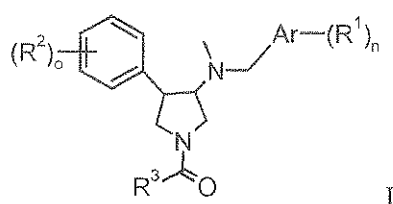


**3-(BENZYLAMINO)-PYRROLIDINE DERIVATIVES AND THEIR USE  
AS NK-3 RECEPTOR ANTAGONISTS**

The present invention relates to a compounds of formula I



wherein

5 Ar is aryl;

R¹ is hydrogen, halogen, lower alkyl, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen, cyano, amino, mono or di-lower alkyl amino, C(O)-lower alkyl, or is aryl or heteroaryl;

10

R² is hydrogen or halogen;

R³ is  $-(CH_2)_p$ -heterocyclyl, optionally substituted by one or two substituents R⁴; or is lower alkyl,

15

lower alkoxy,

$-(CH_2)_p$ -O-lower alkyl,

$-(CH_2)_p$ -CN,

$-O-(CH_2)_p$ -CN,

$-(CH_2)_p$ -heteroaryl,

20

$-(CH_2)_p$ -C(O)-heteroaryl,

$-O-(CH_2)_p$ -heterocyclyl,

$-(CH_2)_p$ -aryl, optionally substituted by lower alkoxy or halogen,

$-(CH_2)_p$ -O-aryl, optionally substituted by lower alkyl,

$-(CH_2)_p$ -NR'-heterocyclyl, optionally substituted by lower alkyl,

-2-

$-(CH_2)_p-NR'R''$ ,  
 $-(CH_2)_p-NR'-CH_2)_p-NR'R''$ ,  
 $-(CH_2)_p-NR'-CH_2)_p-CN$ ,  
 $-(CH_2)_p-C(O)-NR'R''$  or is  
 $-O-(CH_2)_p-NR'R''$ ;

$R^4$  is hydroxy, lower alkyl,  $-(CH_2)_p-OH$ ,  $-(CH_2)_p-NR'R''$ ,  $-NR'-C(O)$ -lower alkyl,  $-(CH_2)_p-CN$ ,  $-S(O)_2$ -lower alkyl,  $-NR'-S(O)_2$ -lower alkyl,  $-S(O)_2-NR'R''$ ,  $-C(O)$ -lower alkyl,  $-C(O)$ -lower cycloalkyl, wherein the cycloalkyl may be substituted by lower alkyl, or is  $-C(O)-NR'R''$ , heterocyclyl, optionally substituted by  $=O$ , or is heteroaryl, optionally substituted by alkoxy or cyano, or is aryl optionally substituted by alkoxy, cyano or is 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl;

$R'$  and  $R''$  are independently from each other hydrogen, lower alkyl or  $-(CH_2)_p-OH$ ;

$n$  is 1 or 2; in case  $n$  is 1 or 2,  $R^1$  may be the same or different;

$o$  is 1 or 2; in case  $o$  is 1 or 2,  $R^2$  may be the same or different;

$p, p'$  are the same or different and are 0, 1, 2, 3 or 4;

or to a pharmaceutically active salt, a racemic mixture, an enantiomer, an optical isomer or a tautomeric form thereof.

The invention includes all stereoisomeric forms, including individual diastereoisomers and enantiomers of the compound of formula (I) as well as racemic and non-racemic mixtures thereof.

It has been found that the present compounds are high potential NK-3 receptor antagonists for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, anxiety and attention deficit hyperactivity disorder (ADHD).

The three main mammalian tachykinins, substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) belong to the family of neuropeptides sharing the common COOH-terminal pentapeptide sequence of Phe-X-Gly-Leu-Met-NH<sub>2</sub>. As neurotransmitters, these peptides exert

their biological activity via three distinct neurokinin (NK) receptors termed as NK-1, NK-2 and NK-3. SP binds preferentially to the NK-1 receptor, NKA to the NK-2 and NKB to the NK-3 receptor.

The NK-3 receptor is characterized by a predominant expression in CNS and its involvement in the modulation of the central monoaminergic system has been shown. These properties make the NK-3 receptor a potential target for central nervous system disorders such as anxiety, depression, bipolar disorders, Parkinson's disease, schizophrenia and pain (*Neurosci. Letters*, 2000, 283, 185-188; *Exp. Opin. Ther. Patents* 2000, 10, 939-960; *Neuroscience*, 1996, 74, 403-414; *Neuropeptides*, 1998, 32, 481-488).

Schizophrenia is one of the major neuropsychiatric disorders, characterized by severe and chronic mental impairment. This devastating disease affects about 1 % of the world's population. Symptoms begin in early adulthood and are followed by a period of interpersonal and social dysfunction. Schizophrenia manifests as auditory and visual hallucinations, paranoia, delusions (positive symptoms), blunted affect, depression, anhedonia, poverty of speech, memory and attention deficits as well as social withdrawal (negative symptoms).

For decades scientists and clinicians have made efforts with the aim of discovering an ideal agent for the pharmacological treatment of schizophrenia. However, the complexity of the disorders, due to a wide array of symptoms, has hampered those efforts. There are no specific focal characteristics for the diagnosis of schizophrenia and no single symptom is consistently present in all patients. Consequently, the diagnosis of schizophrenia as a single disorder or as a variety of different disorders has been discussed but not yet resolved. The major difficulty in the development of a new drug for schizophrenia is the lack of knowledge about the cause and nature of this disease. Some neurochemical hypotheses have been proposed on the basis of pharmacological studies to rationalize the development of a corresponding therapy: the dopamine, the serotonin and the glutamate hypotheses. But taking into account the complexity of schizophrenia, an appropriate multireceptor affinity profile might be required for efficacy against positive and negative signs and symptoms. Furthermore, an ideal drug against schizophrenia would preferably have a low dosage allowing once-per-day dosage, due to the low adherence of schizophrenic patients.

In recent years clinical studies with selective NK1 and NK2 receptor antagonists appeared in the literature showing results for the treatment of emesis, depression, anxiety, pain and migraine (NK1) and asthma (NK2 and NK1). The most exciting data were produced in the treatment of chemotherapy-induced emesis, nausea and depression with NK1 and in asthma with

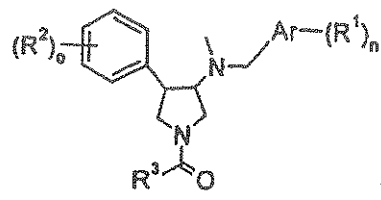
NK2- receptor antagonists. In contrast, no clinical data on NK3 receptor antagonists have appeared in the literature until 2000. Osanetant (SR 142,801) from Sanofi-Synthelabo was the first identified potent and selective non-peptide antagonist described for the NK3 tachykinin receptor for the potential treatment of schizophrenia, which was reported in the literature (*Current Opinion in Investigational Drugs*, 2001,2(7), 950-956 and *Psychiatric Disorders Study 4, Schizophrenia*, June 2003, *Decision Resources, Inc., Waltham, Massachusetts*). The proposed drug SR 142,801 has been shown in a phase II trial as active on positive symptoms of schizophrenia, such as altered behaviour, delusion, hallucinations, extreme emotions, excited motor activity and incoherent speech, but inactive in the treatment of negative symptoms, which are depression, anhedonia, social isolation or memory and attention deficits.

The neurokinin-3 receptor antagonists have been described as useful in pain or inflammation, as well as in schizophrenia, *Exp. Opinion.Ther. Patents* (2000), 10(6), 939-960 and *Current Opinion in Investigational Drugs*, 2001, 2(7), 950-956 956 and *Psychiatric Disorders Study 4, Schizophrenia*, June 2003, *Decision Resources, Inc., Waltham, Massachusetts*).

Objects of the embodiments disclosed herein are novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the disclosure and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as depression, pain, bipolar disorders, psychosis, Parkinson's disease, schizophrenia, anxiety and attention deficit hyperactivity disorder (ADHD).

The preferred indications using the compounds of the present disclosure are depression, psychosis, Parkinson's disease, schizophrenia, anxiety and attention deficit hyperactivity disorder (ADHD).

In a first aspect, there is provided a compound of general formula I



wherein

Ar is aryl selected from the group consisting of phenyl, benzyl, naphthyl or indanyl;

R<sup>1</sup> is hydrogen, halogen, C<sub>1-8</sub>-alkyl, C<sub>1-8</sub>-alkoxy, C<sub>1-8</sub>-alkyl substituted by halogen, C<sub>1-8</sub>-alkoxy substituted by halogen, cyano, amino, mono or di-C<sub>1-8</sub>-alkyl amino, C(O)-C<sub>1-8</sub>-alkyl, or is aryl as defined for Ar, or is heteroaryl selected from the group consisting of quinoxaliny, dihydroisoquinoliny, pyrazin-2-yl, pyrazol-1-yl, 2,4-dihydro-pyrazol-3-one, pyridiny, isoxazolyl, benzo[1,3]dioxol, pyridyl, pyrimidin-4-yl, pyrimidin-5-yl, benzotriazol-5-yl, benzoimidazol-5-yl, [1,3,4]-oxadiazol-2-yl, [1,2,4]triazol-1-yl, [1,6]naphthyridin-2-yl, imidazo[4,5-b]pyridine-6-yl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, furyl, imidazol-1-yl, or benzofuranyl;

R<sup>2</sup> is hydrogen or halogen;

R<sup>3</sup> is -(CH<sub>2</sub>)<sub>p</sub>-heterocyclyl, selected from the group consisting of morpholiny, [1,4]diazepam-1-yl, piperaziny, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl or 1,1-dioxo-λ<sup>6</sup>-thiomorpholiny, optionally substituted by one or two substituents R<sup>4</sup>; or is

C<sub>1-8</sub>-alkyl,

C<sub>1-8</sub>-alkoxy,

-(CH<sub>2</sub>)<sub>p</sub>-O-C<sub>1-8</sub>-alkyl,

-(CH<sub>2</sub>)<sub>p</sub>-CN,

-O-(CH<sub>2</sub>)<sub>p</sub>-CN,

$-(CH_2)_p$ -heteroaryl as defined for  $R^1$ ,  
 $-(CH_2)_p$ -C(O)-heteroaryl as defined for  $R^1$ ,  
 $-O-(CH_2)_p$ -heterocyclyl as defined above,  
 $-(CH_2)_p$ -aryl as defined for Ar, optionally substituted by  $C_{1-8}$ -alkoxy or halogen,  
 $-(CH_2)_p$ -O-aryl as defined for Ar, optionally substituted by  $C_{1-8}$ -alkyl,  
 $-(CH_2)_p$ -NR'-heterocyclyl as defined above, optionally substituted by  $C_{1-8}$ -alkyl,  
 $-(CH_2)_p$ -NR'R'',  
 $-(CH_2)_p$ -NR'- $-(CH_2)_p$ -NR'R'',  
 $-(CH_2)_p$ -NR'- $-(CH_2)_p$ -CN,  
 $-(CH_2)_p$ -C(O)-NR'R'' or is  
 $-O-(CH_2)_p$ -NR'R'';

$R^4$  is hydroxy,  $C_{1-8}$ -alkyl,  $-(CH_2)_p$ -OH,  $-(CH_2)_p$ -NR'R'', -NR'-C(O)- $C_{1-8}$ -alkyl,  $-(CH_2)_p$ -CN, -S(O)<sub>2</sub>- $C_{1-8}$ -alkyl, -NR'-S(O)<sub>2</sub>- $C_{1-8}$ -alkyl, -S(O)<sub>2</sub>-NR'R'', -C(O)- $C_{1-8}$ -alkyl, -C(O)- $C_{3-7}$ -cycloalkyl, wherein the cycloalkyl may be substituted by  $C_{1-8}$ -alkyl, or is -C(O)-NR'R'', heterocyclyl as defined for  $R^3$ , optionally substituted by =O, or is heteroaryl as defined for  $R^1$ , optionally substituted by  $C_{1-8}$ -alkoxy or cyano, or is aryl as defined for Ar, optionally substituted by  $C_{1-8}$ -alkoxy, cyano or is 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl;

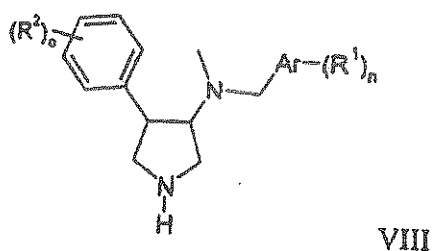
$R'$  and  $R''$  are independently from each other hydrogen,  $C_{1-8}$ -alkyl or  $-(CH_2)_p$ -OH,

$n$  is 1 or 2; in case  $n$  is 1 or 2,  $R^1$  may be the same or different;  
 $o$  is 1 or 2; in case  $o$  is 1 or 2,  $R^2$  may be the same or different;  
 $p, p'$  are the same or different and are 0, 1, 2, 3 or 4;  
 or to a pharmaceutically active salt thereof.

or a pharmaceutically active salt, a racemic mixture, an enantiomer, an optical isomer or a tautomeric form thereof.

In a second aspect, there is provided a process for preparing a compound of formula I as defined above, which process comprises

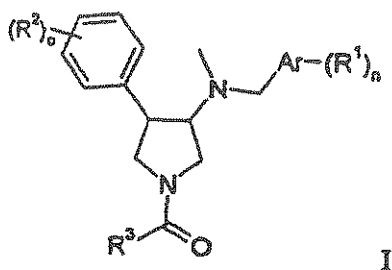
a) coupling a compound of formula



with a suitable acid chloride or carboxylic acid of formula

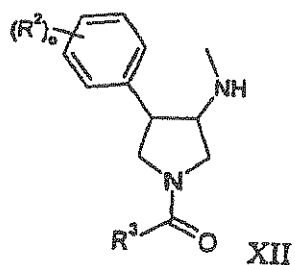


to a compound of formula



wherein the groups Ar, R¹, R² and R³ and the definitions o and n are described above, or

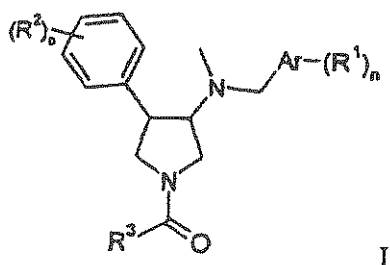
b) alkylating a compound of formula



with a compound of formula



to a compound of formula



wherein the groups Ar, R¹, R² and R³ and the definitions o and n are described above, and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

In a third aspect, there is provided a medicament containing one or more compounds as defined above and pharmaceutically acceptable excipients.

In a fourth aspect, there is provided the use of a compound as defined above for the manufacture of medicaments for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, anxiety and attention deficit hyperactivity disorder (ADHD).

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1-8 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1-4 carbon atoms.

The term "lower alkyl substituted by halogen" denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by halogen, for example -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>CF<sub>2</sub>CF<sub>3</sub> and the like. Preferred lower alkyl substituted by halogen groups are groups having 1-4 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "cycloalkyl" denotes a saturated carbon ring containing from 3-7 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

The term "aryl" denotes a cyclic aromatic hydrocarbon radical consisting of one or more fused rings containing 6-14 carbon atoms in which at least one ring is aromatic in nature, for example phenyl, benzyl, naphthyl or indanyl. Preferred is the phenyl group.

The term "heteroaryl" denotes a cyclic aromatic hydrocarbon radical consisting of one or more fused rings containing 5-14 ring atoms, preferably containing 5-10 ring atoms, in which at least one ring is aromatic in nature, and which contains at least one heteroatom, selected from N, O or S, for example quinoxaliny, dihydroisoquinoliny, pyrazin-2-yl, pyrazol-1-yl, 2,4-dihydro-pyrazol-3-one, pyridiny, isoxazolyl, benzo[1,3]dioxol, pyridyl, pyrimidin-4-yl, pyrimidin-5-yl, benzotriazol-5-yl, benzoimidazol-5-yl, [1,3,4]-oxadiazol-2-yl, [1,2,4]triazol-1-yl, [1,6]naphthyridin-2-yl, imidazo[4,5-b]pyridine-6-yl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, furyl, imidazol-1-yl, or benzofuranyl. Preferred heteroaryl group is pyridine-2,3or 4-yl.

The term heterocyclyl denotes a five or six membered alkyl ring, wherein one or two carbon atoms are replaced by N, S or O, for example the following groups: morpholiny, [1,4]diazepam-1-yl, piperaziny, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl or 1,1-dioxo- $\lambda^6$ -thiomorpholiny.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

Compounds of formula I, wherein Ar is phenyl, are preferred.

Preferred compounds of formula I are those, wherein R<sup>3</sup> is unsubstituted  $-(CH_2)_p$ -heterocyclyl, for example the following compounds:

1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-morpholin-4-yl-pentan-1-one

1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl)-5-morpholin-4-yl-pentan-1-one

1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-piperazin-1-yl-pentan-1-one

1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-pentan-1-one

1-{(3SR,4RS)-3-(3-chloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-morpholin-4-yl-pentan-1-one

1-{(3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-3-morpholin-4-yl-propan-1-one

5 1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-morpholin-4-yl-ethanone

1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-piperazin-1-yl-ethanone or

10 1-{(3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(1,1-dioxo- $\lambda^6$ -thiomorpholin-4-yl)-ethanone.

Preferred compounds of formula I are further those, wherein  $R^3$  is  $-(CH_2)_p$ -heterocyclyl, substituted by one or two substituents  $R^4$ .

Preferred compounds of formula I are those, wherein  $R^4$  is  $-S(O)_2$ -lower alkyl, for example the

15 following compounds:

{(3RS,4SR)-3-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

{(3SR,4RS)-3-(4-chloro-phenyl)-4-[(3,4-dichloro-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

20 [(3RS,4SR)-3-(biphenyl-4-ylmethyl-methyl-amino)-4-(4-chloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3RS,4SR)-3-[(4-chloro-3-fluoro-benzyl)-methyl-amino]-4-(4-chloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

25 {(3SR,4RS)-3-(4-chloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3RS,4SR)-3-[(3,4-dichloro-benzyl)-methyl-amino]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

30 [(3RS,4SR)-3-[(4-chloro-benzyl)-methyl-amino]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

4-({[(3RS,4SR)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-amino}-methyl)-benzonitrile

- {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3,4-difluoro-benzyl)-methyl-amino]-pyrrolidin-1-yl}-  
(4-methanesulfonyl-piperazin-1-yl)-methanone
- {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(2,3-dihydro-benzofuran-6-ylmethyl)-methyl-amino]-  
pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
- 5 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(4-fluoro-3-methyl-benzyl)-methyl-amino]-pyrrolidin-1-  
yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
- {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(1H-indol-6-ylmethyl)-methyl-amino]-pyrrolidin-1-yl}-  
(4-methanesulfonyl-piperazin-1-yl)-methanone
- 4-({[(3RS,4SR)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-  
pyrrolidin-3-yl]-methyl-amino}-methyl)-2-fluoro-benzonitrile
- 10 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidin-1-yl}-(S)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone
- {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidin-1-yl}-(R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone
- 15 {(3SR,4RS)-3-(4-chloro-3-fluoro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-  
amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
- {(3SR,4RS)-3-(4-chloro-3-fluoro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-  
amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-[1,4]diazepan-1-yl)-methanone
- {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-  
20 yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone or
- 1-({(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidin-1-yl}-2-(4-methanesulfonyl-piperazin-1-yl)-ethanone.

Preferred compounds of formula I are those, wherein R<sup>4</sup> is lower alkyl, for example the  
25 following compounds:

- 1-({(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidin-1-yl}-5-(4-methyl-piperazin-1-yl)-pentan-1-one
- 1-({(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidin-1-yl}-2-(4-methyl-piperazin-1-yl)-ethanone
- 30 1-({(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidin-1-yl}-2-(3,5-dimethyl-piperazin-1-yl)-ethanone
- 1-({(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidin-1-yl}-2-(S)-3-methyl-piperazin-1-yl)-ethanone

1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-((R)-3-methyl-piperazin-1-yl)-ethanone or  
 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(2,6-dimethyl-morpholin-4-yl)-ethanone.

5

Preferred compounds of formula I are those, wherein  $R^4$  is  $-S(O)_2-NR'R''$ , for example the following compounds:

4-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl)-piperazine-1-sulfonic acid dimethylamide

- 10 4-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperazine-1-sulfonic acid dimethylamide or  
 4-(5-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-oxo-pentyl)-piperazine-1-sulfonic acid dimethylamide.

- 15 Preferred compounds of formula I are those, wherein  $R^4$  is  $-NR'-S(O)_2$ -lower alkyl, for example the following compounds:

N-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-methanesulfonamide or

- 20 N-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-methanesulfonamide.

Preferred compounds of formula I are those, wherein  $R^4$  is  $-C(O)$ -lower alkyl, for example the following compounds:

- 25 1-(4-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl)-piperazin-1-yl)-ethanone or  
 2-(4-ccetyl-piperazin-1-yl)-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone.

- 30 Preferred compounds of formula I are those, wherein  $R^4$  is  $-NR'-C(O)$ -lower alkyl, for example the following compounds:

N-[1-(5-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-oxo-pentyl)-piperidin-4-yl]-acetamide

N-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-acetamide

N-[(S)-1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-pyrrolidin-3-yl]-acetamide

5 N-[(R)-1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-pyrrolidin-3-yl]-acetamide or

N-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-acetamide.

10 Preferred compounds of formula I are those, wherein  $R^4$  is  $-(CH_2)_p-NR'R''$ -, for example the following compounds:

{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-((R)-3-dimethylamino-pyrrolidin-1-yl)-methanone

1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-ethanone

15 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(3-dimethylamino-propyl)-piperazin-1-yl]-methanone

{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone or

20 1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(4-dimethylamino-piperidin-1-yl)-ethanone.

Preferred compounds of formula I are those, wherein  $R^4$  is heteroaryl, optionally substituted by alkoxy or cyano, for example the following compounds:

25 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone

{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-pyridin-2-yl-piperazin-1-yl)-methanone

{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-pyridin-4-yl-piperazin-1-yl)-methanone

30 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone

2-(4-{{(3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-nicotinonitrile

6-(4-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-nicotinonitrile or

5 {{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(6-methoxy-pyridin-2-yl)-piperazin-1-yl]-methanone.

Preferred compounds of formula I are those, wherein  $R^4$  is aryl, optionally substituted by alkoxy or cyano, for example the following compounds:

10 {{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone

2-(4-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-benzonitrile or

15 4-(4-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-benzonitrile.

Preferred compounds of formula I are those, wherein  $R^4$  is  $-(CH_2)_pOH-$ , for example the following compounds:

20 {{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(3-hydroxy-propyl)-piperazin-1-yl]-methanone

{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone

1-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-[4-(3-hydroxy-propyl)-piperazin-1-yl]-ethanone

25 1-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(4-hydroxy-piperidin-1-yl)-ethanone or

{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-methanone.

30 Preferred compounds of formula I are those, wherein  $R^4$  is  $-C(O)-NR'R''$ , for example the following compound:

4-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazine-1-carboxylic acid diethylamide.

Preferred compounds of formula I are those, wherein  $R^4$  is  $-(CH_2)_pCN-$ , for example the following compounds:

3-(4-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl)-piperazin-1-yl)-propionitrile  
 3-[4-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperazin-1-yl]-propionitrile or  
 1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidine-4-carbonitrile.

10

Preferred compounds of formula I are those, wherein  $R^4$  is heterocyclyl, optionally substituted by  $=O$ , for example the following compounds:

4-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-morpholin-3-one

15 1'-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-[1,4']bipiperidinyl-2-one.

Preferred compounds of formula I are those, wherein  $R^4$  is 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl, for example the following compound:

20 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(1S,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-ethanone.

Preferred compounds of formula I are those, wherein  $R^4$  is  $-C(O)$ -lower cycloalkyl, substituted by lower alkyl, for example the following compound:

25 (3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone.

Preferred compounds of formula I are those, wherein  $R^3$  is  $-(CH_2)_pNR'R''$ , for example the following compounds:

30 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-methylamino-pentan-1-one or

1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-dimethylamino-pentan-1-one

Preferred compounds of formula I are those, wherein  $R^3$  is  $-(CH_2)_p$ -heteroaryl, for example the following compound:

1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-imidazol-1-yl-pentan-1-one.

Preferred compounds of formula I are those, wherein  $R^3$  is  $-(CH_2)_p$ -C(O)-heteroaryl, for example the following compounds:

1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-6-pyridin-2-yl-hexane-1,6-dione.

Preferred compounds of formula I are those, wherein  $R^3$  is  $-(CH_2)_p$ -C(O)-NR'R'', for example the following compound:

6-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-6-oxo-hexanoic acid amide.

Preferred compounds of formula I are those, wherein  $R^3$  is  $-(CH_2)_p$ -O-lower alkyl, for example the following compound:

1-{(3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-methoxy-pentan-1-one.

Preferred compounds of formula I are those, wherein  $R^3$  is  $-(CH_2)_p$ -CN, for example the following compound:

6-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-6-oxo-hexanenitrile.

Preferred compounds of formula I are those, wherein  $R^3$  is  $-(CH_2)_p$ -NR'-(CH<sub>2</sub>)<sub>p</sub>-NR'R'', for example the following compounds:

1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(2-dimethylamino-ethylamino)-ethanone

1-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(3-dimethylamino-propylamino)-ethanone

1-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-[(3-dimethylamino-propyl)-methyl-amino]-ethanone.

5

Preferred compounds of formula I are those, wherein  $R^3$  is  $-(CH_2)_p-NR'-(CH_2)_{p'}-CN$ , for example the following compounds:

3-(2-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-oxo-ethylamino)-propionitrile or

10 3-[(2-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-oxo-ethyl)-methyl-amino]-propionitrile.

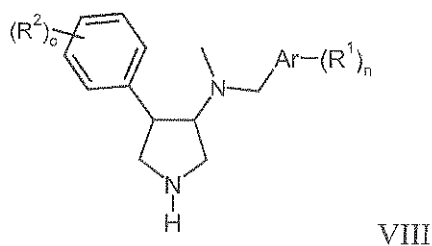
The preparation of compounds of formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the compounds of the invention are  
15 shown in the following schemes. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein before unless indicated to the contrary.

The compounds of formula I can be manufactured by the methods given below, by the  
20 methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in the schemes, however, depending on the starting materials and their respective reactivity the sequence of reaction steps can be freely altered. Starting materials are either commercially available or can be prepared by methods analogous to the methods given  
25 below, by methods described in references cited in the description or in the examples, or by methods known in the art.

