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Priority: 2604/04 - German (DE).

Publication: 2007-04-25 - German (DE).

Language: English.

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Title: PYRRROLIDINE ARYL-ETHER AS NK3 RECEPTOR ANTAGONISTS.

Abstract: The invention relates to a compound of general formula (I) wherein X 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, SO₂ or a further hetero atom, selected from the group consisting of N or O; if X is a carbon atom, O, SO₂ or unsubstituted N, then R₁ is hydrogen, hydroxy, cyano, -(CH₂)ₗ-OH, -(CH₂)ₗ-NR₂, -(CH₂)ₗ-CN, lower alkyl, -SO₂(O)₂-lower alkyl, -NR-S(O)₂-lower alkyl, -(O)₂-lower alkyl, -NR-O(O)₂-lower alkyl, -NR(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 R₂, then R₁ is hydrogen, -(CH₂)ₗ-OH, -(CH₂)ₗ-NR₂, -SO₂(O)₂-lower alkyl, -NR(O)-lower alkyl, -(O)₂-lower alkyl, -(CH₂)ₗ-CN, lower alkyl, -(SO₂)₂-lower alkyl, aryl or a five or six membered heteroaryl or -C(O)-lower alkyl, provided that q is 2 or 3. RTR' are independently from each other hydrogen or lower alkyl; R₂ is hydrogen, halogen, lower alkyl, cyano, lower alkoxy substituted by halogen, lower alkyl substituted by halogen or is a five or six membered heteroaryl; R₃ is hydrogen or halogen; R₄ is hydrogen or lower alkyl; n is 1 or 2; and in case n is 2, R₅ may be the same or different; o is 1 or 2; in case o is 2, R₂ may be the same or different; p is 1 or 2; in case p is 2, R₅ may be the same or different; s is 1, 2 or 3; t is 0, 1, 2, 3 or 4; or to a pharmacologically 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. 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).
PYRROLIDINE ARYL-ETHER AS NK3 RECEPTOR ANTAGONISTS

The invention relates to a compound of general formula

wherein

- Ar is aryl or a five or six membered heteroaryl;
- X is a six to nine membered mono or bi-heterocyclic group, wherein X may be a carbon atom, SO₂ or a further hetero atom, selected from the group consisting of N or O;
- if X is a carbon atom, O, SO₂ or unsubstituted N, then
  - R¹ is hydrogen, hydroxy, cyano, -(CH₂)ₗ-OH, -(CH₂)ₗ-NRR', -(CH₂)ₗ-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 R¹, then
  - R¹ is hydrogen, -(CH₂)ₗ-OH, -(CH₂)ₗ-NRR', -(CH₂)ₗ-CN, lower alkyl, -S(O)₂-lower alkyl, ary1 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;
- if X is a N-atom, substituted by R¹, then
  - R¹ is hydrogen, halogen, lower alkyl, cyano, lower alkoxy substituted by halogen, lower alkyl substituted by halogen or is a five or six membered heteroaryl;
  - R³ is hydrogen or halogen;
  - R⁴ is hydrogen or lower alkyl;
  - n is 1 or 2; in case n is 2, R¹ may be the same or different;
  - o is 1 or 2; in case o is 2, R² may be the same or different;
  - p is 1 or 2; in case p is 2, R³ 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-I, NK-2 and NK-3. SP binds preferentially to the NK-I 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; Neuroptides, 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 -CF₃, -CHF₂, -CH₂F, -CH₂CF₃, -CH₂CH₂CF₃, -CH₂CF₂CF₃ 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 \((R_3^1)\) is 3,4-di-chloro.

- A compound of formula I, wherein \(\text{Ar} \) is phenyl, for example the following compounds

\[
\begin{align*}
(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[((RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone \\
(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[[(SR)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone \\
2-(4-acetyl-piperazin-1-yl)-l-[(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl]-ethanone \\
(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)methanone \\
[(3SR,4RS)-3-[(RS)-1-(4-fluoro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone \\
[(3RS,4SR)-3-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-l-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-ethoxyj-benzonitrile \\
\end{align*}
\]
[(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)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl]-4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone or

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

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

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

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

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

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

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

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

{(3SR,4RS)-3-[(RS)-l-(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 and Ar is phenyl, for example

