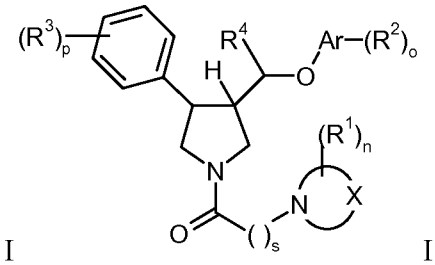
PYRROLIDINE ARYL-ETHER AS NK3 RECEPTOR ANTAGONISTS

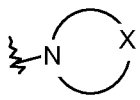
The invention relates to a compound of general formula



I I

wherein

Ar is aryl or a five or six membered heteroaryl;



is a six to nine membered mono or bi-heterocyclic group, wherein X may be a carbon atom, SO_2 or a further hetero atom, selected from the group consisting of N or O;

if X is a carbon atom, O, SO_2 or unsubstituted N, then

R^1 is hydrogen, hydroxy, cyano, -$(CH_2)_q$-OH, -$(CH_2)_q$-NRR', -(CH_2)q-CN, lower alkyl, -$S(O)_2$-lower alkyl, -NR-$S(O)_2$-lower alkyl, -C(O)-lower alkyl, -NR-C(O)-lower alkyl, phenyl, or is a heterocyclic group selected from piperidinyl-2-one;

if X is a N-atom, substituted by R^1, then

R^1 is hydrogen, -$(CH_2)_q$-OH, -$(CH_2)_q$-NRR', -(CH_2)q-CN, lower alkyl, -$S(O)_2$-lower alkyl, aryl or a five or six membered heteroaryl or -C(O)-lower alkyl, provided that q is 2 or 3.

R/R' are independently from each other hydrogen or lower alkyl;

R^2 is hydrogen, halogen, lower alkyl, cyano, lower alkoxy substituted by halogen, lower alkyl substituted by halogen or is a five or six membered heteroaryl;

R^3 is hydrogen or halogen;

R^4 is hydrogen or lower alkyl;

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

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

p is 1 or 2; in case p is 2, R^3 may be the same or different;

q is 1, 2 or 3;

s is 0, 1, 2, 3 or 4;

or to a pharmaceutically active salt 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_2. 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 Recources, 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 Recources, Inc., Waltham, Massachusetts)*.

Objects of the present invention are novel compounds of formula I, their manufacture, medicaments based on a compound in accordance with the invention 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 invention are depression, 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 $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CF_2CF_3$ and the like. Preferred lower alkyl substituted by halogen groups are groups having 1-4 carbon atoms.

The term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above and which is attached via an oxygen atom, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, i-butoxy, 2-butoxy, t-butoxy and the like. Preferred alkoxy groups are groups with 1-4 carbon atoms.

The term "lower alkoxy substituted by halogen" denotes a group wherein the alkyl residue is as defined above "lower alkyl substituted by halogen" and which is attached via an oxygen atom. Preferred lower alkoxy substituted by halogen groups are groups having 1-4 carbon atoms.

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

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.

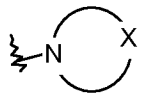
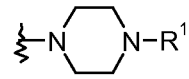
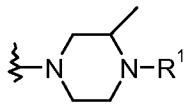
The term "five or six membered heteroaryl" denotes a cyclic aromatic hydrocarbon radical, which contains at least one heteroatom, selected from N, O or S, for example quinoxalinyl, pyrazinyl, pyrazolyl, pyridinyl, pyridyl, pyrimidinyl, oxadiazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, thiophenyl, isoxazolyl, pyrrolyl, furanyl or imidazolyl. Preferred heteroaryl groups are pyridyl, pirimidinyl or imidazolyl.

The term "six membered heterocyclic group, wherein X may be a carbon atom or a further hetero atom, selected from the group consisting of N, O or S" denotes the following groups: piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, 2-oxa-6-aza-spiro[3.3]hept-6-yl, 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl or hexahydro-pyrrolo[1.2-a]pyrazin-6-one.

The term "pharmaceutically acceptable acid addition salt" 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.

The following groups of compounds of formula I are preferred:

- A compound of formula I, wherein $(R^3)_p$ is 3,4-di-chloro.

- A compound of formula I, wherein  is  or  and Ar is phenyl, for example the following compounds

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

2-(4-acetyl-piperazin-1-yl)-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone

(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-((R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone

[(3SR,4RS)-3-[(RS)-1-(3,4-dichloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-((RS)-1-p-tolyloxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

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

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-fluoro-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

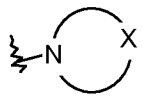
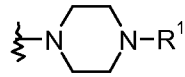
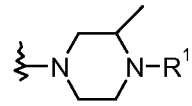
[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

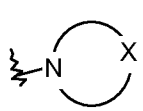
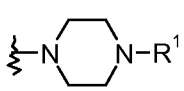
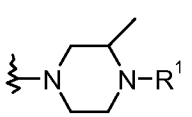
[(3SR,4RS)-3-[(RS)-1-(3-chloro-4-fluoro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

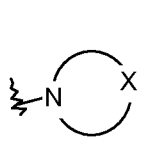
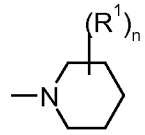
4-{(SR)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-ethoxy}-benzonitrile

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(4-fluoro-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3SR,4RS)-3-[(SR)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone
{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone or
2-(4-acetyl-piperazin-1-yl)-1-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone.

- A compound of formula I, wherein  is  or  and Ar is pyridyl, for example
[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone
[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-((R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone
[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone
{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
[(3SR,4RS)-3-(5-chloro-pyridin-2-yloxymethyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone
{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone.

- A compound of formula I, wherein  is  or  and Ar is pyrimidinyl, for example
{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(pyrimidin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(5-fluoro-pyrimidin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone or
[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyrimidin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone.

- A compound of formula I, wherein  is  and Ar is phenyl, for example

N-(1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine-1-carbonyl}-piperidin-4-yl)-N-methyl-methanesulfonamide

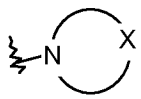
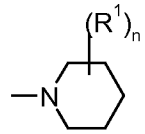
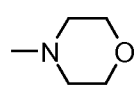
N-[1-(2-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-methanesulfonamide

N-[1-(2-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-piperidin-4-yl]-acetamide

N-(1-{2-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-4-phenyl-piperidin-4-yl)-acetamide

N-(1-{2-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-piperidin-4-yl)-N-methyl-acetamide or

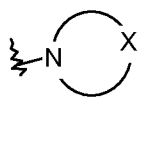
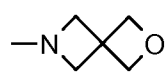
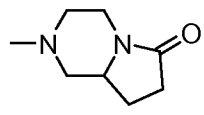
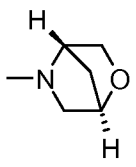
1-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-(4-hydroxymethyl-piperidin-1-yl)-ethanone.

- A compound of formula I, wherein  is  or  and Ar is pyridyl, for example

1-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-5-morpholin-4-yl-pentan-1-one

6-{(SR)-1-[(3RS,4SR)-1-[2-(4-cyano-piperidin-1-yl)-acetyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile or

6-{(SR)-1-[(3RS,4SR)-1-(4-cyano-piperidine-1-carbonyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile.

- A compound of formula I, wherein  is ,  or  and Ar is pyridyl, for example

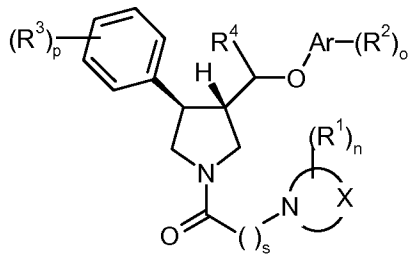
[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(2-oxa-6-aza-spiro[3.3]hept-6-yl)-methanone

2-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl]-hexahydro-pyrrolo[1,2-a]pyrazin-6-one

1-[(3S,4R)-3-[(R)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethanone or

{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-methanone.

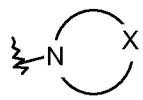
A further embodiment of the invention are compounds of formula



I-1

wherein

Ar is aryl or a five or six membered heteroaryl;



is a six or seven membered heterocyclic group, wherein X may be a carbon atom, SO_2 or a further hetero atom, selected from the group consisting of N or O;

if X is a carbon atom, O, SO_2 or unsubstituted N, then

R^1 is hydrogen, hydroxy, cyano, $-(CH_2)_q$-OH, $-(CH_2)_q$-NRR', $-(CH_2)$q-CN, lower alkyl, $-S(O)_2$-lower alkyl, -NR-$S(O)_2$-lower alkyl, -C(O)-lower alkyl, -NR-C(O)-lower alkyl, or is a heterocyclic group selected from piperidinyl-2-one;

if X is a N-atom, substituted by R^1, then

R^1 is hydrogen, $-(CH_2)_q$-OH, $-(CH_2)_q$-NRR', $-(CH_2)$q-CN, lower alkyl, $-S(O)_2$-lower alkyl, aryl or a five or six membered heteroaryl, -C(O)-lower alkyl, provided than q is 2, 3 or 4

R/R' are independently from each other hydrogen or lower alkyl;

R^2 is hydrogen, halogen, lower alkyl, cyano, lower alkoxy substituted by halogen, lower alkyl substituted by halogen or is a five or six membered heteroaryl;

R^3 is hydrogen or halogen;

R^4 is hydrogen or lower alkyl;

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

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

p is 1 or 2; in case p is 2, R^3 may be the same or different;

q is 1, 2 or 3;

s is 0, 1, 2, 3 or 4;

or to a pharmaceutically active salt thereof.

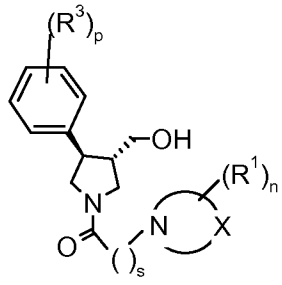
The invention includes all stereoisomeric forms, including individual diastereoisomers and enantiomers of the compound of formula (I) as well as racemic and non-racemic mixtures thereof.

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 shown in the following schemes 1 to 4. 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.

In more detail, the compounds of formula **I** can be manufactured by the methods given below, by the 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 schemes 1 - 4, 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 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 can be prepared by processes described below, which process comprises

a) reacting a compound of formula

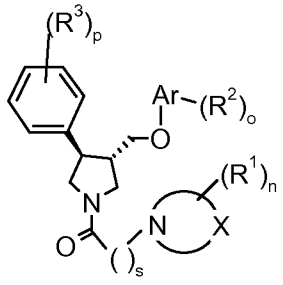


VII

with a compound of formula

$HO\text{-}Ar\text{-}(R^2)_o$

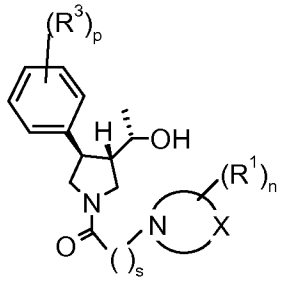
to a compound of formula



I-C

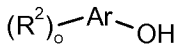
wherein the definitions have same meanings as described above, or

b) reacting a compound of formula

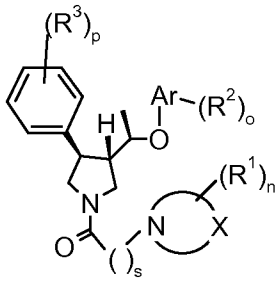


XII-B

with a compound of formula



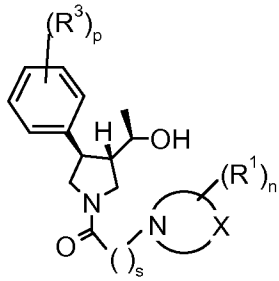
to a compound of formula



I-B,

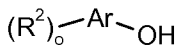
wherein the definitions are as above, or

c) reacting a compound of formula

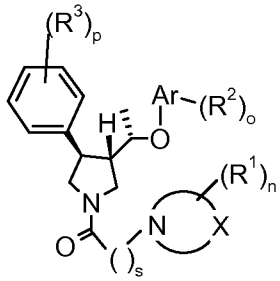


XII-A

with a compound of formula



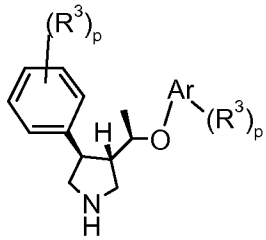
to a compound of formula



I-A,

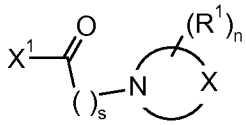
wherein the definitions are as above,

d) reacting a compound of formula

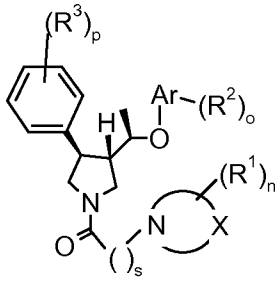


XV-B

with a compound of formula



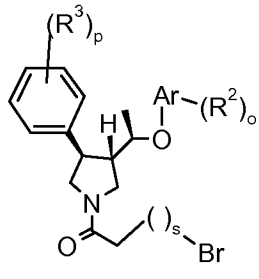
to a compound of formula



I-B

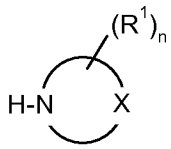
wherein X^1 is halogen, and the other definitions are as above,