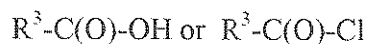
The present compounds of formula I and their pharmaceutically acceptable salts may be prepared by methods, known in the art, for example by the process variants described below, which process comprises

30 a) coupling a compound of formula

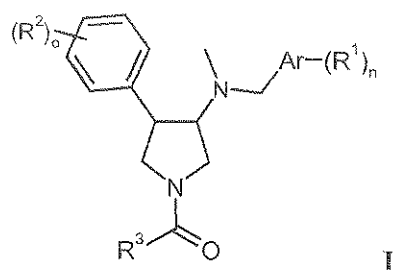
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with a suitable acid chloride or carboxylic acid of formula

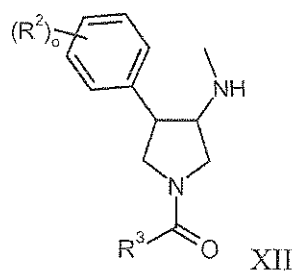


to a compound of formula

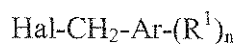


wherein the groups Ar, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> and the definitions o and n are described above, or

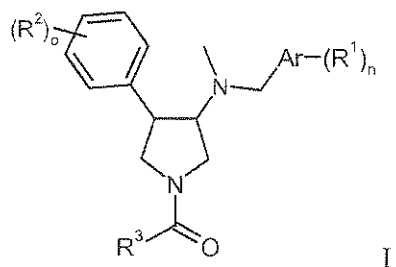
b) alkylating a compound of formula



with a compound of formula



to a compound of formula



wherein the groups Ar, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> and the definitions o and n are described above, and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

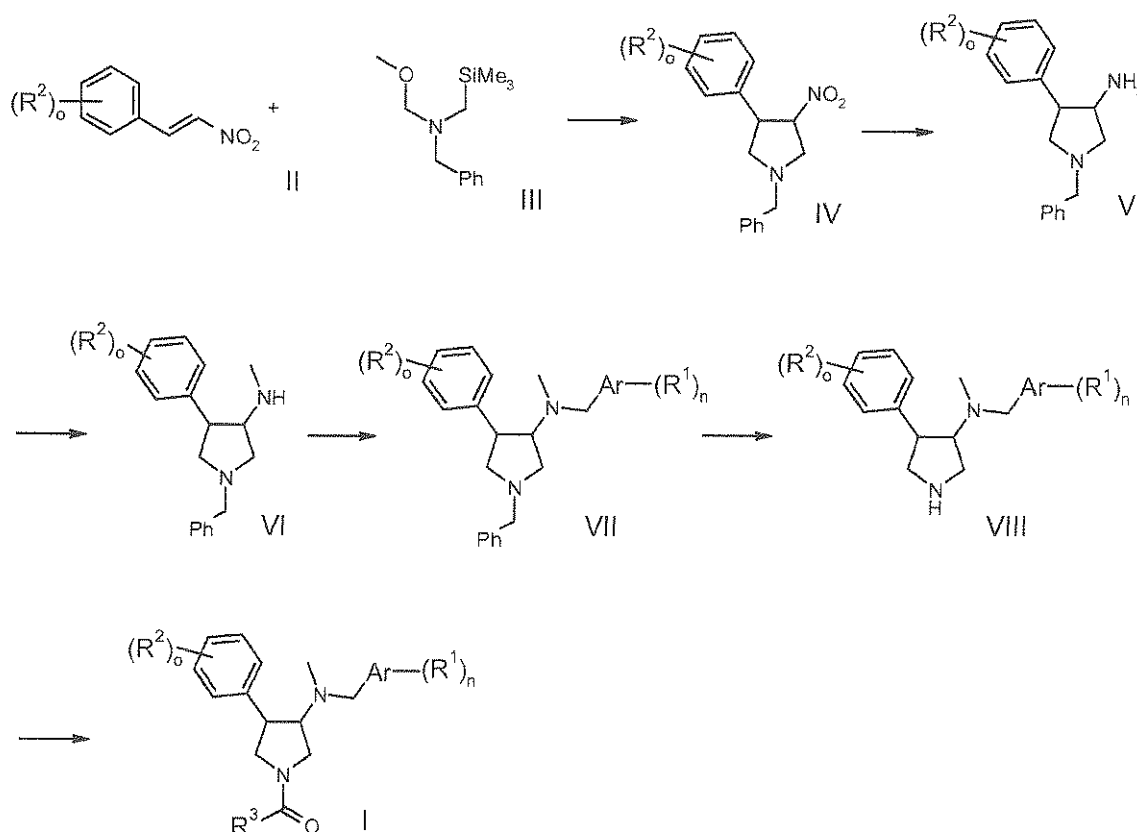
The preparation of compounds of formula I is further described in more detail in general schemes I – 4, in general procedures I – VIII and in examples 1 – 149.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are antagonists of neurokinin 3 (NK-3) receptors. The compounds were investigated in accordance with the tests given hereinafter.

### Experimental procedure

The compounds were investigated in accordance with the tests given hereinafter.

#### General scheme 1

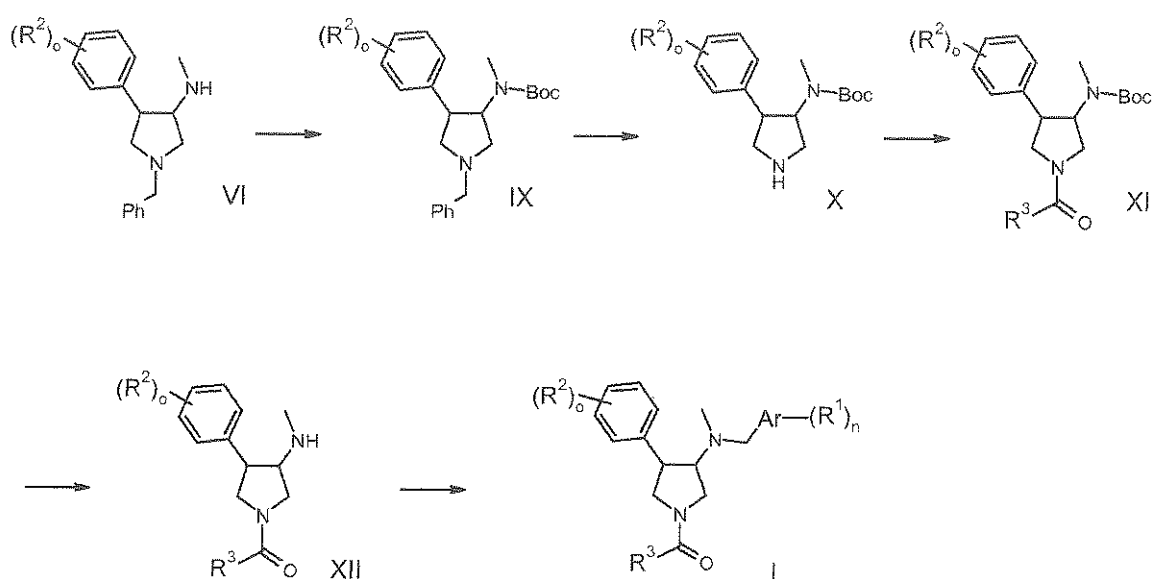


The pyrrolidines IV were prepared *via* a stereo specific 1,3-dipolar cycloaddition between 2-nitrostyrene derivatives II and the azomethine ylide generated *in situ* from the N-

(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine III in the presence of a catalytic amount of acid, such as TFA. Reduction of the nitro moiety using standard conditions for example SnCl<sub>2</sub>.H<sub>2</sub>O yielded V. The amino moiety was subsequently methylated in a two step

sequence, involving first the preparation of the ethyl carbamate followed by its reduction with borane to produce **VI**. Reductive amination reaction between **VI** and an aldehyde yielded **VII**. Alternatively, **VII** could be prepared by alkylation. Selective N-debenzylation was then carried out using several known procedures which are compatible with the substitution patterns of the aromatic rings to afford **VIII**. Finally derivatives **I** were prepared *via* a coupling with a corresponding acid chloride or carboxylic acid.

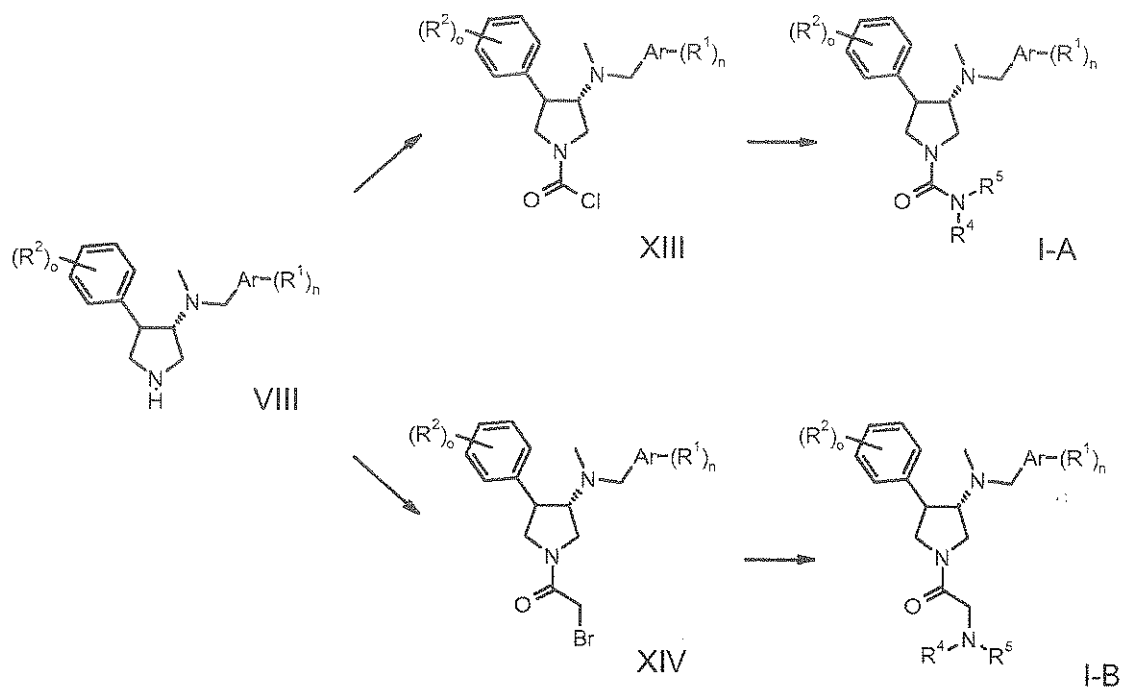
General scheme 2



Alternatively, the pyrrolidine derivatives **I**, were also prepared via the route highlighted scheme 2. The secondary amine of the intermediate **VI** can be BOC-protected to afford **IX**. Selective N-debenzylation was then carried out using several known procedures which are compatible with the substitution patterns of the aromatic rings to afford **X**. Standard coupling reaction with an acid chloride or carboxylic acid gave **XI**, which could then undergo a deprotection with for instance TFA to give **XII**. The secondary amine was then alkylated via a standard reductive amination or via an alkylation with an alkyl-halide to afford the derivatives **I**.

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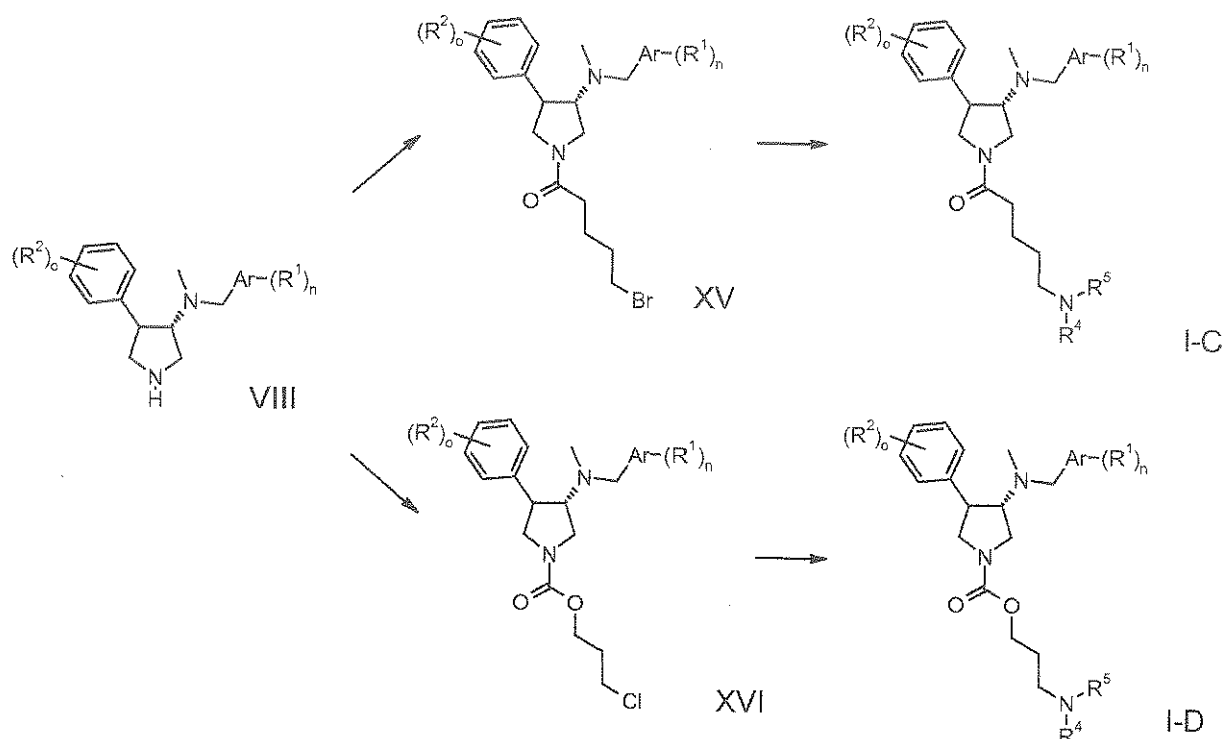
## General scheme 3



Alternatively, intermediates VIII could be converted in a two step sequence into final compound I-A or I-B. For instance, the treatment of derivatives VIII with triphosgene in a presence of a base, preferably pyridine and at low temperature yielded pyrrolidine-1-carbonyl chloride derivatives XIII. The coupling between compounds XIII and a primary or secondary amine gave access to urea of formula I-A. The treatment of derivatives VIII with bromo-acetyl chloride in a presence of a base yielded intermediates XIV. A nucleophilic substitution reaction between XIV and a primary or secondary amine gave access to amide of formula I-B.

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## General scheme 4



Alternatively, intermediates **VIII** could be converted in a two step sequence into final compound **I-C** or **I-D**. For instance, the treatment of derivatives **VIII** with 5-Bromo-pentanoyl chloride yielded pyrrolidine derivatives of general formula **XV**. A nucleophilic substitution reaction yielded final derivatives of the types **I-C**. The treatment of derivatives **VIII** with 3-chloropropyl chloroformate in a presence of a base yielded intermediates **XVI**. A nucleophilic substitution reaction yielded pyrrolidine derivatives of the types **I-D**. Nucleophiles could be a primary or secondary amines.

## Experimental part

## Abbreviations:

CH<sub>2</sub>Cl<sub>2</sub> = dichloromethane;

DMAP = dimethylaminopyridine;

HOBt = 1-hydroxy-benzotriazol hydrat;

EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;

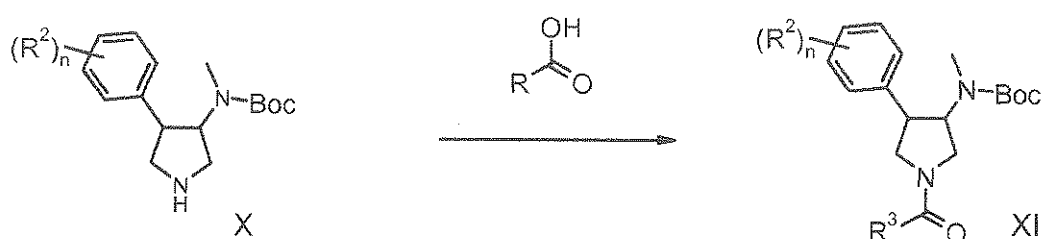
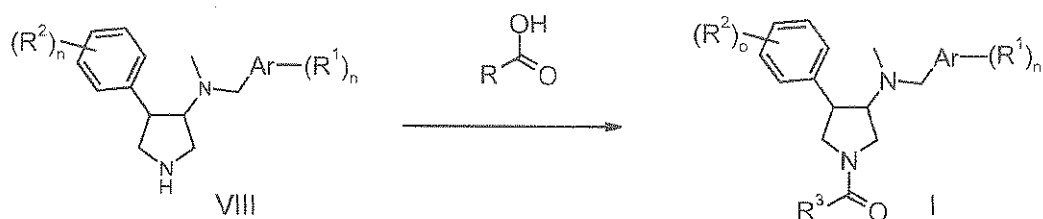
Et<sub>3</sub>N = triethylamine;

EtOAc = ethyl acetate;

H = hexane;

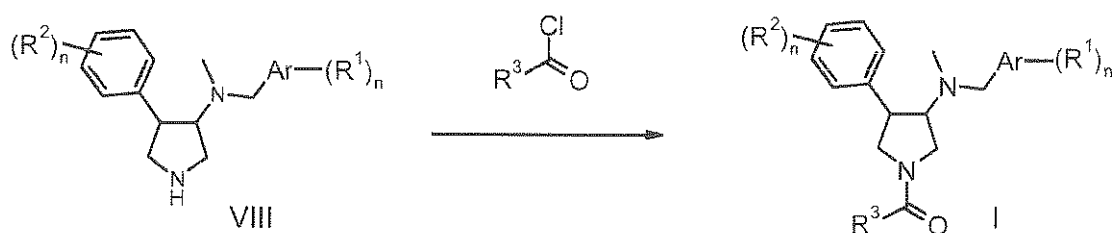
RT = room temperature;

### General procedure I (amide coupling)



To a stirred solution of a carboxylic acid derivative (commercially available or known in the literature) (1 mmol) in 10 mL of  $\text{CH}_2\text{Cl}_2$  was added (1.3 mmol) of EDC, (1.3 mmol) of HOBT and  $\text{Et}_3\text{N}$  (1.3 mmol). After one hour at RT, was added a pyrrolidine intermediate of general formula (VIII or X). The mixture was stirred at RT over night and then poured onto water and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuo. Flash chromatography or preparative HPLC afforded the title compound.

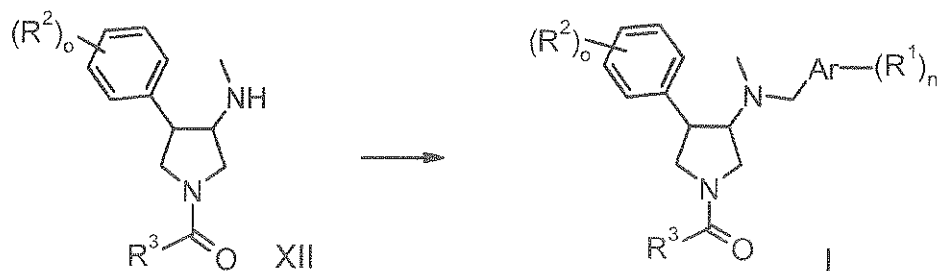
### 15 General procedure II (amid or urea preparation)



To a stirred solution of a pyrrolidine intermediate VIII (1 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 ml) at RT were added ethyl-diisopropyl-amine (2 mmol) and an acid chloride or carbamoyl chlorid or chloroformate derivative of formula  $\text{RCOCl}$  (1.1 mmol). Stirring was continued until completion

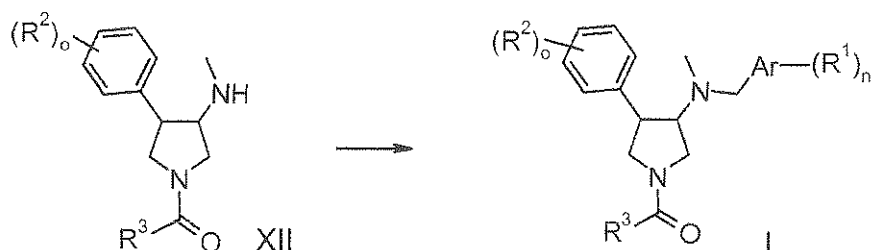
of the reaction. The reaction mixture was then concentrated under vacuo and purification by flash chromatography on SiO<sub>2</sub> or preparative HPLC.

### General procedure III (reductive amination)



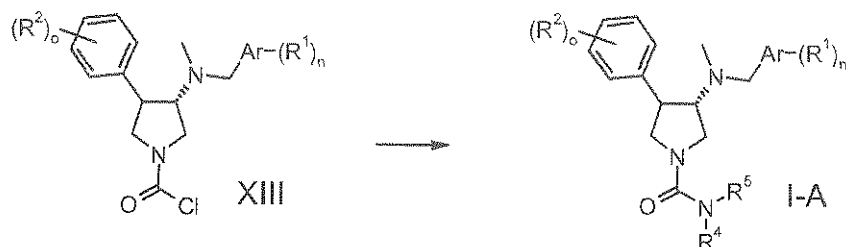
To a stirred solution of a pyrrolidine intermediate XII (1.00 mmol) in MeOH (6 ml) was added the aldehyde (1.20 mmol). Then a solution of NaBH<sub>3</sub>CN (1.3 mol) in MeOH (1.5 ml) and AcOH (0.01 ml) were added. The reaction mixture was stirred overnight at RT, concentrated under vacuo, diluted with EtOAc, washed with H<sub>2</sub>O. The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the product purified by flash chromatography (SiO<sub>2</sub>) or preparative HPLC to afford the desired compound.

### 15 General procedure IV (alkylation)



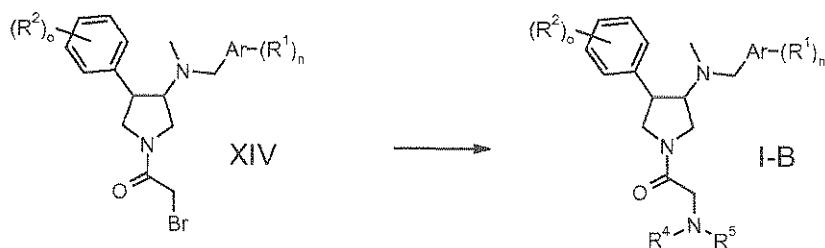
To a stirred solution of a pyrrolidine intermediate XII (1.00 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 ml) was added a substituted benzyl bromide derivative (1.20 mmol) and N,N-diisopropylethylamine (1.50 mmol). The reaction mixture was stirred at 45°C overnight, washed with H<sub>2</sub>O. The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the product purified by flash chromatography (SiO<sub>2</sub>) or preparative HPLC to afford the desired compound.

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**General procedure V:**

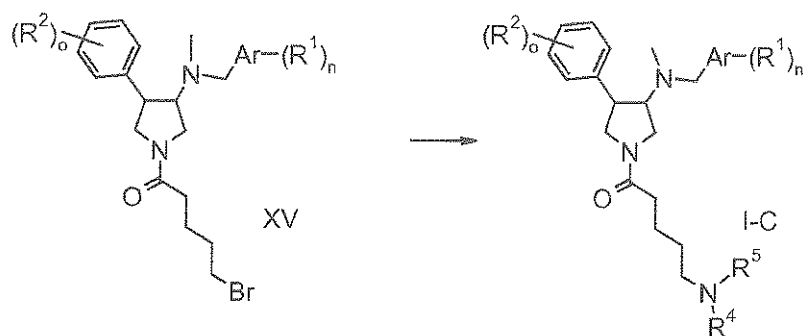
To a stirred solution of a pyrrolidine carbonyl chloride intermediate **XIII** (1 mmol) in  $\text{CH}_2\text{Cl}_2$

- 5 (15 ml) at RT were added ethyl-diisopropyl-amine (1.2 mmol) and a primary or secondary amine (1.1 mmol). Stirring was continued until completion of the reaction. The reaction mixture was then concentrated under vacuo and purification by flash chromatography on  $\text{SiO}_2$  or preparative HPLC yielded **I-A**.

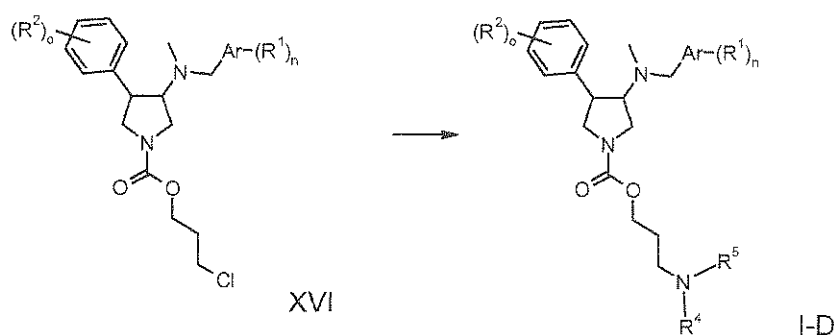
10 **General procedure VI:**

To a stirred solution of a pyrrolidine acetyl bromid intermediate **XIV** (1 mmol) in THF (15 ml)

- 15 at RT were added ethyl-diisopropyl-amine (1.2 mmol) and a primary or secondary amine (4 mmol). Stirring was continued until completion of the reaction. The reaction mixture was then concentrated under vacuo and purification by flash chromatography on  $\text{SiO}_2$  or preparative HPLC yielded **I-B**.

**General procedure VII:**

To a stirred solution of a pyrrolidine intermediate **XV** (1 mmol) in THF (15 ml) at RT were added ethyl-diisopropyl-amine (1.2 mmol) and a primary or secondary amine (4 mmol). Stirring was continued until completion of the reaction. The reaction mixture was then concentrated under vacuo and purification by flash chromatography on SiO<sub>2</sub> or preparative HPLC yielded **I-C**.

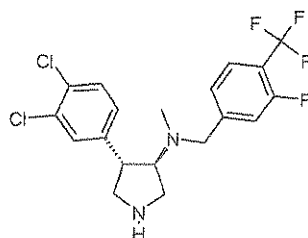
**General procedure VIII:**

To a stirred solution of a pyrrolidine intermediate **XVI** (1 mmol) in THF (15 ml) at RT were added ethyl-diisopropyl-amine (1.2 mmol) and a primary or secondary amine (4 mmol). Stirring was continued until completion of the reaction. The reaction mixture was then concentrated under vacuo and purification by flash chromatography on SiO<sub>2</sub> or preparative HPLC yielded **I-D**.