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

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

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

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

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

A compound of formula I, wherein pyridyl, for example

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

6-[(SR)-l-{[(3RS,4SR)-l-[(4-cyano-piperidin-l-carbonyl)]-4-(3,4-dichloro-phenyl)]-pyrrolidin-3-yl]-ethoxyj-nicotinonitrile or

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

A compound of formula I, wherein and Ar is pyridyl, for example
[(3SR,4RS)-3-[(RS)-l-(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)-l-(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)-l-(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)-l-(5-trifluoromethyl-pyridin-2-yloxy)-
elyl]-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

![Structure I-1](image)

wherein

- **Ar** is aryl or a five or six membered heteroaryl;
- **X** is a six or seven membered heterocyclic group, wherein X may be a carbon atom, SO₂ or a further hetero atom, selected from the group consisting of **N** or **O**;

if **X** is a carbon atom, **O**, **SO₂** or unsubstituted **N**, then

- **R¹** is hydrogen, hydroxy, cyano, -(CH₂)ₙ-OH, -(CH₂)ₙ-NRR', -(CH₂)ₙ-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 **R¹**, then

- **R¹** is hydrogen, -(CH₂)ₙ-OH, -(CH₂)ₙ-NRR', -(CH₂)ₙ-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;

- **R²** is hydrogen, halogen, lower alkyl, cyano, lower alkoxy substituted by halogen, lower alkyl substituted by halogen or is a five or six membered heteroaryl;

- **R³** is hydrogen or halogen;

- **R⁴** is hydrogen or lower alkyl;

- **n** is 1 or 2; in case **n** is 2, **R¹** may be the same or different;

- **o** is 1 or 2; in case **o** is 2, **R²** 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 to 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

\[
\begin{align*}
\text{(R^3)_p} & \quad \text{(R^1)_n} \\
\text{VII} & \quad \text{X}
\end{align*}
\]

with a compound of formula
to a compound of formula

wherein the definitions have same meanings as described above, or

b) reacting a compound of formula

with a compound of formula

wherein the definitions are as above, or

c) reacting a compound of formula
with a compound of formula

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

to a compound of formula

wherein the definitions are as above,

d) reacting a compound of formula

with a compound of formula

XV-B

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

\[
\begin{align*}
&\text{(R)}_p &\text{Ar} \sim \text{(R)}_o \\
&\text{H} &\text{O} \\
&\text{O} &\text{(X)}_r \\
&\text{Br} &\text{XVI-B}
\end{align*}
\]

with a compound of formula

\[
\begin{align*}
&\text{(R)}_n \\
&\text{H} &\text{N} \\
&\text{X} &\text{X}
\end{align*}
\]

5
to a compound of formula

\[
\begin{align*}
&\text{(R)}_p &\text{Ar} \sim \text{(R)}_o \\
&\text{H} &\text{O} \\
&\text{O} &\text{(X)}_r \\
&\text{N} &\text{X} &\text{(R)}_n &\text{X} \\
&\text{I-D}
\end{align*}
\]

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 \textit{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.
Preparation of derivatives of formula I-A and I-B wherein R⁴ is methyl:

X¹ 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 LiBH₄ yielded the two diastereoisomers 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.
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 diastereoisomers 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.

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:**

- CH2Cl2 = dichloromethane;
- DMAP = dimethylaminopyridine;
- HOBt = 1-hydroxy-benzotriazol hydrat;
- EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
- Et3N = triethylamine;
- EtOAc = ethyl acetate;
- H = hexane;
- RT = room temperature;
- PPh3 = 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 CH2Cl2 was added (1.3 mmol) of EDC, (1.3 mmol) of HOBt and Et3N (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 CH2Cl2. The combined organic phases were dried over Na2SO4 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 CH2Cl2 (10 mL) was treated with Et3N (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 CH2Cl2. The combined organic phases were dried over Na2SO4 and concentrated under vacuo. Purification by preparative HPLC yielded the title compound.

### General procedure III

**Mitsunobu reaction**

PPh3 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 Na₂SO₄. 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 (NR₄R₅)
To a stirred solution of the bromide intermediate XVI-B (1 mmol) in CH₂Cl₂ (20 mL) at RT were added the amine of formula NR₄R₅ (3 mmol) and Et₃N (4 mmol). Stirring was continued overnight. The reaction mixture was washed H₂O and the organic phase was dried over Na₂SO₄. 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.