e) reacting a compound of formula

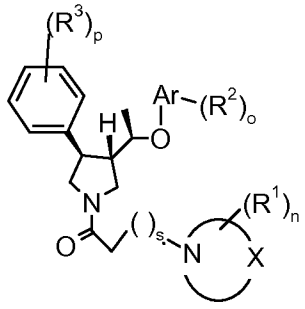


XVI-B

with a compound of formula



to a compound of formula



I-D

wherein the definitions are as above,

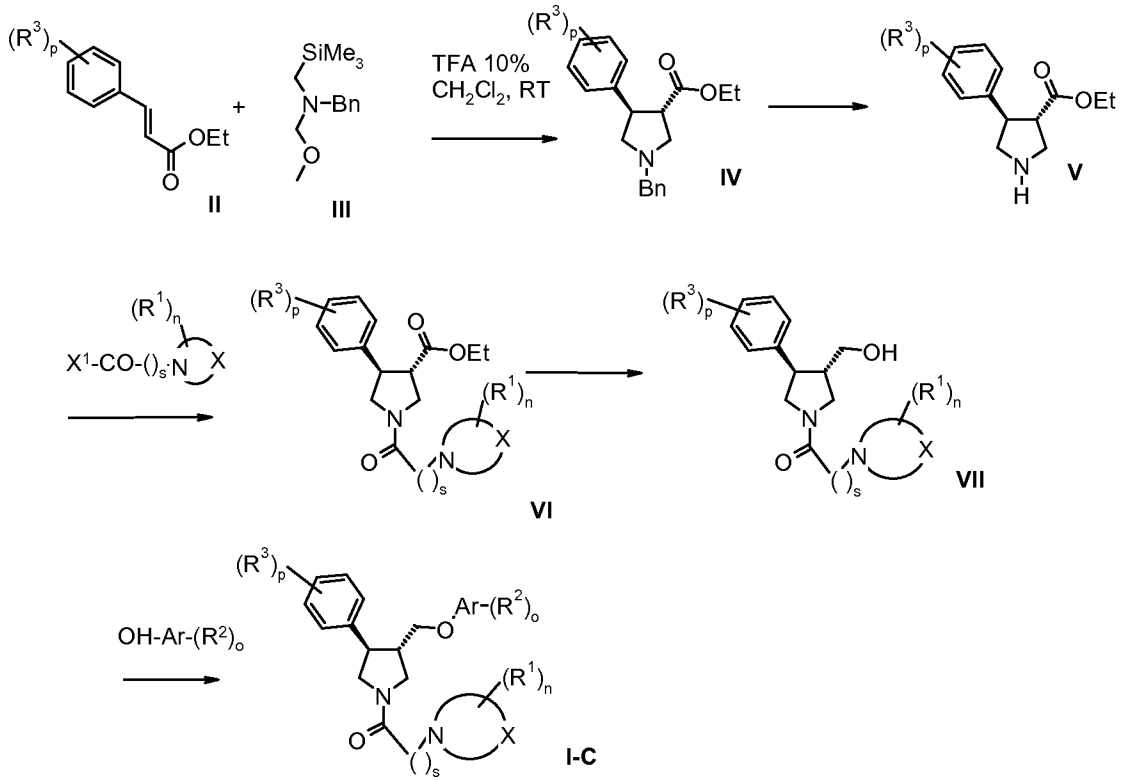
and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The process is described in more detail in schemes 1 to 4 and in examples 1 – 73.

Scheme 1

Preparation of derivatives of formula I-C wherein R^4 is hydrogen

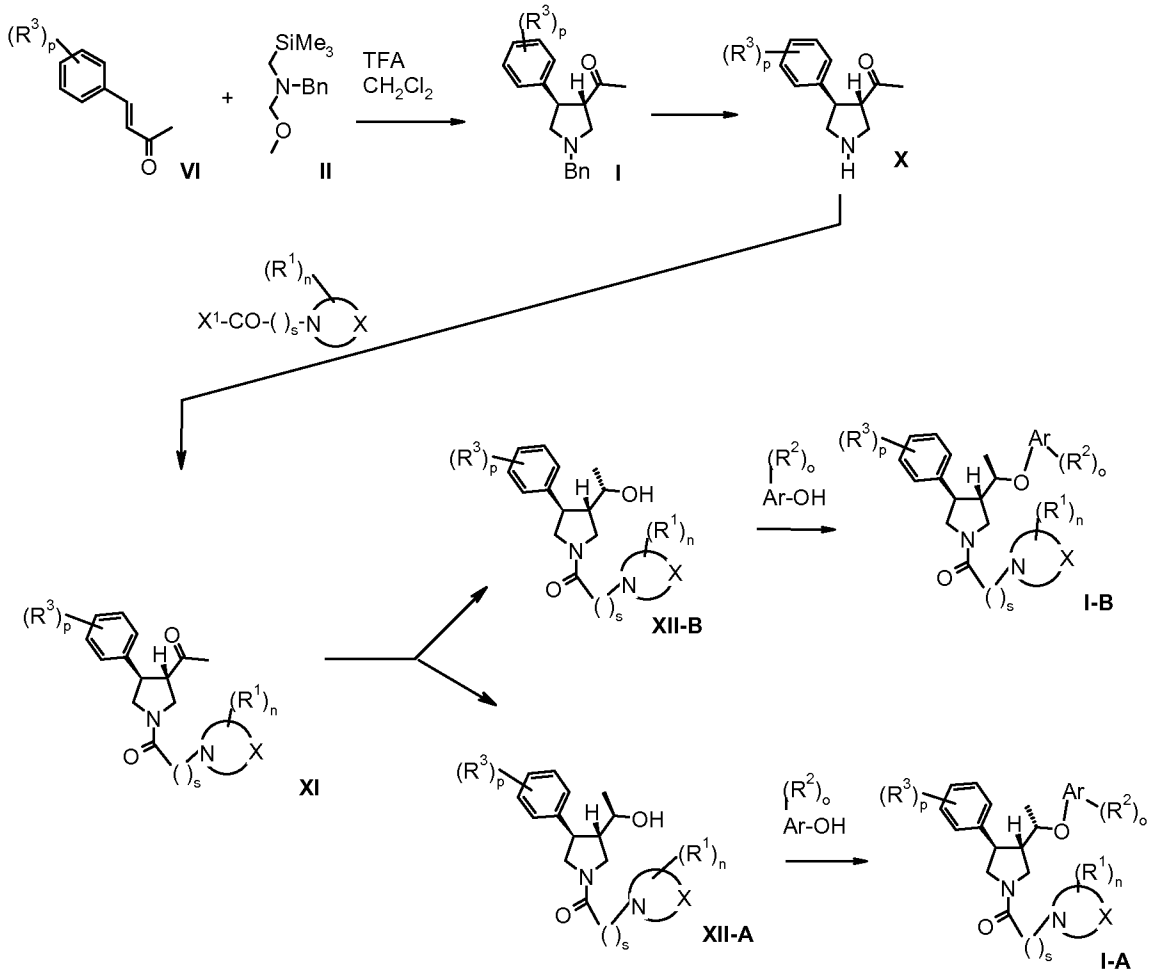


X^1 is halogen and the other definitions are as described above.

The 3,4-disubstituted pyrrolidines **IV** were prepared *via* a stereo specific 1,3-dipolar cycloaddition between the (E)-3-substituted phenyl-acrylic acid ethyl ester 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. Selective N-debenzylation was then carried out using several known procedures which are compatible with the substitution patterns of the aromatic ring to afford **V**. A coupling with a suitable acid chloride, carboxylic acid or carbamoyl chloride using known methods gave **VI**. Reduction of the ester moiety using standard conditions for example $LiBH_4$ yielded the alcohol **VII**. Standard Mitsunobu reaction with for example a phenol, pyridin-ol or pyrimidin-ol gave the aryl-ether **I-C**..

Scheme 2

Preparation of derivatives of formula I-A and I-B wherein R^4 is methyl:

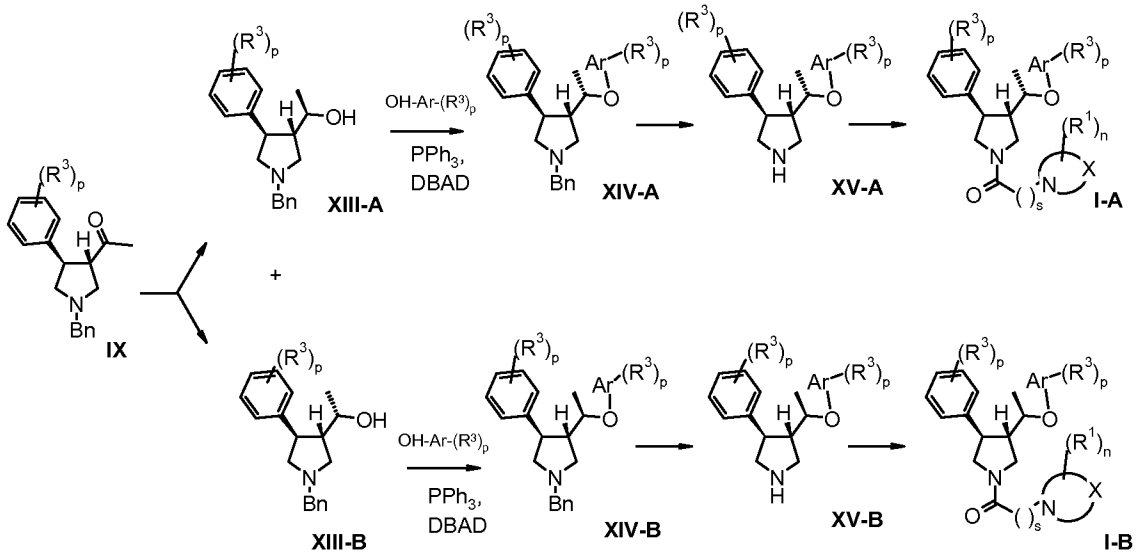


X^1 is halogen and the other definitions are as described above.

The 3,4-disubstituted pyrrolidines **IX** were prepared *via* a stereo specific 1,3-dipolar cycloaddition between substituted (E)-4-phenyl-but-3-en-2-one derivative **VIII** 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. Selective N-debenzylation was then carried out using several known procedures which are compatible with the substitution patterns of the aromatic ring to afford **X**. A coupling with a suitable acid chloride, carboxylic acid or carbamoyl chloride using known methods gave **XI**. Reduction of the acetyl moiety using standard conditions for example $LiBH_4$ yielded the two diasteroisomers **XII-A** and **XII-B** which were subsequently separated by column chromatography. Each of the diastereoisomers were then separately converted to the final derivatives **I-A** and **I-B** via a standard Mitsunobu reaction with for example a phenol, pyridin-ol or pyrimidin-ol.

Scheme 3

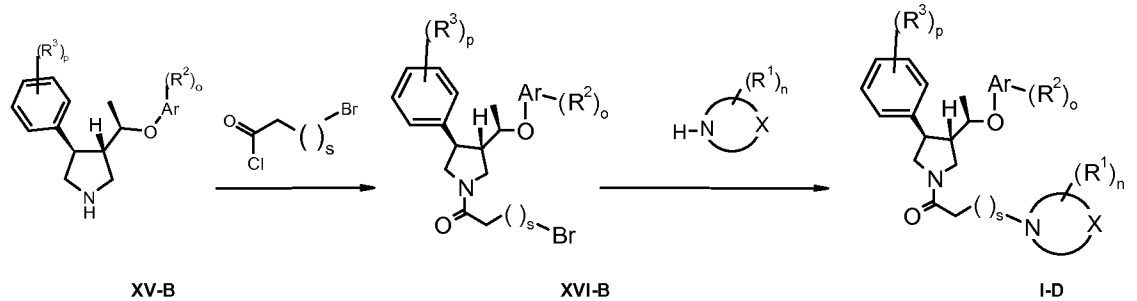
Preparation of derivatives of formula I-A and I-B wherein R^4 is methyl:



Alternatively, reduction of the acetyl moiety of **IX** was achieved with for instance $LiAlH_4$, and produced the two diastereoisomeres **XIII-A** and **XIII-B** which were separated by column chromatography. Both underwent a standard Mitsunobu reaction with for example a phenol, pyridin-ol or pyrimidin-ol to give the aryl-ether derivatives **XIV-A** and **XIV-B**. Selective N-debenzylation using several known procedures which are compatible with the substitution patterns of the aromatic rings to afforded respectively **XV-A** and **XV-B**. Coupling with a suitable acid chloride, carboxylic acide or carbamoyl chloride using known methods yielded respectively **I-A** and **I-B**.

Scheme 4

Preparation of derivatives of formula I-D, wherein R^4 is methyl



Alternatively, derivatives **XV-B** could react with bromo-acetyl chloride to yield **XVI-B**. Nucleophilic substitution reaction with primary or secondary amines gave derivatives of general formula **I-D**.

Abbreviations:

CH_2Cl_2 = dichloromethane;
DMAP = dimethylaminopyridine;
HOBt = 1-hydroxy-benzotriazol hydrat;
EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
Et_3N = triethylamine;
EtOAc = ethyl acetate;
H = hexane;
RT = room temperature;
PPh_3 = triphenylphosphine;
DBAD = di-tert-butyl azodicarboxylate

General procedure I

Amid coupling (pyrrolidine V, X or XV and carboxylic acid)

To a stirred solution of a carboxylic acid derivative (commercially available or known in the literature) (1 mmol) in 10 mL of CH_2Cl_2 was added (1.3 mmol) of EDC, (1.3 mmol) of HOBt and Et_3N (1.3 mmol). After one hour at RT, was added a pyrrolidine intermediate of general formula (**XII**). The mixture was stirred at RT over night and then poured onto water and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuo. Flash chromatography or preparative HPLC afforded the title compound.

General procedure II

Coupling between a compound of formula V, X or XV and an acid chloride or carbamoyl chloride

A solution of the pyrrolidine (1 mmol) of formula (**V, X, XV**) in CH_2Cl_2 (10 mL) was treated with Et_3N (1.2 mmol) and an acid chloride or carbamoyl chloride (1.2 mmol) and stirred at RT overnight. The reaction mixture was then poured onto water and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuo. Purification by preparative HPLC yielded the title compound.

General procedure III

Mitsunobu reaction

PPh_3 bound on resin (2.2 mmol) was put in suspension in THF (50 mL). Then the DBAD (1.6 mmol) and the phenol, pyridin-ol or pyrimidin-ol (1.5 mmol) were added. After 5

min at RT, the alcohol of formula **VII**, **XII** or **XIII** was added and stirring was continued at RT overnight. The reaction mixture was filtered on celite and then concentrated under vacuo. The crude was dissolved in EtOAc, washed with aq. NaOH (1M) and the organic phase was dried over Na_2SO_4. Column chromatography or preparative HPLC yielded the title compound.