**Process for preparation of pyrrolidine intermediates of formula VIII****Pyrrolidine VIII-1**

**[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine**

-23-



a) (3SR,4RS)-1-Benzyl-3-(3,4-dichloro-phenyl)-4-nitro-pyrrolidine

A solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine (1.96 g, 8.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added drop wise, over a 30 minutes period, to a stirred solution of 1,2-dichloro-4-((E)-2-nitro-vinyl)-benzene (1.0 g, 4.58 mmol) and trifluoroacetic acid (52 mg, 4.45 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) at 0 °C. The ice bath was removed, and the solution was stirred at 25 °C for an additional 48 h. It was then concentrated and purification by flash chromatography (SiO<sub>2</sub>, EtOAc/H 1:4) afforded 1.00 g (62 %) of the title compound as a colorless oil. ES-MS m/e: 351.4 (M+H<sup>+</sup>).

b) (3RS,4SR)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-ylamine

To a stirred solution of (3SR,4RS)-1-benzyl-3-(3,4-dichloro-phenyl)-4-nitro-pyrrolidine (15.0 g, 0.0427 mol) in EtOAc (200 ml) was added portionwise SnCl<sub>2</sub>·2H<sub>2</sub>O (43.36 g, 0.192 mol). The reaction mixture was then heated at reflux for 4 hours, cooled down to RT and a saturated aqueous solution of NaHCO<sub>3</sub> (500 ml) was added. The salts were filtered off and the product extracted with EtOAc. The organic phases were then dried over Na<sub>2</sub>SO<sub>4</sub>, and concentration under vacuum gave 9.30 g (75 %) of the title compound as a light yellow oil. The product was then used in the next step without further purification. ES-MS m/e: 321.1 (M+H<sup>+</sup>).

c) [(3RS,4SR)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-amine

To a solution of (3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-ylamine (9.2 g, 0.028 mol) in THF (100 ml) was added a solution of K<sub>2</sub>CO<sub>3</sub> (7.91 g, 0.057 mol) in H<sub>2</sub>O (35 ml). After 10 minutes, ethyl chloroformate (2.86 ml, 0.030 mol) was added and stirring was continued at RT for an additional 4 h. The intermediate carbamate was then extracted with Et<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo to give viscous oil. The oil was taken up in THF (100 ml) and a solution of borane in THF (1M) was added (114.5 ml). The reaction mixture was then heated at 65 °C over night, cooled to RT and carefully quenched with conc. HCl (100 ml). The mixture was then heated at 80 °C for 2 h, cooled to RT, concentrated under vacuo, diluted with Et<sub>2</sub>O (100 ml) and neutralized with an aqueous solution of NaHCO<sub>3</sub>. The organic phases were

dried over  $\text{Na}_2\text{SO}_4$  and the product purified by flash chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9:1) to afford 7.31 g (76 %) of the title compound as a colorless oil. ES-MS  $m/e$ : 335.3 ( $\text{M}+\text{H}^+$ ).

d) [(3RS,4SR)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine

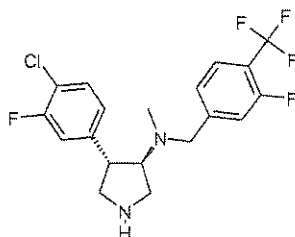
To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-amine (3.5 g, 0.010 mol) in MeOH (60 ml) was added 3-fluoro-4-trifluoromethyl-benzaldehyde (2.10 g, 0.0109 mol). Then a solution of  $\text{NaBH}_3\text{CN}$  (0.79 g, 0.012 mol) in MeOH (15 ml) and AcOH (0.1 ml) were added. The reaction mixture was stirred overnight at RT, concentrated under vacuo, diluted with EtOAc, washed with  $\text{H}_2\text{O}$ . The organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the product purified by flash chromatography ( $\text{SiO}_2$ , EtOAc/Heptane 1:4) to afford 3.31 g (62 %) of the title compound as a colorless oil.

e) [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (3.30 g, 6.45 mmol) in  $\text{CH}_3\text{CN}$  (45 ml) at RT, was added 2,2,2-trichloroethyl chloroformate (1.30 ml, 9.67 mmol). The reaction mixture was stirred at RT for 3 hours, concentrated under vacuo. The residue was dissolved in AcOH (10 ml) and zinc dust (1.0 g) was added portion wise over 3 hours. The solvent was evaporated, the residue diluted in EtOAc and the organic phase was washed with an aqueous solution of  $\text{NaHCO}_3$ . The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , concentrated under vacuo to afford 1.43 g (53 %) of the title compound as a colorless oil. ES-MS  $m/e$ : 421.0 ( $\text{M}+\text{H}^+$ ).

**Pyrrolidine VIII-2**

[(3RS,4SR)-4-(4-Chloro-3-fluoro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine



a) (3SR,4RS)-1-Benzyl-3-(4-chloro-3-fluoro-phenyl)-4-nitro-pyrrolidine

A solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine (1.00 g, 4.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added drop wise, over a 30 minutes period, to a stirred solution of 1-chloro-2-fluoro-4-((E)-2-nitro-vinyl)-benzene (0.68 g, 3.37 mmol) and trifluoroacetic acid (30 ul) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) at 0 °C. The ice bath was removed, and the solution was stirred at 25 °C for an additional 48 h. It was then concentrated and purification by flash chromatography (SiO<sub>2</sub>, EtOAc/H 1:4) afforded 0.78 g (55 %) of the title compound as a colorless oil. ES-MS m/e: 335.2 (M+H<sup>+</sup>).

b) (3RS,4SR)-1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidin-3-ylamine

To a stirred solution of (3SR,4RS)-1-benzyl-3-(4-chloro-3-fluoro-phenyl)-4-nitro-pyrrolidine (0.78 g, 2.33 mmol) in EtOAc (15 ml) was added portion wise SnCl<sub>2</sub>.2H<sub>2</sub>O (2.63 g, 11.6 mmol). The reaction mixture was then heated at reflux for 4 hours, cooled down to RT and a saturated aqueous solution of NaHCO<sub>3</sub> (500 ml) was added. The salts were filtered off and the product extracted with EtOAc. The organic phases were then dried over Na<sub>2</sub>SO<sub>4</sub>, and concentration under vacuum. A column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95/5) gave 0.46 g (65 %) of the title compound as a light brown oil. ES-MS m/e: 305.1 (M+H<sup>+</sup>).

c) [(3RS,4SR)-1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidin-3-yl]-methyl-amine

To a solution of (3RS,4SR)-1-benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidin-3-ylamine (0.46 g, 1.51 mmol) in THF (5 ml) was added a solution of K<sub>2</sub>CO<sub>3</sub> (0.419 g, 3.0 mmol) in H<sub>2</sub>O (2 ml). After 10 minutes, ethyl chloroformate (0.3 ml, 3.0 mmol) was added and stirring was continued at RT for an additional 4 h. The intermediate carbamate was then extracted with Et<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo to give viscous oil. The oil was taken up in THF (10 ml) and a solution of borane in THF (1M) was added (6.0 ml). The reaction mixture was then heated at 65 °C over night, cooled to RT and carefully quenched with conc. HCl (5 ml). The mixture was then heated at 80 °C for 2 h, cooled to RT, concentrated under vacuo, diluted with Et<sub>2</sub>O (10 ml) and neutralized with an aqueous solution of NaHCO<sub>3</sub>. The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the product purified by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) to afford 0.34 g (70 %) of the title compound as a colorless oil. ES-MS m/e: 319.1 (M+H<sup>+</sup>).

d) [(3RS,4SR)-1-Benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine

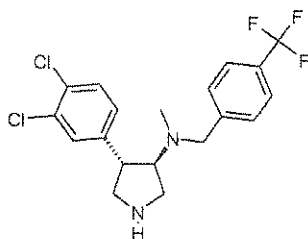
To a stirred solution of [(3RS,4SR)-1-benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidin-3-yl]-methyl-amine (340 mg, 1.06 mmol) in MeOH (6 ml) was added 3-fluoro-4-trifluoromethyl-benzaldehyde (230 mg, 1.20 mmol). Then a solution of NaBH<sub>3</sub>CN (85 mg, 1.3 mol) in MeOH (1.5 ml) and AcOH (0.01 ml) were added. The reaction mixture was stirred overnight at RT, concentrated under vacuo, diluted with EtOAc, washed with H<sub>2</sub>O. The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the product purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Heptane 1:4) to afford 145 mg (28 %) of the title compound as a colorless oil.

e) [(3RS,4SR)-4-(4-Chloro-3-fluoro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(4-chloro-3-fluoro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (145 mg, 0.29 mmol) in CH<sub>3</sub>CN (2 ml) at RT, was added 2,2,2-trichloroethyl chloroformate (0.06 ml, 0.44 mmol). The reaction mixture was stirred at RT for 3 hours, concentrated under vacuo. The residue was dissolved in AcOH (3 ml) and zinc dust (60 mg) was added portion wise over 3 hours. The solvent was evaporated, the residue diluted in EtOAc and the organic phase was washed with an aqueous solution of NaHCO<sub>3</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuo to afford 80 mg (67 %) of the title compound as a colorless oil. ES-MS m/e: 405.3 (M+H<sup>+</sup>).

**Pyrrolidine VIII-3**

**[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine**



a) [(3RS,4SR)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-amine (0.35 g, 1.04 mmol) in THF (6 ml) was added 1-bromomethyl-4-trifluoromethyl-benzene (0.27 g, 1.15 mmol) and Et<sub>3</sub>N (0.148 ml, 1.45 mmol). The reaction mixture was stirred overnight at RT and concentrated under vacuo. The product purified by flash chromatography (SiO<sub>2</sub>,

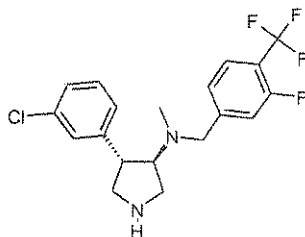
EtOAc/Heptane 1:4) to afford 130 mg (29 %) of the title compound as a colorless oil. ES-MS  $m/e$ : 492.9 ( $M+H^+$ ).

b) [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine (160 mg, 0.32 mmol) in  $CH_3CN$  (5 ml) at RT, was added 2,2,2-trichloroethyl chloroformate (0.070 ml, 0.48 mmol). The reaction mixture was stirred at RT for 3 hours, concentrated under vacuo. The residue was dissolved in AcOH (3 ml) and zinc dust (80 mg) was added portion wise over 1 hours. The solvent was evaporated, the residue diluted in EtOAc and the organic phase was washed with an aqueous solution of  $NaHCO_3$ . The organic phase was dried over  $Na_2SO_4$  and concentrated under vacuo. The product was purified by column chromatography ( $CH_2Cl_2$ / MeOH: 9/1) to afford 85 mg (65 %) of the tile compound as a colorless oil. ES-MS  $m/e$ : 403.4 ( $M+H^+$ ).

**Pyrrolidine VIII-4**

**[(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine**



a) (3SR,4RS)-1-Benzyl-3-(3-chloro-phenyl)-4-nitro-pyrrolidine

A solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine (9.69 g, 41 mmol) in  $CH_2Cl_2$  (40 ml) was added drop wise, over a 30 minutes period, to a stirred solution of 1-chloro-3-((E)-2-nitro-vinyl)-benzene (0.68 g, 3.37 mmol) and trifluoroacetic acid (0.21 ml) in  $CH_2Cl_2$  (40 ml) at 0 °C. The ice bath was removed, and the solution was stirred at 25 °C for an additional 48 h. It was then concentrated and purification by flash chromatography ( $SiO_2$ , EtOAc/H 1:4) afforded 6.30 g (73 %) of the title compound as a colorless oil. ES-MS  $m/e$ : 317.1 ( $M+H^+$ ).

b) (3RS,4SR)-1-Benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-ylamine

To a stirred solution of (3SR,4RS)-1-benzyl-3-(3-chloro-phenyl)-4-nitro-pyrrolidine (6.30 g, 19.8 mmol) in EtOAc (150 ml) was added portion wise  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (22.43 g, 99 mmol). The reaction mixture was then heated at reflux for 4 hours, cooled down to RT and a saturated aqueous solution of  $\text{NaHCO}_3$  (500 ml) was added. The salts were filtered off and the product  
5 extracted with EtOAc. The organic phases were then dried over  $\text{Na}_2\text{SO}_4$ , and concentration under vacuum. A column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95/5) gave 4.47 g (78 %) of the title compound as a light yellow oil. ES-MS m/e: 287.0 ( $\text{M}+\text{H}^+$ ).

c) [(3RS,4SR)-1-Benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-yl]-methyl-amine

- 10 To a solution of (3RS,4SR)-1-benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-ylamine (4.47 g, 16.0 mmol) in THF (50 ml) was added a solution of  $\text{K}_2\text{CO}_3$  (4.31 g, 31 mmol) in  $\text{H}_2\text{O}$  (35 ml). After 10 minutes, ethyl chloroformate (2.97 ml, 31 mmol) was added and stirring was continued at RT for an additional 4 h. The intermediate carbamate was then extracted with  $\text{Et}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuo to give viscous oil. The oil was taken up in THF (10 ml)  
15 and a solution of borane in THF (1M) was added (62 ml). The reaction mixture was then heated at 65 °C over night, cooled to RT and carefully quenched with conc. HCl (5 ml). The mixture was then heated at 80 °C for 2 h, cooled to RT, concentrated under vacuo, diluted with  $\text{Et}_2\text{O}$  (50 ml) and neutralized with an aqueous solution of  $\text{NaHCO}_3$ . The organic phases were dried over  $\text{Na}_2\text{SO}_4$  and the product purified by flash chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9:1) to afford  
20 2.68 g (57 %) of the title compound as a colorless oil. ES-MS m/e: 301.2 ( $\text{M}+\text{H}^+$ ).

d) [(3RS,4SR)-1-Benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine

- To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-yl]-methyl-amine  
25 (2.20 g, 7.31 mmol) in THF (70 ml) was added 4-bromomethyl-2-fluoro-1-trifluoromethyl-benzene (2.25 g, 8.75 mmol) and  $\text{Et}_3\text{N}$  (1.21 ml, 8.75 mmol). The reaction mixture was stirred overnight at 40 °C, concentrated under vacuo, diluted with EtOAc, washed with  $\text{H}_2\text{O}$ . The organic phase was dried over  $\text{Na}_2\text{SO}_4$  and the product purified by flash chromatography ( $\text{SiO}_2$ , EtOAc/Heptane 1:3) to afford 2.0 g (57 %) of the title compound as a colorless oil.

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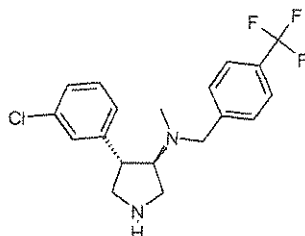
e) [(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (2.0 g, 4.19 mmol) in CH<sub>3</sub>CN (28 ml) at RT, was added 2,2,2-trichloroethyl chloroformate (0.85 ml, 6.3 mmol). The reaction mixture was stirred at RT for 3 hours, concentrated under vacuo. The residue was dissolved in AcOH (25 ml) and zinc dust (800 mg) was added portion wise over 3 hours. The solvent was evaporated, the residue diluted in EtOAc and the organic phase was washed with an aqueous solution of NaHCO<sub>3</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuo to afford 0.90 g (44 %) of the title compound as a light brown oil. ES-MS m/e: 387.2 (M+H<sup>+</sup>).

10

## Pyrrolidine VIII-5

[(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine



a) [(3RS,4SR)-1-Benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine

15 To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-yl]-methyl-amine (0.46 g, 1.59 mmol) in THF (15 ml) was added 1-bromomethyl-4-trifluoromethyl-benzene (0.44 g, 1.86 mmol) and Et<sub>3</sub>N (0.155 ml, 1.59 mmol). The reaction mixture was stirred overnight at RT and concentrated under vacuo. The product purified by flash chromatography (SiO<sub>2</sub>, EtOAc/Heptane 1:4) to afford 500 mg (71 %) of the title compound as a colorless oil. ES-MS

20 m/e: 459.3 (M+H<sup>+</sup>).

b) [(3RS,4SR)-4-(3-chloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3-chloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine (500 mg, 1.09 mmol) in CH<sub>3</sub>CN (7 ml) at RT, was added 2,2,2-trichloroethyl chloroformate (0.22 ml, 1.63 mmol). The reaction mixture was stirred at RT for 3 hours, concentrated under vacuo. The residue was dissolved in AcOH (5 ml) and zinc dust (200 mg) was added portion wise over 1 hours. The solvent was evaporated, the residue diluted in EtOAc and the organic phase was washed with an aqueous solution of NaHCO<sub>3</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo. The product was purified by

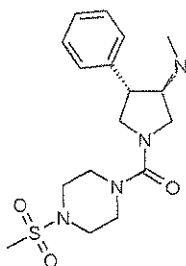
column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) to afford 305 mg (76 %) of the title compound as a colorless oil. ES-MS m/e: 369.2 (M+H<sup>+</sup>).

Process for preparation of pyrrolidine intermediates of formula XII

5

**Pyrrolidine XII-1**

**(4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone**



a) (3RS,4SR)-1-Benzyl-3-nitro-4-phenyl-pyrrolidine

- 10 A solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine (0.50 g, 2.02 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml) was added drop wise, over a 30 minutes period, to a stirred solution of ((E)-2-nitro-vinyl)-benzene (0.30 g, 2.02 mmol) and trifluoroacetic acid (0.17 ml, 0.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at 0 °C. The ice bath was removed, and the solution was stirred at 25 °C for an additional 48 h. It was then concentrated and purification by flash chromatography (SiO<sub>2</sub>, EtOAc/H 1:6) afforded 0.38 g (68 %) of the title compound as a colorless oil. ES-MS m/e: 283 (M+H<sup>+</sup>).
- 15

b) (3RS,4SR)-1-Benzyl-4-phenyl-pyrrolidin-3-ylamine

- To a stirred solution of (3RS,4SR)-1-benzyl-3-nitro-4-phenyl-pyrrolidine (1.0 g, 3.54 mmol) in EtOAc (50 ml) was added in one portion SnCl<sub>2</sub>·2H<sub>2</sub>O (3.99 g, 17.70 mmol). The reaction mixture was then heated at reflux for 2 hours, cooled down to RT and a saturated aqueous solution of NaHCO<sub>3</sub> (100 ml) was added. The salts were filtered off and the product extracted with EtOAc. The organic phases were then dried over Na<sub>2</sub>SO<sub>4</sub>, and concentration under vacuum gave 0.72 g (80 %) of (3RS,4SR)-1-benzyl-4-phenyl-pyrrolidin-3-ylamine as a light yellow oil.
- 20
- 25 The product was then used in the next step without further purification.

c) ((3RS,4SR)-1-Benzyl-4-phenyl-pyrrolidin-3-yl)-methyl-amine

To a solution of (3RS,4SR)-1-benzyl-4-phenyl-pyrrolidin-3-ylamine (0.25 g, 1.0 mmol) in THF (5 ml) was added a solution of K<sub>2</sub>CO<sub>3</sub> (0.25 g, 1.8 mmol) in H<sub>2</sub>O (2 ml). After 10 minutes, ethyl

chloroformate (0.119 g, 1.1 mmol) was added and stirring was continued at RT for an additional 4 h. The intermediate carbamate was then extracted with Et<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo to give viscous oil. The oil was taken up in THF (5 ml) and a solution of borane in THF (1M) was added (3.5 ml). The reaction mixture was then heated at 65 °C over night, cooled to RT and carefully quenched with conc. HCl (0.5 ml). The mixture was then heated at 80 °C for 2 h, cooled to RT, concentrated under vacuo, diluted with Et<sub>2</sub>O (20 ml) and neutralized with an aqueous solution of NaHCO<sub>3</sub>. The organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and the product purified by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) to afford 0.21 g (82 %) of *rac*-((3S,4R)-1-benzyl-4-phenyl-pyrrolidin-3-yl)-methyl-amine as a colorless oil.

d) ((3RS,4SR)-1-Benzyl-4-phenyl-pyrrolidin-3-yl)-methyl-carbamic acid tert-butyl ester

To a stirred solution of [(3RS,4SR)-1-benzyl-4-phenyl]-pyrrolidin-3-yl]-methyl-amine (2.00 g, 7.55 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added Et<sub>3</sub>N (1.80 ml, 15.1 mmol), DMAP (81 mg, 0.66 mmol) and (Boc)<sub>2</sub>O (1.75 g, 8.02 mmol). After one hour at RT, the organic phase was washed with H<sub>2</sub>O, then dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography (Heptane/EtOAc: 3/1) afforded 2.04 g (74 %) of the title compound as a yellow oil.

e) Methyl-((3RS,4SR)-4-phenyl-pyrrolidin-3-yl)-carbamic acid tert-butyl ester

To a stirred solution of ((3RS,4SR)-1-Benzyl-4-phenyl-pyrrolidin-3-yl)-methyl-carbamic acid tert-butyl ester (2.03 g, 5.56 mmol) in MeOH (20 ml) at RT, was added ammonium formate (1.60 g, 25.4 mmol) and palladium on charcoal (0.40 g, 10 %). The reaction mixture was stirred for 2 hours, filtrate on celite and concentrated under vacuo. The residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1) to give 0.57 g (41 %) of the title product as a waxy solid. ES-MS m/e: 277.1 (M+H<sup>+</sup>).

e) [(3RS,4SR)-1-(4-Methanesulfonyl-piperazine-1-carbonyl)-4-phenyl-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester

Using the general procedure II for the preparation of urea, 640 mg of the title compound was produced from methyl-((3RS,4SR)-4-phenyl-pyrrolidin-3-yl)-carbamic acid tert-butyl ester and 4-methanesulfonyl-piperazine-1-carbonyl chloride as a white solid. ES-MS m/e: 467.3 (M+H<sup>+</sup>).

4-Methanesulfonyl-piperazine-1-carbonyl chloride:

To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (1.81 g, 6.09 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0 °C, was added a solution of 1-methanesulfonyl-piperazine (2.0 g, 12.2

mmol) and pyridine (1.08 mL, 13.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub>. Purification by flash chromatography (SiO<sub>2</sub>, EtOAc) yielded 2.20 g (79 %) of the title compound as white solid.

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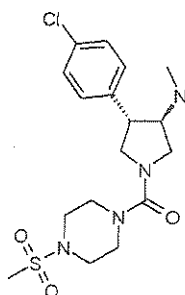
f) (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone

To a stirred solution of [(3RS,4SR)-1-(4-Methanesulfonyl-piperazine-1-carbonyl)-4-phenyl-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester (640 mg, 1.37 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10ml) was added TFA (2 ml). The reaction mixture was stirred at RT for 2 hours, aqueous NaHCO<sub>3</sub> was added until pH=8 and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phase were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under vacuo gave 500 mg (99 %) of the title product as a white solid. ES-MS m/e: 367.1 (M+H<sup>+</sup>).

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**Pyrrolidine XII-2**

**[(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone**



a) (3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-4-nitro-pyrrolidine

20 A solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine (6.70 g, 28.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added drop wise, over a 30 minutes period, to a stirred solution of 1-chloro-4-((E)-2-nitro-vinyl)-benzene (4.97 g, 27.1 mmol) and trifluoroacetic acid (0.31 g, 2.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (150 ml) at 0 °C. The ice bath was removed, and the solution was stirred at 25 °C for an additional 48 h. It was then concentrated and purification by flash

25 chromatography (SiO<sub>2</sub>, EtOAc/H 1:4) afforded 6.75 g (79 %) of the title compound as a colorless oil.

b) (3RS,4SR)-1-Benzyl-4-(4-chloro-phenyl)-pyrrolidin-3-ylamine

Titanium (IV) chloride (0.36 g, 1.89 mmol) was added drop wise to a suspension of zinc powder (0.25 g, 3.78 mmol) in THF (3 ml). This solution was heated at 68 °C for one hour, then cooled to RT before (3SR,4RS)-1-benzyl-3-(4-chloro-phenyl)-4-nitro-pyrrolidine (0.20 g, 0.63 mmol) in THF (2 ml) was added. The reaction mixture was then stirred at reflux over night. The reaction  
5 was cooled to RT, diluted with 300 ml of Et<sub>2</sub>O, washed with an aqueous solution of NaHCO<sub>3</sub> and the organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>. Flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9:1) yielded 0.10 g (57 %) of (3RS,4SR)-1-benzyl-4-(4-chloro-phenyl)-pyrrolidin-3-ylamine as a light yellow oil.

10 c) [(3RS,4SR)-1-Benzyl-4-(4-chloro-phenyl)-pyrrolidin-3-yl]-methyl-amine

To a solution of (3RS,4SR)-1-benzyl-4-(4-chloro-phenyl)-pyrrolidin-3-ylamine (1.86 g, 6.51 mmol) in THF (20 ml) was added a solution of K<sub>2</sub>CO<sub>3</sub> (1.80 g, 13.02 mmol) in H<sub>2</sub>O (15 ml). After 10 minutes, ethyl chloroformate (0.68 ml, 7.16 mmol) was added and stirring was continued at RT for an additional 4 h. The intermediate carbamate was then extracted with Et<sub>2</sub>O,  
15 dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo to give viscous oil. The oil was taken up in THF (20 ml) and a solution of borane in THF (1M) was added (26 ml). The reaction mixture was then heated at 65 °C over night, cooled to RT and carefully quenched with conc. HCl (5 ml). The mixture was then heated at 80 °C for 2 h, cooled to RT, concentrated under vacuo, diluted with Et<sub>2</sub>O (100 ml) and neutralized with an aqueous solution of NaHCO<sub>3</sub>. The organic phases were  
20 dried over Na<sub>2</sub>SO<sub>4</sub> and the product purified by flash chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) to afford 1.51 g (77 %) of rac-[(3S,4R)-1-benzyl-4-(4-chloro-phenyl)-pyrrolidin-3-yl]-methyl-amine as a colorless oil.

25 d) [(3RS,4SR)-1-Benzyl-4-(4-chloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(4-chloro-phenyl)-pyrrolidin-3-yl]-methyl-amine (2.75 g, 9.14 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 ml) was added Et<sub>3</sub>N (2.50 ml, 18.2 mmol), DMAP (112 mg, 0.91 mmol) and (Boc)<sub>2</sub>O (2.39 g, 10.95 mmol). After one hour at RT, the organic phase was washed with H<sub>2</sub>O, then dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography (Heptane/EtOAc: 3/1)  
30 afforded 2.60 g (71 %) of the title compound as a yellow oil. ES-MS m/e: 401.3 (M+H<sup>+</sup>).

e) [(3RS,4SR)-4-(4-Chloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(4-chloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester (1.30 g, 3.20 mmol) in toluene (30 ml) at RT, was added 1-chloroethyl chloroformate (0.53 ml, 4.80 mmol). The reaction mixture was stirred at 90 °C overnight and concentrated under vacuo. The residue was dissolved in MeOH (30 ml) and the reaction mixture was heated at 80 °C for 2 hours. . The solvent was evaporated and the crude product was directly used in the next step without further purification.

e) [(3RS,4SR)-4-(4-Chloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester

- 10 Using the general procedure II for the preparation of urea, 871 mg of the title compound was produce from 765 mg of [(3RS,4SR)-4-(4-chloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester and 4-methanesulfonyl-piperazine-1-carbonyl chloride as a white solid. ES-MS m/e: 501.43 (M+H<sup>+</sup>).

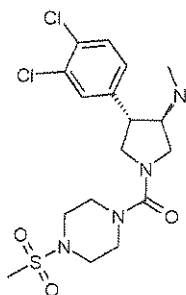
- 15 f) [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

To a stirred solution of [(3RS,4SR)-4-(4-Chloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester (860 mg, 1.72 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 ml) was added TFA (2 ml). The reaction mixture was stirred at RT for 2 hours, aqueous

- 20 NaHCO<sub>3</sub> was added until pH=8 and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phase were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under vacuo gave 680 mg (98 %) of the title product as a white solid. ES-MS m/e: 401.3 (M+H<sup>+</sup>).

### Pyrrolidine XII-3

- 25 [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



a) [(3RS,4SR)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-amine (1.00 g, 2.98 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was added Et<sub>3</sub>N (0.83 ml, 5.96 mmol), DMAP (73 mg, 0.59 mmol) and (Boc)<sub>2</sub>O (1.43 g, 6.55 mmol). After one hour at RT, the organic phase was washed with H<sub>2</sub>O, then dried over Na<sub>2</sub>SO<sub>4</sub>. Column chromatography (Heptane/EtOAc: 3/1) afforded 0.93 g (71 %) of the title compound as a yellow oil. ES-MS m/e: 435.3 (M+H<sup>+</sup>).

b) [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester

To a stirred solution of [(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester (928 mg, 2.13 mmol) in CH<sub>3</sub>CN (10 ml) at RT, was added 2,2,2-trichloroethyl chloroformate (0.45 ml, 2.13 mmol). The reaction mixture was stirred at RT for 3 hours, concentrated under vacuo. The residue was dissolved in AcOH (5 ml) and zinc dust (400 mg) was added portion wise over 1 hours. The solvent was evaporated, the residue diluted in EtOAc and the organic phase was washed with an aqueous solution of NaHCO<sub>3</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo to afford 415 mg (98 %) of the tile compound as a light yellow oil. ES-MS m/e: 345.2 (M+H<sup>+</sup>).

c) [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester

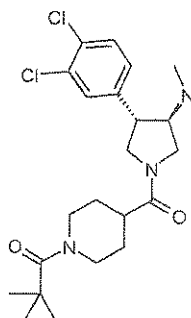
Using the general procedure II for the preparation of urea, 133 mg of the title compound was produce from [(3RS,4SR)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester and 4-methanesulfonyl-piperazine-1-carbonyl chloride as a white solid. ES-MS m/e: 535.1 (M+H<sup>+</sup>).

d) [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

To a stirred solution of [(3RS,4SR)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester (130mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added TFA (1 ml). The reaction mixture was stirred at RT for 2 hours, aqueous NaHCO<sub>3</sub> was added until pH=8 and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phase were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration under vacuo gave 100 mg (93 %) of the title product as a light yellow oil. ES-MS m/e: 435.8 (M+H<sup>+</sup>).