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 g for 10 min at 4 °C, the pellets were resuspended in the 50 mM Tris-HCl, 4 mM MnCl₂, 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 Kᵢ 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., Zurich, Switzerland) and shaking for 1 h. Inhibition curves were fitted according to the Hill equation:

\[ y = \frac{100}{1 + \left(x/IC_{50}\right)^{nH}} \]

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

\[ K_i = \frac{IC_{50}}{1 + [L]/K_D} \]

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

Tables of the following composition are manufactured in the usual manner:

<table>
<thead>
<tr>
<th>mg / tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
</tr>
<tr>
<td>Lactose</td>
</tr>
<tr>
<td>Corn starch</td>
</tr>
<tr>
<td>Macrocystalline cellulose</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
</tbody>
</table>

Tablet weight 100

Example B

Capsules of the following composition are manufactured:

<table>
<thead>
<tr>
<th>mg / capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
</tr>
<tr>
<td>Lactose</td>
</tr>
<tr>
<td>Corn starch</td>
</tr>
<tr>
<td>Talc</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>mg / supp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
</tr>
<tr>
<td>Suppository mass</td>
</tr>
</tbody>
</table>

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-I

![Chemical structure](image)

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

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 CH2Cl2 (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 CH2Cl2 (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 (SiO2, EtOAc/H2O 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 CH3CN (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. NaHCO3 (basic pH). The organic phases were dried on Na2SO4 and column chromatography (SiO2, CH2Cl2/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) - l-(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 A-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 (SiO2, 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 CH2Cl2 (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 CH2Cl2 (5 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H2O, dried over Na2SO4. Purification by flash chromatography (SiO2, EtOAc) yielded 2.20 g (79%) of the title compound as white solid.

d) [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-pyrrolidin-l-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone
To a stirred solution of (3SR,4RS)-4-(3,4-Dichloro-phenyl)-l-(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 LiBH4 (434 mg, 19.9 mmol). After 2 hours, addition of a second portion of LiBH4 (1.30 g, 59.7 mmol) and stirring was continued for 2 days. The reaction mixture was poured on H2O, extracted with EtOAc and the combined organic phases were dried over Na2SO4. Flash chromatography (SiO2, 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-I and XII-B-I
[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-l-hydroxy-ethyl)-pyrrolidin-l-yl]-4-methanesulfonyl-piperazin-1-yl) -methanone (XII-A-I)
and
[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-l-yl]-4-methanesulfonyl-piperazin-1-yl) -methanone (XII-B-I)
a) 1-[(3SR,4RS)-1-Benzyl-4-(3,4-dichloro-phenyl)-Pyrrolidin-3-yl]-ethanone (IX-I)
A solution of N-(methoxymethyl) -N-(phenylmethyl) -N-(trimethylsilyl)methylamine (32.78 g, 0.138 mol) in CH₂Cl₂ (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 CH₂Cl₂ (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 (SiO₂, CH₂Cl₂/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-I)
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 CH₃CN (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. NaHCO₃ (basic pH). The organic phases were dried on Na₂SO₄ and column chromatography (SiO₂, CH₂Cl₂/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-I)
Using the general procedure II, the coupling between 1-[(3SR,4RS)-1-benzyl-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 (SiO₂, EtOAc).

d) [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-1-hydroxy-ethyl)-pyrrolidin-1-yll-(4- methanesulfonyl-piperazin-1-vD-methanone (XH-A-I) and (3RS,4SR)-3-(3,4-Dichloro-
phenyl)-4-((SR)-1-hydroxy-ethyl)-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)methanone (XH-B-I) 

To a stirred solution of 1-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-pyrrolidin-3-yl]-ethanone (XI-I) (2.00 g, 4.46 mmol) in MeOH (40 mL) at -78°C was added LiBH₄ (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 H₂O. The product was extracted with EtOAc, the combined organic phases were dried over Na₂SO₄. The two diastereoisomers were separated by column chromatography (SiO₂) 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-I) 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-I) as a white solid ES-MS m/e: 450.1 (M+H⁺).

