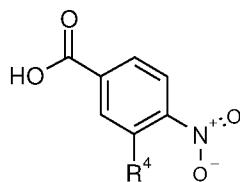
- 5 wherein

$R^5$  denotes  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_4$ -alkyl- $C_3$ - $C_{10}$ -cycloalkyl or  $C_3$ - $C_{10}$ -cycloalkyl,

$R^4$  denotes hydrogen or a group selected from among -CN, hydroxy,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_5$ -alkyloxy and  $C_1$ - $C_6$ -alkylthio,

wherein

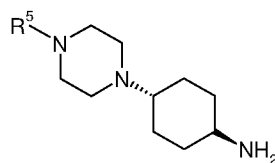
- 10 a compound of general formula (7)



(7)

wherein

- $R^4$  is as hereinbefore defined, optionally converted into an acyl halide compound, is  
15 reacted with the amine compound of formula (6)

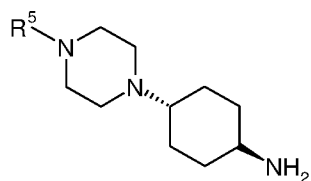


(6)

wherein

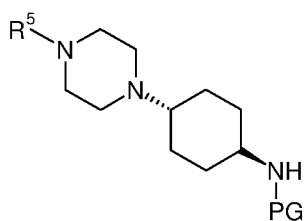
- $R^5$  is as hereinbefore defined,  
20 using an alkali or alkaline earth hydroxide as base and a protic solvent.

2. The process of claim 1, wherein the compound of formula (6)



(6)

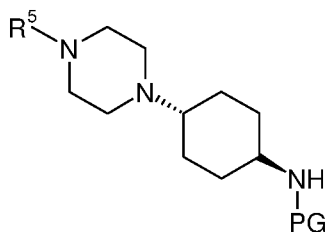
is obtained by removing the protecting group PG in a compound of general formula (5)



(5)

by acidic hydrolysis using p-toluenesulfonic acid (TsOH).

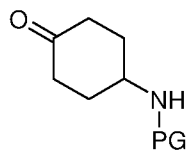
3. The process of claim 2, wherein the compound of formula (5)



(5)

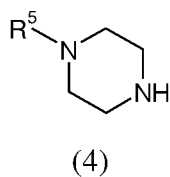
is obtained by reacting

a compound of formula (3)



(3)

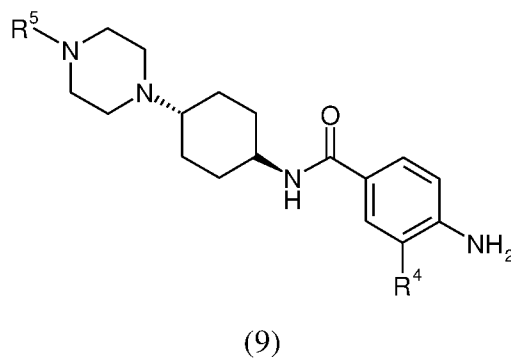
wherein PG is a protecting group with a compound of general formula (4)



via an enamine intermediate which is hydrogenated in the presence of a metal catalyst and  
5 a solvent or a mixture of solvents.

4. A process according to any one of claims 1 to 3 wherein the alkali or alkaline earth hydroxide as base used is NaOH or KOH.

5. A process for manufacturing a compound of formula (9)



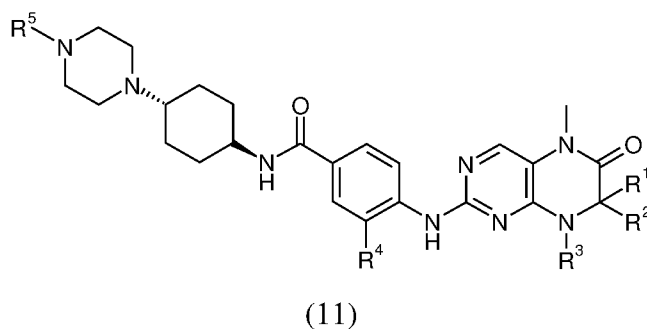
10

wherein

$R^4$  and  $R^5$  are as hereinbefore defined,

using any one of the preceding claims 1, 2, 3 and/or 4.