General procedure IV

Nucleophilic substitution reaction: Coupling of XVI-B and an primary or secondary amine (NR^4R^5)

To a stirred solution of the bromide intermediate **XVI-B** (1 mmol) in CH_2Cl_2 (20 mL) at RT were added the amine of formula NR^4R^5 (3 mmol) and Et_3N (4 mmol). Stirring was continued overnight. The reaction mixture was washed H_2O and the organic phase was dried over Na_2SO_4. Column chromatography or preparative HPLC yielded the title compound.

The salt formation is effected at room temperature in accordance with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates, methan-sulphonates, p-toluenesulphonates and the like are examples of such salts.

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.

[^{3}H]SR142801 competition binding assay

hNK3 receptor binding experiment were performed using [^{3}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 $MnCl_2$, 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 [^{3}H]SR142801 at a concentration equal to K_D 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: $y = 100/(1+(x/IC_{50})^{nH})$, where n_H = slope factor using Excel-fit 4 software (Microsoft). IC_{50} values were derived from the inhibition curve and the affinity constant (K_i) 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_D 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_i values was calculated.

Some results of preferred compounds of the hNK-3 receptor affinity are shown in the following Table 1.

Table 1

Example No.	K_i NK3 h (µM)	Example No.	K_i NK3 h (µM)
16	0.0288	52	0.0425
17	0.0468	53	0.0068
18	0.0779	54	0.002
20	0.0595	55	0.02
24	0.0589	56	0.0026
25	0.0597	57	0.0647
27	0.0096	59	0.0126
30	0.0796	61	0.039
31	0.0589	62	0.024
33	0.0756	63	0.012
34	0.0401	64	0.019
36	0.0211	65	0.02
39	0.0029	66	0.011
41	0.049	67	0.053
42	0.0699	68	0.027

45	0.0954	69	0.0056
46	0.0497	70	0.086
48	0.068	71	0.0087
51	0.0237	73	0.093

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.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

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:

	mg / tablet
Active substance	5
Lactose	45
Corn starch	15
Microcrystalline cellulose	34
Magnesium stearate	1
Tablet weight	100

Example B

Capsules of the following composition are manufactured:

	mg / capsule
Active substance	10
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 gelatine capsules.

Example C

Suppositories of the following composition are manufactured:

	mg / supp.
Active substance	15
Suppository mass	1285
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

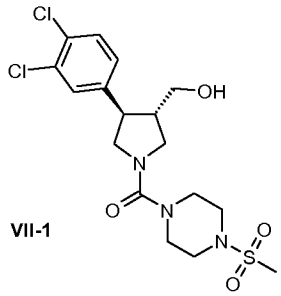
of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

Description of pyrrolidine intermediates of formula VII, XII-A, XII-B, XV-B, XVI-B

Pyrrolidine intermediates of formula VII

Pyrrolidine VII-1

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



VII-1

a) (3SR,4RS)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidine-3-carboxylic acid ethyl ester

A solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine (2.46 g, 10.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise, over a 30 minutes period, to a stirred solution of (E)-3-(3,4-dichloro-phenyl)-acrylic acid ethyl ester (2.40 g, 10.4 mmol) and trifluoroacetic acid (0.08 mL, 1 mmol) in CH_2Cl_2 (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_2, EtOAc/H 1:4) afforded 2.48 g (66%) of the title compound as a yellow oil. ES-MS m/e: 379.3 ($M+H^+$).

b) (3SR,4RS)-4-(3,4-Dichloro-phenyl)-pyrrolidine-3-carboxylic acid ethyl ester

To a solution of (3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidine-3-carboxylic acid ethyl ester 2.50 g (6.61 mmol) dissolved in CH_3CN (55 mL) was added 1.34 mL (9.91 mmol) of 2,2,2-trichloroethyl chloroformate and stirring was continued for 4 hours at RT. Volatiles were removed under vacuo, and the residue was dissolved in AcOH (25 mL) before a total of 1.20 g of Zn dust was added portion wise. After three hours at RT, the reaction mixture was filtered on celite, the solvent removed under vacuo, followed by an extraction with EtOAc/aq. $NaHCO_3$ (basic pH). The organic phases were dried on Na_2SO_4 and column chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) yielded 1.85 g (97%) of the title compound as a light yellow oil. ES-MS m/e: 288.1 ($M+H^+$).

c) (3SR,4RS)-4-(3,4-Dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidine-3-carboxylic acid ethyl ester

Using the general procedure II, the coupling between (3SR,4RS)-4-(3,4-Dichloro-phenyl)-pyrrolidine-3-carboxylic acid ethyl ester (1.89 g, 6.55 mmol) and 4-methanesulfonyl-piperazine-1-carbonyl chloride (1.63 g, 7.2 mmol) yielded the title product (2.40 g, 77%) as a colorless oil after purification by flash chromatography (SiO_2, EtOAc). ES-MS m/e: 478.1 ($M+H^+$).

4-Methanesulfonyl-piperazine-1-carbonyl chloride:

To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (1.81 g, 6.09 mmol) in CH_2Cl_2 (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_2Cl_2 (5 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Purification by flash chromatography (SiO_2, EtOAc) yielded 2.20 g (79%) of the title compound as white solid.

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

To a stirred solution of (3SR,4RS)-4-(3,4-Dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidine-3-carboxylic acid ethyl ester (2.39 g, 5.00 mmol) in MeOH (80 mL)at RT was added $LiBH_4$ (434 mg, 19.9 mmol). After 2 hours, addition of a second portion of $LiBH_4$ (1.30 g, 59.7 mmol) and stirring was continued for 2 days. The reaction mixture was poured on H_2O, extracted with EtOAc and the combined organic phases were dried over Na_2SO_4. Flash chromatography (SiO_2, EtOAc, then EtOAc/MeOH 9:1) yielded the title product 1.76 g (81%) as a white solid. ES-MS m/e: 436.1 ($M+H^+$).

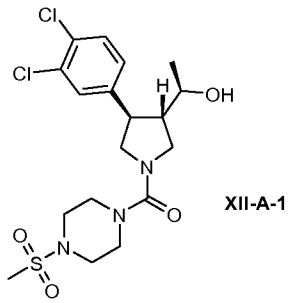
Pyrrolidine intermediates of formula XII

Pyrrolidine XII-A-1 and XII-B-1

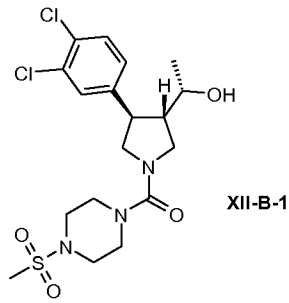
[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-A-1)

and

[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-B-1)



XII-A-1



XII-B-1

a) 1-[(3SR,4RS)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanone (IX-1)

A solution of N-(methoxymethyl)-N-(phenylmethyl)-N-(trimethylsilyl)methylamine (32.78 g, 0.138 mol) in CH_2Cl_2 (50 mL) was added drop wise, over a 30 minutes period, to a stirred solution of (E)-4-(3,4-dichloro-phenyl)-but-3-en-2-one (19.80 g, 0.092 mol) and trifluoroacetic acid (1.05 mL, 0.009 mol) in CH_2Cl_2 (100 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, CH_2Cl_2/MeOH 98:2) afforded 28.3 g (88 %) of the title compound as a yellow oil. ES-MS m/e: 348.2 ($M+H^+$).

b) 1-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethanone (X-1)

To a solution of 1-[(3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanone 4.00 g (9.20 mmol) dissolved in CH_3CN (50 mL) was added 2.48 mL (18.40 mmol) of 2,2,2-trichloroethyl chloroformate and stirring was continued for 3 hours at RT. Volatiles were removed under vacuo, and the residue was dissolved in AcOH (30 mL) before a total of 1.5 g of Zn dust was added portion wise. After three hours at RT, the reaction mixture was filtered on celite, the solvent removed under vacuo, followed by extraction with EtOAc/aq. $NaHCO_3$ (basic pH). The organic phases were dried on Na_2SO_4 and column chromatography (SiO_2, CH_2Cl_2/MeOH 9:1 to 8:2) yielded 1.50 g (63 %) of the title compound as a colorless oil. ES-MS m/e: 258.0 ($M+H^+$).

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

Using the general procedure II, the coupling between 1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanone (1.88 g, 7.28 mmol) and 4-methanesulfonyl-piperazine-1-carbonyl chloride (1.98 g, 8.74 mmol) yielded the title product (2.40 g, 74 %) as a colorless oil after purification by flash chromatography (SiO_2, EtOAc).

d) [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-A-1) and (3RS,4SR)-3-(3,4-Dichloro-

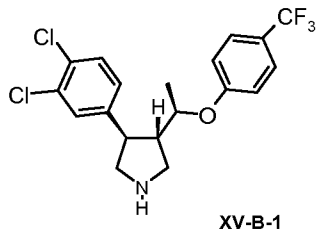
phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (XII-B-1)

To a stirred solution of 1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-ethanone (**XI-1**)(2.00 g, 4.46 mmol) in MeOH (40 mL) at -78°C was added $LiBH_4$ (0.13 g, 4.68 mmol). The temperature was slowly raised to RT (over 1 hour), and the reaction mixture was quenched by addition of H_2O. The product was extracted with EtOAc, the combined organic phases were dried over Na_2SO_4. The two diastereoisomers were separated by column chromatography (SiO_2) to yield 0.31 g (16%) of [(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**) as a white solid ES-MS m/e: 450.1 ($M+H^+$) and 1.02 g (51 %) of [(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**) as a white solid ES-MS m/e: 450.1 ($M+H^+$).

Pyrrolidine intermediates of formula XV

Pyrrolidine XV-B-1

(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine



XV-B-1

a) (RS)-1-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (XIII-A-1) and (SR)-1-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (XIII-B-1)

To a solution of 1-[(3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanone (**IX-1**) (14.90 g, 0.043 mol) in THF (300 mL) at 0°C were added portionwise $LiAlH_4$ (2.05 g, 0.051 mol). Stirring was continued for one hour, and the reaction mixture was carefully quenched by addition of aq. NH_4Cl, concentrated under vacuo and the product extracted with EtOAC. The combined organic phases were dried on Na_2SO_4 and concentrated under vacuo. The two diastereoisomeres were separated by column chromatography (SiO_2, EtOAc/H, 1:1) to yield (SR)-1-[(3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (**XIII-B-1**) 4.69 g (31%) as a white solid ES-MS m/e: 350.2 ($M+H^+$) and (RS)-1-[(3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (**XIII-A-1**) 5.30 g (35 %) as a white solid ES-MS m/e: 350.2 ($M+H^+$).

b) (3RS,4SR)-1-Benzyl-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (XIV-B-1)

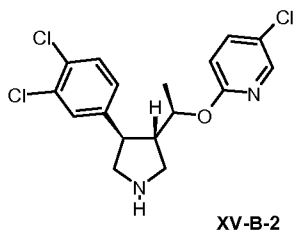
To a suspension of PPh_3 (PPh_3 polymer bound, 3 mmol PPh_3/g resin) (1.80g, 5.59 mmol) in THF (40 mL)at 0°C were added 4-trifluoromethyl-phenol(0.618 g, 3.81 mmol) and then DBAD (0.936 g, 4.07 mmol). After 5 minutes was added (SR)-1-[(3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (**XIII-B-1**) (0.89 g, 2.54 mmol). The reaction mixture was stirred over night at RT, filtered on celite and concentrated under vacuo. Extraction with EtOAc/aq.NaOH 1M, followed by column chromatography (SiO_2, EtOAc/H, 1:6) yielded 0.990 g (79 %) of the title compound as a colorless oil. ES-MS m/e: 493.0 ($M+H^+$).

c) (3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (XV-B-1)

To a solution of (3RS,4SR)-1-benzyl-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (**XIV-B-1**) 0.99 g (2.00 mmol) dissolved in CH_3CN (25 mL) was added 0.40 mL (3.00 mmol) of 2,2,2-trichloroethyl chloroformate and stirring was continued for 4 hours at RT. Volatiles were removed under vacuo, and the crude was dissolved in AcOH (20 mL) before a total of 800 mg of Zn dust was added portion wise. After three hours at RT, the reaction mixture was filtered on celite, the solvent removed under vacuo, followed by an extraction with EtOAc/aq. $NaHCO_3$ (basic pH). The organic phases were dried on Na_2SO_4 and column chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) yielded 0.54 g (67 %) of the title compound as a colorless oil. ES-MS m/e: 404.2 ($M+H^+$).

Pyrrolidine XV-B-2

5-Chloro-2-{(RS)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine



XV-B-2

a) 2-{(RS)-1-[(3SR,4RS)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-chloro-pyridine (XIV-B-2)

To a suspension of PPh_3 (PPh_3 polymer bound, 3 mmol PPh_3/g resin) (3.05 g, 9.17 mmol) in THF (50 mL)at 0 °C were added 5-chloro-pyridin-2-ol (0.81 g, 6.25 mmol) and then DBAD (1.53 g, 6.67 mmol). After 5 minutes was added (SR)-1-[(3SR,4RS)-1-

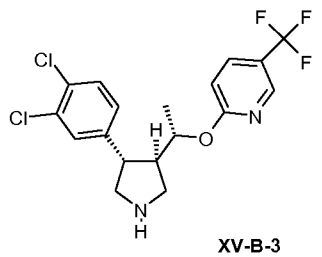
benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (**XIII-B-1**) (1.46 g, 4.17 mmol). The reaction mixture was stirred over night at RT, filtered on celite and concentrated under vacuo. Extraction with EtOAc/aq.NaOH 1M, followed by column chromatography (SiO_2, EtOAc/H, 1:6) yielded 1.57 g (82 %) of the title compound as a colorless oil. ES-MS m/e: 461.2 ($M+H^+$).

c) 5-Chloro-2-{(RS)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine (XV-B-2)

To a solution of 2-{(RS)-1-[(3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-chloro-pyridine (**XIV-B-2**) 1.57g (3.40 mmol) dissolved in CH_3CN (40 mL) was added 1.08 mL (5.10 mmol) of 2,2,2-trichloroethyl chloroformate and stirring was continued for 3 hours at RT. Volatiles were removed under vacuo, and the residue was dissolved in AcOH (30 mL) before a total of 1.20 g of Zn dust was added portion wise. After three hours at RT, the reaction mixture was filtered on celite, the solvent removed under vacuo, followed by an extraction with EtOAc/aq. $NaHCO_3$ (basic pH). The organic phases were dried on Na_2SO_4 and column chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) yielded 0.54 g (67 %) of the title compound as a colorless oil. ES-MS m/e: 356.3 ($M+H^+$).