## Pyrrolidine XII-4

[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone



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a) [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester

Using the general procedure I for the preparation of amide, 3.06 g of the title compound was produce from [(3RS,4SR)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl ester and 1-(1-Methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid as a light brown foam. ES-MS m/e: 538.3 (M+H<sup>+</sup>).

1-(1-Methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid:

First step: Using the general procedure I for the preparation of amide, 2.60 g of 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid ethyl ester was prepared from 1.89 g of piperidine-4-carboxylic acid ethyl ester and 1.40 g of 1-methyl-cyclopropanecarboxylic acid as a light yellow oil. ES-MS m/e: 240.3 (M+H<sup>+</sup>). Second step: To a stirred solution of 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid ethyl ester (2.60 g, 0.011 mmol) in THF, EtOH, H<sub>2</sub>O (50 ml, 1/1/1) was added LiOH.H<sub>2</sub>O (686 mg, 16.3 mmol). After two hours at RT, the reaction mixture was concentrated under vacuo. The crude residue was diluted in CH<sub>2</sub>Cl<sub>2</sub> and aqueous HCl (1N) was added until pH = 2. The organic phase was collected, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo to afforded 1.98 g (86 %) of the title product as a white powder. ES-MS m/e: 212.1 (M+H<sup>+</sup>).

b) [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone

To a stirred solution of [(3RS,4SR)-4-(3,4-dichloro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-pyrrolidin-3-yl]-methyl-carbamic acid tert-butyl

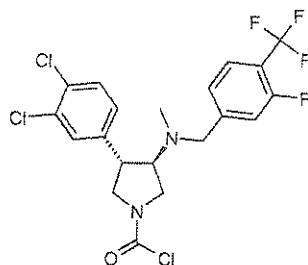
-37-

ester (3.02 g, 5.61 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 ml) was added TFA (4.3 ml). The reaction mixture was stirred at RT for 20 hours, aqueous  $\text{NaHCO}_3$  was added until pH=8 and the product was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phase were dried over  $\text{Na}_2\text{SO}_4$ . The product was purified by column chromatography ( $\text{SiO}_2$ , H / EtOAc / MeOH, 50:50:0 to 0: 90 : 10) to afford 1.79 g (73 %) of the title product as a light brown oil. ES-MS m/e: 338.3 ( $\text{M}+\text{H}^+$ ).

### Process for preparation of pyrrolidine intermediates of formula XIII

#### Pyrrolidine XIII-1

(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride



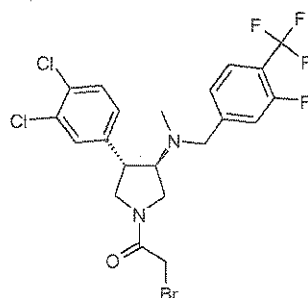
To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (37 mg, 0.125 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 ml) at  $-78^\circ\text{C}$ , was added a solution of [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (Intermediate VIII-1), (130 mg, 0.31 mmol) and pyridine (0.05 ml, 0.68 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 ml) over 30 minutes. The temperature was raised to RT, and stirring was continued for 2 hours. The organic phase was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ . Purification by flash chromatography ( $\text{SiO}_2$ , EtOAc/Hx 1:2) yielded 83 mg (55 %) of the title compound as a light yellow oil. ES-MS m/e: 483.0 ( $\text{M}+\text{H}^+$ ).

### Process for preparation of pyrrolidine intermediates of formula XIV

#### Pyrrolidine XIV-1

2-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone

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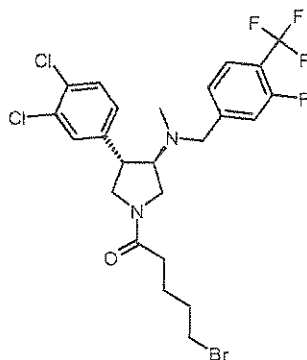
To a stirred solution of bromo-acetyl chloride (0.146 ml, 1.75 mmol) in THF (15 ml) at RT was added over 1 hour a solution of [(3RS,4SR)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (Intermediate VIII-1, 0.70 g, 1.66 mmol) and triethyl  
 5 amine (0.25 ml, 1.83 mmol) in THF (10 mL). The reaction was stirred over night, quenched by addition of an aqueous solution of NaHCO<sub>3</sub>, and the product extracted with EtOAc. Purification by flash chromatography (SiO<sub>2</sub>, EtOAc/Hx 1:1) yielded 0.63 g (70 %) of the title compound as a white solid. ES-MS m/e: 542.6 (M+H<sup>+</sup>).

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**Process for preparation of pyrrolidine intermediates of formula XV**

**Pyrrolidine XV-1**

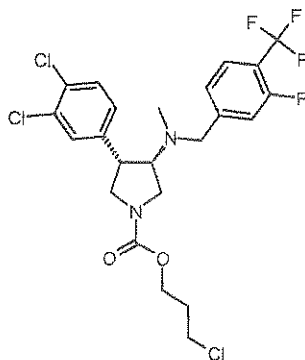
**5-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-pentan-1-one**



- 15 To a stirred solution of 5-bromo-pentanoyl chloride (0.167 ml, 1.25 mmol) in THF (10 ml) at RT was added over 1 hour a solution of [(3RS,4SR)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (Intermediate VIII-1, 0.50 g, 1.19 mmol) and triethyl amine (0.18 ml, 1.30 mmol) in THF (5 mL). The reaction was stirred over night, quenched by addition of an aqueous solution of NaHCO<sub>3</sub>, and the product extracted with EtOAc.
- 20 Purification by flash chromatography (SiO<sub>2</sub>, EtOAc/Hx 1:1) yielded 0.58 g (83 %) of the title compound as a white solid. ES-MS m/e: 584.4 (M+H<sup>+</sup>).

Process for preparation of pyrrolidine intermediates of formula XVI**Pyrrolidine XVI-1**

**(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid 3-chloro-propyl ester**



5

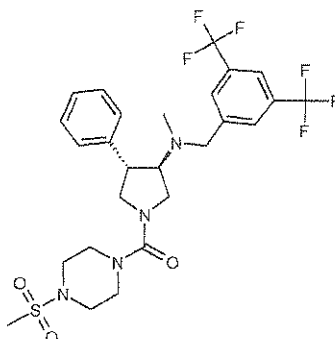
To a stirred solution of 3-chloropropyl chloroformate (0.058 ml, 0.47 mmol) in THF (5 ml) at RT was added over 1 hour a solution of [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (Intermediate VIII-1, 0.187 g, 0.44 mmol) and triethyl amine (0.068 ml, 0.48 mmol) in THF (2 mL). The reaction was stirred over night, quenched by addition of an aqueous solution of NaHCO<sub>3</sub>, and the product extracted with EtOAC. The organic phases were concentrated under vacuo to yielded 0.25 g (99 %) of the title compound as a light yellow oil. The product was used in the next steps without further rpurification. ES-MS m/e: 542.7 (M+H<sup>+</sup>).

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**Example 1**

**{(3RS,4SR)-3-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



Alkylation according to general procedure IV:

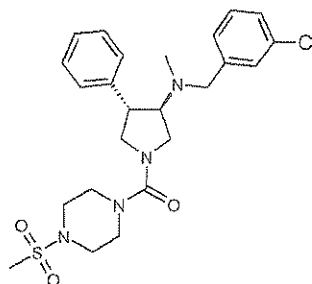
20 - Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (XII-1),

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- Electrophile: 1-Bromomethyl-3,5-bis-trifluoromethyl-benzene (commercially available),  
ES-MS m/e: 593.4 (M+H<sup>+</sup>).

### Example 2

**{{(3RS,4SR)-3-[(3-Chloro-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



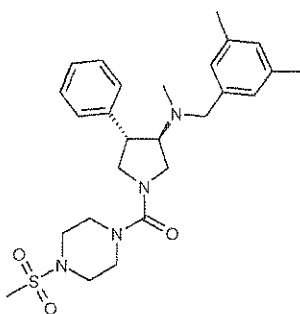
Alkylation according to general procedure IV:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

10 - Electrophile: 1-Bromomethyl-3-chloro-benzene (commercially available),  
ES-MS m/e: 491.3 (M+H<sup>+</sup>).

### Example 3

**{{(3RS,4SR)-3-[(3,5-Dimethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



15 Alkylation according to general procedure IV:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

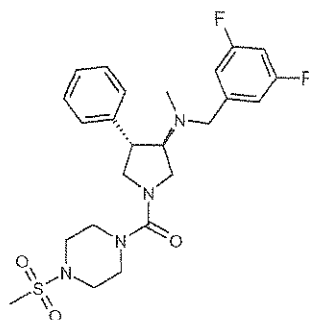
- Electrophile: 1-Bromomethyl-3,5-dimethyl-benzene (commercially available),

20 ES-MS m/e: 485.4 (M+H<sup>+</sup>).

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## Example 4

**{(3RS,4SR)-3-[(3,5-Difluoro-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



5 Alkylation according to general procedure IV:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

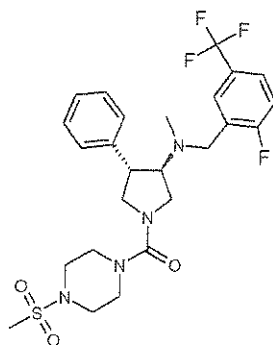
- Electrophile: 1-Bromomethyl-3,5-difluoro-benzene (commercially available),

ES-MS m/e: 493.3 (M+H<sup>+</sup>).

10

## Example 5

**{(3RS,4SR)-3-[(2-Fluoro-5-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



Reductive amination according to general procedure III:

15 - Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

- Aldehyde: 2-Fluoro-5-trifluoromethyl-benzaldehyde (commercially available),

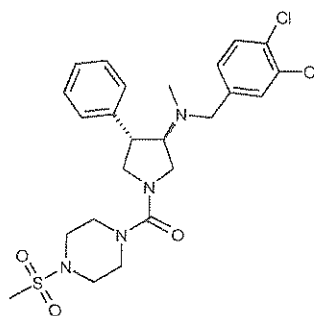
ES-MS m/e: 543.4 (M+H<sup>+</sup>).

## Example 6

20

**{(3RS,4SR)-3-[(3,4-Dichloro-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-42-



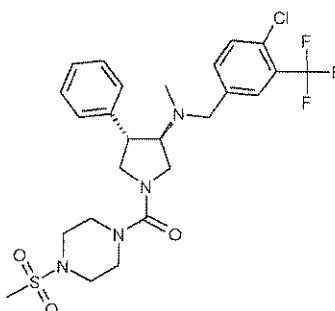
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

- 5 - Aldehyde: 3,4-Dichloro-benzaldehyde (commercially available),  
ES-MS m/e: 525.3 (M+H<sup>+</sup>).

#### Example 7

**{{(3RS,4SR)-3-[(4-Chloro-3-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

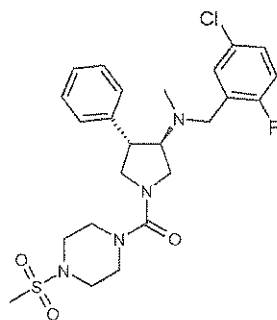
- Aldehyde: 4-Chloro-3-trifluoromethyl-benzaldehyde (commercially available),

- 15 ES-MS m/e: 593.4 (M+H<sup>+</sup>).

#### Example 8

**{{(3RS,4SR)-3-[(5-Chloro-2-fluoro-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-43-



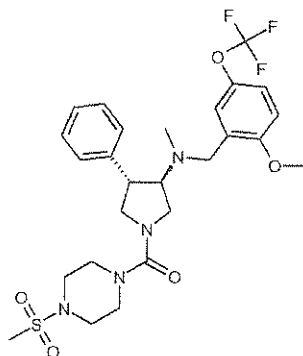
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

- 5 - Aldehyde: 5-Chloro-2-fluoro-benzaldehyde (commercially available),  
ES-MS m/e: 543.3 ( $M+H^+$ ).

#### Example 9

(4-Methanesulfonyl-piperazin-1-yl)-{(3RS,4SR)-3-[(2-methoxy-5-trifluoromethoxy-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-methanone



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

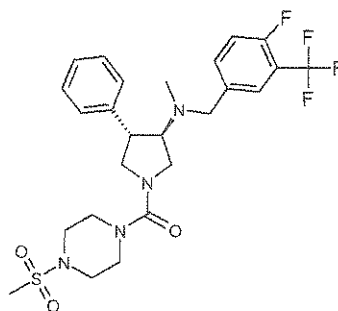
- Aldehyde: 2-Methoxy-5-trifluoromethoxy-benzaldehyde (commercially available),

- 15 ES-MS m/e: 571.3 ( $M+H^+$ ).

#### Example 10

{(3RS,4SR)-3-[(4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}- (4-methanesulfonyl-piperazin-1-yl)-methanone

-44-



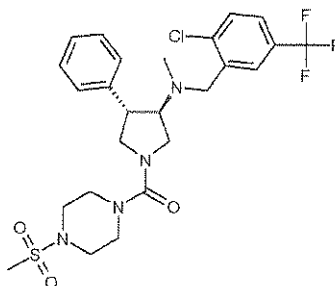
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

- 5 - Aldehyde: 4-Fluoro-3-trifluoromethyl-benzaldehyde (commercially available),  
ES-MS m/e: 543.3 (M+H<sup>+</sup>).

#### Example 11

**{{(3RS,4SR)-3-[(2-Chloro-5-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

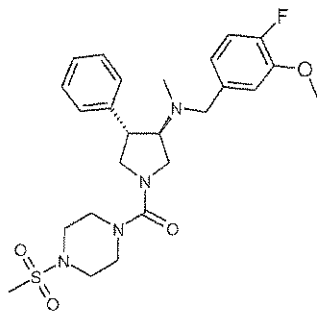
- Aldehyde: 2-Chloro-5-trifluoromethyl-benzaldehyde (commercially available),

- 15 ES-MS m/e: 559.3 (M+H<sup>+</sup>).

#### Example 12

**{{(3RS,4SR)-3-[(4-Fluoro-3-methoxy-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-45-



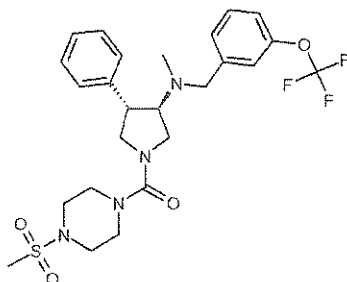
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

- 5 - Aldehyde: 4-Fluoro-3-methoxy-benzaldehyde (commercially available),  
ES-MS m/e: 505.3 ( $M+H^+$ ).

### Example 13

(4-Methanesulfonyl-piperazin-1-yl)-{(3RS,4SR)-3-[methyl-(3-trifluoromethoxy-benzyl)-amino]-4-phenyl-pyrrolidin-1-yl}-methanone



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

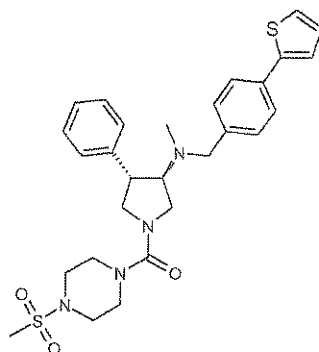
- Aldehyde: 3-Trifluoromethoxy-benzaldehyde (commercially available),

- 15 ES-MS m/e: 541.4 ( $M+H^+$ ).

### Example 14

(4-Methanesulfonyl-piperazin-1-yl)-{(3RS,4SR)-3-[methyl-(4-thiophen-2-yl-benzyl)-amino]-4-phenyl-pyrrolidin-1-yl}-methanone

-46-



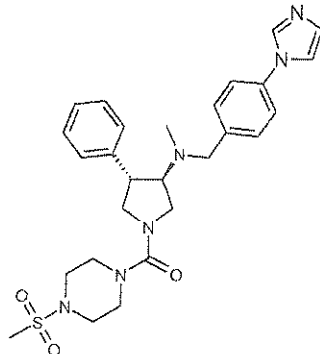
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

- 5 - Aldehyde: 4-Thiophen-2-yl-benzaldehyde (commercially available),  
ES-MS m/e: 539.4 (M+H<sup>+</sup>).

#### Example 15

**{{(3RS,4SR)-3-[(4-Imidazol-1-yl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

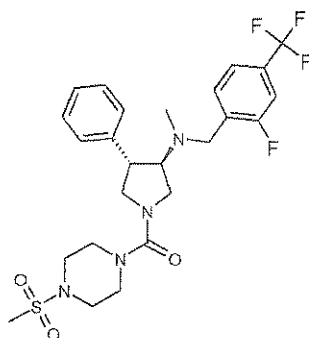
- Aldehyde: 4-Imidazol-1-yl-benzaldehyde (commercially available),

- 15 ES-MS m/e: 523.5 (M+H<sup>+</sup>).

#### Example 16

**{{(3RS,4SR)-3-[(2-Fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-47-



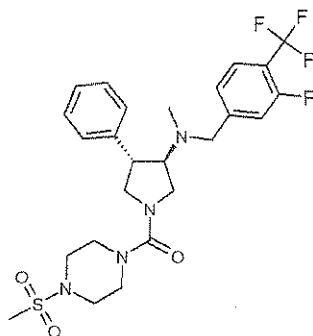
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

- 5 - Aldehyde: 2-Fluoro-4-trifluoromethyl-benzaldehyde (commercially available),  
ES-MS m/e: 543.3 (M+H<sup>+</sup>).

#### Example 17

{(3RS,4SR)-3-[(3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

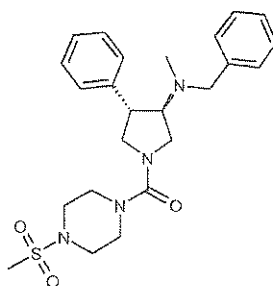
- Aldehyde: 3-Fluoro-4-trifluoromethyl-benzaldehyde (commercially available),

- 15 ES-MS m/e: 543.5 (M+H<sup>+</sup>).

#### Example 18

[(3RS,4SR)-3-(Benzyl-methyl-amino)-4-phenyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

-48-



Reductive amination according to general procedure III:

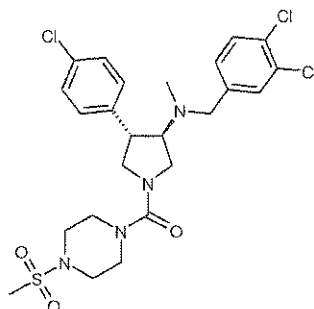
- Pyrrolidine intermediate: (4-Methanesulfonyl-piperazin-1-yl)-((3RS,4SR)-3-methylamino-4-phenyl-pyrrolidin-1-yl)-methanone (**XII-1**),

5 - Aldehyde: benzaldehyde (commercially available),

ES-MS m/e: 457.5 (M+H<sup>+</sup>).

### Example 19

**{{(3SR,4RS)-3-(4-Chloro-phenyl)-4-[(3,4-dichloro-benzyl)-methyl-amino]-pyrrolidin-1-yl}-  
(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-2**),

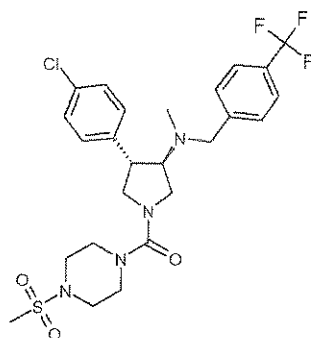
- Aldehyde: 3,4-Dichloro-benzaldehyde (commercially available),

15 ES-MS m/e: 561.1 (M+H<sup>+</sup>).

### Example 20

**{{(3SR,4RS)-3-(4-Chloro-phenyl)-4-[(4-chloro-3-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-49-



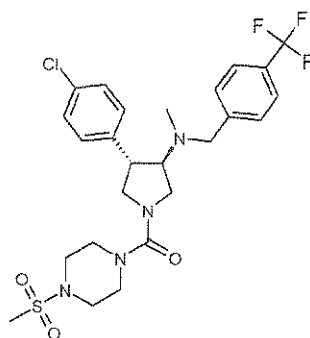
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-2**),

- 5 - Aldehyde: 4-Chloro-3-trifluoromethyl-benzaldehyde (commercially available),  
ES-MS m/e: 593.81 (M+H<sup>+</sup>).

### Example 21

{(3SR,4RS)-3-(4-Chloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-2**),

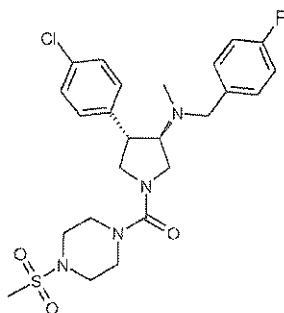
- Aldehyde: 4-Trifluoromethyl-benzaldehyde (commercially available),

- 15 ES-MS m/e: 559.3 (M+H<sup>+</sup>).

### Example 22

{(3SR,4RS)-3-(4-Chloro-phenyl)-4-[(4-fluoro-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

-50-



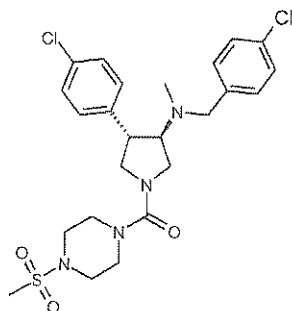
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-2),

- 5 - Aldehyde: 4-Fluoro-benzaldehyde (commercially available),  
ES-MS m/e: 509.2(M+H<sup>+</sup>).

### Example 23

**[(3RS,4SR)-3-[(4-Chloro-benzyl)-methyl-amino]-4-(4-chloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-2),

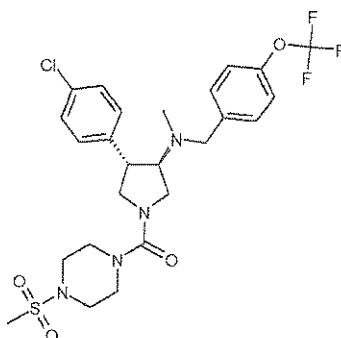
- Aldehyde: 4-chloro-benzaldehyde (commercially available),

- 15 ES-MS m/e: 525.3 (M+H<sup>+</sup>).

### Example 24

**{(3SR,4RS)-3-(4-Chloro-phenyl)-4-[methyl-(4-trifluoromethoxy-benzyl)-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-51-



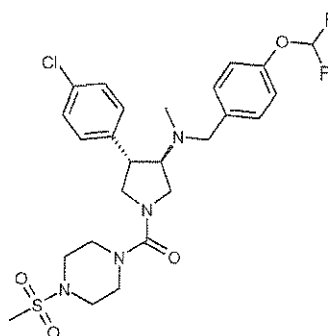
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-2),

- 5 - Aldehyde: 4-Trifluoromethoxy-benzaldehyde (commercially available),  
ES-MS m/e: 575.3 (M+H<sup>+</sup>).

#### Example 25

**{(3SR,4RS)-3-(4-Chloro-phenyl)-4-[(4-difluoromethoxy-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-2),

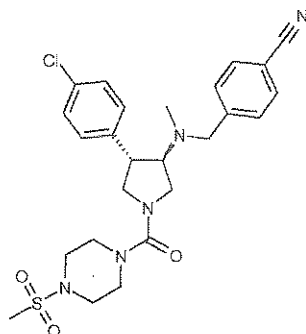
- Aldehyde: 4-Difluoromethoxy-benzaldehyde (commercially available),

- 15 ES-MS m/e: 557.1 (M+H<sup>+</sup>).

#### Example 26

**4-([[(3RS,4SR)-4-(4-Chloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-amino]-methyl)-benzonitrile**

-52-



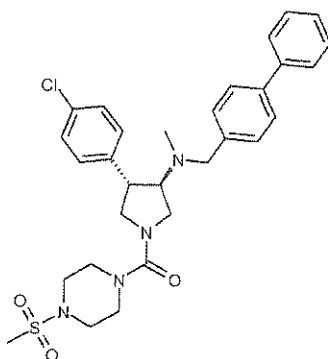
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-2**),

- 5 - Aldehyde: 4-Formyl-benzonitrile (commercially available),  
ES-MS m/e: 516.3 (M+H<sup>+</sup>).

#### Example 27

[(3RS,4SR)-3-(Biphenyl-4-ylmethyl-methyl-amino)-4-(4-chloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-2**),

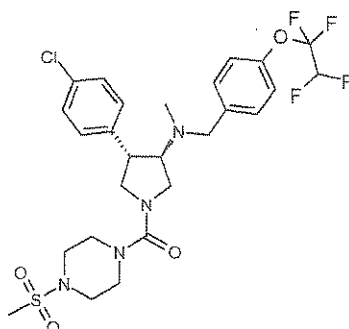
- Aldehyde: Biphenyl-4-carbaldehyde (commercially available),

- 15 ES-MS m/e: 567.4 (M+H<sup>+</sup>).

#### Example 28

((3SR,4RS)-3-(4-Chloro-phenyl)-4-{methyl-[4-(1,1,2,2-tetrafluoro-ethoxy)-benzyl]-amino}-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone

-53-



Reductive amination according to general procedure III:

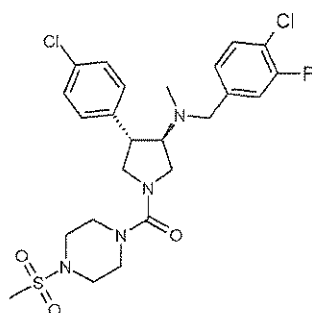
- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-2),

5 - Aldehyde: 4-(1,1,2,2-Tetrafluoro-ethoxy)-benzaldehyde (commercially available),

ES-MS m/e: 607.3 (M+H<sup>+</sup>).

#### Example 29

[(3RS,4SR)-3-[(4-Chloro-3-fluoro-benzyl)-methyl-amino]-4-(4-chloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-2),

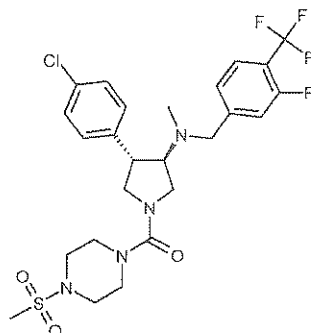
- Aldehyde: 4-Chloro-3-fluoro-benzaldehyde (commercially available),

15 ES-MS m/e: 543.2 (M+H<sup>+</sup>).

#### Example 30

{(3SR,4RS)-3-(4-Chloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

-54-



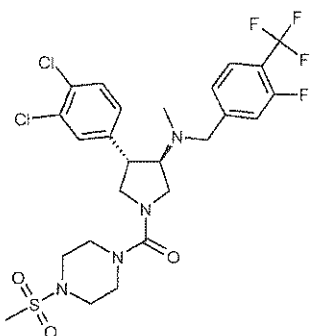
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(4-Chloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-2),

- 5 - Aldehyde: 3-Fluoro-4-trifluoromethyl-benzaldehyde (commercially available),  
ES-MS m/e: 577.3 (M+H<sup>+</sup>).