Pyrrolidine intermediates of formula XV

Pyrrolidine XV-B-I

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

![Pyrrolidine XV-B-I](image)

20 a) (RS)-1-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl11-ethanol (XIH-A-I) and
(SR)-1-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl11-ethanol (XIH-B-I)

To a solution of 1-[(3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanone (IX-I) (14.90 g, 0.043 mol) in THF (300 mL) at 0°C were added portionwise LiAIH₄ (2.05 g, 0.051 mol). Stirring was continued for one hour, and the reaction mixture was carefully quenched by addition of aq. NH₄Cl, concentrated under vacuo and the product extracted with EtOAC. The combined organic phases were dried on Na₂SO₄ and concentrated under vacuo. The two diastereoisomers were separated by column chromatography (SiO₂, EtOAc/H, 1:1) to yield (SR)-1-[(3SR,4RS)-1-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl11-ethanol (XIII-B-I) 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-yl11-ethanol (XIII-A-I) 5.30 g (35%) as a white solid ES-MS m/e: 350.2 (M+H⁺).
b) (3RS,4SR)-l-Benzyl-3-(3,4-dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (XIV-B-I)

To a suspension of PPh₃ (PPh₃ polymer bound, 3 mmol PPh₃/g resin) (1.80 g, 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-I) (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 IM, followed by column chromatography (SiO₂, EtOAc/H₂O, 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)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (XV-B-I)

To a solution of (3RS,4SR)-l-benzyl-3-(3,4-dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (XIV-B-I) 0.99 g (2.00 mmol) dissolved in CH₃CN (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. NaHCO₃ (basic pH). The organic phases were dried on Na₂SO₄ and column chromatography (SiO₂, CH₂CVMeOH 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)-l-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine

![XV-B-2](image)

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

To a suspension of PPh₃ (PPh₃ polymer bound, 3 mmol PPh₃/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-I) (1.46 g, 4.17 mmol). The reaction mixture was stirred overnight at RT, filtered on celite and concentrated under vacuo. Extraction with EtOAc/aq.NaOH IM, followed by column chromatography (SiO₂, EtOAc/H₂O, 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-[4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-pyridine (XV-B-2)

To a solution of 2-{(RS)-1-[4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-chloro-pyridine (XIV-B-2) 1.57g (3.40 mmol) dissolved in CH₂CN (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. NaHCO₃ (basic pH). The organic phases were dried on Na₂SO₄ and column chromatography (SiO₂, CH₂CVMeOH 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-[4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-5-trifluoromethyl-pyridine

![Diagram](image.png)

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

To a suspension of PPh₃ (PPh₃ polymer bound, 3 mmol PPh₃/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-[4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethanol (0.41 g, 1.17 mmol, described herein above). The reaction mixture was stirred overnight at RT, filtered on celite and concentrated under vacuo. Extraction with EtOAc/aq.NaOH IM, followed by column chromatography (SiO₂,
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)-l-[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy]-5-trifluoromethyl-pyridine (XV-B-3)

To a solution of 2-([(3RS,4SR)-l-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 (SiO₂, CH₂Cl₂/MeOH 9:1) yielded 0.32 g (87%) of the title compound as a light yellow oil. ES-MS m/e: 405.9 (M+H+).

Pyrrolidine XV-B-4

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

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

To a suspension of PPh₃ (PPh₃ polymer bound, 3 mmol PPh₃/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)-l-[(3RS,4SR)-l-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 (SiO₂, 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)-l-[(3RS,4SR)-4-(3,4-Dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy]-nicotinonitrile (XV-B-4)
To a solution of 6-{(SR)-I-[(3RS,4SR)-l-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile 0.75 g (1.70 mmol) dissolved in CH₃CN (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. NaHCO₃ (basic pH). The organic phases were dried on Na₂SO₄ and column chromatography (SiO₂, CH₂Cl₂/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-I

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

To a stirred solution of (3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (XV-B-I) 0.25 g (0.62 mmol) in CH₂Cl₂ (30 mL) at RT, 0.10 mL (0.74 mmol) OfEt₃N 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 H₂O. The organic phase was dried over Na₂SO₄ and the product was purified by flash chromatography (SiO₂, EtOAc) to yield the title product 0.275 g (85%) as a colorless oil.