Pyrrolidine XV-B-3

2-{(SR)-1-[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-trifluoromethyl-pyridine



XV-B-3

a) 2-{(SR)-1-[(3RS,4SR)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-trifluoromethyl-pyridine (XIV-B-3)

To a suspension of PPh_3 (PPh_3 polymer bound, 3 mmol PPh_3/g resin) (0.77 g) in THF (25 mL) at 0°C were added 5-trifluoromethyl-pyridin-2-ol (0.28 g, 1.75 mmol) and then DBAD (0.43 g). After 5 minutes was added (RS)-1-[(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (0.41 g, 1.17 mmol, described herein above). The reaction mixture was stirred over night at RT, filtered on celite and concentrated under vacuo. Extraction with EtOAc/aq.NaOH 1M, followed by column chromatography (SiO_2,

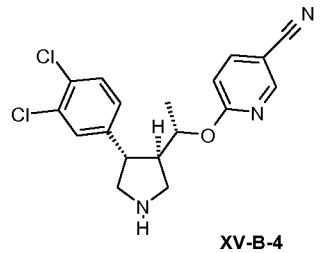
EtOAc/H, 1:4) yielded 0.45 g (78 %) of the title compound as a colorless oil. ES-MS m/e: 495.8 ($M+H^+$).

b) 2-{(SR)-1-[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-trifluoromethyl-pyridine (XV-B-3)

To a solution of 2-{(SR)-1-[(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-trifluoromethyl-pyridine 0.45 g (0.91 mmol) dissolved in toluene (5 mL) were added 0.30 mL (2.7 mmol) of 1-chloroethyl chloroformate and 0.46 mL of Hunig's base. The reaction mixture was heated at 100°C for one hour. After cooling down to RT, volatiles were removed under vacuo and the crude was dissolved in MeOH (5 mL). The reaction mixture was heated at 85°C for 30 minutes and after cooling down to RT, volatiles were removed under vacuo and the residue was directly purified on column chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) yielded 0.32g (87 %) of the title compound as a light yellow oil. ES-MS m/e: 405.9 ($M+H^+$).

Pyrrolidine XV-B-4

6-{(SR)-1-[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile



XV-B-4

a) 6-{(SR)-1-[(3RS,4SR)-1-Benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile (XVI-B-4)

To a suspension of PPh_3 (PPh_3 polymer bound, 3 mmol PPh_3/g resin) (1.97 g) in THF (300 mL)at 0°C were added 6-hydroxy-nicotinonitrile (0.61 g, 5.1 mmol) and then DBAD (1.10 g). After 5 minutes was added (RS)-1-[(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (1.20 g, 3.4 mmol, described herein above). The reaction mixture was stirred over night at RT, filtered on celite and concentrated under vacuo. Extraction with EtOAc/aq.NaOH 1M, followed by column chromatography (SiO_2, EtOAc/H, 1:4) yielded 1.02 g (66%) of the title compound as a colorless oil. ES-MS m/e: 452.0 ($M+H^+$).

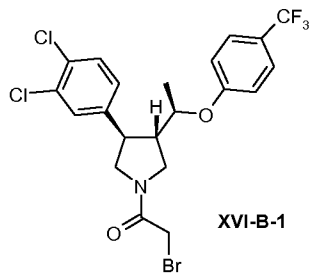
b) 6-{(SR)-1-[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile (XV-B-4)

To a solution of 6-{(SR)-1-[(3RS,4SR)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile 0.75 g (1.70 mmol) dissolved in CH_3CN (50 mL) was added 0.56 mL (4.14 mmol) of 2,2,2-trichloroethyl chloroformate and stirring was continued for 4 hours at RT. Volatiles were removed under vacuo, and the crude was dissolved in AcOH (30 mL) before a total of 0.45 g of Zn dust was added portion wise. After three hours at RT, the reaction mixture was filtered on celite, the solvent removed under vacuo, followed by an extraction with EtOAc/aq. $NaHCO_3$ (basic pH). The organic phases were dried on Na_2SO_4 and column chromatography (SiO_2, CH_2Cl_2/MeOH 9:1) yielded 0.36g (60%) of the title compound as a colorless oil. ES-MS m/e: 362.3 ($M+H^+$).

Pyrrolidine intermediates of formula XVI

Pyrrolidine XVI-B-1

2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone

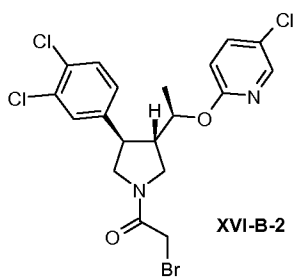


XVI-B-1

To a stirred solution of (3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (**XV-B-1**) 0.25 g (0.62 mmol) in CH_2Cl_2 (30 mL) at RT, 0.10 ml (0.74 mmol) of Et_3N and 0.062 mL (0.74 mmol) of bromo-acetyl chloride were added. Stirring was continued over night and then concentrated under vacuo. The crude residue was dissolved in EtOAc, washed with H_2O. The organic phase was dried over Na_2SO_4 and the product was purified by flash chromatography (SiO_2, EtOAc) to yield the title product 0.275 g (85%) as a colorless oil.

Pyrrolidine XVI-B-2

2-Bromo-1-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone

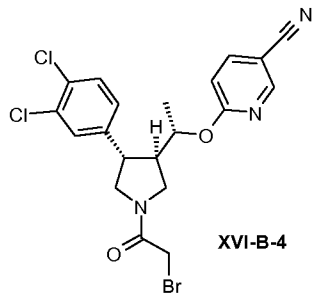


XVI-B-2

To a stirred solution of 5-chloro-2-{(RS)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine (XV-B-2) 0.12 g (0.32 mmol) in CH_2Cl_2 (10 mL) at RT, 0.055 ml (0.38 mmol) of Et_3N and 0.032 mL (0.33 mmol) of bromo-acetyl chloride were added. Stirring was continued over night and then concentrated under vacuo. The crude residue was dissolved in EtOAc, washed with H_2O. The organic phase was dried over Na_2SO_4 and the product was purified by flash chromatography (SiO_2, EtOAc) to yield the title product 0.15 g (92%) as a colorless oil.

Pyrrolidine XVI-B-4

6-{(SR)-1-[(3RS,4SR)-1-(2-Bromo-acetyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile

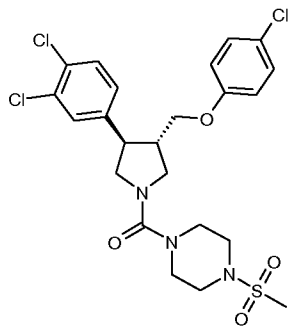


XVI-B-4

To a stirred solution of 6-{(SR)-1-[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile (XV-B-4) 30 mg (0.083 mmol) in CH_2Cl_2 (3 mL) at RT, 0.013 ml (0.01 mmol) of Et_3N and 0.0083 mL (0.01 mmol) of bromo-acetyl chloride were added. Stirring was continued over night and then concentrated under vacuo. The crude residue was dissolved in EtOAc, washed with H_2O. The organic phase was dried over Na_2SO_4 and the product was purified by flash chromatography (SiO_2, EtOAc) to yield the title product 34 mg (85%) as a colorless oil.

Example 1

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



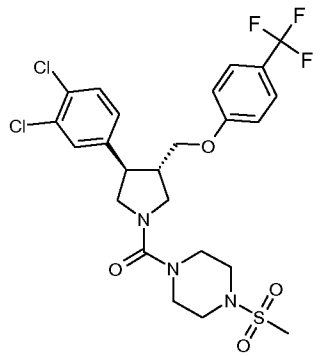
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 4-Chloro-phenol (commercially available),

ES-MS m/e: 545.7 ($M+H^+$).

Example 2

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



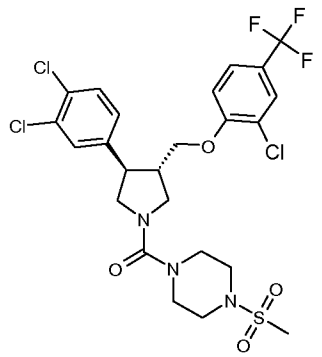
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 4-Trifluoromethyl-phenol (commercially available),

ES-MS m/e: 581.0 ($M+H^+$).

Example 3

[(3SR,4RS)-3-(2-Chloro-4-trifluoromethyl-phenoxymethyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



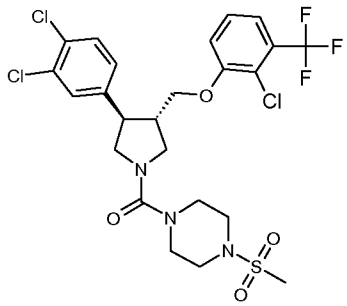
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 2-Chloro-4-trifluoromethyl-phenol (commercially available),

ES-MS m/e: 616.0 ($M+H^+$).

Example 4

[(3SR,4RS)-3-(2-Chloro-3-trifluoromethyl-phenoxymethyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



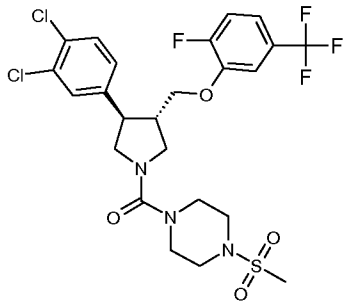
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 2-Chloro-3-trifluoromethyl-phenol (commercially available),

ES-MS m/e: 616.0 ($M+H^+$).

Example 5

[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-(2-fluoro-5-trifluoromethyl-phenoxymethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



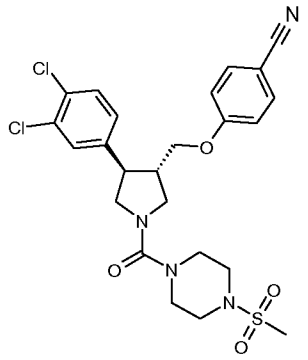
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 2-Fluoro-5-trifluoromethyl-phenol (commercially available),

ES-MS m/e: 598.2 ($M+H^+$).

Example 6

4-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-ylmethoxy]-benzonitrile



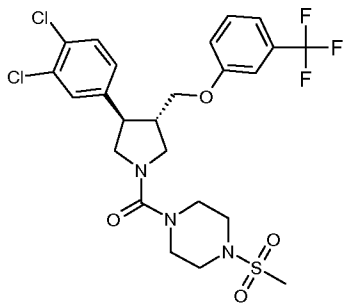
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 4-Hydroxy-benzonitrile (commercially available),

ES-MS m/e: 537.2 ($M+H^+$).

Example 7

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



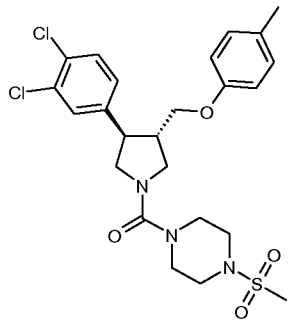
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 3-Trifluoromethyl-phenol (commercially available),

ES-MS m/e: 581.0 ($M+H^+$).

Example 8

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



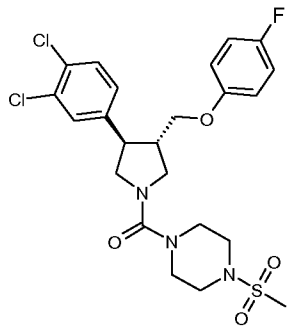
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 4-Methyl-phenol (commercially available),

ES-MS m/e: 525.8 ($M+H^+$).

Example 9

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



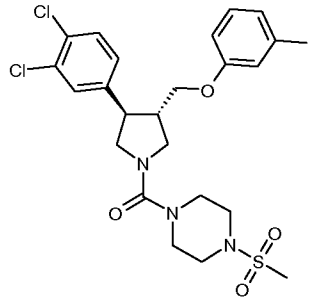
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 4-Fluoro-phenol (commercially available),

ES-MS m/e: 529.7 ($M+H^+$).

Example 10

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



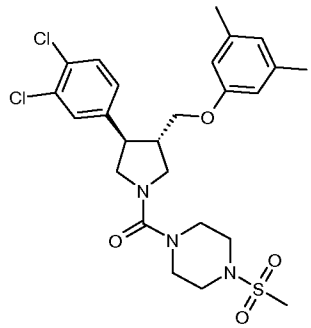
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 3-Methyl-phenol (commercially available),

ES-MS m/e: 525.8 ($M+H^+$).

Example 11

[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-(3,5-dimethyl-phenoxymethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



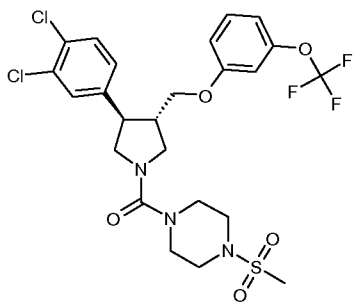
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 3,5-Dimethyl-phenol (commercially available),

ES-MS m/e: 539.7 ($M+H^+$).

Example 12

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



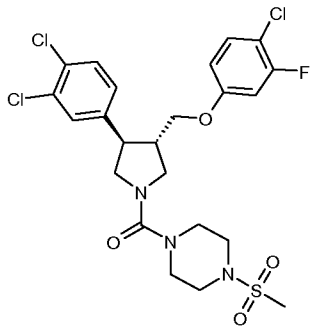
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 3-Trifluoromethoxy-phenol (commercially available),

ES-MS m/e: 595.6 ($M+H^+$).