### Example 31

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

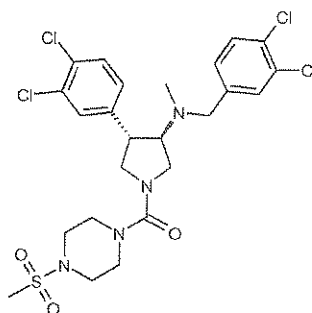
- Aldehyde: 3-Fluoro-4-trifluoromethyl-benzaldehyde (commercially available),

- 15 ES-MS m/e: 611.2 (M+H<sup>+</sup>).

### Example 32

**[(3RS,4SR)-3-[(3,4-Dichloro-benzyl)-methyl-amino]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-55-



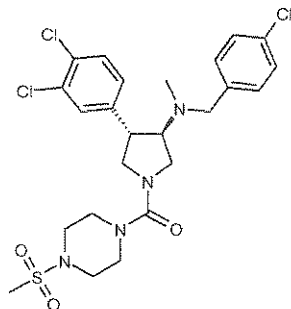
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-  
(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-3**),

5 - Aldehyde: 3,4-Dichloro-benzaldehyde (commercially available),  
ES-MS m/e: 595.2 (M+H<sup>+</sup>).

### Example 33

**[(3RS,4SR)-3-[(4-Chloro-benzyl)-methyl-amino]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-  
(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-  
(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-3**),

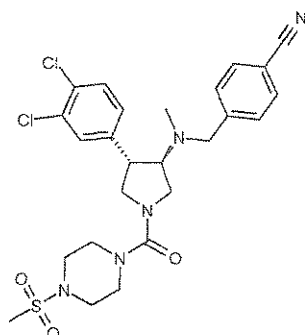
- Aldehyde: 4-Chloro-benzaldehyde (commercially available),

15 ES-MS m/e: 561.1 (M+H<sup>+</sup>).

### Example 34

**4-([[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-  
pyrrolidin-3-yl]-methyl-amino}-methyl)-benzonitrile**

-56-



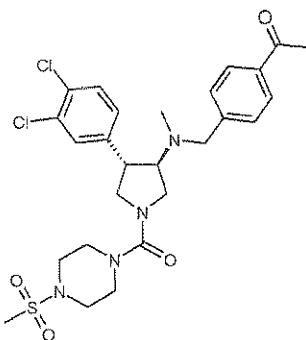
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-  
(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

5 - Aldehyde: 4-Formyl-benzonitrile (commercially available),  
ES-MS m/e: 550.3 (M+H<sup>+</sup>).

### Example 35

1-[4-([(3RS,4SR)-4-(3,4-Dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-  
pyrrolidin-3-yl]-methyl-amino)-methyl]-phenyl]-ethanone



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-  
(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

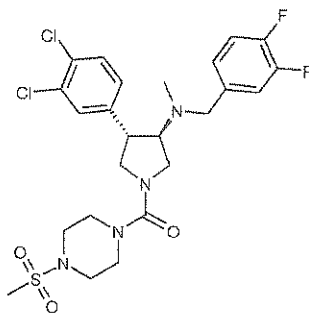
- Aldehyde: 4-Acetyl-benzaldehyde (commercially available),

15 ES-MS m/e: 567.3 (M+H<sup>+</sup>).

### Example 36

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3,4-difluoro-benzyl)-methyl-amino]-pyrrolidin-1-  
yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

-57-



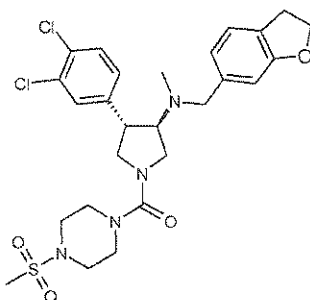
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-3**),

- 5 - Aldehyde: 3,4-Difluoro-benzaldehyde (commercially available),  
ES-MS m/e: 561.3 (M+H<sup>+</sup>).

#### Example 37

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(2,3-dihydro-benzofuran-6-ylmethyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-3**),

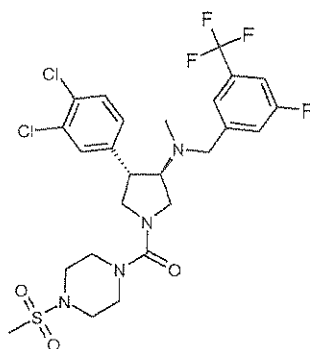
- Aldehyde: 2,3-Dihydro-benzofuran-6-carbaldehyde (commercially available),

- 15 ES-MS m/e: 567.3 (M+H<sup>+</sup>).

#### Example 38

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-5-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-58-



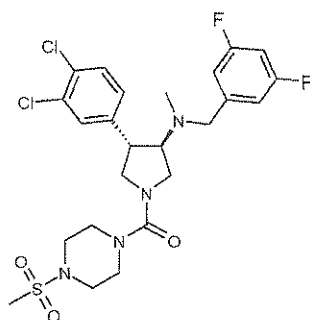
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

- 5 - Aldehyde: 3-Fluoro-5-trifluoromethyl-benzaldehyde (commercially available),  
ES-MS m/e: 611.2 (M+H<sup>+</sup>).

### Example 39

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3,5-difluoro-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

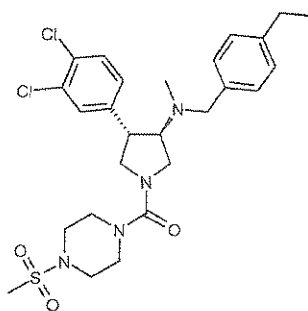
- Aldehyde: 3,5-Difluoro-benzaldehyde (commercially available),

- 15 ES-MS m/e: 561.2 (M+H<sup>+</sup>).

### Example 40

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(4-ethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-59-



Reductive amination according to general procedure III:

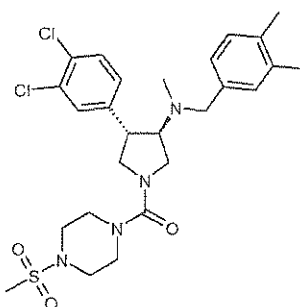
- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

5 - Aldehyde: 4-Ethyl-benzaldehyde (commercially available),

ES-MS m/e: 553.2 (M+H<sup>+</sup>).

#### Example 41

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3,4-dimethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

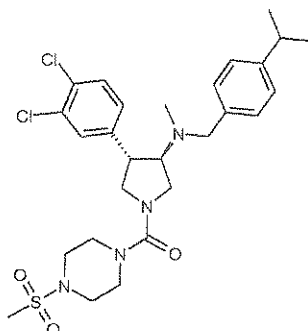
- Aldehyde: 3,4-Dimethyl-benzaldehyde (commercially available),

15 ES-MS m/e: 553.2 (M+H<sup>+</sup>).

#### Example 42

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(4-isopropyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-60-



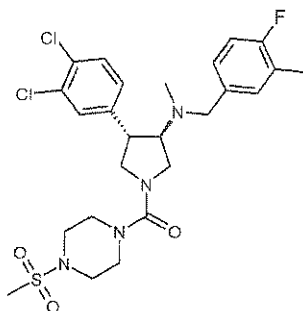
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

5 - Aldehyde: 4-Isopropyl-benzaldehyde (commercially available),  
ES-MS m/e: 567.3 (M+H<sup>+</sup>).

#### Example 43

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(4-fluoro-3-methyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),

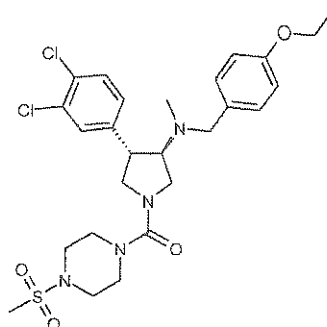
- Aldehyde: 4-Fluoro-3-methyl-benzaldehyde (commercially available),

15 ES-MS m/e: 557.2 (M+H<sup>+</sup>).

#### Example 44

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(4-ethoxy-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

-61-



Reductive amination according to general procedure III:

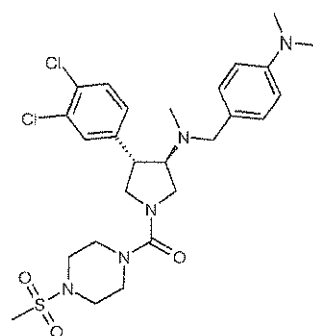
- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-3**),

5 - Aldehyde: 4-Ethoxy-benzaldehyde (commercially available),

ES-MS m/e: 559.2 (M+H<sup>+</sup>).

#### Example 45

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(4-dimethylamino-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-3**),

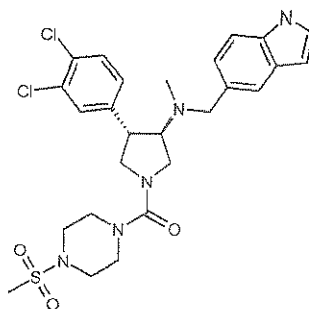
- Aldehyde: 4-Dimethylamino-benzaldehyde (commercially available),

15 ES-MS m/e: 568.2 (M+H<sup>+</sup>).

#### Example 46

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(1H-indol-5-ylmethyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

-62-

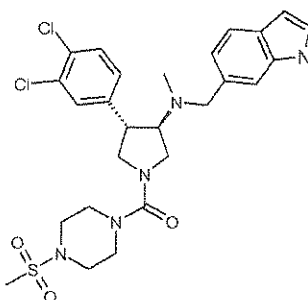


Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-  
(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),
- 5 - Aldehyde: 1H-Indole-5-carbaldehyde (commercially available),  
ES-MS m/e: 564.4 (M+H<sup>+</sup>).

#### Example 47

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(1H-indol-6-ylmethyl)-methyl-amino]-pyrrolidin-1-yl}-  
(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

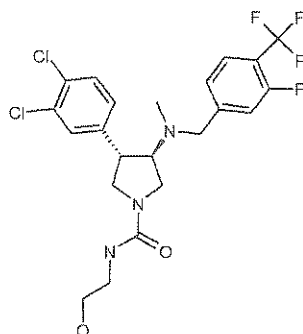
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-  
(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-3),
- Aldehyde: 1H-Indole-6-carbaldehyde (commercially available),
- 15 ES-MS m/e: 564.4 (M+H<sup>+</sup>).

#### Example 48

**(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-  
pyrrolidine-1-carboxylic acid (2-hydroxy-ethyl)-amide**

-63-



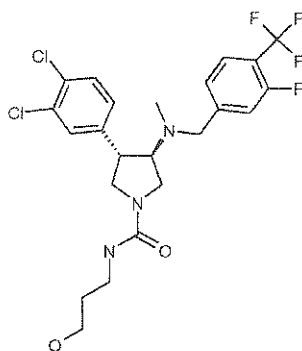
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: 2-Amino-ethanol (commercially available),  
ES-MS m/e: 508.2 (M+H<sup>+</sup>).

#### Example 49

(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid (3-hydroxy-propyl)-amide



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

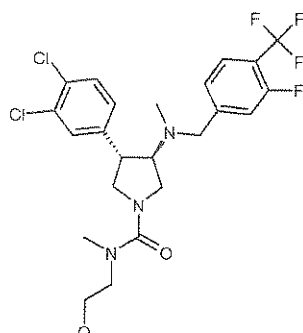
- Amine: 3-Amino-propan-1-ol (commercially available),

- 15 ES-MS m/e: 522.3 (M+H<sup>+</sup>).

#### Example 50

(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid (2-hydroxy-ethyl)-methyl-amide

-64-

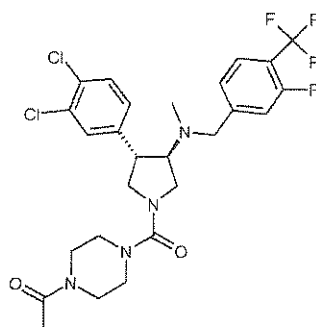


Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),
  - 5 - Amine: 2-Methylamino-ethanol (commercially available),
- ES-MS m/e: 522.3 ( $M+H^+$ ).

#### Example 51

**1-(4-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl]-piperazin-1-yl)-ethanone**



10

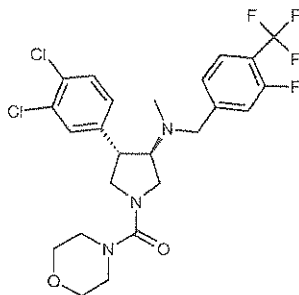
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),
- Amine: 1-Piperazin-1-yl-ethanone (commercially available),
- 15 ES-MS m/e: 575.3 ( $M+H^+$ ).

#### Example 52

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-morpholin-4-yl-methanone**

-65-



Coupling reaction according to general procedure V:

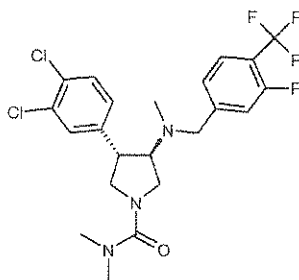
- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

5 - Amine: Morpholine (commercially available),

ES-MS m/e: 534.2 (M+H<sup>+</sup>).

### Example 53

**(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid dimethylamide**



10

Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine] (**VIII-1**),

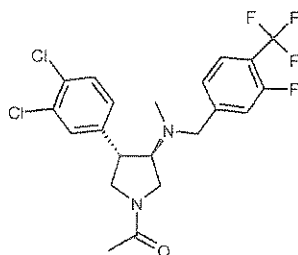
- Carbamoyl chloride: N,N-dimethyl carbamoyl chloride (commercially available),

15 ES-MS m/e: 492.3 (M+H<sup>+</sup>).

### Example 54

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone**

-66-



Coupling reaction according to general procedure II:

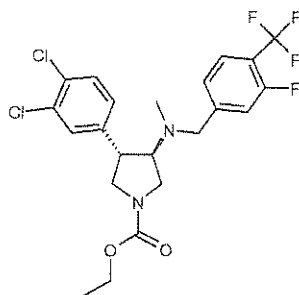
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

5 - Acid chloride: acetyl chloride (commercially available),

ES-MS m/e: 463.2 (M+H<sup>+</sup>).

### Example 55

**(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid ethyl ester**



10

Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

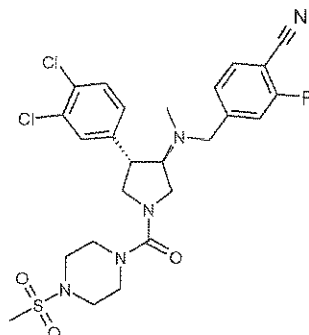
- chloroformate: ethyl chloroformate (commercially available),

15 ES-MS m/e: 493.2 (M+H<sup>+</sup>).

### Example 56

**4-([(3RS,4SR)-4-(3,4-Dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-amino}-methyl)-2-fluoro-benzonitrile**

-67-



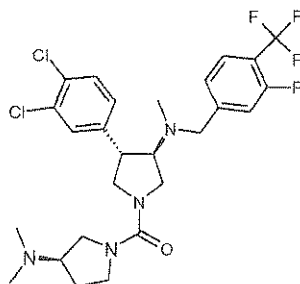
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-3**),

- 5 - Aldehyde: 2-Fluoro-4-formyl-benzonitrile (commercially available),  
ES-MS m/e: 568.2 (M+H<sup>+</sup>).

#### Example 57

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-((R)-3-dimethylamino-pyrrolidin-1-yl)-methanone



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

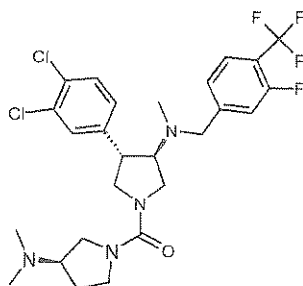
- Amine: Dimethyl-(R)-pyrrolidin-3-yl-amine (commercially available),

- 15 ES-MS m/e: 561.1 (M+H<sup>+</sup>).

#### Example 58

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-((S)-3-dimethylamino-pyrrolidin-1-yl)-methanone

-68-



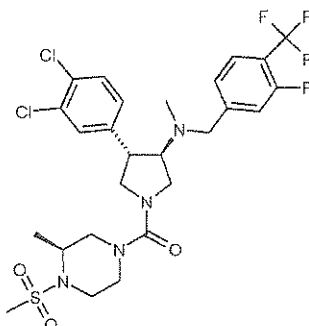
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: Dimethyl-(S)-pyrrolidin-3-yl-amine (commercially available),  
ES-MS m/e: 561.2 (M+H<sup>+</sup>).

### Example 59

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-((S)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone**



10

Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

- carbamoyl chloride: (S)-4-Methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride,

- 15 ES-MS m/e: 625.2 (M+H<sup>+</sup>).

#### (S)-4-Methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride:

First step: To a stirred solution of commercially available (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (2.38 g, 12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at 0°C were added pyridine (1.91 mL, 24 mmol) and methanesulfonyl chloride (0.92 mL, 12 mmol). Stirring was continued at RT  
20 overnight, the reaction was poured onto water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried on Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo. The crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and TFA (4 mL) was added. After 2 hours at RT, the volatiles were removed

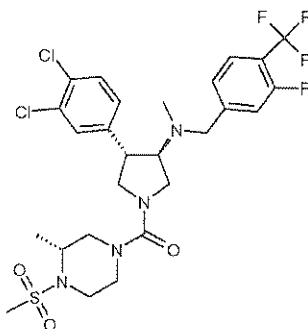
-69-

under vacuo, the crude was dissolved in  $\text{CH}_2\text{Cl}_2$  and washed with aq.  $\text{NaHCO}_3$  (until pH = 8). The organic phase was dried on  $\text{Na}_2\text{SO}_4$  and concentrated under vacuo to yield 0.83 g (39%) of (s)-1-methanesulfonyl-2-methyl-piperazine as a light yellow oil.

Second step: To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (560 mg, 1.88 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $-78^\circ\text{C}$ , was added a solution of (S)-1-methanesulfonyl-2-methyl-piperazine (838 mg, 4.70 mmol) and pyridine (0.74 mL, 9.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) over 1 hour. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ . Concentration under vacuo and flash chromatography ( $\text{SiO}_2$ , EtOAc/H, 1:1) yielded 0.70 g (62 %) of (S)-4-methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride as a light yellow solid.

### Example 60

**{{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-((R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone**



Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

- carbamoyl chloride: (R)-4-Methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride,

ES-MS m/e: 625.2 ( $\text{M}+\text{H}^+$ ).

(R)-4-Methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride:

First step: To a stirred solution of commercially available (R)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (8.78 g, 44 mmol) in  $\text{CH}_2\text{Cl}_2$  (80 mL) at  $0^\circ\text{C}$  were added  $\text{Et}_3\text{N}$  (12.15 mL, 88 mmol) and methanesulfonyl chloride (5.09 mL, 66 mmol). Stirring was continued at RT

overnight, the reaction was poured onto water and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried on  $\text{Na}_2\text{SO}_4$  and concentrated under vacuo. The crude product was dissolved in  $\text{CH}_2\text{Cl}_2$  (50 mL) and TFA (15 mL) was added. After 2 hours at RT, the volatiles were removed

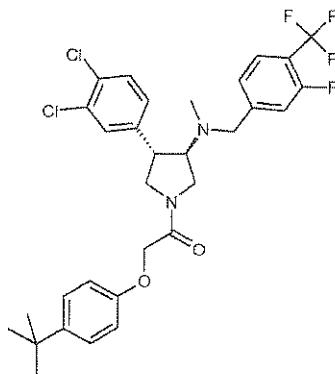
-70-

under vacuo, the crude was dissolved in  $\text{CH}_2\text{Cl}_2$  and washed with aq.  $\text{NaHCO}_3$  (until  $\text{pH} = 8$ ). The organic phase was dried on  $\text{Na}_2\text{SO}_4$  and concentrated under vacuo to yield 2.63 g (34%) of (R)-1-methanesulfonyl-2-methyl-piperazine as a light yellow oil.

Second step: To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (1.17 g, 3.95 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) at  $-78^\circ\text{C}$ , was added a solution of (R)-1-methanesulfonyl-2-methyl-piperazine (1.76 g, 9.9 mmol) and pyridine (1.60 mL, 20 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) over 1 hour. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$ . Concentration under vacuo and flash chromatography ( $\text{SiO}_2$ ,  $\text{EtOAc}/\text{H}$ , 1:1) yielded 1.70 g (71 %) of (R)-4-methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride as a light yellow solid.

### Example 61

**2-(4-tert-Butyl-phenoxy)-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone**



Coupling reaction according to general procedure I:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

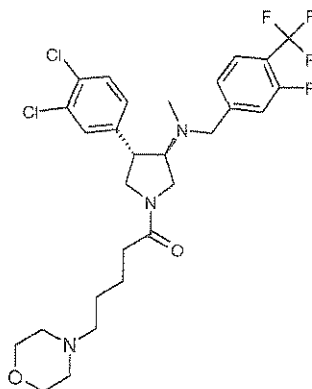
- Carboxylic acid: (4-tert-Butyl-phenoxy)-acetic acid (commercially available),

ES-MS  $m/e$ : 611.2 ( $\text{M}+\text{H}^+$ ).

### Example 62

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-5-morpholin-4-yl-pentan-1-one**

-71-



Coupling reaction according to general procedure I:

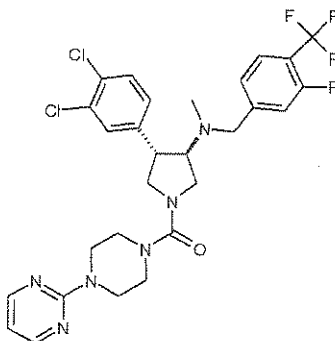
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

5 - Carboxylic acid: 5-Morpholin-4-yl-pentanoic acid (described in J. Molecular Structure 2001, 560, p.261),

ES-MS m/e: 590.5 (M+H<sup>+</sup>).

### Example 63

10 {(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone



Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

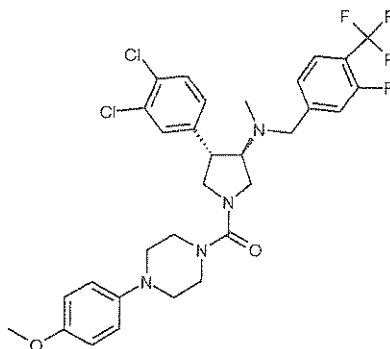
15 - Amine: 2-Piperazin-1-yl-pyrimidine (commercially available),

ES-MS m/e: 611.5 (M+H<sup>+</sup>).

### Example 64

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone

-72-



Coupling reaction according to general procedure V:

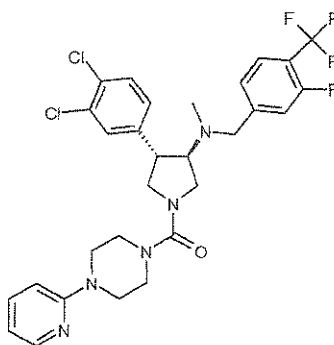
- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

5 - Amine: 1-(4-Methoxy-phenyl)-piperazine (commercially available),

ES-MS m/e: 639.5 (M+H<sup>+</sup>).

### Example 65

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-pyridin-2-yl-piperazin-1-yl)-methanone**



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

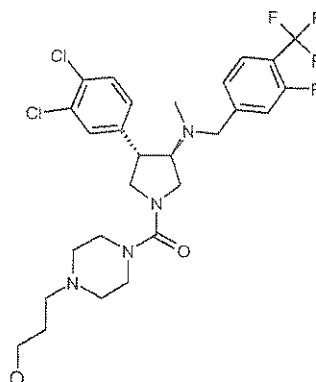
- Amine: 1-Pyridin-2-yl-piperazine (commercially available),

15 ES-MS m/e: 610.5 (M+H<sup>+</sup>).

### Example 66

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(3-hydroxy-propyl)-piperazin-1-yl]-methanone**

-73-



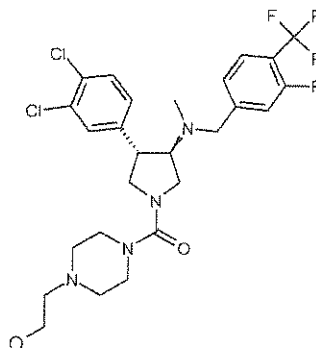
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: 3-Piperazin-1-yl-propan-1-ol (commercially available),  
ES-MS m/e: 591.5 (M+H<sup>+</sup>).

#### Example 67

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone**



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

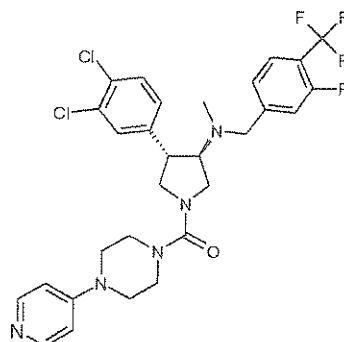
- Amine: 3-Piperazin-1-yl-ethan-1-ol (commercially available),

- 15 ES-MS m/e: 577.4 (M+H<sup>+</sup>).

#### Example 68

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-pyridin-4-yl-piperazin-1-yl)-methanone**

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Coupling reaction according to general procedure V:

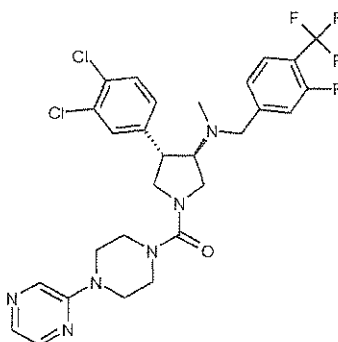
- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

5 - Amine: 1-Pyridin-4-yl-piperazine (commercially available),

ES-MS  $m/e$ : 610.5 ( $M+H^+$ ).

#### Example 69

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone**



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

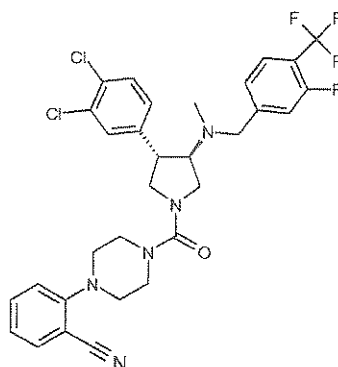
- Amine: 3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl (commercially available),

15 ES-MS  $m/e$ : 611.2 ( $M+H^+$ ).

#### Example 70

**2-(4-{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-benzonitrile**

-75-



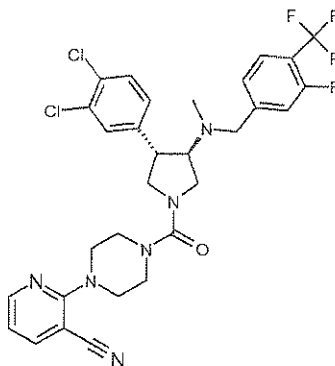
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: 2-Piperazin-1-yl-benzonitrile (commercially available),  
ES-MS m/e: 634.2 (M+H<sup>+</sup>).

#### Example 71

**2-(4-[(3SR,4R)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl]-piperazin-1-yl)-nicotinonitrile**



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

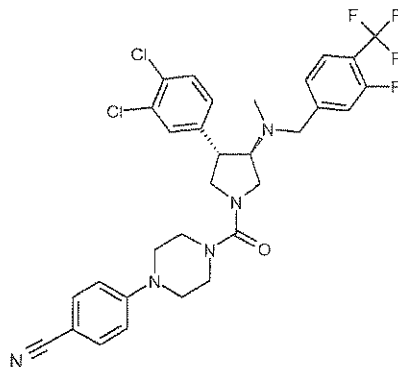
- Amine: 2-Piperazin-1-yl-nicotinonitrile (commercially available),

- 15 ES-MS m/e: 635.2 (M+H<sup>+</sup>).