6. A process for manufacturing a compound of formula (11)



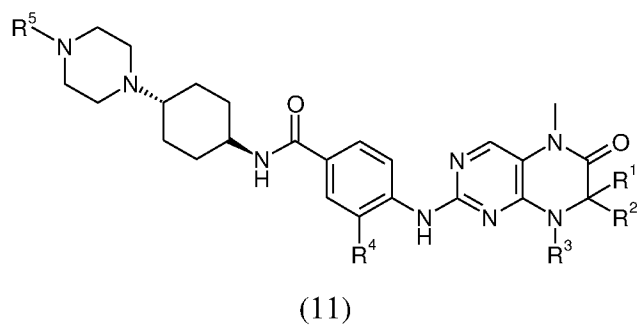
15

wherein

$R^1$  to  $R^5$  are as hereinbefore defined,

using any one of the preceding claims 1, 2 and/or 3.

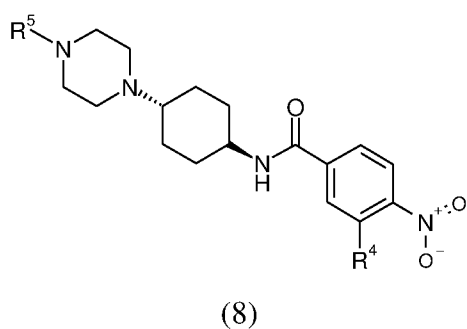
7. A process for manufacturing a compound of formula (11)



wherein

$R^1$  to  $R^5$  are as hereinbefore defined,

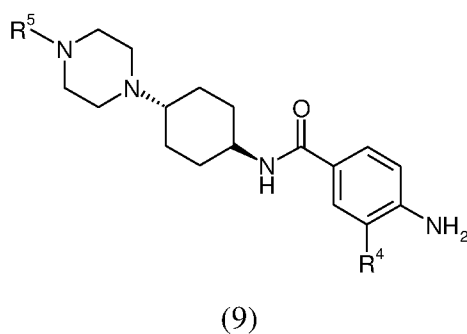
using a compound of formula (8)



obtained using the process of claim 1;

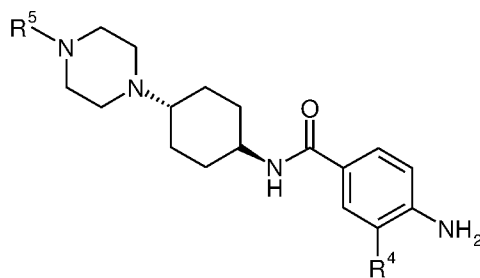
or

using a compound of formula (9)



using the process of claim 5.

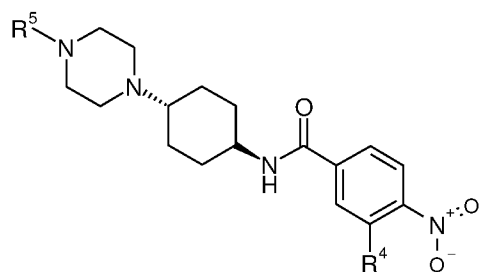
8. A process for manufacturing a compound of formula (9)



(9)

wherein

- 5 a compound of general formula (8)



(8)

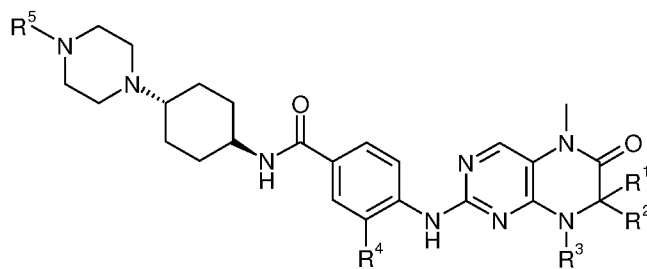
wherein

R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined,

- 10 is hydrogenated,

wherein the compound of formula (8) is obtained using the process according to any one of the preceding claims 1, 2, 3 and/or 4.