Pyrrolidine XVI-B-2

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

To a solution of 6-{(SR)-I-[(3RS,4SR)-l-benzyl-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile 0.75 g (1.70 mmol) dissolved in CH₃CN (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. NaHCO₃ (basic pH). The organic phases were dried on Na₂SO₄ and column chromatography (SiO₂, CH₂Cl₂/MeOH 9:1) yielded 0.36g (60%) of the title compound as a colorless oil. ES-MS m/e: 362.3 (M+H⁺).
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 CH₂Cl₂ (10 mL) at RT, 0.055 mL (0.38 mmol) of Et₃N and 0.032 mL (0.33 mmol) of bromo-acetyl chloride were added. Stirring was continued overnight and then concentrated under vacuo. The crude residue was dissolved in EtOAc, washed with H₂O. The organic phase was dried over Na₂SO₄ and the product was purified by flash chromatography (SiO₂, EtOAc) to yield the title product 0.15 g (92%) as a colorless oil.

**Pyrrolidine XVI-B-4**

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

To a stirred solution of 6-{(SR)-l-[3RS,4SR)-l-(2-Bromo-acetyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxy}-nicotinonitrile (XV-B-4) 30 mg (0.083 mmol) in CH₂Cl₂ (3 mL) at RT, 0.013 mL (0.01 mmol) of Et₃N and 0.0083 mL (0.01 mmol) of bromo-acetyl chloride were added. Stirring was continued overnight and then concentrated under vacuo. The crude residue was dissolved in EtOAc, washed with H₂O. The organic phase was dried over Na₂SO₄ and the product was purified by flash chromatography (SiO₂, EtOAc) to yield the title product 34 mg (85%) as a colorless oil.

**Example 1**

[(3SR,4RS)-3-(4-Chloro-phenoxy)methyl]-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-I),
- 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-I),
- 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-I),
- 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 \text{ (VII-I)}\),
- 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 \text{ (VII-I)}\),
- 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)-l-(4-methanesulfonyl-piperazine-l-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-I),
- Phenol: 4-Hydroxy-benzonitrile (commercially available),
ES-MS m/e: 537.2 (M+H \(^+\)).

Example 7
\([(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-(3-trifluoromethyl-phenoxy)methyl-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone\)

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-I),
- 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-I),
- 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-I),
- 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-I),
- 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-I),
- 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-l-yl]-(4-methanesulfonyl-piperazin-l-yl)-methanone  (VII-I),
- Phenol: 3-Trifluoromethoxy-phenol (commercially available),
ES-MS m/e: 595.6 (M+H +).

Example 13

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

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-
  pyrrolidin-l-yl]-(4-methanesulfonyl-piperazin-l-yl)-methanone  (VII-I),
- 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-l-yl-phenoxymethyl)-pyrrolidin-
  l-yl]-(4-methanesulfonyl-piperazin-l-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-hydroxymethyl-
  pyrrolidin-l-yl]-(4-methanesulfonyl-piperazin-l-yl)-methanone  (VII-I),
- Phenol: 4-Imidazol-l-yl-phenol (commercially available),
ES-MS m/e: 577.6 (M+H+).

Example 15

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

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-I),
- Phenol: 4-Trifluoromethoxy-phenol (commercially available),
ES-MS m/e: 595.6 (M+H+).

Example 16

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

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: \([(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-\{(SR)-l-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-((RS)-l-(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)-l-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-(l-\{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-l-(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-[(R S)-l-(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+).
To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (0.61 g, 2.08 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (20 mL) over 1 hour. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H₂O, dried over Na₂SO₄. 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-I),
- 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)-l-
(4-trifluoromethyl-phenoxy) -ethyl]-pyrrolidin-1-yl]-ethanone (XVI-B-I),
- Amine: N-Methyl-N-piperidin-4-yl-methanesulfonamide (preparation described in the patent GB2000 136),
ES-MS m/e: 635.6 (M+H+).

Example 21

l’-(2-[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-l-(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)-l-
(4-trifluoromethyl-phenoxy) -ethyl]-pyrrolidin-1-yl]-ethanone (XVI-B-I),
- 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)-l-(4-trifluoromethyl-phenoxy)-
ethyl]-pyrrolidin-1-yl]-2-oxo-ethyl]-piperidin-4-yl] -N-methyl-acetamide

Coupling reaction according to general procedure IV:
Example 23

1-{{3RS,4SR}-3-(3,4-Dichloro-phenyl)-4-[i(RS)-l-(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-l-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[i(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (XVI-B-I),
- Amine: 1-Methanesulfonyl-piperazine (commercially available),
ES-MS m/e: 609.4 (M+H+).