#### Example 72

**4-(4-[(3SR,4R)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl]-piperazin-1-yl)-benzonitrile**

-76-



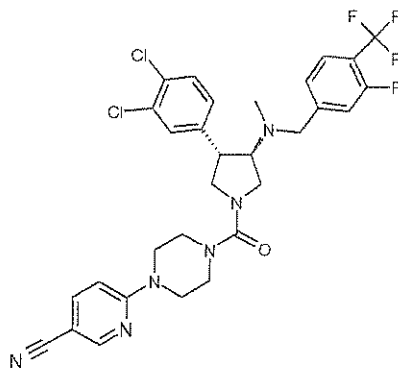
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: 4-Piperazin-1-yl-benzonitrile (commercially available),  
ES-MS m/e: 634.2 (M+H<sup>+</sup>).

### Example 73

**6-(4-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl]-piperazin-1-yl)-nicotinonitrile**



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

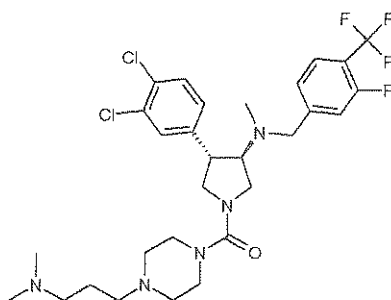
- Amine: 6-Piperazin-1-yl-nicotinonitrile (commercially available),

- 15 ES-MS m/e: 635.2 (M+H<sup>+</sup>).

### Example 74

**{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(3-dimethylamino-propyl)-piperazin-1-yl]-methanone**

-77-



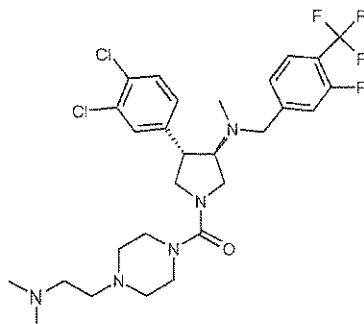
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: Dimethyl-(3-piperazin-1-yl-propyl)-amine (commercially available),  
ES-MS  $m/e$ : 618.2 ( $M+H^+$ ).

#### Example 75

**{{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone**



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

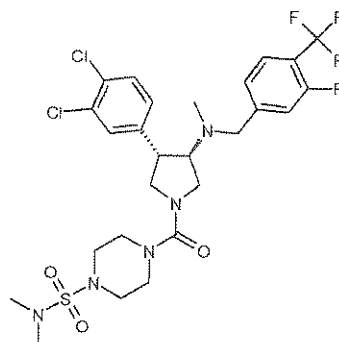
- Amine: Dimethyl-(2-piperazin-1-yl-ethyl)-amine (commercially available),

- 15 ES-MS  $m/e$ : 604.2 ( $M+H^+$ ).

#### Example 76

**4-{{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazine-1-sulfonic acid dimethylamide**

-78-



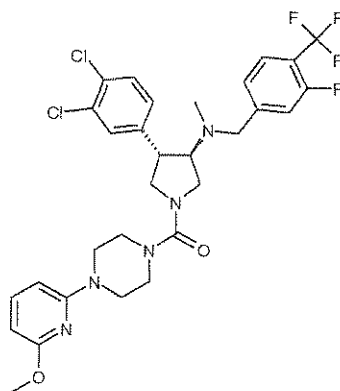
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: Piperazine-1-sulfonic acid dimethylamide (commercially available),  
ES-MS m/e: 642.2 (M+H<sup>+</sup>).

#### Example 77

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(6-methoxy-pyridin-2-yl)-piperazin-1-yl]-methanone



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

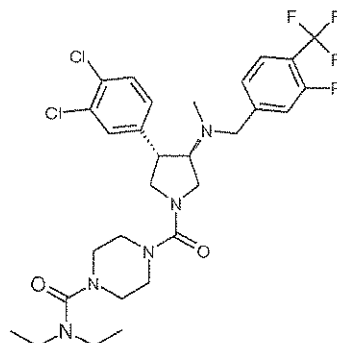
- Amine: 1-(6-Methoxy-pyridin-2-yl)-piperazine (commercially available),

- 15 ES-MS m/e: 640.2 (M+H<sup>+</sup>).

#### Example 78

4-{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazine-1-carboxylic acid diethylamide

-79-



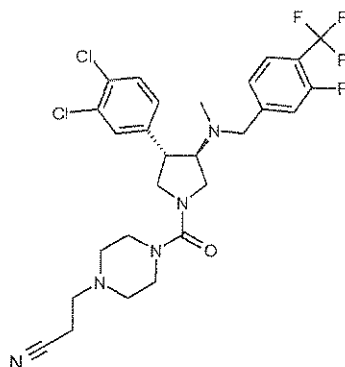
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: Piperazine-1-carboxylic acid diethylamide (commercially available),  
ES-MS m/e: 632.2 ( $M+H^+$ ).

#### Example 79

3-(4-{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-propionitrile



10

Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

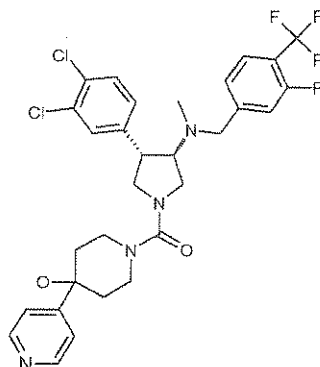
- Amine: 3-Piperazin-1-yl-propionitrile (commercially available),

- 15 ES-MS m/e: 580.3 ( $M+H^+$ ).

#### Example 80

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-methanone

-80-



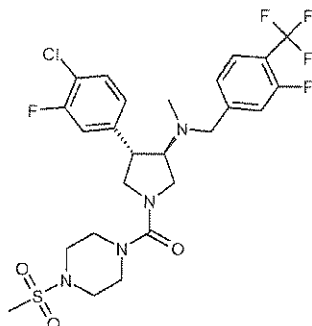
Coupling reaction according to general procedure V:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl chloride (**XIII-1**),

- 5 - Amine: 2,3,5,6-Tetrahydro-1H-[4,4']bipyridinyl-4-ol (commercially available),  
ES-MS m/e: 625.2 (M+H<sup>+</sup>).

#### Example 81

**{{(3SR,4RS)-3-(4-Chloro-3-fluoro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



10

Coupling reaction according to general procedure II:

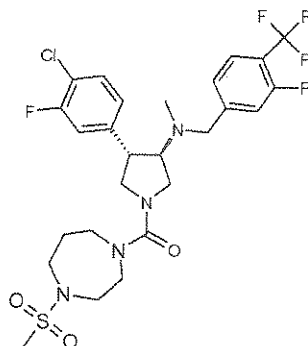
- Pyrrolidine intermediate: [(3RS,4SR)-4-(4-Chloro-3-fluoro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-2**),

- carbamoyl chloride: 4-methanesulfonyl-piperazine-1-carbonyl chloride (described herein above  
15 in the intermediate part),  
ES-MS m/e: 594.7 (M+H<sup>+</sup>).

#### Example 82

**{{(3SR,4RS)-3-(4-Chloro-3-fluoro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-[1,4]diazepan-1-yl)-methanone**

-81-



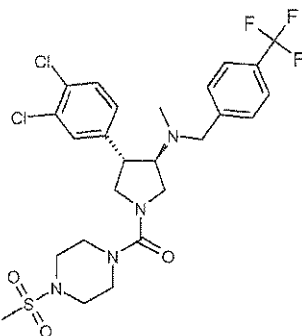
Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(4-Chloro-3-fluoro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-2**),

- 5 - carbamoyl chloride: 4-Methanesulfonyl-[1,4]diazepane-1-carbonyl chloride (this compound was prepared from 1-Methanesulfonyl-[1,4]diazepane using the same procedure as for the preparation of 4-methanesulfonyl-piperazine-1-carbonyl chloride),  
ES-MS m/e: 625.2 (M+H<sup>+</sup>).

### Example 83

- 10 **{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



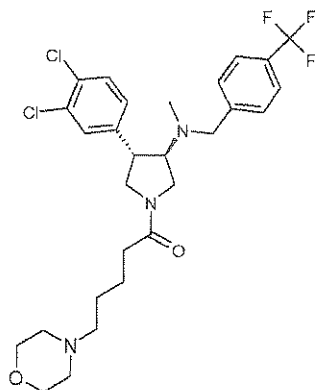
Reductive amination according to general procedure III:

- Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-3**),  
15 - Aldehyde: 4-Trifluoromethyl-benzaldehyde (commercially available),  
ES-MS m/e: 592.8 (M+H<sup>+</sup>).

### Example 84

- 20 **1-{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl}-5-morpholin-4-yl-pentan-1-one**

-82-



Coupling reaction according to general procedure I:

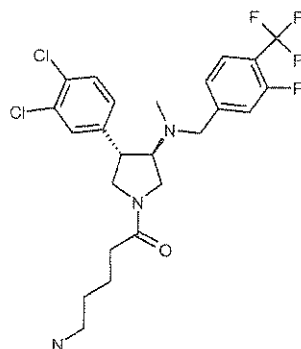
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine (**VIII-3**),

5 - Carboxylic acid: 5-Morpholin-4-yl-pentanoic acid (described in J. Molecular Structure 2001, 560, p.261),

ES-MS m/e: 573.7 (M+H<sup>+</sup>).

#### Example 85

5-Amino-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-pentan-1-one



Nucleophilic substitution reaction according to general procedure VII:

- Pyrrolidine intermediate: 5-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-pentan-1-one (**XV-1**),

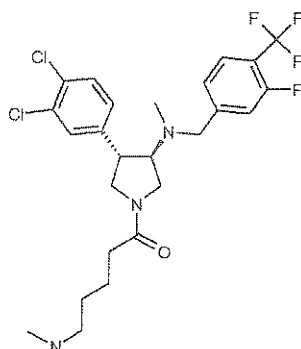
15 - Amine: aqueous ammonia (commercially available),

ES-MS m/e: 519.9 (M+H<sup>+</sup>).

#### Example 86

1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-5-methylamino-pentan-1-one

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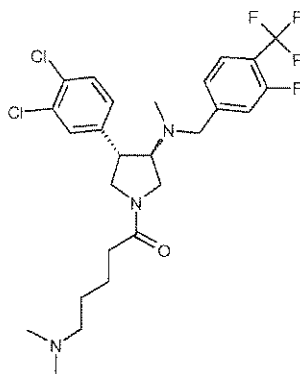
Nucleophilic substitution reaction according to general procedure VII:

- Pyrrolidine intermediate: 5-Bromo-1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-pentan-1-one (XV-1),

- 5 - Amine: methyl amine (THF solution) (commercially available),  
ES-MS m/e: 533.8 ( $M+H^+$ ).

#### Example 87

1-{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-dimethylamino-pentan-1-one



10

Nucleophilic substitution reaction according to general procedure VII:

- Pyrrolidine intermediate: 5-Bromo-1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-pentan-1-one (XV-1),

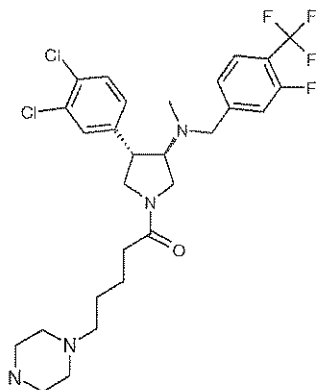
- Amine: dimethyl-amine (commercially available),

- 15 ES-MS m/e: 547.9 ( $M+H^+$ ).

#### Example 88

1-{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-piperazin-1-yl-pentan-1-one

-84-



Nucleophilic substitution reaction according to general procedure VII:

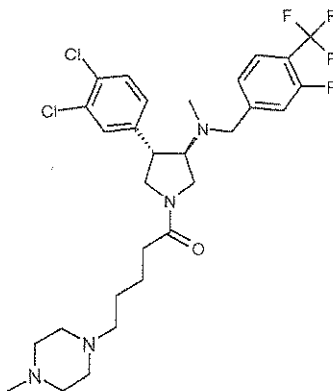
- Pyrrolidine intermediate: 5-Bromo-1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-pentan-1-one (**XV-1**),

5 - Amine: Piperazine (commercially available),

ES-MS m/e: 588.8 ( $M+H^+$ ).

#### Example 89

**1-{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-(4-methyl-piperazin-1-yl)-pentan-1-one**



10

Nucleophilic substitution reaction according to general procedure VII:

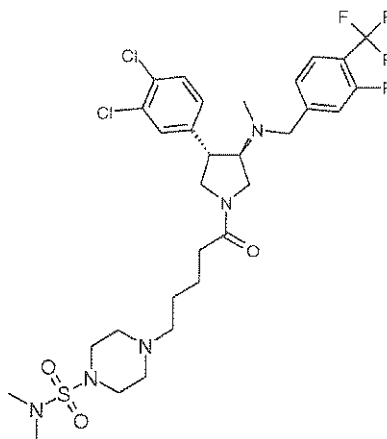
- Pyrrolidine intermediate: 5-Bromo-1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-pentan-1-one (**XV-1**),

- Amine: 1-Methyl-piperazine (commercially available),

15 ES-MS m/e: 602.8( $M+H^+$ ).

**Example 90**

**4-(5-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-5-oxo-pentyl)-piperazine-1-sulfonic acid dimethylamide**

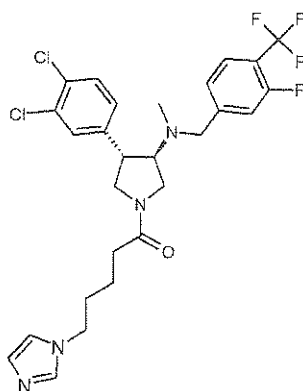


- 5 Nucleophilic substitution reaction according to general procedure VII:
- Pyrrolidine intermediate: 5-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-pentan-1-one (**XV-1**),
  - Amine: Piperazine-1-sulfonic acid dimethylamide (commercially available),
- ES-MS m/e: 695.8 (M+H<sup>+</sup>).

10

**Example 91**

**1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-5-imidazol-1-yl-pentan-1-one**



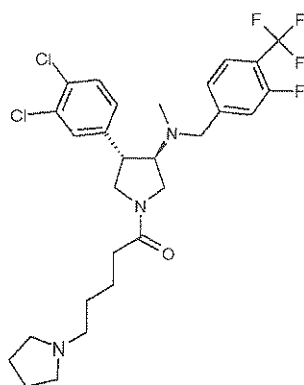
Nucleophilic substitution reaction according to general procedure VII:

- 15 - Pyrrolidine intermediate: 5-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-pentan-1-one (**XV-1**),
- Amine: 1H-Imidazole (commercially available),

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ES-MS m/e: 570.6 ( $M+H^+$ ).**Example 92**

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-5-pyrrolidin-1-yl-pentan-1-one**



5

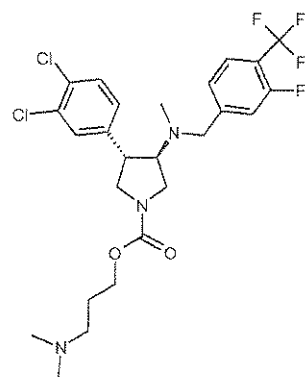
Nucleophilic substitution reaction according to general procedure VII:

- Pyrrolidine intermediate: 5-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-pentan-1-one (XV-1),
- Amine: pyrrolidine (commercially available),

10 ES-MS m/e: 573.7 ( $M+H^+$ ).

**Example 93**

**(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid 3-dimethylamino-propyl ester**



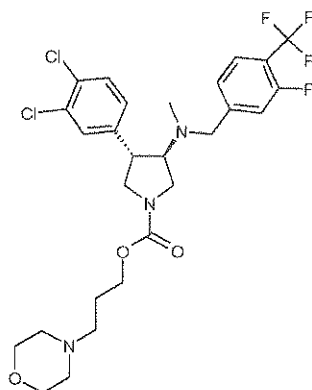
15 Nucleophilic substitution reaction according to general procedure VIII:

- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid 3-chloro-propyl ester (XVI-1),
- Amine: dimethyl-amine (commercially available),

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ES-MS m/e: 550.3 ( $M+H^+$ ).**Example 94**

**(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid 3-morpholin-4-yl-propyl ester**



5

Nucleophilic substitution reaction according to general procedure VIII:

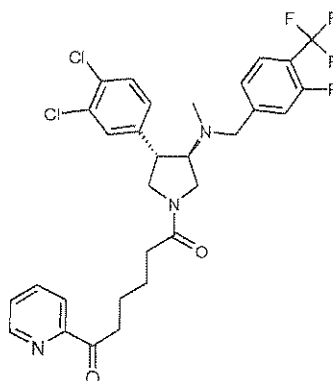
- Pyrrolidine intermediate: (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid 3-chloro-propyl ester (**XVI-1**),

- Amine: morpholine (commercially available),

10 ES-MS m/e: 591.8 ( $M+H^+$ ).

**Example 95**

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-6-pyridin-2-yl-hexane-1,6-dione**



15 Coupling reaction according to general procedure I:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

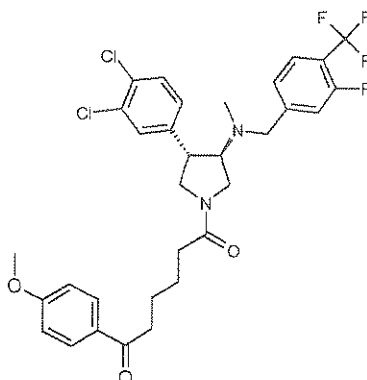
-88-

- Carboxylic acid: 6-Oxo-6-pyridin-2-yl-hexanoic acid (Journal fuer Praktischer Chemie, 1966, 34, 272),

ES-MS m/e: 610.1 ( $M+H^+$ ).

### Example 96

5 **1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-6-(4-methoxy-phenyl)-hexane-1,6-dione**



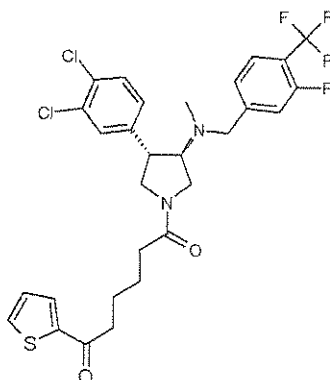
Coupling reaction according to general procedure I:

10 - Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

- Carboxylic acid: 6-(4-Methoxy-phenyl)-6-oxo-hexanoic acid (commercially available),  
ES-MS m/e: 611.2 ( $M+H^+$ ).

### Example 97

15 **1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-6-thiophen-2-yl-hexane-1,6-dione**



Coupling reaction according to general procedure I:

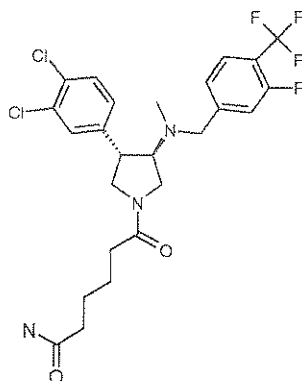
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

-89-

- Carboxylic acid: 6-Oxo-6-thiophen-2-yl-hexanoic acid (commercially available),  
ES-MS m/e: 587.1 ( $M+H^+$ ).

**Example 98**

6-{{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-6-oxo-hexanoic acid amide



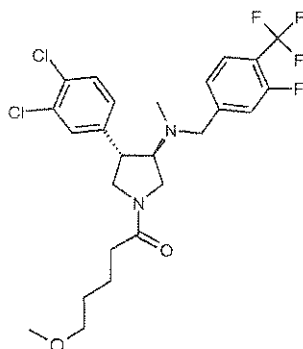
Coupling reaction according to general procedure I:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

10 - Carboxylic acid: 5-Carbamoyl-pentanoic acid (commercially available),  
ES-MS m/e: 548.2 ( $M+H^+$ ).

**Example 99**

1-{{(3S,4R)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-methoxy-pentan-1-one



Coupling reaction according to general procedure I:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

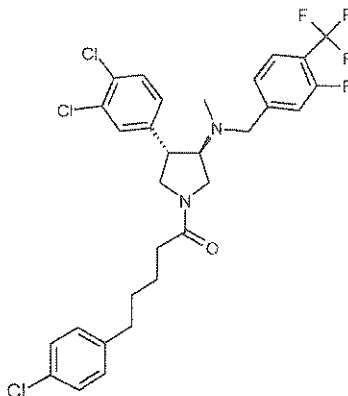
- Carboxylic acid: 5-Methoxy-pentanoic acid (commercially available),

20 ES-MS m/e: 535.1 ( $M+H^+$ ).

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**Example 100**

**5-(4-Chloro-phenyl)-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-pentan-1-one**

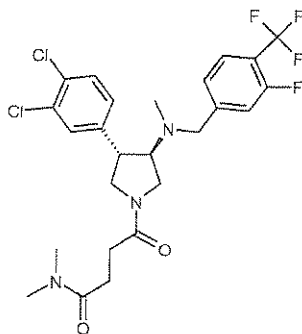


- 5 Coupling reaction according to general procedure I:
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),
  - Carboxylic acid: 5-(4-Chloro-phenyl)-pentanoic acid (commercially available),
- ES-MS m/e: 615.1 ( $M+H^+$ ).

10

**Example 101**

**4-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-N,N-dimethyl-4-oxo-butamide**

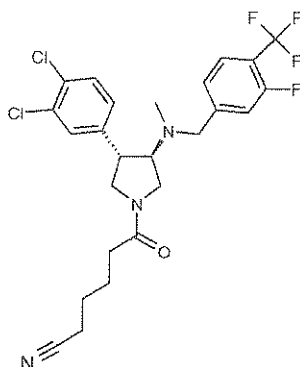


Coupling reaction according to general procedure I:

- 15 - Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),
- Carboxylic acid: N,N-Dimethyl-succinamic acid (commercially available),
- ES-MS m/e: 548.2 ( $M+H^+$ ).

**Example 102**

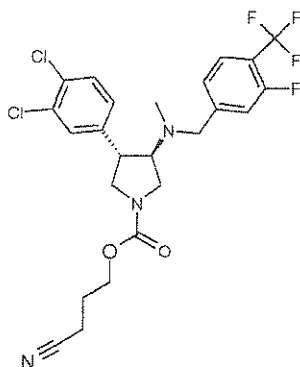
**6-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-6-oxo-hexanenitrile**



- 5 To a stirred solution of 5-bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-pentan-1-one (**XV-1**) (40 mg, 0.068 mmol) in DMF (2 ml) was added potassium cyanide (5.0 mg, 0.077 mmol) and 18 crown 6-ether (18 mg, 0.068 mmol). The reaction mixture was stirred at 40 °C overnight, concentrated under vacuo. The product was purified by preparation HPLC to yield 3.2 mg (9 %) of the title product
- 10 as a colorless oil. ES-MS  $m/e$ : 530.1 ( $M+H^+$ ).

**Example 103**

**(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid 3-cyano-propyl ester**

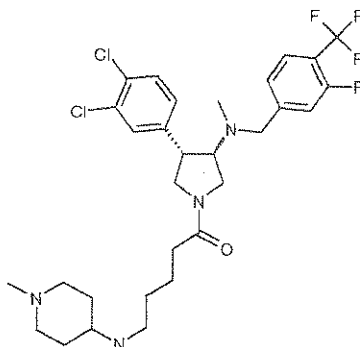


- 15 To a stirred solution of (3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carboxylic acid 3-chloro-propyl ester (**XVI-1**) (40 mg, 0.068 mmol) in DMF (2 ml) was added potassium cyanide (5.0 mg, 0.077 mmol) and 18 crown 6-ether (18 mg, 0.068 mmol). The reaction mixture was stirred at 40 °C overnight, concentrated

under vacuo. The product was purified by preparation HPLC to yield 18 mg (45 %) of the title product as a colorless oil. ES-MS  $m/e$ : 532.1 ( $M+H^+$ ).

#### Example 104

1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-5-(1-methyl-piperidin-4-ylamino)-pentan-1-one



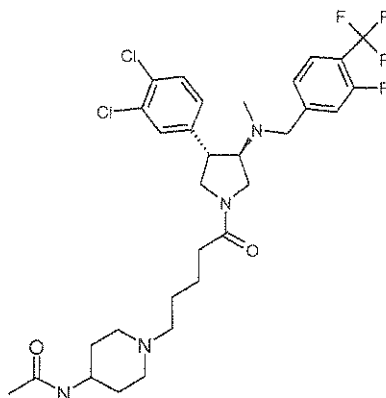
Nucleophilic substitution reaction according to general procedure VII:

- Pyrrolidine intermediate: 5-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-pentan-1-one (XV-1),

10 - Amine: 1-Methyl-piperidin-4-ylamine (commercially available),  
ES-MS  $m/e$ : 617.3 ( $M+H^+$ ).

#### Example 105

N-[1-(5-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-5-oxo-pentyl)-piperidin-4-yl]-acetamide



Nucleophilic substitution reaction according to general procedure VII:

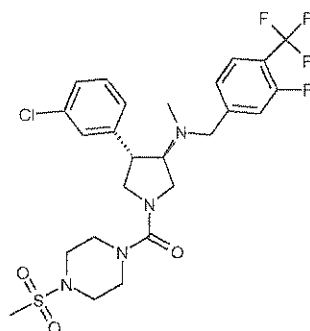
- Pyrrolidine intermediate: 5-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-pentan-1-one (XV-1),

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- Amine: N-Piperidin-4-yl-acetamide (commercially available),  
ES-MS m/e: 645.4 (M+H<sup>+</sup>).

**Example 106**

**{(3SR,4RS)-3-(3-Chloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**



Coupling reaction according to general procedure II:

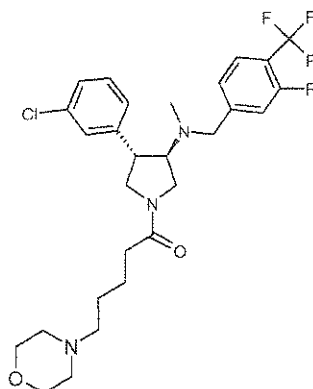
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-4**),

10 - Carbamoyl chloride: 4-Methanesulfonyl-piperazine-1-carbonyl chloride (described herein above),

ES-MS m/e: 576.8 (M+H<sup>+</sup>).

**Example 107**

**1-{(3SR,4RS)-3-(3-Chloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-morpholin-4-yl-pentan-1-one**



Coupling reaction according to general procedure II:

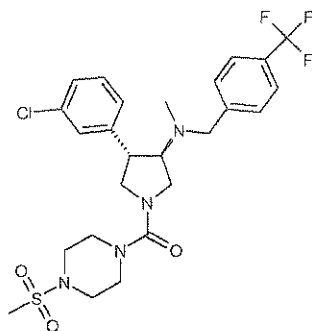
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-4**),

- Carboxylic acid: 5-Morpholin-4-yl-pentanoic acid (described in J. Molecular Structure 2001, 560, p.261),

ES-MS m/e: 555.8 ( $M+H^+$ ).

### Example 108

- 5    **{(3SR,4RS)-3-(3-Chloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone**

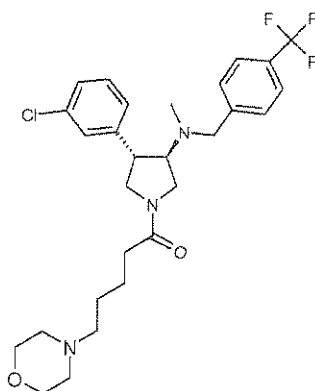


Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: [(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine (**VIII-5**),  
 10    - Carbamoyl chloride: 4-Methanesulfonyl-piperazine-1-carbonyl chloride (described herein above),  
 ES-MS m/e: 558.6 ( $M+H^+$ ).