9. A process for manufacturing a compound of formula (11)

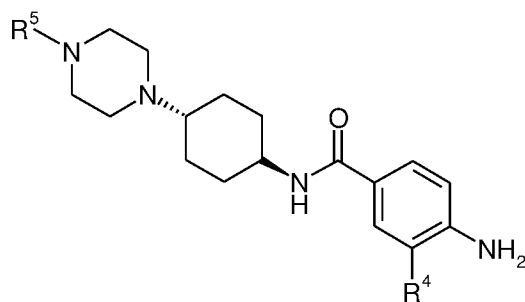


(11)

wherein

R<sup>1</sup> to R<sup>5</sup> are as hereinbefore defined,

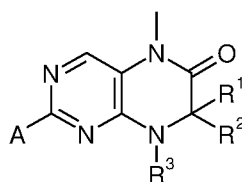
wherein a compound of formula (9)



(9)

wherein

- 5  $R^4$  and  $R^5$  are as hereinbefore defined,  
is reacted with a compound of formula (10)

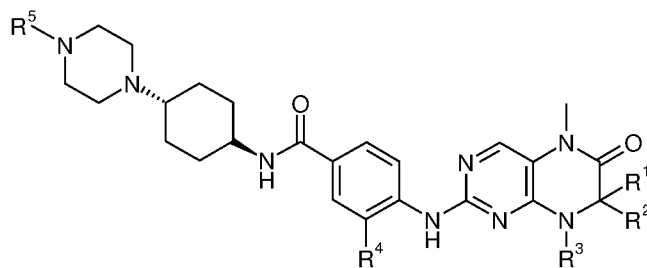


(10)

wherein  $R^1$ ,  $R^2$  and  $R^3$  are as hereinbefore defined and A is a leaving group,

- 10 wherein the compound of formula (9) is obtained using the process according to claim 8.

10. A process for manufacturing a compound of formula (11)



(11)

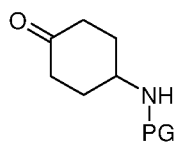
wherein

- 15  $R^1$  to  $R^5$  are as hereinbefore defined,

comprising the following steps:

step 1: a compound of formula (3)

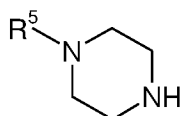
37



(3)

wherein PG is a protecting group

is reacted with a compound of general formula (4)



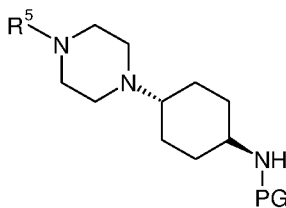
(4)

wherein

R<sup>5</sup> is as hereinbefore defined,

via an enamine intermediate which is hydrogenated in the presence of a metal catalyst and  
a solvent or a mixture of solvents

to obtain a compound of formula (5)



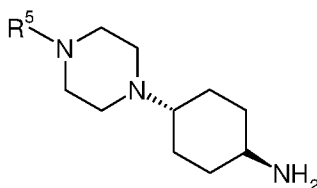
(5)

wherein R<sup>5</sup> and PG are as hereinbefore and hereinafter defined;

step 2: in a compound of formula (5) as hereinbefore defined,

the protecting group PG is removed by acidic hydrolysis using p-toluenesulfonic acid (TsOH),

to obtain a compound of formula (6)





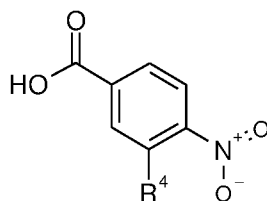
38

(6)

wherein

$R^5$  is as hereinbefore defined;

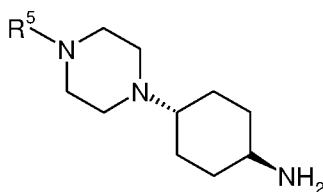
step 3: a compound of general formula (7)



(7)

wherein

$R^4$  is as hereinbefore defined, optionally converted into an acyl halide compound, is reacted with the amine compound of formula (6)



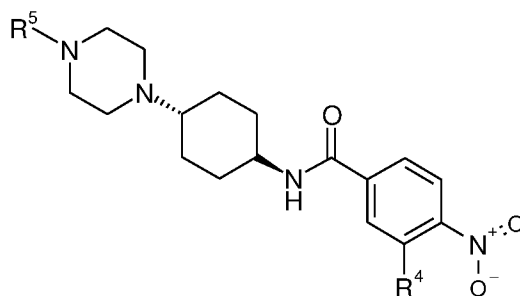
(6)

wherein

$R^5$  is as hereinbefore defined,

using an alkali or alkaline earth hydroxide as base and a protic solvent,

to obtain a compound of formula (8)