Example 13

[(3SR,4RS)-3-(4-Chloro-3-fluoro-phenoxymethyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



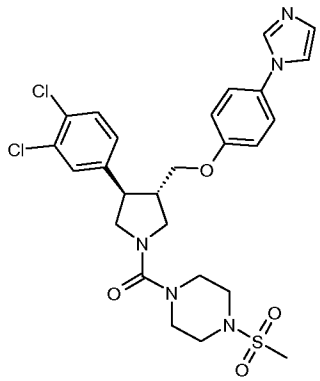
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 4-Chloro-3-fluoro-phenol (commercially available),

ES-MS m/e: 565.7 ($M+H^+$).

Example 14

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



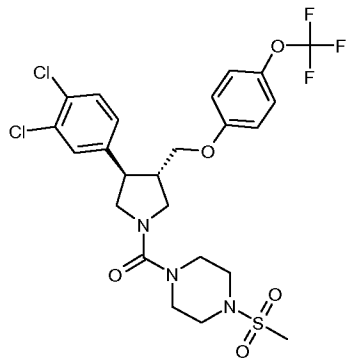
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 4-Imidazol-1-yl-phenol (commercially available),

ES-MS m/e: 577.6 ($M+H^+$).

Example 15

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



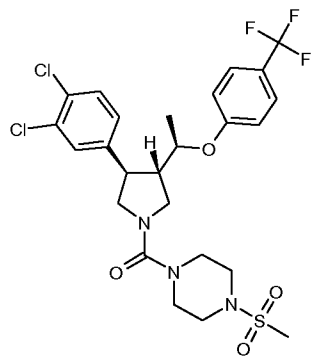
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 4-Trifluoromethoxy-phenol (commercially available),

ES-MS m/e: 595.6 ($M+H^+$).

Example 16

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



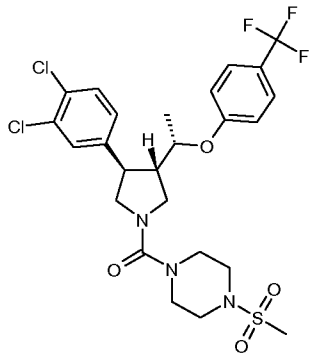
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 4-Trifluoromethyl-phenol (commercially available),

ES-MS m/e: 594.2 ($M+H^+$).

Example 17

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



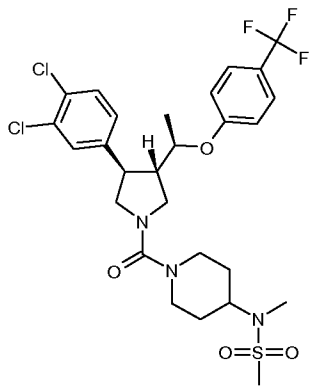
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**),
- Phenol: 4-Trifluoromethyl-phenol (commercially available),

ES-MS m/e: 594.2 ($M+H^+$).

Example 18

N-(1-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine-1-carbonyl}-piperidin-4-yl)-N-methyl-methanesulfonamide



Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: (3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (**XV-B-1**),
- Carbamoyl chloride: 4-(Methanesulfonyl-methyl-amino)-piperidine-1-carbonyl chloride,

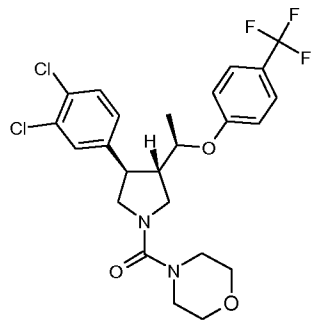
ES-MS m/e: 623.6 ($M+H^+$).

4-(Methanesulfonyl-methyl-amino)-piperidine-1-carbonyl chloride:

To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (0.61 g, 2.08 mmol) in CH_2Cl_2 (30 mL) at -78 °C, was added a solution of N-Methyl-N-piperidin-4-yl-methanesulfonamide (preparation described in the patent GB2000136) (1.00 g, 5.20 mmol) and pyridine (0.92 mL, 11.4 mmol) in CH_2Cl_2 (20 mL) over 1 hour. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo yielded 0.53 g (40%) of the title compound as a light yellow solid.

Example 19

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-morpholin-4-yl-methanone



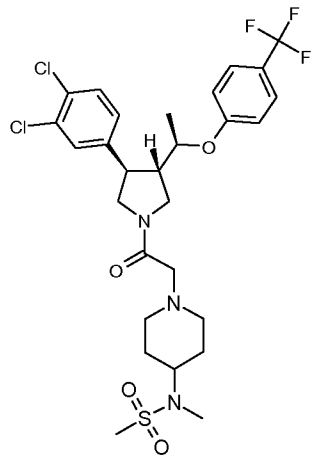
Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: (3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (**XV-B-1**),
- Carbamoyl chloride: Morpholine-4-carbonyl chloride (commercially available),

ES-MS m/e: 516.8 ($M+H^+$).

Example 20

N-[1-(2-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-methanesulfonamide



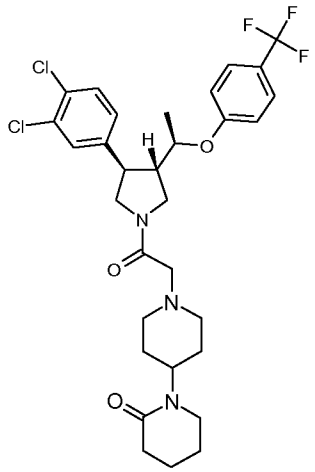
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (XVI-B-1),
- Amine: N-Methyl-N-piperidin-4-yl-methanesulfonamide (preparation described in the patent GB2000136),

ES-MS m/e: 635.6 ($M+H^+$).

Example 21

1'-(2-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-[1,4']bipiperidinyl-2-one



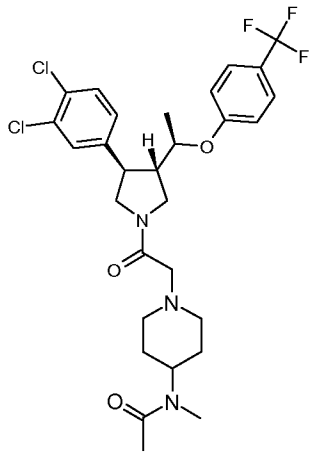
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (XVI-B-1),
- Amine: [1,4']Bipiperidinyl-2-one (commercially available),

ES-MS m/e: 625.8 ($M+H^+$).

Example 22

N-[1-(2-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-acetamide



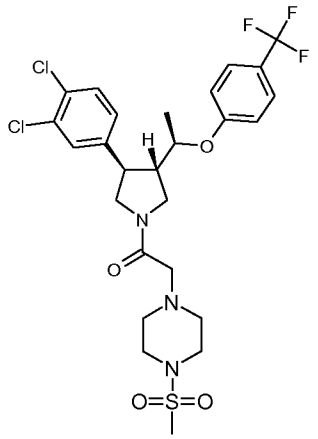
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (XVI-B-1),
- Amine: N-Methyl-N-piperidin-4-yl-acetamide (preparation described in the patent US5576333),

ES-MS m/e: 599.7 ($M+H^+$).

Example 23

1-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-(4-methanesulfonyl-piperazin-1-yl)-ethanone



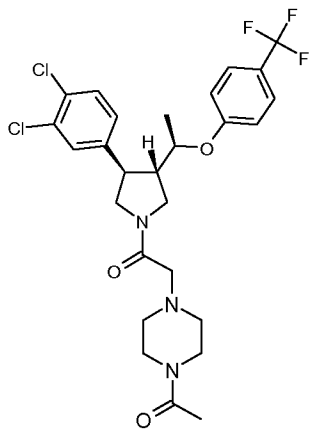
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (XVI-B-1),
- Amine: 1-Methanesulfonyl-piperazine (commercially available),

ES-MS m/e: 609.4 ($M+H^+$).

Example 24

2-(4-Acetyl-piperazin-1-yl)-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone



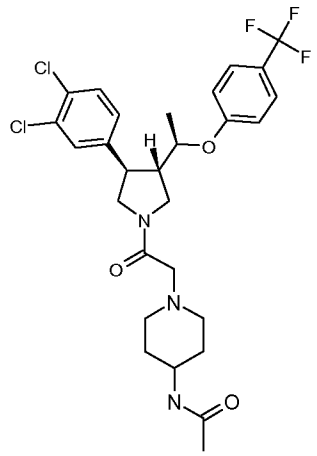
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (XVI-B-1),
- Amine: 1-Piperazin-1-yl-ethanone (commercially available),

ES-MS m/e: 573.6 ($M+H^+$).

Example 25

N-[1-(2-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-piperidin-4-yl]-acetamide



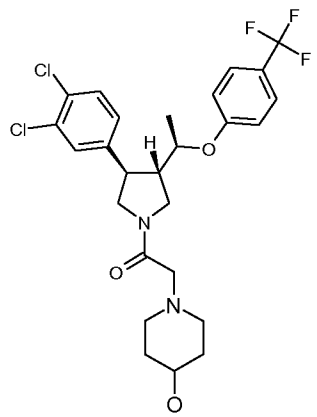
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (XVI-B-1),
- Amine: N-Piperidin-4-yl-acetamide (commercially available),

ES-MS m/e: 587.7 ($M+H^+$).

Example 26

1-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-(4-hydroxy-piperidin-1-yl)-ethanone



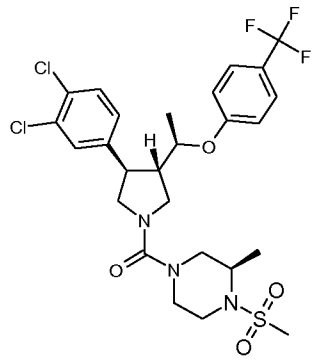
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (**XVI-B-1**),
- Amine: Piperidin-4-ol (commercially available),

ES-MS m/e: 545.2 ($M+H^+$).

Example 27

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-((R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone



Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: (3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (**XV-B-1**),
- Carbamoyl chloride: (R)-4-Methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride,

ES-MS m/e: 609.6 ($M+H^+$).

<u>(R)-4-Methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride:</u>

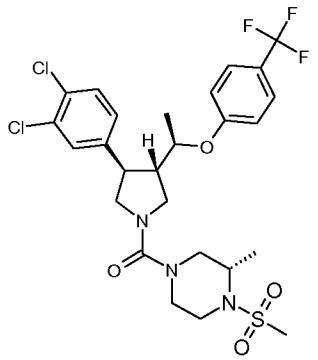
First step: To a stirred solution of commercially available (R)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (8.78 g, 44 mmol) in CH_2Cl_2 (80 mL) at 0°C were added Et_3N (12.15 mL, 88 mmol) and methanesulfonyl chloride (5.09 mL, 66 mmol). Stirring was continued at RT overnight, the reaction was poured onto water and extracted with CH_2Cl_2. The combined organic phases were dried on Na_2SO_4 and concentrated under vacuo. The crude product was dissolved in CH_2Cl_2 (50 mL) and TFA (15 mL) was added. After 2 hours at RT, the volatiles were removed under vacuo, the crude was dissolved in CH_2Cl_2 and washed with aq. $NaHCO_3$ (until pH = 8). The organic phase was dried on Na_2SO_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 CH_2Cl_2 (20 mL) at -78 °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 CH_2Cl_2 (20 mL) over 1 hour. The temperature was raised to RT, and stirring

was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo and flash chromatography (SiO_2, EtOAc/H, 1:1) yielded 1.70 g (71%) of (R)-4-methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride as a light yellow solid.

Example 28

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-((S)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone



Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: (3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (**XV-B-1**),
- Carbamoyl chloride: (S)-4-Methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride,

ES-MS m/e: 609.6 ($M+H^+$).

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

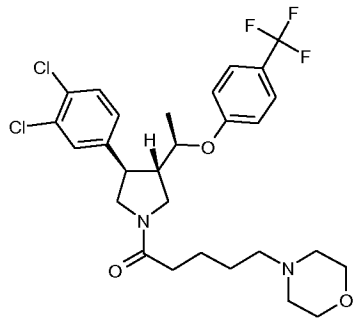
First step: To a stirred solution of commercially available (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (2.38 g, 12 mmol) in CH_2Cl_2 (25 mL) at 0°C were added pyridine (1.91 mL, 24 mmol) and methanesulfonyl chloride (0.92 mL, 12 mmol). Stirring was continued at RT overnight, the reaction was poured onto water and extracted with CH_2Cl_2. The combined organic phases were dried on Na_2SO_4 and concentrated under vacuo. The crude product was dissolved in CH_2Cl_2 (20 mL) and TFA (4 mL) was added. After 2 hours at RT, the volatiles were removed under vacuo, the crude was dissolved in CH_2Cl_2 and washed with aq. $NaHCO_3$ (until pH = 8). The organic phase was dried on Na_2SO_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 CH_2Cl_2 (10 mL) at -78 °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 CH_2Cl_2 (10 mL) over 1 hour. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4.

Concentration under vacuo and flash chromatography (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 29

1-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-5-morpholin-4-yl-pentan-1-one



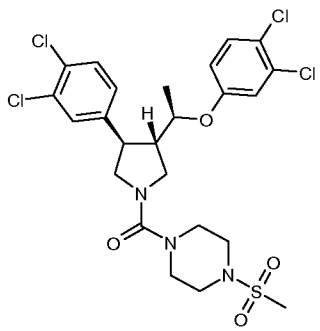
Amide coupling according to general procedure I:

- Pyrrolidine intermediate: (3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (**XV-B-1**),
- Carboxylic acid: 5-Morpholin-4-yl-pentanoic acid (described in *J. Molecular Structure*, 2001, 560, p.261),

ES-MS m/e: 573.1 ($M+H^+$).

Example 30

[(3SR,4RS)-3-[(RS)-1-(3,4-Dichloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



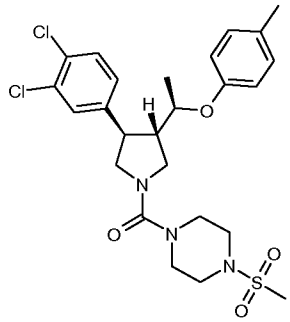
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 3,4-Dichloro-phenol (commercially available),

ES-MS m/e: 594.1 ($M+H^+$).