Example 24

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

Coupling reaction according to general procedure IV:
- Pyrrolidine intermediate: 2-Bromo-l-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-l-yl}-ethanone (XVI-B-I),
- Amine: 1-Piperazin-l-yl-ethanone (commercially available),
ES-MS m/e: 573.6 (M+H ^+).

Example 25
N-l-(2-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin- l-yl}-2-oxo-ethyl)-piperidin-4-yl]-acetamide

Coupling reaction according to general procedure IV:

Example 26
l-{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-l-yl}-2-(4-hydroxy-piperidin-l-yl)-ethanone

Coupling reaction according to general procedure IV:
- Pyrrolidine intermediate: 2-Bromo-l-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-l-yl}-ethanone (XVI-B-I).
- 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)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-l-yl}-(R)-4-methanesulfonyl-3-methyl-piperazin-l-yl)-methanone

Coupling reaction according to general procedure II:
- Pyrrolidine intermediate: (3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (XV-B-I).
- Carbamoyl chloride: (R)-4-Methanesulfonyl-3-methyl-piperazine-l-carbonyl chloride,
ES-MS m/e: 609.6 (M+H +).

(R)^-Methanesulfonyl-S-methyl-piperazine-l-carbonyl chloride:
First step: To a stirred solution of commercially available (R)-3-methyl-piperazine-l-carboxylic acid tert-butyl ester (8.78 g, 44 mmol) in CH₂Cl₂ (80 mL) at 0°C were added Et₃N (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 CH₂Cl₂. The combined organic phases were dried on Na₂SCu and concentrated under vacuo. The crude product was dissolved in CH₂Cl₂ (50 mL) and TFA (15 mL) was added. After 2 hours at RT, the volatiles were removed under vacuo, the crude was dissolved in CH₂Cl₂ and washed with aq. NaHCO₃ (until pH = 8). The organic phase was dried on Na₂SCu and concentrated under vacuo to yield 2.63 g (34%) of (R)-l-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 CH₂Cl₂ (20 mL) at -78°C, was added a solution of (R)-l-methanesulfonyl-2-methyl-piperazine (1.76 g, 9.9 mmol) and pyridine (1.60 mL, 20 mmol) in CH₂Cl₂ (20 mL) over 1 hour. The temperature was raised to RT, and stirring
was continued over night. The organic phase was washed with H₂O, dried over Na₂SO₄. Concentration under vacuo and flash chromatography (SiO₂, EtOAc/H₂O, 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-I),
- 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 CH₂Cl₂ (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 CH₂Cl₂. The combined organic phases were dried on Na₂SO₄ and concentrated under vacuo. The crude product was dissolved in CH₂Cl₂ (20 mL) and TFA (4 mL) was added. After 2 hours at RT, the volatiles were removed under vacuo, the crude was dissolved in CH₂Cl₂ and washed with aq. NaHCO₃ (until pH = 8). The organic phase was dried on Na₂SO₄ 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 CH₂Cl₂ (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 CH₂Cl₂ (10 mL) over 1 hour. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H₂O, dried over Na₂SO₄.
Concentration under vacuo and flash chromatography (Si θ 2 , EtOAc/H, 1:1) yielded 0.70 g (62%) of (S)-4-methanesulfonyl-3-methyl-piperazine-l-carbonyl chloride as a light yellow solid.

Example 29

\begin{equation}
1-(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-\{((RS)-l-(4-trifluoromethyl-phenoxy) -ethyl\}-pyrrolidin-1-yl\}-5-morpholin-4-yl-pentan-1-one
\end{equation}

Amide coupling according to general procedure I:
- Pyrrolidine intermediate: \((3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-\{((RS)-l-(4-trifluoromethyl-phenoxy) -ethyl\}-pyrrolidine \text{ (XV-B-I)},\)
- Carboxylic acid: 5-Morpholin-4-yl-pentanoic acid (described in \textit{Molecular Structure}, 2001, 560, p.261),
ES-MS m/e: 573.1 (M+H + ).