### Example 109

- 15    **1-[(3SR,4RS)-3-(3-Chloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl]-5-morpholin-4-yl-pentan-1-one**



Coupling reaction according to general procedure II:

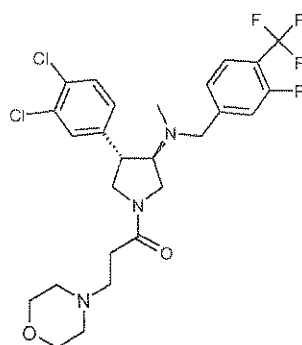
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine (**VIII-5**),  
 20    - 5-morpholin-4-yl-pentan-1-one

- Carboxylic acid: 5-Morpholin-4-yl-pentanoic acid (described in J. Molecular Structure 2001, 560, p.261),

ES-MS m/e: 537.9 (M+H<sup>+</sup>).

### Example 110

5 1-{(3S,4R)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-3-morpholin-4-yl-propan-1-one



Coupling reaction according to general procedure I:

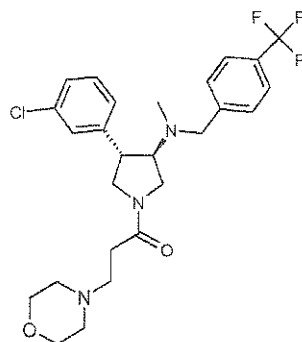
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-1**),

- Carboxylic acid: 3-Morpholin-4-yl-propionic acid (commercially available),

ES-MS m/e: 561.8 (M+H<sup>+</sup>).

### Example 111

15 1-{(3SR,4RS)-3-(3-Chloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl}-3-morpholin-4-yl-propan-1-one



Coupling reaction according to general procedure I:

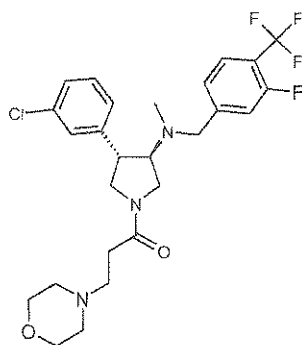
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-methyl-(4-trifluoromethyl-benzyl)-amine (**VIII-5**),

20 - Carboxylic acid: 3-Morpholin-4-yl-propionic acid (commercially available),

ES-MS m/e: 510.1 ( $M+H^+$ ).

### Example 112

**1-[(3SR,4RS)-3-(3-Chloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-3-morpholin-4-yl-propan-1-one**



5

Coupling reaction according to general procedure I:

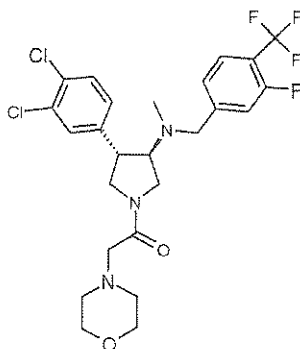
- Pyrrolidine intermediate: [(3RS,4SR)-4-(3-Chloro-phenyl)-pyrrolidin-3-yl]-(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine (**VIII-4**),

- Carboxylic acid: 3-Morpholin-4-yl-propionic acid (commercially available),

10 ES-MS m/e: 527.7 ( $M+H^+$ ).

### Example 113

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-morpholin-4-yl-ethanone**



15 Coupling reaction according to general procedure VI:

2-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone (**XIV-1**)

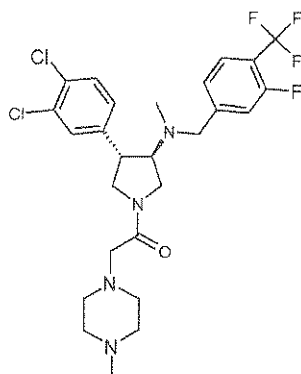
- Amine: Morpholine (commercially available),

ES-MS m/e: 547.8( $M+H^+$ ).

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**Example 114**

**1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(4-methyl-piperazin-1-yl)-ethanone**



5 Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

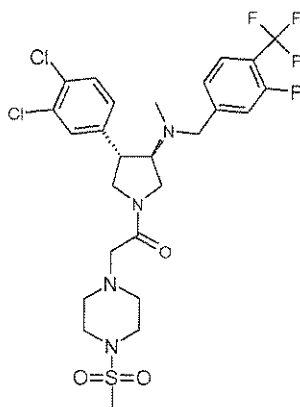
- Amine: 1-Methyl-piperazine (commercially available),

ES-MS m/e: 560.7 ( $M+H^+$ ).

10

**Example 115**

**1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(4-methanesulfonyl-piperazin-1-yl)-ethanone**



Coupling reaction according to general procedure VI:

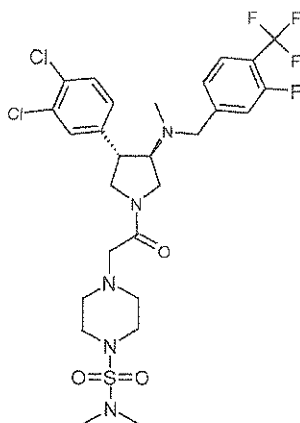
15 2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- Amine: 1-Methanesulfonyl-piperazine (commercially available),

ES-MS m/e: 624.5 ( $M+H^+$ ).

**Example 116**

**4-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperazine-1-sulfonic acid dimethylamide**



5 Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

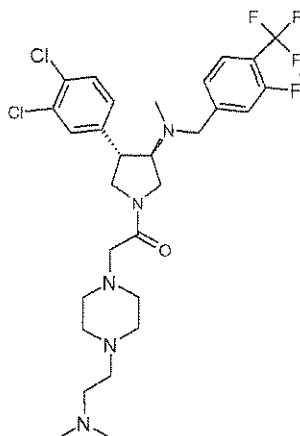
- Amine: Piperazine-1-sulfonic acid dimethylamide (commercially available),

ES-MS m/e: 653.7 (M+H<sup>+</sup>).

10

**Example 117**

**1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-ethanone**



Coupling reaction according to general procedure VI:

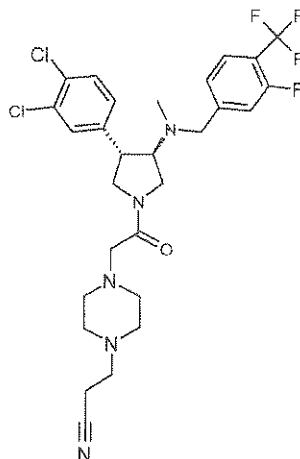
15 2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- Amine: Dimethyl-(2-piperazin-1-yl-ethyl)-amine (commercially available),

ES-MS m/e: 617.8 (M+H<sup>+</sup>).

**Example 118**

**3-[4-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperazin-1-yl]-propionitrile**



5 Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

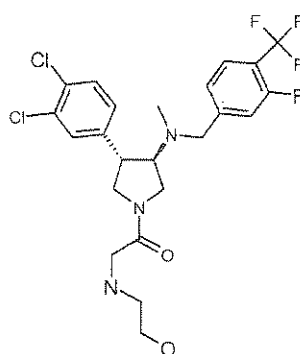
- Amine: 3-Piperazin-1-yl-propionitrile (commercially available),

ES-MS m/e: 599.7 (M+H<sup>+</sup>).

10

**Example 119**

**1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(2-hydroxy-ethylamino)-ethanone**



Coupling reaction according to general procedure VI:

15 2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

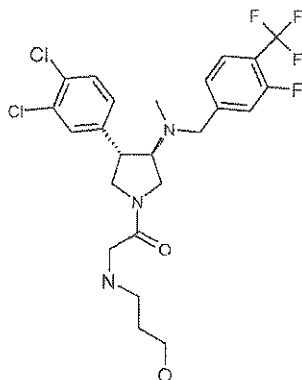
- Amine: 2-Amino-ethanol (commercially available),

ES-MS m/e: 521.9 (M+H<sup>+</sup>).

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**Example 120**

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-(3-hydroxy-propylamino)-ethanone**



5 Coupling reaction according to general procedure VI:

2-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone (**XIV-1**)

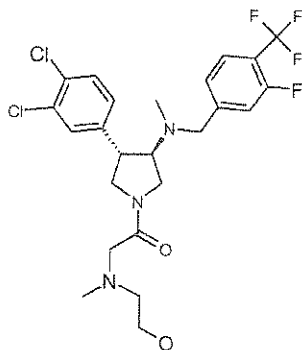
- Amine: 3-Amino-propan-1-ol (commercially available),

ES-MS m/e: 535.8 (M+H<sup>+</sup>).

10

**Example 121**

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-[(2-hydroxy-ethyl)-methyl-amino]-ethanone**



Coupling reaction according to general procedure VI:

15 2-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone (**XIV-1**)

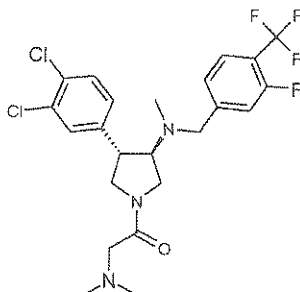
- Amine: 2-Methylamino-ethanol (commercially available),

ES-MS m/e: 535.8 (M+H<sup>+</sup>).

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**Example 122**

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-dimethylamino-ethanone**



5 Coupling reaction according to general procedure VI:

2-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone (**XIV-1**)

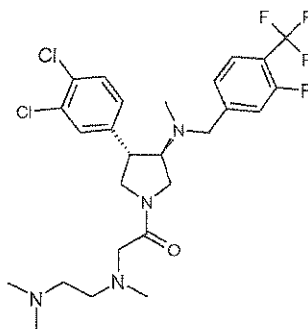
- Amine: Dimethyl-amine (commercially available),

ES-MS m/e: 505.9 (M+H<sup>+</sup>).

10

**Example 123**

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-[(2-dimethylamino-ethyl)-methyl-amino]-ethanone**



Coupling reaction according to general procedure VI:

15 2-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone (**XIV-1**)

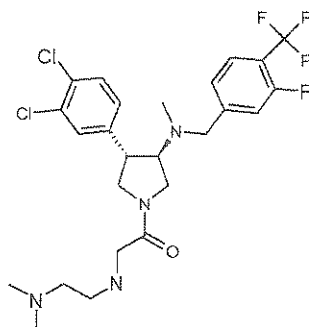
- Amine: N,N,N'-Trimethyl-ethane-1,2-diamine (commercially available),

ES-MS m/e: 562.9 (M+H<sup>+</sup>).

**Example 124**

20 **1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-(2-dimethylamino-ethylamino)-ethanone**

-102-



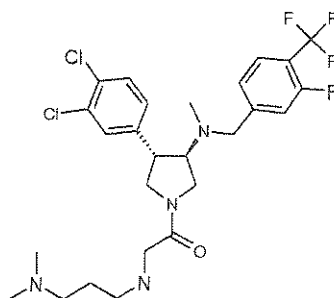
Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichlorophenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- 5 - Amine: N,N-Dimethyl-ethane-1,2-diamine (commercially available),  
ES-MS m/e: 549.7 ( $M+H^+$ ).

#### Example 125

1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-2-(3-dimethylamino-propylamino)-ethanone



10

Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichlorophenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-ethanone (**XIV-1**)

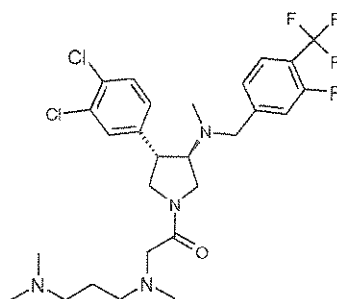
- Amine: N,N-Dimethyl-propane-1,3-diamine (commercially available),

- 15 ES-MS m/e: 563.2 ( $M+H^+$ ).

#### Example 126

1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-2-((3-dimethylamino-propyl)-methyl-amino)-ethanone

-103-



Coupling reaction according to general procedure VI:

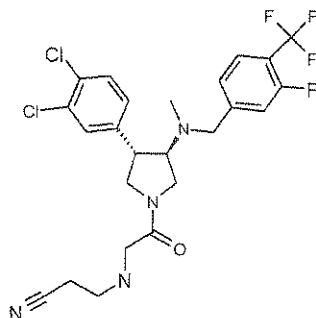
2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

5 - Amine: N,N,N'-Trimethyl-propane-1,3-diamine (commercially available),

ES-MS m/e: 576.8 (M+H<sup>+</sup>).

#### Example 127

3-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethylamino)-propionitrile



10

Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

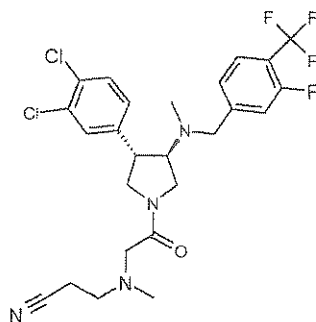
- Amine: 3-Amino-propionitrile (commercially available),

15 ES-MS m/e: 530.8 (M+H<sup>+</sup>).

#### Example 128

3-[(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-methyl-amino]-propionitrile

-104-



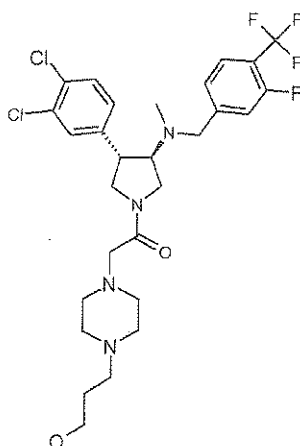
Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- 5 - Amine: 3-Methylamino-propionitrile (commercially available),  
ES-MS m/e: 544.9 (M+H<sup>+</sup>).

#### Example 129

1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-2-[4-(3-hydroxy-propyl)-piperazin-1-yl]-ethanone



10

Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-ethanone (**XIV-1**)

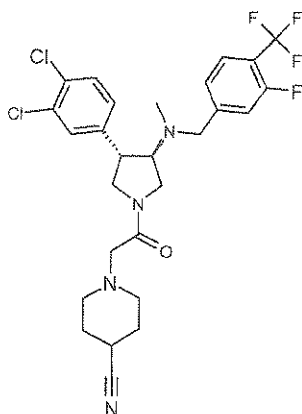
- Amine: 3-Piperazin-1-yl-propan-1-ol (commercially available),

- 15 ES-MS m/e: 605.3 (M+H<sup>+</sup>).

#### Example 130

1-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidine-4-carbonitrile

-105-



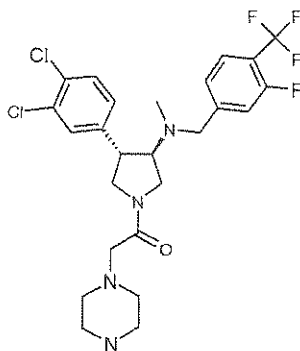
Coupling reaction according to general procedure VI:

2-Bromo-1-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-ethanone (**XIV-1**)

- 5 - Amine: Piperidine-4-carbonitrile (commercially available),  
ES-MS m/e: 570.7 (M+H<sup>+</sup>).

#### Example 131

1-{{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-piperazin-1-yl-ethanone



10

Coupling reaction according to general procedure VI:

2-Bromo-1-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-ethanone (**XIV-1**)

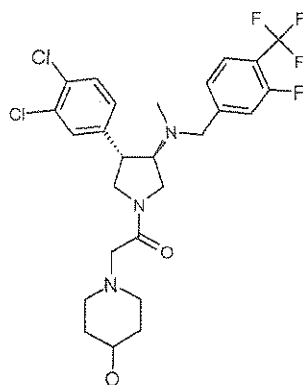
- Amine: Piperazine (commercially available),

- 15 ES-MS m/e: 546.7 (M+H<sup>+</sup>).

#### Example 132

1-{{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(4-hydroxy-piperidin-1-yl)-ethanone

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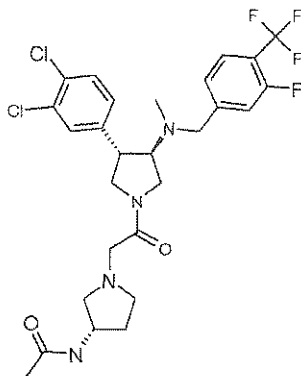
Coupling reaction according to general procedure VI:

2-Bromo-1-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}}-ethanone (**XIV-1**)

- 5 - Amine: Piperidin-4-ol (commercially available),  
ES-MS m/e: 561.8 (M+H<sup>+</sup>).

### Example 133

**N-[(S)-1-(2-{{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}}-2-oxo-ethyl)-pyrrolidin-3-yl]-acetamide**



10

Coupling reaction according to general procedure VI:

2-Bromo-1-{{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}}-ethanone (**XIV-1**)

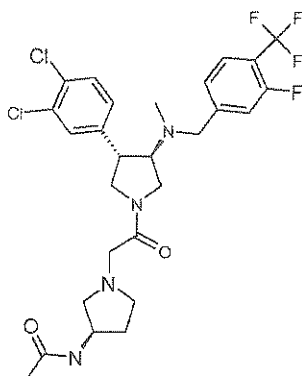
- Amine: (S)-N-Pyrrolidin-3-yl-acetamide (commercially available),

- 15 ES-MS m/e: 588.8 (M+H<sup>+</sup>).

### Example 134

**N-[(R)-1-(2-{{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}}-2-oxo-ethyl)-pyrrolidin-3-yl]-acetamide**

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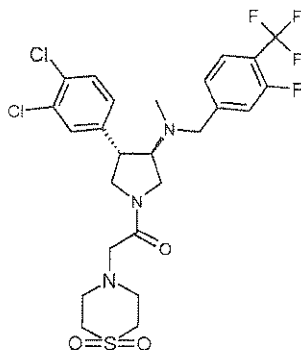
Coupling reaction according to general procedure VI:

2-Bromo-1-((3S,4R)-3-(3,4-dichlorophenyl)-4-((3-fluoro-4-(trifluoromethyl)benzyl)methylamino)pyrrolidin-1-yl)ethanone (**XIV-1**)

- 5 - Amine: (R)-N-Pyrrolidin-3-yl-acetamide (commercially available),  
ES-MS m/e: 588.8 (M+H<sup>+</sup>).

### Example 135

1-((3S,4R)-3-(3,4-Dichlorophenyl)-4-((3-fluoro-4-(trifluoromethyl)benzyl)methylamino)pyrrolidin-1-yl)-2-(1,1-dioxo-λ<sup>6</sup>-thiomorpholin-4-yl)ethanone



10

Coupling reaction according to general procedure VI:

2-Bromo-1-((3S,4R)-3-(3,4-dichlorophenyl)-4-((3-fluoro-4-(trifluoromethyl)benzyl)methylamino)pyrrolidin-1-yl)ethanone (**XIV-1**)

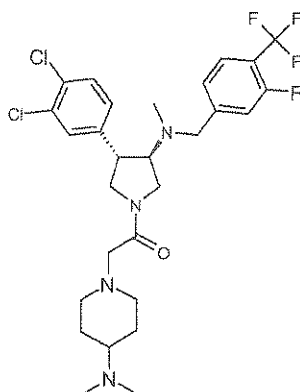
- Amine: Thiomorpholine 1,1-dioxide (commercially available),

- 15 ES-MS m/e: 595.6 (M+H<sup>+</sup>).

### Example 136

1-((3S,4R)-3-(3,4-Dichlorophenyl)-4-((3-fluoro-4-(trifluoromethyl)benzyl)methylamino)pyrrolidin-1-yl)-2-(4-dimethylamino-piperidin-1-yl)ethanone

-108-



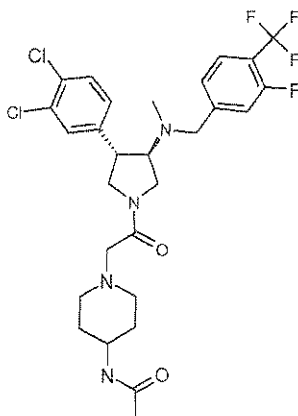
Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- 5 - Amine: Dimethyl-piperidin-4-yl-amine (commercially available),  
ES-MS m/e: 588.8 ( $M+H^+$ ).

#### Example 137

N-[1-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-acetamide



10

Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

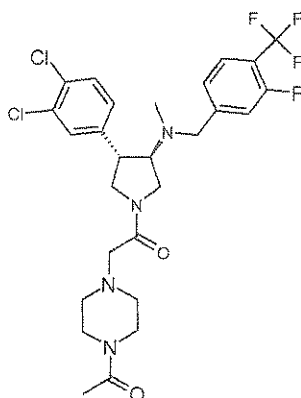
- Amine: N-Piperidin-4-yl-acetamide (commercially available),

- 15 ES-MS m/e: 602.8 ( $M+H^+$ ).

#### Example 138

2-(4-Acetyl-piperazin-1-yl)-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone

-109-



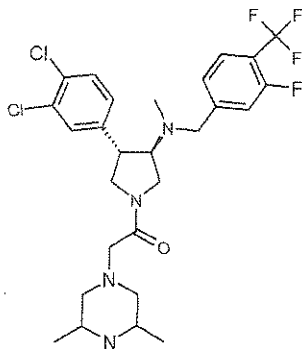
Coupling reaction according to general procedure VI:

2-Bromo-1-((3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- 5 - Amine: 1-Piperazin-1-yl-ethanone (commercially available),  
ES-MS m/e: 588.8 (M+H<sup>+</sup>).

### Example 139

1-((3S,4R)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(3,5-dimethyl-piperazin-1-yl)-ethanone



10

Coupling reaction according to general procedure VI:

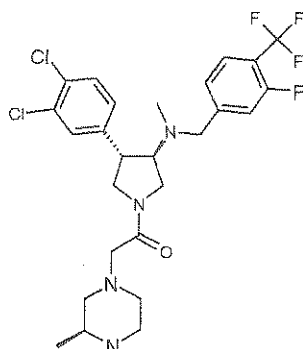
2-Bromo-1-((3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- Amine: 2,6-Dimethyl-piperazine (commercially available),  
15 ES-MS m/e: 574.9 (M+H<sup>+</sup>).

### Example 140

1-((3S,4R)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-((S)-3-methyl-piperazin-1-yl)-ethanone

-110-



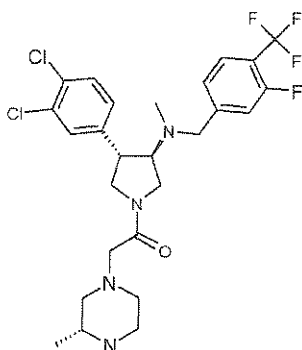
Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichlorophenyl)-4-((3-fluoro-4-trifluoromethylbenzyl)methylamino)pyrrolidin-1-yl)ethanone (**XIV-1**)

- 5 - Amine: (S)-2-Methyl-piperazine (commercially available),  
ES-MS m/e: 560.8 (M+H<sup>+</sup>).

#### Example 141

1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-2-((R)-3-methyl-piperazin-1-yl)-ethanone



10

Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichlorophenyl)-4-((3-fluoro-4-trifluoromethylbenzyl)methylamino)pyrrolidin-1-yl)ethanone (**XIV-1**)

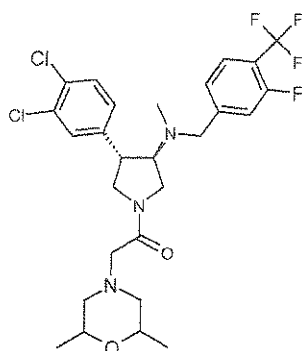
- Amine: (R)-2-Methyl-piperazine (commercially available),

- 15 ES-MS m/e: 560.8 (M+H<sup>+</sup>).

#### Example 142

1-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-2-(2,6-dimethyl-morpholin-4-yl)-ethanone

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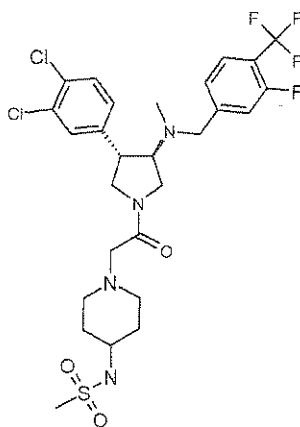
Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- 5 - Amine: 2,6-Dimethyl-morpholine (commercially available),  
ES-MS m/e: 575.8 (M+H<sup>+</sup>).

#### Example 143

**N-[1-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-methanesulfonamide**



10

Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

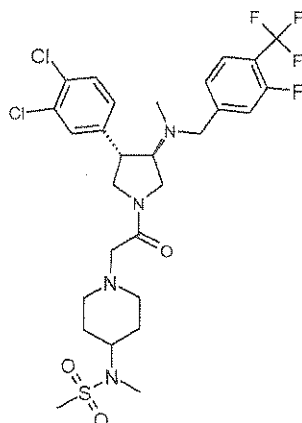
- Amine: N-Piperidin-4-yl-methanesulfonamide (commercially available),

- 15 ES-MS m/e: 638.9 (M+H<sup>+</sup>).

#### Example 144

**N-[1-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-methanesulfonamide**

-112-



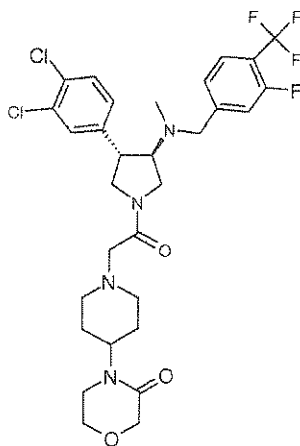
Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- 5 - Amine: N-Methyl-N-piperidin-4-yl-methanesulfonamide (described in WO20080707740),  
ES-MS m/e: 652.7 (M+H<sup>+</sup>).

#### Example 145

4-[1-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-morpholin-3-one



10

Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-ethanone (**XIV-1**)

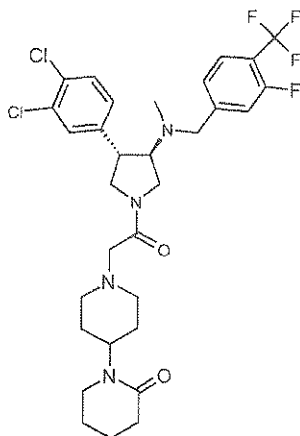
- Amine: 4-Piperidin-4-yl-morpholin-3-one (described in WO2006/055951),

- 15 ES-MS m/e: 644.8 (M+H<sup>+</sup>).

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**Example 146**

**1'-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-[1,4']bipiperidiny-2-one**



5 Coupling reaction according to general procedure VI:

2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

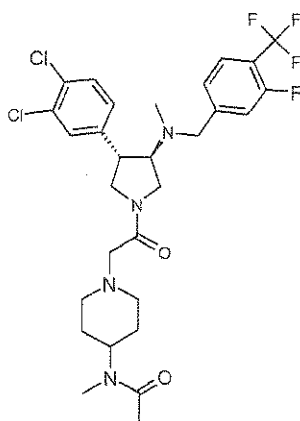
- Amine: [1,4']Bipiperidiny-2-one (described in WO2006/055951),

ES-MS m/e: 642.8 (M+H<sup>+</sup>).

10

**Example 147**

**N-[1-(2-((3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-acetamide**



Coupling reaction according to general procedure VI:

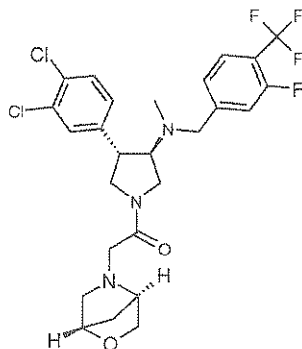
15 2-Bromo-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone (**XIV-1**)

- Amine: N-Methyl-N-piperidin-4-yl-acetamide (commercially available),

ES-MS m/e: 617.2 (M+H<sup>+</sup>).