Example 31

[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-p-tolyloxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



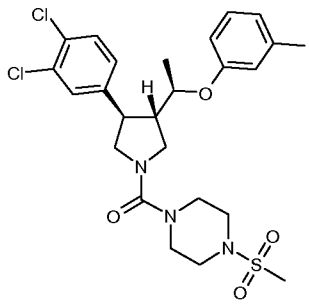
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 4-Methyl-phenol (commercially available),

ES-MS m/e: 540.2 ($M+H^+$).

Example 32

[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-m-tolyloxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



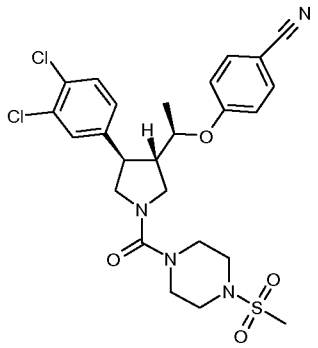
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 3-Methyl-phenol (commercially available),

ES-MS m/e: 540.2 ($M+H^+$).

Example 33

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



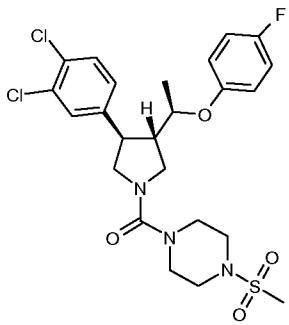
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 4-Hydroxy-benzonitrile (commercially available),

ES-MS m/e: 551.3 ($M+H^+$).

Example 34

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



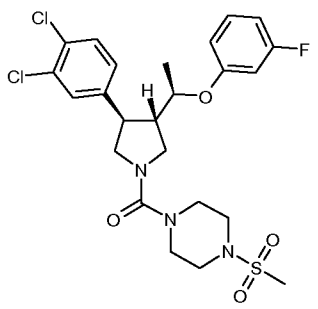
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 4-Fluoro-phenol (commercially available),

ES-MS m/e: 544.3 ($M+H^+$).

Example 35

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



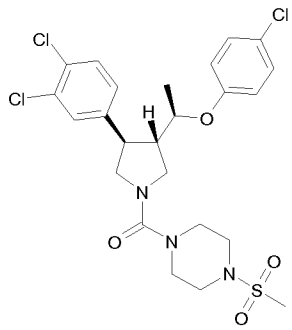
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 3-Fluoro-phenol (commercially available),

ES-MS m/e: 544.3 ($M+H^+$).

Example 36

[(3SR,4RS)-3-[(R)-1-(4-Chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



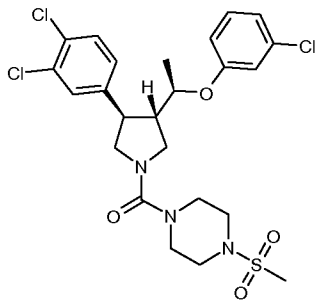
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 4-Chloro-phenol (commercially available),

ES-MS m/e: 560.2 ($M+H^+$).

Example 37

[(3SR,4RS)-3-[(RS)-1-(3-Chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



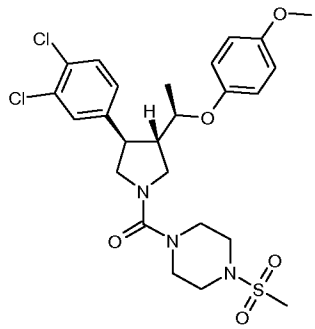
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 3-Chloro-phenol (commercially available),

ES-MS m/e: 562.2 ($M+H^+$).

Example 38

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-methoxy-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



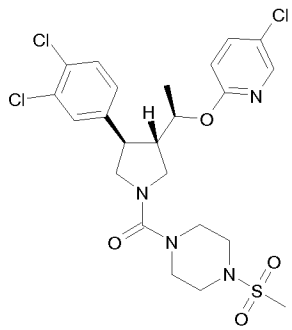
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 4-Methoxy-phenol (commercially available),

ES-MS m/e: 558.3 ($M+H^+$).

Example 39

[(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



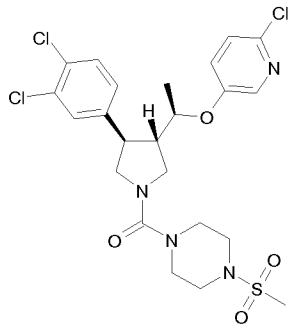
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Pyridinol: 5-Chloro-pyridin-2-ol (commercially available),

ES-MS m/e: 561.2 ($M+H^+$).

Example 40

[(3SR,4RS)-3-[(RS)-1-(6-Chloro-pyridin-3-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



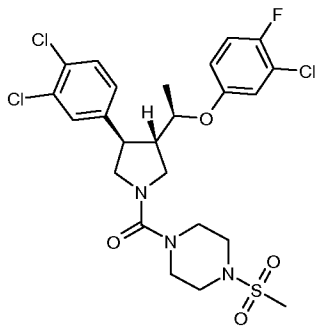
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Pyridinol: 6-Chloro-pyridin-3-ol (commercially available),

ES-MS m/e: 563.1 ($M+H^+$).

Example 41

[(3SR,4RS)-3-[(RS)-1-(3-Chloro-4-fluoro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



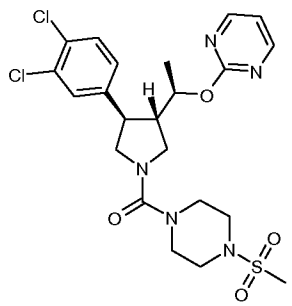
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 3-Chloro-4-fluoro-phenol (commercially available),

ES-MS m/e: 579.0 ($M+H^+$).

Example 42

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(pyrimidin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



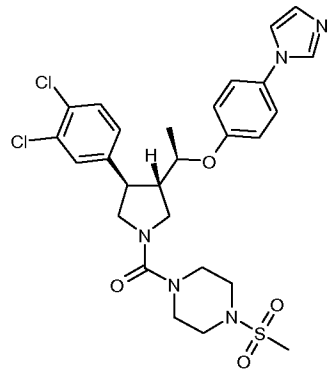
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Pyrimidinol: Pyrimidin-2-ol (commercially available),

ES-MS m/e: 528.0 ($M+H^+$).

Example 43

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-imidazol-1-yl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



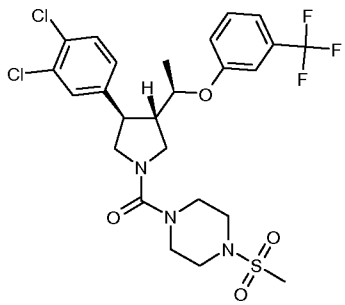
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 4-Imidazol-1-yl-phenol (commercially available),

ES-MS m/e: 592.1 ($M+H^+$).

Example 44

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(3-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



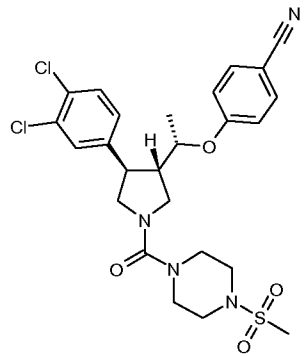
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Phenol: 3-Trifluoromethyl-phenol (commercially available),

ES-MS m/e: 594.2 ($M+H^+$).

Example 45

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



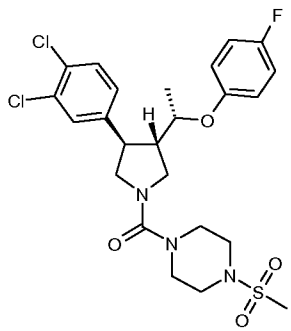
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**),
- Phenol: 4-Hydroxy-benzonitrile (commercially available),

ES-MS m/e: 551.2 ($M+H^+$).

Example 46

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



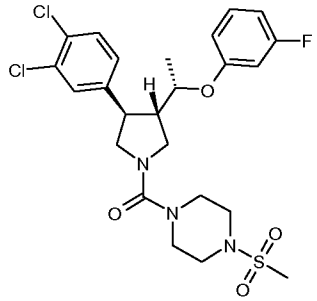
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**),
- Phenol: 4-Fluoro-phenol (commercially available),

ES-MS m/e: 546.2 ($M+H^+$).

Example 47

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



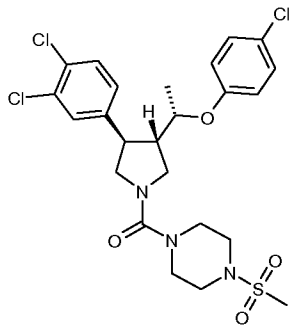
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**),
- Phenol: 3-Fluoro-phenol (commercially available),

ES-MS m/e: 544.3 ($M+H^+$).

Example 48

[(3SR,4RS)-3-[(SR)-1-(4-Chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



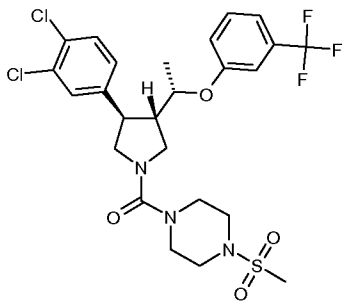
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**),
- Phenol: 4-Chloro-phenol (commercially available),

ES-MS m/e: 562.2 ($M+H^+$).

Example 49

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(3-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



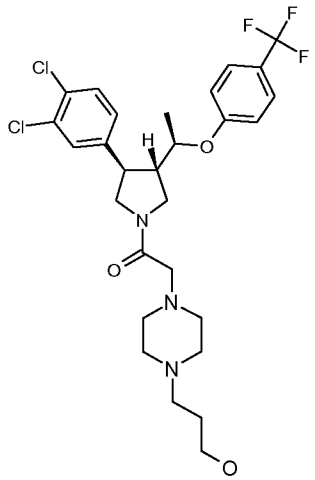
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**),
- Phenol: 3-Trifluoromethyl-phenol (commercially available),

ES-MS m/e: 594.2 ($M+H^+$).

Example 50

1-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-[4-(3-hydroxy-propyl)-piperazin-1-yl]-ethanone



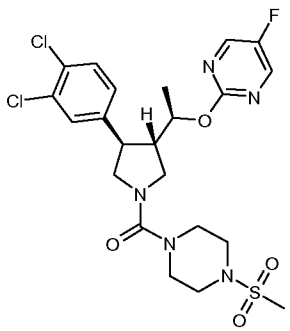
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (**XVI-B-1**),
- Amine: 3-Piperazin-1-yl-propan-1-ol (commercially available),

ES-MS m/e: 588.1 ($M+H^+$).

Example 51

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(5-fluoro-pyrimidin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



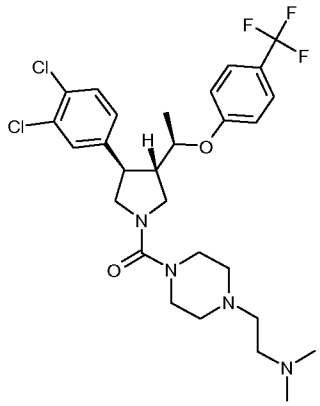
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Pyrimidinol: 5-Fluoro-pyrimidin-2-ol (commercially available),

ES-MS m/e: 545.7 ($M+H^+$).

Example 52

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone



a) (3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine-1-carbonyl chloride

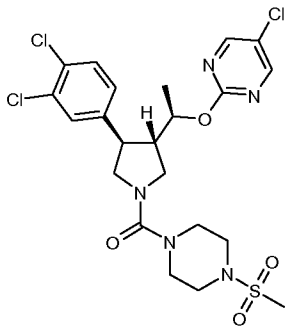
To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (29 mg, 0.098 mmol) in CH_2Cl_2 (2 mL) at -78 °C, was added a solution of (3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (intermediate **XV-B-1**) (100 mg, 0.25 mmol) and pyridine (0.043 mL, 0.54 mmol) in CH_2Cl_2 (2 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo yielded 58 mg (50%) of the title compound as a light yellow solid.

b) {(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]pyrrolidin-1-yl}-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone

To a stirred solution of (3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine-1-carbonyl chloride (58 mg, 0.12 mmol) in CH_2Cl_2 (2 ml) were added Et_3N (0.02 mL, 0.15 mmol) and dimethyl-(2-piperazin-1-yl-ethyl)-amine (0.03 mL) (commercially available).Stirring was continued overnight, and the reaction mixture was concentrated under vacuo and directly purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH/NH_3, 9/4/1) to yield 46 mg (63%) of the title compound as light yellow oil. ES-MS m/e: 587.3 ($M+H^+$).

Example 53

[(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyrimidin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



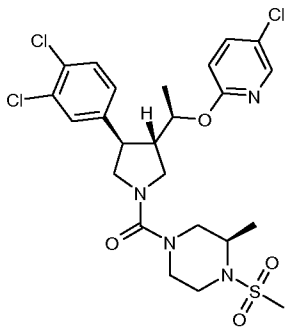
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Pyrimidinol: 5-Chloro-pyrimidin-2-ol (commercially available),

ES-MS m/e: 562.7 ($M+H^+$).

Example 54

[(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-((R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone



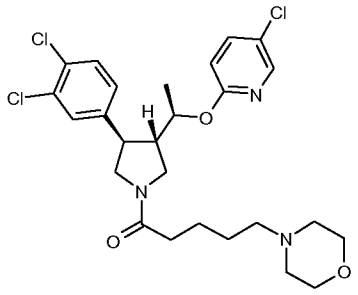
Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: 5-Chloro-2-{(RS)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine (**XV-B-2**),
- Carbamoyl chloride: (R)-4-Methanesulfonyl-3-methyl-piperazine-1-carbonyl chloride,

ES-MS m/e: 577.2 ($M+H^+$).