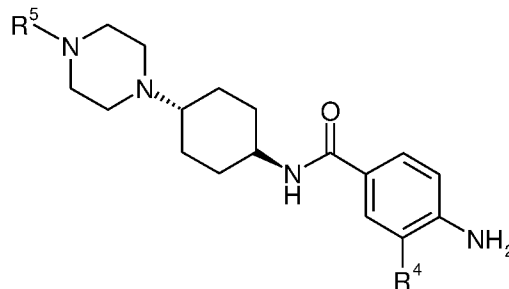
(8)

wherein

$R^4$  and  $R^5$  are as hereinbefore defined;

step 4: a compound of general formula (8) as hereinbefore defined

is hydrogenated to obtain a compound of formula (9)



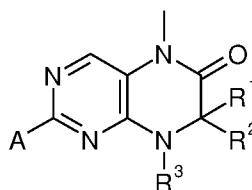
(9)

5 wherein

R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined;

step 5: a compound of formula (9) as hereinbefore defined,

is reacted with a compound of formula (10)

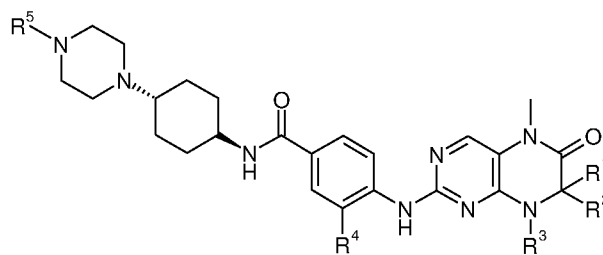


(10)

10

wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as hereinbefore defined and A is a leaving group,

to obtain a compound of formula (11)



(11)

15 wherein

R<sup>1</sup> to R<sup>5</sup> are as hereinbefore defined.

11. The process according to claim 10, wherein in step 1 the metal catalyst is selected from Pt/C or platinum-IV-oxide (PtO<sub>2</sub>), preferably platinum-IV-oxide (PtO<sub>2</sub>).

12. The process according to claim 10, wherein in step 1 the solvent is selected from  
- an aprotic organic solvent which is preferably selected from dichloromethane,  
5 acetone, ethylene glycol dimethyl ether, diglyme, toluene, tetrahydrofuran (THF), more preferably toluene or THF, most preferably toluene,

or

- an alcohol, which is preferably selected from ethanol, methanol, isopropanol, n-propanol, n-butanol and/or tert.-butanol, more preferably ethanol or methanol,

10 or

- a mixture of an aprotic solvent and an alcohol, preferably a mixture of toluene and an alcohol, most preferably a mixture of toluene/ethanol.

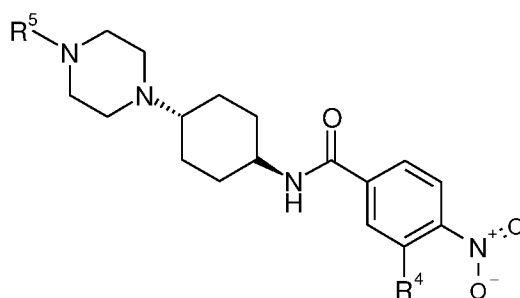
13. The process according to claim 12, wherein the ratio toluene : alcohol, preferably toluene : ethanol, is adjusted in the range of 4 - 5 : 1.

15 14. The process according to any one of the preceding claims, wherein the compounds produced may be in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the salts thereof.

15. A process according to any one of the preceding claims, characterized in that the metal catalyst is selected from the group consisting of a Ni catalyst, Pd catalyst or a Pt catalyst.  
20

16. A process according to any one of the preceding claims, wherein the metal catalyst is Pt/C or platinum-IV-oxide (PtO<sub>2</sub>).

17. A compound of formula (8)

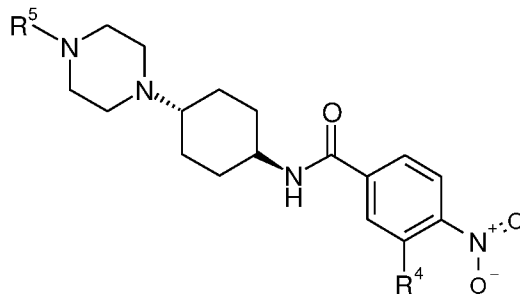


(8)

25

as defined in claim 1, prepared according to the process of claim 1.

18. A process for manufacturing a compound of formula (8)



(8)

5 as defined in claim 1 and substantially as hereinbefore described with reference to any one of the Examples.

**Boehringer Ingelheim International GmbH**

**Patent Attorneys for the Applicant/Nominated Person  
SPRUSON & FERGUSON**