**Example 148**

**1-[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-(1S,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-ethanone**



- 5 Coupling reaction according to general procedure VI:

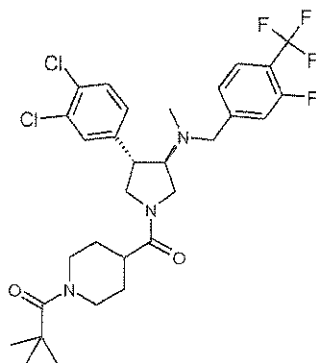
2-Bromo-1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-ethanone (**XIV-1**)

- Amine: (1S,4R)-2-Oxa-5-aza-bicyclo[2.2.1]heptane (commercially available),  
ES-MS m/e: 561.8 (M+H<sup>+</sup>).

10

**Example 149**

**[(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone**



Reductive amination according to general procedure III:

- 15 - Pyrrolidine intermediate: [(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-methylamino-pyrrolidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone

(**XII-4**),

- Aldehyde: 3-Fluoro-4-trifluoromethyl-benzaldehyde (commercially available),  
ES-MS m/e: 614.3 (M+H<sup>+</sup>)

## EXPERIMENTAL PROCEDURES

As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are antagonists of neurokinin 3 (NK-3) receptors. The compounds were investigated in accordance with the tests given hereinafter.

**Experimental procedure**

The compounds were investigated in accordance with the tests given hereinafter

**[<sup>3</sup>H]SR142801 competition binding assay**

hNK3 receptor binding experiment were performed using [<sup>3</sup>H]SR142801 (Catalog No. TRK1035, specific activity: 74.0 Ci/mmol, Amersham, GE Healthcare UK limited, Buckinghamshire, UK) and membrane isolated from HEK293 cells transiently expressing recombinant human NK3 receptor. After thawing, the membrane homogenates were centrifuged at 48,000 X g for 10 min at 4 °C, the pellets were resuspended in the 50 mM Tris-HCl, 4 mM MnCl<sub>2</sub>, 1 μM phosphoramidon, 0.1 % BSA binding buffer at pH 7.4 to a final assay concentration of 5 μg protein/well. For inhibition experiments, membranes were incubated with [<sup>3</sup>H]SR142801 at a concentration equal to K<sub>D</sub> value of radioligand and 10 concentrations of the inhibitory compound (0.0003-10 μM) (in a total reaction volume of 500 μl) for 75 min at room temperature (RT). At the end of the incubation, membranes were filtered onto unitfilter (96-well white microplate with bonded GF/C filter preincubated 1 h in 0.3% PEI + 0.3% BSA, Packard BioScience, Meriden, CT) with a Filtermate 196 harvester (Packard BioScience) and washed 4 times with ice-cold 50 mM Tris-HCl, pH 7.4 buffer. Nonspecific binding was measured in the presence of 10 μM SB222200 for both radioligands. The radioactivity on the filter was counted (5 min) on a Packard Top-count microplate scintillation counter with quenching correction after addition of 45 μl of microscint 40 (Canberra Packard S.A., Zürich, Switzerland) and shaking for 1 h. Inhibition curves were fitted according to the Hill equation:  $y = 100 / (1 + (x / IC_{50})^{n_H})$ , where n<sub>H</sub> = slope factor using Excel-fit 4 software (Microsoft). IC<sub>50</sub> values were derived from the inhibition curve and the affinity constant (K<sub>i</sub>) values were calculated using the Cheng-Prussoff equation  $K_i = IC_{50} / (1 + [L] / K_D)$  where [L] is the concentration of radioligand and K<sub>D</sub> is its dissociation constant at the receptor, derived from the saturation isotherm. All experiments were performed in duplicate and the mean ± standard error (SEM) of the individual K<sub>i</sub> values was calculated.

Some results of preferred compounds with a hNK-3 receptor affinity <0.10  $\mu\text{M}$  were shown in the following table 1.

Table 1

| Example | Data $K_i$<br>[ $\mu\text{M}$ ] | Example | Data $K_i$ [ $\mu\text{M}$ ] |
|---------|---------------------------------|---------|------------------------------|
| 17      | 0.0909                          | 88      | 0.0247                       |
| 19      | 0.0807                          | 89      | 0.0269                       |
| 23      | 0.091                           | 90      | 0.0086                       |
| 26      | 0.0825                          | 91      | 0.0572                       |
| 27      | 0.078                           | 92      | 0.0466                       |
| 29      | 0.0699                          | 95      | 0.0243                       |
| 30      | 0.0284                          | 98      | 0.0527                       |
| 31      | 0.0083                          | 99      | 0.0366                       |
| 32      | 0.0333                          | 102     | 0.0708                       |
| 33      | 0.0336                          | 105     | 0.0622                       |
| 34      | 0.0322                          | 107     | 0.0812                       |
| 36      | 0.0526                          | 110     | 0.0267                       |
| 37      | 0.0762                          | 113     | 0.0457                       |
| 43      | 0.0849                          | 114     | 0.0402                       |
| 47      | 0.0691                          | 115     | 0.013                        |
| 51      | 0.0173                          | 116     | 0.0169                       |
| 52      | 0.0713                          | 117     | 0.0193                       |
| 56      | 0.022                           | 118     | 0.0112                       |
| 57      | 0.0748                          | 124     | 0.0964                       |
| 59      | 0.0154                          | 125     | 0.0768                       |
| 60      | 0.0036                          | 126     | 0.0805                       |
| 62      | 0.011                           | 127     | 0.0997                       |
| 63      | 0.0086                          | 128     | 0.072                        |
| 64      | 0.0028                          | 129     | 0.0171                       |
| 65      | 0.0041                          | 130     | 0.0254                       |
| 66      | 0.003                           | 131     | 0.0334                       |
| 67      | 0.0062                          | 132     | 0.0263                       |

|    |        |     |        |
|----|--------|-----|--------|
| 68 | 0.0059 | 133 | 0.0232 |
| 69 | 0.0047 | 134 | 0.0432 |
| 70 | 0.0105 | 135 | 0.0437 |
| 71 | 0.0134 | 136 | 0.0189 |
| 72 | 0.0027 | 137 | 0.0087 |
| 73 | 0.0019 | 138 | 0.0088 |
| 74 | 0.0054 | 139 | 0.0249 |
| 75 | 0.0046 | 140 | 0.0479 |
| 76 | 0.0018 | 141 | 0.0597 |
| 77 | 0.0268 | 142 | 0.0197 |
| 78 | 0.0048 | 143 | 0.012  |
| 79 | 0.0019 | 144 | 0.0059 |
| 80 | 0.0208 | 145 | 0.0137 |
| 81 | 0.0146 | 146 | 0.0149 |
| 82 | 0.0397 | 147 | 0.0138 |
| 83 | 0.006  | 148 | 0.0251 |
| 84 | 0.0155 | 149 | 0.0031 |
| 86 | 0.0976 |     |        |
| 87 | 0.0512 |     |        |

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

5        Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

10        Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

#### Example A

Tablets of the following composition are manufactured in the usual manner:

|                            | <u>mg / tablet</u> |
|----------------------------|--------------------|
| Active substance           | 5                  |
| 20    Lactose              | 45                 |
| Corn starch                | 15                 |
| Microcrystalline cellulose | 34                 |
| Magnesium stearate         | 1                  |
| Tablet weight              | 100                |

#### Example B

Capsules of the following composition are manufactured:

|                     | <u>mg / capsule</u> |
|---------------------|---------------------|
| Active substance    | 10                  |
| 30    Lactose       | 155                 |
| Corn starch         | 30                  |
| Talc                | 5                   |
| Capsule fill weight | 200                 |

The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelantine capsules.

5

Example C

Suppositories of the following composition are manufactured:

|                  | <u>mg / supp.</u> |
|------------------|-------------------|
| Active substance | 15                |
| Suppository mass | 1285              |
| 10               | Total 1300        |

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45 °C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

15

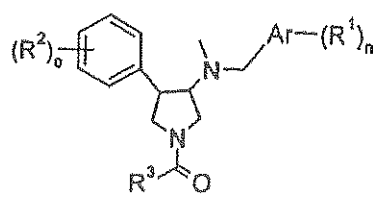
20

25

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Claims

1. A compound of general formula I



wherein

Ar is aryl selected from the group consisting of phenyl, benzyl, naphthyl or indanyl;

R¹ is hydrogen, halogen, C<sub>1-8</sub>-alkyl, C<sub>1-8</sub>-alkoxy, C<sub>1-8</sub>-alkyl substituted by halogen, C<sub>1-8</sub>-alkoxy substituted by halogen, cyano, amino, mono or di-C<sub>1-8</sub>-alkyl amino, C(O)-C<sub>1-8</sub>-alkyl, or is aryl as defined for Ar, or is heteroaryl selected from the group consisting of quinoxaliny, dihydroisoquinoliny, pyrazin-2-yl, pyrazol-1-yl, 2,4-dihydro-pyrazol-3-one, pyridiny, isoxazolyl, benzo[1,3]dioxol, pyridyl, pyrimidin-4-yl, pyrimidin-5-yl, benzotriazol-5-yl, benzoimidazol-5-yl, [1,3,4]-oxadiazol-2-yl, [1,2,4]triazol-1-yl, [1,6]naphthyridin-2-yl, imidazo[4,5-b]pyridine-6-yl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, furyl, imidazol-1-yl, or benzofuranyl;

R² is hydrogen or halogen;

R³ is -(CH<sub>2</sub>)<sub>p</sub>-heterocyclyl, selected from the group consisting of morpholiny, [1,4]diazepam-1-yl, piperaziny, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl or 1,1-dioxo-λ<sup>6</sup>-thiomorpholiny, optionally substituted by one or two substituents R<sup>4</sup>; or is  
 C<sub>1-8</sub>-alkyl,  
 C<sub>1-8</sub>-alkoxy,  
 -(CH<sub>2</sub>)<sub>p</sub>-O-C<sub>1-8</sub>-alkyl,  
 -(CH<sub>2</sub>)<sub>p</sub>-CN,  
 -O-(CH<sub>2</sub>)<sub>p</sub>-CN,

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$-(CH_2)_p$ -heteroaryl as defined for  $R^1$ ,  
 $-(CH_2)_p$ -C(O)-heteroaryl as defined for  $R^1$ ,  
 $-O-(CH_2)_p$ -heterocyclyl as defined above,  
 $-(CH_2)_p$ -aryl as defined for Ar, optionally substituted by  $C_{1-8}$ -alkoxy or halogen,  
 $-(CH_2)_p$ -O-aryl as defined for Ar, optionally substituted by  $C_{1-8}$ -alkyl,  
 $-(CH_2)_p$ -NR'-heterocyclyl as defined above, optionally substituted by  $C_{1-8}$ -alkyl,  
 $-(CH_2)_p$ -NR'R'',  
 $-(CH_2)_p$ -NR'- $-(CH_2)_p$ -NR'R'',  
 $-(CH_2)_p$ -NR'- $-(CH_2)_p$ -CN,  
 $-(CH_2)_p$ -C(O)-NR'R'' or is  
 $-O-(CH_2)_p$ -NR'R'';

$R^4$  is hydroxy,  $C_{1-8}$ -alkyl,  $-(CH_2)_p$ -OH,  $-(CH_2)_p$ -NR'R'', -NR'-C(O)- $C_{1-8}$ -alkyl,  $-(CH_2)_p$ -CN, -S(O)<sub>2</sub>- $C_{1-8}$ -alkyl, -NR'-S(O)<sub>2</sub>- $C_{1-8}$ -alkyl, -S(O)<sub>2</sub>-NR'R'', -C(O)- $C_{1-8}$ -alkyl, -C(O)- $C_{3-7}$ -cycloalkyl, wherein the cycloalkyl may be substituted by  $C_{1-8}$ -alkyl, or is  
 $-C(O)$ -NR'R'', heterocyclyl as defined for  $R^3$ , optionally substituted by =O, or is heteroaryl as defined for  $R^1$ , optionally substituted by  $C_{1-8}$ -alkoxy or cyano, or is aryl as defined for Ar, optionally substituted by  $C_{1-8}$ -alkoxy, cyano or is 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl;

$R'$  and  $R''$  are independently from each other hydrogen,  $C_{1-8}$ -alkyl or  $-(CH_2)_p$ -OH,

$n$  is 1 or 2; in case  $n$  is 1 or 2,  $R^1$  may be the same or different;

$o$  is 1 or 2; in case  $o$  is 1 or 2,  $R^2$  may be the same or different;

$p, p'$  are the same or different and are 0, 1, 2, 3 or 4;

or to a pharmaceutically active salt thereof.

or a pharmaceutically active salt, a racemic mixture, an enantiomer, an optical isomer or a tautomeric form thereof.

2. A compound of formula I according to claim 1, wherein Ar is phenyl.
3. A compound of formula I according to claim 2, wherein R<sup>3</sup> is unsubstituted  $-(CH_2)_p$ -heterocyclyl selected from the group consisting of morpholinyl, [1,4]diazepam-1-yl, piperazinyl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl or 1,1-dioxo- $\lambda^6$ -thiomorpholinyl.
4. A compound of formula I according to claim 3, wherein the compounds are
  - 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-morpholin-4-yl-pentan-1-one
  - 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl)-5-morpholin-4-yl-pentan-1-one
  - 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-piperazin-1-yl-pentan-1-one
  - 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-pentan-1-one
  - 1-((3SR,4RS)-3-(3-chloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-morpholin-4-yl-pentan-1-one
  - 1-((3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-3-morpholin-4-yl-propan-1-one
  - 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-morpholin-4-yl-ethanone
  - 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-piperazin-1-yl-ethanone or
  - 1-((3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(1,1-dioxo- $\lambda^6$ -thiomorpholin-4-yl)-ethanone.
5. A compound of formula I according to claim 2, wherein R<sup>3</sup> is  $-(CH_2)_p$ -heterocyclyl selected from the group consisting of morpholinyl, [1,4]diazepam-1-yl, piperazinyl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl or 1,1-dioxo- $\lambda^6$ -thiomorpholinyl, substituted by one or two substituents R<sup>4</sup>.
6. A compound of formula I according to claim 5, wherein R<sup>4</sup> is  $-S(O)_2-C_{1-8}$ -alkyl.
7. A compound of formula I according to claim 6, wherein the compounds are

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{(3RS,4SR)-3-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-4-phenyl-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 {(3SR,4RS)-3-(4-chloro-phenyl)-4-[(3,4-dichloro-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 [(3RS,4SR)-3-(biphenyl-4-ylmethyl-methyl-amino)-4-(4-chloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 [(3RS,4SR)-3-[(4-chloro-3-fluoro-benzyl)-methyl-amino]-4-(4-chloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 {(3SR,4RS)-3-(4-chloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 [(3RS,4SR)-3-[(3,4-dichloro-benzyl)-methyl-amino]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 [(3RS,4SR)-3-[(4-chloro-benzyl)-methyl-amino]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 4-({[(3RS,4SR)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-amino}-methyl)-benzonitrile  
 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3,4-difluoro-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(2,3-dihydro-benzofuran-6-ylmethyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(4-fluoro-3-methyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(1H-indol-6-ylmethyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone  
 4-({[(3RS,4SR)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-methyl-amino}-methyl)-2-fluoro-benzonitrile  
 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-((S)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone  
 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-((R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone  
 {(3SR,4RS)-3-(4-chloro-3-fluoro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

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{(3SR,4RS)-3-(4-chloro-3-fluoro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-[1,4]diazepan-1-yl)-methanone  
 {(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[methyl-(4-trifluoromethyl-benzyl)-amino]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone or  
 1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(4-methanesulfonyl-piperazin-1-yl)-ethanone.

8. A compound of formula I according to claim 5, wherein  $R^4$  is  $C_{1-8}$ -alkyl.

9. A compound of formula I according to claim 8, wherein the compounds are

1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-(4-methyl-piperazin-1-yl)-pentan-1-one  
 1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(4-methyl-piperazin-1-yl)-ethanone  
 1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(3,5-dimethyl-piperazin-1-yl)-ethanone  
 1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-((S)-3-methyl-piperazin-1-yl)-ethanone  
 1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-((R)-3-methyl-piperazin-1-yl)-ethanone or  
 1-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-(2,6-dimethyl-morpholin-4-yl)-ethanone.

10. A compound of formula I according to claim 5, wherein  $R^4$  is  $-S(O)_2-NR'R''$ .

11. A compound of formula I according to claim 10, wherein the compounds are:

4-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazine-1-sulfonic acid dimethylamide  
 4-(2-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-2-oxo-ethyl)-piperazine-1-sulfonic acid dimethylamide or  
 4-(5-{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-5-oxo-pentyl)-piperazine-1-sulfonic acid dimethylamide.

12. A compound of formula I according to claim 5, wherein  $R^4$  is  $-NR'-S(O)_2-C_{1-8}$ -alkyl.

13. A compound of formula I according to claim 12, wherein the compounds are  
 N-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-methanesulfonamide or  
 N-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-methanesulfonamide.
14. A compound of formula I according to claim 5, wherein  $R^4$  is  $-C(O)-C_{1-8}$ -alkyl.
15. A compound of formula I according to claim 14, wherein the compounds are  
 1-(4-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl)-piperazin-1-yl)-ethanone or  
 2-(4-ccetyl-piperazin-1-yl)-1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-ethanone.
16. A compound of formula I according to claim 5, wherein  $R^4$  is  $-NR'-C(O)-C_{1-8}$ -alkyl.
17. A compound of formula I according to claim 16, wherein the compounds are:  
 N-[1-(5-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-oxo-pentyl)-piperidin-4-yl]-acetamide  
 N-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-acetamide  
 N-[(S)-1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-pyrrolidin-3-yl]-acetamide  
 N-[(R)-1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-pyrrolidin-3-yl]-acetamide or  
 N-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-acetamide.
18. A compound of formula I according to claim 5, wherein  $R^4$  is  $-(CH_2)_p-NR'R''$ .
19. A compound of formula I according to claim 18, wherein the compounds are  
 ((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-((R)-3-dimethylamino-pyrrolidin-1-yl)-methanone

1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-ethanone  
 ((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-[4-(3-dimethylamino-propyl)-piperazin-1-yl]-methanone  
 ((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone or  
 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(4-dimethylamino-piperidin-1-yl)-ethanone.

20. A compound of formula I according to claim 5, wherein R<sup>4</sup> is heteroaryl selected from the group consisting of quinoxaliny, dihydroisoquinoliny, pyrazin-2-yl, pyrazol-1-yl, 2,4-dihydro-pyrazol-3-one, pyridiny, isoxazolyl, benzo[1,3]dioxol, pyridyl, pyrimidin-4-yl, pyrimidin-5-yl, benzotriazol-5-yl, benzoimidazol-5-yl, [1,3,4]-oxadiazol-2-yl, [1,2,4]triazol-1-yl, [1,6]naphthyridin-2-yl, imidazo[4,5-b]pyridine-6-yl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, furyl, imidazol-1-yl, or benzofuranyl, optionally substituted by C<sub>1-8</sub>-alkoxy or cyano.

21. A compound of formula I according to claim 20, wherein the compounds are  
 ((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-(4-pyrimidin-2-yl-piperazin-1-yl)-methanone  
 ((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-(4-pyridin-2-yl-piperazin-1-yl)-methanone  
 ((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-(4-pyridin-4-yl-piperazin-1-yl)-methanone  
 ((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone  
 2-(4-((3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl)-piperazin-1-yl)-nicotinonitrile  
 6-(4-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl)-piperazin-1-yl)-nicotinonitrile or  
 ((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-[4-(6-methoxy-pyridin-2-yl)-piperazin-1-yl]-methanone.

22. A compound of formula I according to claim 5, wherein R<sup>4</sup> is aryl, optionally substituted by C<sub>1-8</sub>-alkoxy or cyano.

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23. A compound of formula I according to claim 22, wherein the compounds are  
{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone  
2-(4-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-benzonitrile or  
4-(4-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-benzonitrile.
24. A compound of formula I according to claim 5, wherein  $R^4$  is  $-(CH_2)_pOH$ .
25. A compound of formula I according to claim 24, wherein the compounds are  
{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(3-hydroxy-propyl)-piperazin-1-yl]-methanone  
{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone  
1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-[4-(3-hydroxy-propyl)-piperazin-1-yl]-ethanone  
1-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl]-2-(4-hydroxy-piperidin-1-yl)-ethanone or  
{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl}-(4-hydroxy-3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-methanone.
26. A compound of formula I according to claim 5, wherein  $R^4$  is  $-C(O)-NR'R''$ .
27. A compound of formula I according to claim 26, wherein the compound is  
4-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl]-piperazine-1-carboxylic acid diethylamide.
28. A compound of formula I according to claim 5, wherein  $R^4$  is  $-(CH_2)_pCN$ .
29. A compound of formula I according to claim 28, wherein the compounds are  
3-(4-[(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidine-1-carbonyl}-piperazin-1-yl)-propionitrile

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3-[4-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperazin-1-yl]-propionitrile or  
1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidine-4-carbonitrile.

30. A compound of formula I according to claim 5, wherein  $R^4$  is heterocyclyl, selected from the group consisting of morpholinyl, [1,4]diazepam-1-yl, piperazinyl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl or 1,1-dioxo- $\lambda^6$ -thiomorpholinyl, optionally substituted by =O.

31. A compound of formula I according to claim 30, wherein the compounds are  
4-[1-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-piperidin-4-yl]-morpholin-3-one  
1'-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-[1,4']bipiperidinyl-2-one.

32. A compound of formula I according to claim 5, wherein  $R^4$  is 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl.

33. A compound of formula I according to claim 32, wherein the compound is  
1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(1S,4R)-2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl-ethanone.

34. A compound of formula I according to claim 5, wherein  $R^4$  is  $-C(O)-C_{3-7}$ -cycloalkyl, substituted by  $C_{1-8}$ -alkyl.

35. A compound of formula I according to claim 34, wherein the compound is  
(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone.

36. A compound of formula I according to claim 2, wherein  $R^3$  is  $-(CH_2)_pNR'R''$ .

37. A compound of formula I according to claim 36, wherein the compounds are  
1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-methylamino-pentan-1-one or

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1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-5-dimethylamino-pentan-1-one.

38. A compound of formula I according to claim 2, wherein  $R^3$  is  $-(CH_2)_p$ -heteroaryl, selected from the group consisting of quinoxaliny, dihydroisoquinoliny, pyrazin-2-yl, pyrazol-1-yl, 2,4-dihydro-pyrazol-3-one, pyridiny, isoxazolyl, benzo[1,3]dioxol, pyridyl, pyrimidin-4-yl, pyrimidin-5-yl, benzotriazol-5-yl, benzoimidazol-5-yl, [1,3,4]-oxadiazol-2-yl, [1,2,4]triazol-1-yl, [1,6]naphthyridin-2-yl, imidazo[4,5-b]pyridine-6-yl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, furyl, imidazol-1-yl, or benzofuranyl.

39. A compound of formula I according to claim 38, wherein the compound is 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-5-imidazol-1-yl-pentan-1-one.

40. A compound of formula I according to claim 2, wherein  $R^3$  is  $-(CH_2)_p-C(O)$ -heteroaryl selected from the group consisting of quinoxaliny, dihydroisoquinoliny, pyrazin-2-yl, pyrazol-1-yl, 2,4-dihydro-pyrazol-3-one, pyridiny, isoxazolyl, benzo[1,3]dioxol, pyridyl, pyrimidin-4-yl, pyrimidin-5-yl, benzotriazol-5-yl, benzoimidazol-5-yl, [1,3,4]-oxadiazol-2-yl, [1,2,4]triazol-1-yl, [1,6]naphthyridin-2-yl, imidazo[4,5-b]pyridine-6-yl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, furyl, imidazol-1-yl, or benzofuranyl.

41. A compound of formula I according to claim 40, wherein the compound is 1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-6-pyridin-2-yl-hexane-1,6-dione.

42. A compound of formula I according to claim 2, wherein  $R^3$  is  $-(CH_2)_p-C(O)-NR'R''$ .

43. A compound of formula I according to claim 42, wherein the compound is 6-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-((3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino)-pyrrolidin-1-yl)-6-oxo-hexanoic acid amide.

44. A compound of formula I according to claim 2, wherein  $R^3$  is  $-(CH_2)_p-O-C_{1-8}$ -alkyl.

45. A compound of formula I according to claim 44, wherein the compound is

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1-((3S,4R)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-5-methoxy-pentan-1-one.

46. A compound of formula I according to claim 2, wherein  $R^3$  is  $-(CH_2)_p-CN$ .

47. A compound of formula I according to claim 46, wherein the compound is 6-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-6-oxo-hexanenitrile.

48. A compound of formula I according to claim 2, wherein  $R^3$  is  $-(CH_2)_p-NR'-(CH_2)_p-NR'R''$ .

49. A compound of formula I according to claim 48, wherein the compounds are  
1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(2-dimethylamino-ethylamino)-ethanone  
1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-(3-dimethylamino-propylamino)-ethanone  
1-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-[(3-dimethylamino-propyl)-methyl-amino]-ethanone.

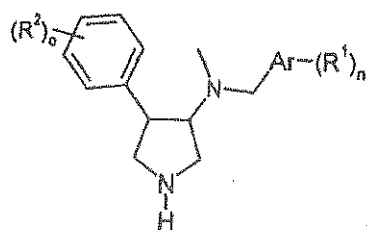
50. A compound of formula I according to claim 2, wherein  $R^3$  is  $-(CH_2)_p-NR'-(CH_2)_p-CN$ .

51. A compound of formula I according to claim 50, wherein the compounds are  
3-(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethylamino)-propionitrile or  
3-[(2-((3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(3-fluoro-4-trifluoromethyl-benzyl)-methyl-amino]-pyrrolidin-1-yl)-2-oxo-ethyl)-methyl-amino]-propionitrile.

52. A process for preparing a compound of formula I as defined in claim 1, which process comprises

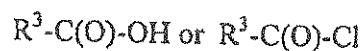
a) coupling a compound of formula

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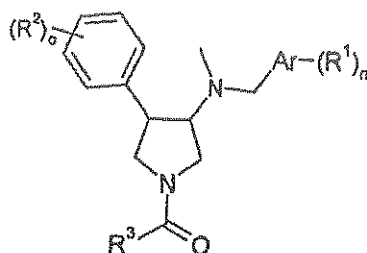


VIII

with a suitable acid chloride or carboxylic acid of formula

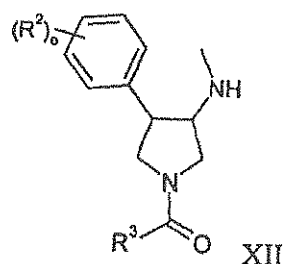


to a compound of formula



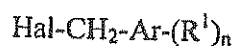
I

wherein the groups Ar, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> and the definitions o and n are described in claim 1, or  
b) alkylating a compound of formula

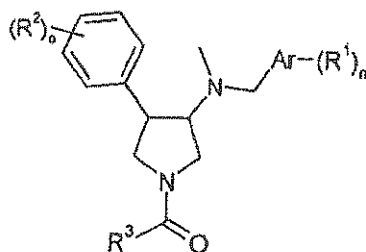


XII

with a compound of formula



to a compound of formula



I

wherein the groups Ar, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> and the definitions o and n are described in claim 1, and,  
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

53. A medicament containing one or more compounds as claimed in any one of claims 1-51 and pharmaceutically acceptable excipients.

54. A medicament according to claim 53 for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, anxiety and attention deficit hyperactivity disorder (ADHD).

55. The use of a compound as claimed in any one of claims 1-51 for the manufacture of medicaments for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, anxiety and attention deficit hyperactivity disorder (ADHD).

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