Example 55

1-[(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-5-morpholin-4-yl-pentan-1-one



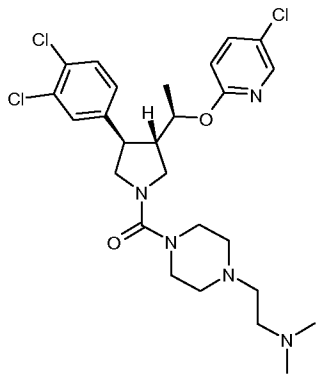
Amid coupling according to general procedure I:

- Pyrrolidine intermediate: 5-Chloro-2-{(RS)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine (**XV-B-2**),
- Carboxylic acid: 5-Morpholin-4-yl-pentanoic acid (described in *J. Molecular Structure*, 2001, 560, p.261),

ES-MS m/e: 542.3 ($M+H^+$).

Example 56

[(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone



a) (3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl chloride

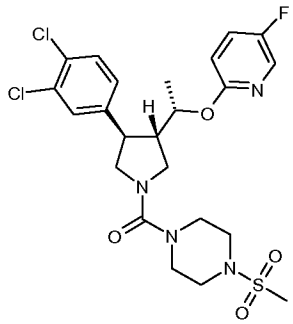
To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (22 mg, 0.074 mmol) in CH_2Cl_2 (3 mL) at -78 °C, was added a solution of 5-chloro-2-{(RS)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine (intermediate **XV-B-2**) (70 mg, 0.19 mmol) and pyridine (0.033 mL, 0.41 mmol) in CH_2Cl_2 (2 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H, 1:1) yielded 80 mg (98%) of the title compound as a light yellow solid.

b) [(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone

To a stirred solution of (3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl chloride (80 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were added Et_3N (0.03 mL, 0.15 mmol) and dimethyl-(2-piperazin-1-yl-ethyl)-amine (0.035 mL) (commercially available). Stirring was continued overnight, and the reaction mixture was concentrated under vacuo and directly purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH/NH_3, 9/4/1) to yield 36 mg (35%) the title compound as light yellow oil. ES-MS m/e: 553.8($M+H^+$).

Example 57

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



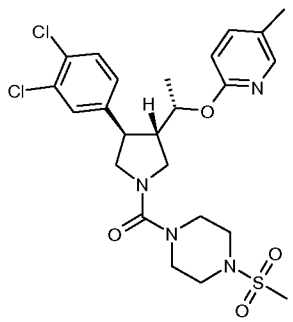
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**),
- Pyridinol: 5-Fluoro-pyridin-2-ol (commercially available),

ES-MS m/e: 545.1 ($M+H^+$).

Example 58

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-methyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



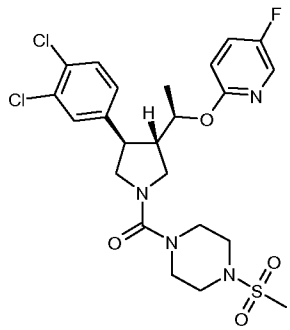
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-A-1**),
- Pyridinol: 5-Methyl-pyridin-2-ol (commercially available),

ES-MS m/e: 542.7 ($M+H^+$).

Example 59

{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



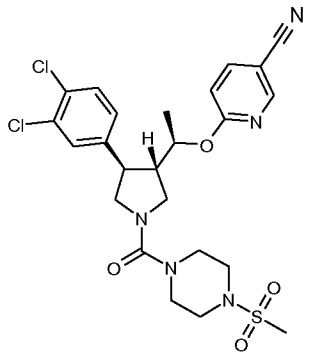
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Pyridinol: 5-Fluoro-pyridin-2-ol (commercially available),

ES-MS m/e: 546.8 ($M+H^+$).

Example 60

6-{(RS)-1-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile



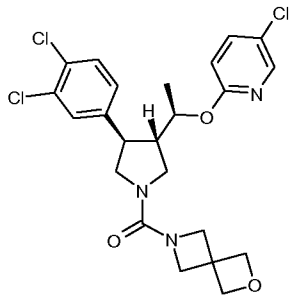
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**XII-B-1**),
- Pyridinol: 6-Hydroxy-nicotinonitrile (commercially available),

ES-MS m/e: 551.7 ($M+H^+$).

Example 61

[(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(2-oxa-6-aza-spiro[3.3]hept-6-yl)-methanone



a) (3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl chloride

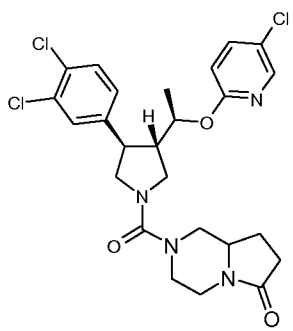
To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (48 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) at -78 °C, was added a solution of 5-chloro-2-{(RS)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine (intermediate **XV-B-2**) (150 mg, 0.40 mmol) and pyridine (0.072 mL, 0.88 mmol) in CH_2Cl_2 (5 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H, 1:1) yielded 90 mg (50%) of the title compound as a viscous colorless oil.

b) [(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(2-oxa-6-aza-spiro[3.3]hept-6-yl)-methanone

To a stirred solution of (3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl chloride (22 mg, 0.051 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.022 mL, 0.16 mmol) and 2-oxa-6-aza-spiro[3.3]heptane (6 mg, 0.060 mmol). Stirring was continued overnight, and the reaction mixture was concentrated under vacuo and directly purified by flash chromatography (SiO_2, EtOAc) to yield 7 mg (28%) the title compound as light yellow oil. ES-MS m/e: 497.1 ($M+H^+$).

Example 62

2-[(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl]-hexahydro-pyrrolo[1,2-a]pyrazin-6-one



a) (3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl chloride

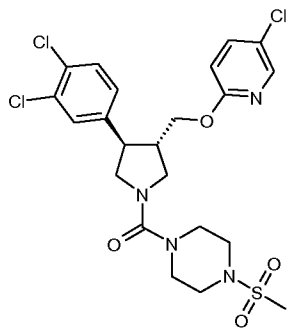
To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (48 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) at -78 °C, was added a solution of 5-chloro-2-{(RS)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine (intermediate **XV-B-2**) (150 mg, 0.40 mmol) and pyridine (0.072 mL, 0.88 mmol) in CH_2Cl_2 (5 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H, 1:1) yielded 90 mg (50%) of the title compound as a viscous colorless oil.

b) 2-[(3SR,4RS)-3-[(RS)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl]-hexahydro-pyrrolo[1,2-a]pyrazin-6-one

To a stirred solution of (3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl chloride (22 mg, 0.051 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.015 mL, 0.11 mmol) and hexahydro-pyrrolo[1,2-a]pyrazin-6-one (commercially available) (9 mg, 0.064 mmol). Stirring was continued overnight, and the reaction mixture was concentrated under vacuo and directly purified by flash chromatography (SiO_2, EtOAc) to yield 7 mg (25%) the title compound as light yellow oil. ES-MS m/e: 539.2 ($M+H^+$).

Example 63

[(3SR,4RS)-3-(5-Chloro-pyridin-2-yloxymethyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



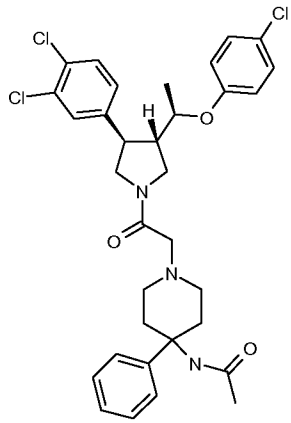
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**VII-1**),
- Phenol: 5-Chloro-pyridin-2-ol (commercially available),

ES-MS m/e: 549.2 ($M+H^+$).

Example 64

N-(1-{2-[(3SR,4RS)-3-[(RS)-1-(4-Chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-4-phenyl-piperidin-4-yl)-acetamide



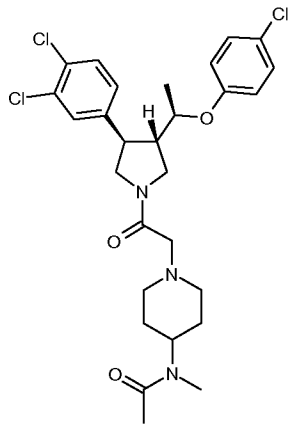
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone (XVI-B-2),
- Amine: N-(4-Phenyl-piperidin-4-yl)-acetamide (commercially available),

ES-MS m/e: 630.9 ($M+H^+$).

Example 65

N-(1-{2-[(3SR,4RS)-3-[(RS)-1-(4-Chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-piperidin-4-yl)-N-methyl-acetamide



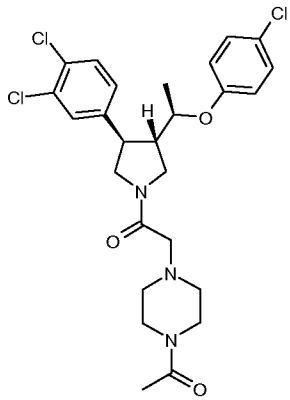
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone (XVI-B-2),
- Amine: N-Methyl-N-piperidin-4-yl-acetamide (commercially available),

ES-MS m/e: 568.7 ($M+H^+$).

Example 66

2-(4-Acetyl-piperazin-1-yl)-1-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone



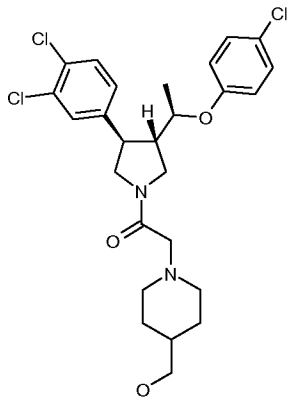
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone (XVI-B-2),
- Amine: 1-Piperazin-1-yl-ethanone (commercially available),

ES-MS m/e: 538.8 ($M+H^+$).

Example 67

1-[(3SR,4RS)-3-[(RS)-1-(4-Chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-(4-hydroxymethyl-piperidin-1-yl)-ethanone



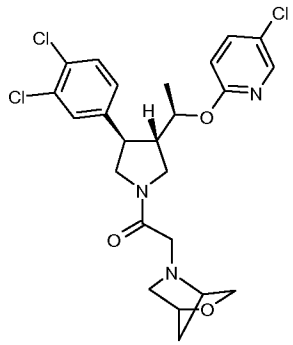
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone (XVI-B-2),
- Amine: Piperidin-4-yl-methanol (commercially available),

ES-MS m/e: 527.6 ($M+H^+$).

Example 68

1-[(3S,4R)-3-[(R)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethanone



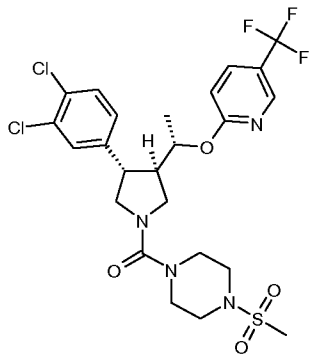
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 2-Bromo-1-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone (**XVI-B-2**),
- Amine: 2-Oxa-5-aza-bicyclo[2.2.1]heptane (commercially available),

ES-MS m/e: 512.0 ($M+H^+$).

Example 69

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



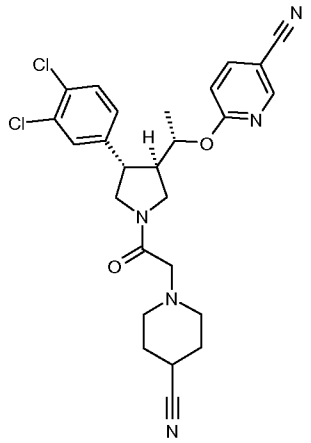
Coupling reaction according to general procedure II:

- Pyrrolidine intermediate: 2-{(SR)-1-[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-trifluoromethyl-pyridine (**XV-B-3**),
- Carbamoyl chloride: 4-Methanesulfonyl-piperazine-1-carbonyl chloride (described herein above),

ES-MS m/e: 595.2 ($M+H^+$).

Example 70

6-{(SR)-1-[(3RS,4SR)-1-[2-(4-Cyano-piperidin-1-yl)-acetyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile



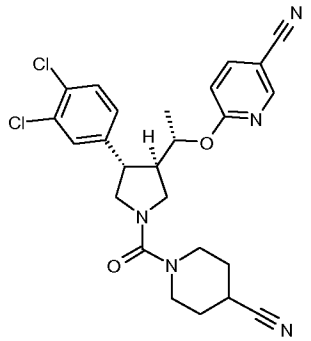
Coupling reaction according to general procedure IV:

- Pyrrolidine intermediate: 6-{(SR)-1-[(3RS,4SR)-1-(2-Bromo-acetyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile (**XVI-B-4**),
- Amine: Piperidine-4-carbonitrile (commercially available),

ES-MS m/e: 512.0 ($M+H^+$).

Example 71

6-{(SR)-1-[(3RS,4SR)-1-(4-Cyano-piperidine-1-carbonyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile



a) (3RS,4SR)-3-[(SR)-1-(5-Cyano-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl chloride

To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (67 mg, 0.22 mmol) in CH_2Cl_2 (14 mL) at -78 °C, was added a solution of 6-{(SR)-1-[(3RS,4SR)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile (intermediate **XV-B-4**) (210 mg, 0.56 mmol) and pyridine (0.10 mL, 1.23 mmol) in CH_2Cl_2 (7 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H, 1:1) yielded 144 mg (57%) of the title compound as a viscous colorless oil.

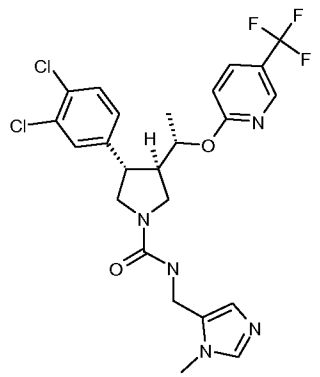
b) 6-{(SR)-1-[(3RS,4SR)-1-(4-Cyano-piperidine-1-carbonyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile

To a stirred solution of (3RS,4SR)-3-[(SR)-1-(5-Cyano-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl chloride (30 mg, 0.070 mmol) in CH_2Cl_2 (4 mL) were added Et_3N (0.015 mL, 0.11 mmol) and piperidine-4-carbonitrile (commercially available) (9 mg, 0.084 mmol). Stirring was continued overnight, and the reaction mixture was concentrated under vacuo and directly purified by flash chromatography (SiO_2, EtOAc) to yield 24 mg (69%) the title compound as light yellow oil. ES-MS m/e: 498.0 ($M+H^+$).