Example 30

\begin{equation}
[(3SR,4RS)-3-\{(RS)-l-(3,4-Dichloro-phenoxy)-ethyl\}]\-4-(3,4-dichloro-phenyl)-pyrrolidin-\ 1-yl\}-(4-methanesulfonyl-piperazin-\ 1-yl)-methanone
\end{equation}

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: \([(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-\ 1-yl\}-(4-methanesulfonyl-piperazin-\ 1-yl)-methanone \text{ (XII-B-1)},\)
- Phenol: 3,4-Dichloro-phenol (commercially available),
ES-MS m/e: 594.1 (M+H + ).
Example 31

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

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: \([(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-1-yl)-(4-methanesulfonyle-piperazin-1-yl)-methanone \] (XII-B-1),
- Phenol: 4-Methyl-phenol (commercially available),
ES-MS m/e: 540.2 (M+H⁺).

Example 32

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

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: \([(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-1-yl)-(4-methanesulfonyle-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)-l-\[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-l-(4-methanesulfonyle-piperazine-1-carbonyl)-pyrrolidin-3-yl\]-ethoxy\}-benzonitrile
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: \([(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-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)-l-(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)-l-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)-l-(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)-l-hydroxy-ethyl)-pyrrolidin-1-yl]-\(\textit{N}\)-(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-[\textit{L}(R)-1-(4-Chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-\(\textit{N}\)-(4-methanesulfonyl-piperazin-1-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: \[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-1-yl]-\(\textit{N}\)-(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-[\textit{L}(R)-1-(3-Chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-\(\textit{N}\)-(4-methanesulfonyl-piperazin-1-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: \[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-1-yl]-\(\textit{N}\)-(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)-l-(4-methoxy-phenoxy)-ethyl]-pyrroli- 

din-l-yl\}-(4-methanesulfonyl-piperazin-l-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: \{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy- 

ethyl)-pyrroli-din- l-yl\}-(4-methanesulfonyl-piperazin- l-yl)-methanone (XII-B- 1),

- Phenol: 4-Methoxy-phenol (commercially available),
ES-MS m/e: 558.3 (M+H +).

Example 39

\{(3SR,4RS)-3-[l-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrroli- 

din- l-yl\}-(4-methanesulfonyl-piperazin- l-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: \{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy- 

-eethyl)-pyrroli-din-l-yl\}-(4-methanesulfonyl-piperazin-l-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-[l-(6-Chloro-pyridin-3-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)- 

-pyrroli-din-l-yl\}-(4-methanesulfonyl-piperazin-l-yl)-methanone
Mitsunobu reaction according to general procedure III:

- Pyrrolidine intermediate: \([(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone\) (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)-l-(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: \([(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-1-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone\) (XII-B-1),

- Phenol: 3-Chloro-4-fluoro-phenol (commercially available),

ES-MS m/e: 579.0 (M+H⁺).

Example 42

\([(3SR,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-l-(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)-l-hydroxy-ethyl)-pyrrolidin-\text{-}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\textsuperscript{+}).

Example 43
{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-l-(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)-l-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\textsuperscript{+}).

Example 44
{(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-[(RS)-l-(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)-l-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\textsuperscript{+}).
Example 45

4-{(SR)-1-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-l-(4-methanesulfonyl-piperazine-l-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-l-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-l-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)-l-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]-l-(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)-l-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)-l-(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)-l-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)-l-(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-l-{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[((RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-ethanone (XVI-B-I),
- 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)-l-(5-fluoro-pyrimidin-2-yloxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: 
\[(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-hydroxy-ethyl)-pyrrolidin-1-yl\] - (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)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidin-1-yl}-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-methanone

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

To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (29 mg, 0.098 mmol) in CH2Cl2 (2 mL) at -78 °C, was added a solution of (3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(RS)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine (intermediate XV-B-D (100 mg, 0.25 mmol) and pyridine (0.043 mL, 0.54 mmol) in CH2Cl2 (2 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued overnight. The organic phase was washed with H2O, dried over Na2SO4, and 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)-l-(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)-l-(4-trifluoromethyl-phenoxy)-ethyl]-pyrrolidine-1-carbonyl chloride (58 mg, 0.12 mmol) in CH2Cl2 (2 mL) were added Et3N (0.02 mL, 0.15 mmol) and dimethyl-(2-piperazin-l-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 (SiO2, CH2Cl2/MeOH/NH3, 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

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

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-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

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

Coupling reaction according to general procedure II:
- Pyrrolidine intermediate: 5-Chloro-2-\{((RS)-l-[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl] -ethoxy\} -pyridine (XV-B-2),
- Carbamoyl chloride: (R)-4-Methanesulfonfyl-3-methyl-piperazine-1-carbonyl chloride, ES-MS m/e: 577.2 (M+H +).