Example 72

(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidine-1-carboxylic acid (3-methyl-3H-imidazol-4-ylmethyl)-amide

(not encompassed by formula I)



a) (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidine-1-carbonyl chloride

To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (22 mg, 0.074 mmol) in CH_2Cl_2 (3 mL) at -78 °C, was added a solution of 2-{(SR)-1-[(3RS,4SR)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-trifluoromethyl-pyridine (intermediate **XV-B-3**) (76 mg, 0.19 mmol) and pyridine (0.03 mL, 0.42 mmol) in CH_2Cl_2 (1 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H, 1:4) yielded 36 mg (41%) of the title compound as a viscous colorless oil.

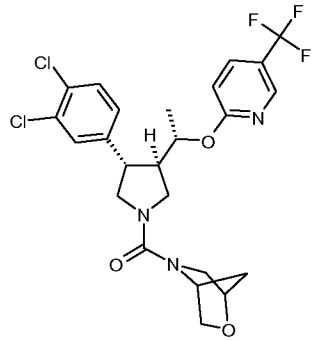
b) (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidine-1-carboxylic acid (3-methyl-3H-imidazol-4-ylmethyl)-amide

To a stirred solution of (3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidine-1-carbonyl chloride (30 mg, 0.064 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.015 mL, 0.11 mmol) and C-(3-Methyl-3H-

imidazol-4-yl)-methylamine (commercially available) (8 mg, 0.070 mmol). Stirring was continued overnight, and the reaction mixture was concentrated under vacuo and directly purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 98/2) to yield 14 mg (40%) the title compound as a white solid. ES-MS m/e: 542.2 ($M+H^+$).

Example 73

{(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-methanone



a) (3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidine-1-carbonyl chloride

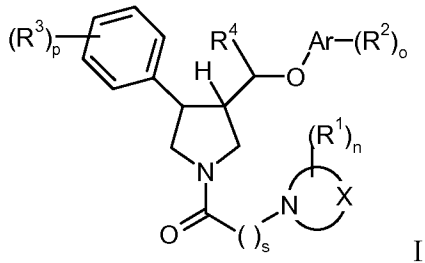
To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (22 mg, 0.074 mmol) in CH_2Cl_2 (3 mL) at -78 °C, was added a solution of 2-{(SR)-1-[(3RS,4SR)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-trifluoromethyl-pyridine (intermediate **XV-B-3**) (76 mg, 0.19 mmol) and pyridine (0.03 mL, 0.42 mmol) in CH_2Cl_2 (1 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H_2O, dried over Na_2SO_4. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H, 1:4) yielded 36 mg (41%) of the title compound as a viscous colorless oil.

b) {(3SR,4RS)-3-(3,4-Dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-methanone

To a stirred solution of (3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidine-1-carbonyl chloride (30 mg, 0.064 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.015 mL, 0.11 mmol) and 2-Oxa-5-aza-bicyclo[2.2.1]heptane (commercially available) (7 mg, 0.070 mmol). Stirring was continued overnight, and the reaction mixture was concentrated under vacuo and directly purified by flash chromatography (SiO_2, EtOAc) to yield 27 mg the title compound as a white solid. ES-MS m/e: 530.1 ($M+H^+$).

Claims

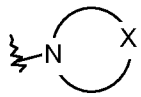
1. A compound of formula



I

wherein

Ar is aryl or a five or six membered heteroaryl;



is a six to nine membered mono or bi-heterocyclic group, wherein X may be a carbon atom, SO_2 or a further hetero atom, selected from the group consisting of N or O;

if X is a carbon atom, O, SO_2 or unsubstituted N, then

R^1 is hydrogen, hydroxy, cyano, $-(CH_2)_q$-OH, $-(CH_2)_q$-NRR', -(CH$_2$)q-CN, lower alkyl, $-S(O)_2$-lower alkyl, -NR-$S(O)_2$-lower alkyl, -C(O)-lower alkyl, -NR-C(O)-lower alkyl, phenyl, or is a heterocyclic group selected from piperidinyl-2-one;

if X is a N-atom, substituted by R^1, then

R^1 is hydrogen, $-(CH_2)_q$-OH, $-(CH_2)_q$-NRR', -(CH$_2$)q-CN, lower alkyl, $-S(O)_2$-lower alkyl, aryl or a five or six membered heteroaryl or -C(O)-lower alkyl, provided that q is 2 or 3.

R/R' are independently from each other hydrogen or lower alkyl;

R^2 is hydrogen, halogen, lower alkyl, cyano, lower alkoxy substituted by halogen, lower alkyl substituted by halogen or is a five or six membered heteroaryl;

R^3 is hydrogen or halogen;

R^4 is hydrogen or lower alkyl;

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

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

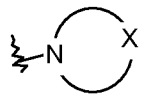
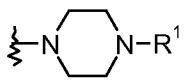
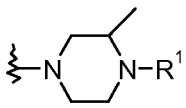
p is 1 or 2; in case p is 2, R^3 may be the same or different;

q is 1, 2 or 3;

s is 0, 1, 2, 3 or 4;

or a pharmaceutically active salt thereof, including all stereoisomeric forms, individual diastereoisomers and enantiomers of the compound of formula (I) as well as racemic and non-racemic mixtures thereof.

2. A compound of formula I according to claim 1, wherein $(R^3)_p$ is 3,4-dichloro.

3. A compound of formula I according to claim 2, wherein  is  or  and Ar is phenyl.

4. A compound of formula I according to claim 3, wherein the compounds are

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

2-(4-acetyl-piperazin-1-yl)-1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone

(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-((R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone

[(3SR,4RS)-3-[(RS)-1-(3,4-dichloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-((RS)-1-p-tolyloxy-ethyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

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

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-fluoro-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3SR,4RS)-3-[(RS)-1-(3-chloro-4-fluoro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

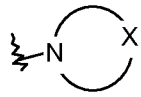
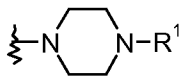
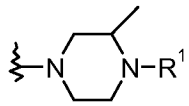
4-{(SR)-1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-ethoxy}-benzonitrile

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(4-fluoro-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3SR,4RS)-3-[(SR)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

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

2-(4-acetyl-piperazin-1-yl)-1-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone.

5. A compound of formula I according to claim 2, wherein  is  or  and Ar is pyridyl.

6. A compound of formula I according to claim 5, wherein the compounds are

[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-((R)-4-methanesulfonyl-3-methyl-piperazin-1-yl)-methanone

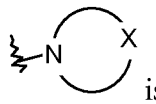
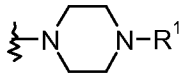
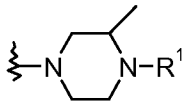
[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

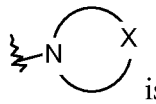
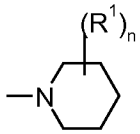
{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

[(3SR,4RS)-3-(5-chloro-pyridin-2-yloxymethyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

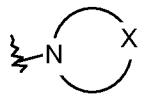
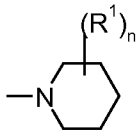
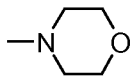
{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone.

7. A compound of formula I according to claim 2, wherein  is  or  and Ar is pyrimidinyl.

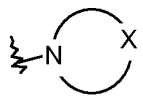
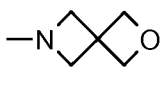
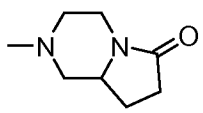
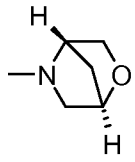
8. A compound of formula I according to claim 7, wherein the compounds are
{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(pyrimidin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(5-fluoro-pyrimidin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone or
[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyrimidin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone.

9. A compound of formula I according to claim 2, wherein  is  and Ar is phenyl.

10. A compound of formula I according to claim 9, wherein the compounds are
N-(1-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine-1-carbonyl}-piperidin-4-yl)-N-methyl-methanesulfonamide
N-[1-(2-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-piperidin-4-yl]-N-methyl-methanesulfonamide
N-[1-(2-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-2-oxo-ethyl)-piperidin-4-yl]-acetamide
N-(1-{2-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-4-phenyl-piperidin-4-yl)-acetamide
N-(1-{2-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-oxo-ethyl}-piperidin-4-yl)-N-methyl-acetamide or
1-[(3SR,4RS)-3-[(RS)-1-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-(4-hydroxymethyl-piperidin-1-yl)-ethanone.

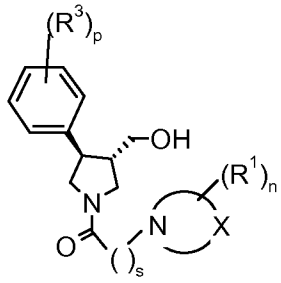
11. A compound of formula I according to claim 2, wherein  is  or  and Ar is pyridyl.

12. A compound of formula I according to claim 11, wherein the compounds are
1-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-5-morpholin-4-yl-pentan-1-one
6-{(SR)-1-[(3RS,4SR)-1-[2-(4-cyano-piperidin-1-yl)-acetyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile or
6-{(SR)-1-[(3RS,4SR)-1-(4-cyano-piperidine-1-carbonyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile.

13. A compound of formula I according to claim 2, wherein  is ,  or  and Ar is pyridyl.

14. A compound of formula I according to claim 13, wherein the compounds are
[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-(2-oxa-6-aza-spiro[3.3]hept-6-yl)-methanone
2-[(3SR,4RS)-3-[(RS)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl]-hexahydro-pyrrolo[1,2-a]pyrazin-6-one
1-[(3S,4R)-3-[(R)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethanone or
{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-methanone.

15. A process for preparation of the compound according to any one of claims 1-14, which process comprises
a) reacting a compound of formula

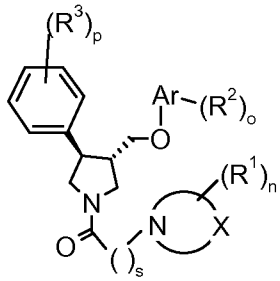


VII

with a compound of formula

$$HO\text{-}Ar\text{-}(R^2)_o$$

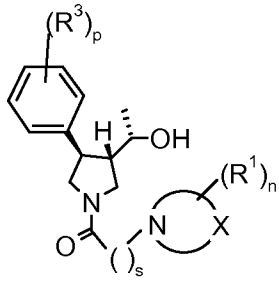
to a compound of formula



I-C

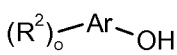
wherein the definitions have same meanings as described in claim 1, or

b) reacting a compound of formula

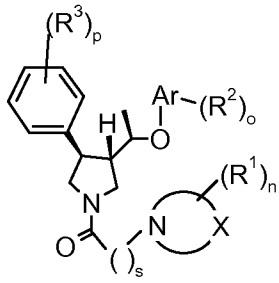


XII-B

with a compound of formula



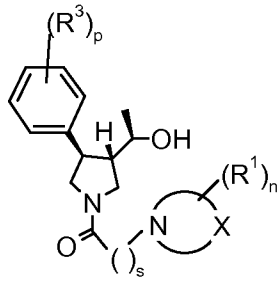
to a compound of formula



I-B,

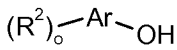
wherein the definitions are as in claim 1, or

c) reacting a compound of formula

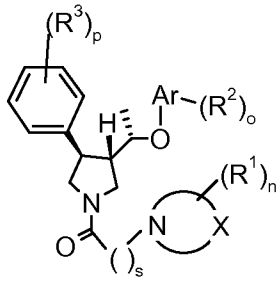


XII-A

with a compound of formula



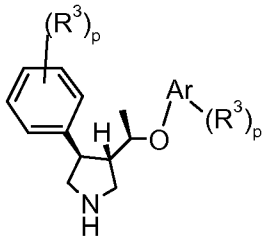
to a compound of formula



I-A,

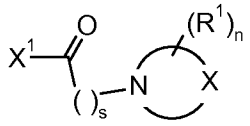
wherein the definitions are as in claim 1,

d) reacting a compound of formula

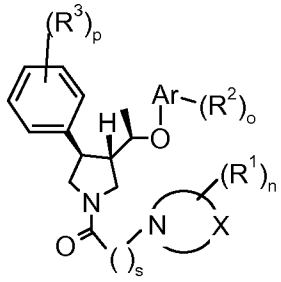


XV-B

with a compound of formula



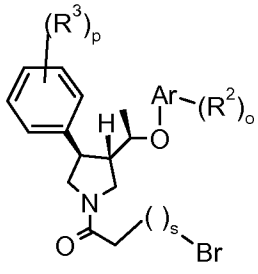
to a compound of formula



I-B

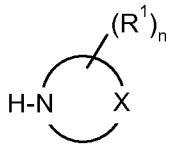
wherein X^1 is halogen, and the other definitions are as in claim 1,

e) reacting a compound of formula

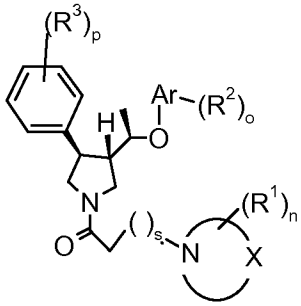


XVI-B

with a compound of formula



to a compound of formula



I-D

wherein the definitions are as in claim 1

and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

16. A compound according to claim 1, whenever prepared by a process as claimed in claim 15 or by an equivalent method.

17. A medicament containing one or more compounds as claimed in any one of claims 1-14 and a pharmaceutically acceptable excipient.

18. A medicament according to claim 17 for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, anxiety or attention deficit hyperactivity disorder (ADHD).

19. The use of a compound as claimed in any one of claims 1-14 for the manufacture of a medicament for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, anxiety or attention deficit hyperactivity disorder (ADHD).

20. The invention as herein before described.

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