Example 55

1\{[(3SR,4RS)-3-[(RS)-l-(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)-l-\[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl\] -ethoxy\} -pyridine (XV-B-2),
- Carboxylic acid: 5-Morpholin-4-yl-pentanoic acid (described in \textit{Molecular Structure}, 2001, 560, p.261),
ES-MS m/e: 542.3 (M+H +).

Example 56

\[(3SR,4RS)-3-\{(RS)-l-(5-Chloro-pyridin-2-yloxy)-ethyl\}-4-(3,4-dichloro-phenyl)-pyrroldin-1-yl\]-[4-(2-dimethylamino-ethyl)-piperazine-1-yl]-methanone

\[\text{To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (22 mg, 0.074 mmol) in CH2Cl2 (3 mL) at -78 }^\circ\text{C, was added a solution of 5-chloro-2-\{(RS)-l-\[(3SR,4RS)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl\] -ethoxy\} -pyridine (intermediate XV-B-2) (70 mg, 0.19 mmol) and pyridine (0.033 mL, 0.41 mmol) in CH2Cl2 (2 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H2O, dried over Na2SCU. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H2O, 1:1) yielded 80 mg (98%) of the title compound as a light yellow solid.}

b) \[(3SR,4RS)-3-\{(RS)-l-(5-Chloro-pyridin-2-yloxy)-ethyl\}-4-(3,4-dichloro-phenyl)-pyrroldin-1-yl\]-[4-(2-dimethylamino-ethyl) -piperazine-1-yl]-methanone
To a stirred solution of (3RS,4RS)-3-[(RS)-l-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl) -pyrrolidine- 1-carbonyl chloride (80 mg, 0.18 mmol) in CH2Cl2 (2 mL) were added Et3N (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 (SiO2, CH2Cl2/MeOH/NH3, 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)-l-(5-fluoro-pyridin-2-yloxy)-ethyl]- pyrrolidin-l-yl)-(4-methanesulfonyl-piperazin-l-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-l-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)-l-(5-methyl-pyridin-2-yloxy)-ethyl]- pyrrolidin-l-yl}-(4-methanesulfonyl-piperazin-l-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((RS)-l-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)-l-(5-fluoro-pyridin-2-yloxy)-ethyl]-
pyrrolidin-l-yl]-(4-methanesulfonyl-piperazin-l-yl)-methanone

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-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)-l-[(3SR,4RS)-4-(3,4-Dichloro-phenyl)-l-(4-methanesulfonyl-piperazine-l-
carbonyl)-pyrrolidin-3-yl]-ethoxy]-nicotinonitrile

Mitsunobu reaction according to general procedure III:
- Pyrrolidine intermediate: [(3RS,4SR)-3-(3,4-Dichloro-phenyl)-4-((SR)-l-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-l-(5-Chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-
pyrrolidin-l-yl]-[2-oxa-6-aza-spiro[3.3]hept-6-yl]-methanone
To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (48 mg, 0.16 mmol) in CH2Cl2 (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 CH2Cl2 (5 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued overnight. The organic phase was washed with H2O, dried over Na2SO4. 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.

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 CH2Cl2 (3 mL) were added Et3N (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 (SiO2, 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-r(RS)-l-(5-Chloro-pyridin-2-yloxy)-ethyl-4-(3,4-dichloro-phenyl)pyrrolidine-1-carbonyl chloride

To a stirred solution of carbonic acid ditrichromethyl ester (triphosgene) (48 mg, 0.16 mmol) in CH2Cl2 (10 mL) at -78 °C, was added a solution of 5-chloro-2-[(RS)-I-[(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 CH2Cl2 (5 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued overnight. The organic phase was washed with H2O, dried over Na2SCU. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H2O, 1:1) yielded 90 mg (50%) of the title compound as a viscous colorless oil.

b) 2-[(3SR,4RS)-3-[(RS)-l-(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)-l-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl) -pyrrolidine-1-carbonyl chloride (22 mg, 0.051 mmol) in CH2Cl2 (3 mL) were added Et3N (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 (SiO2, 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-yloxyethyl)-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-I),
- Phenol: 5-Chloro-pyridin-2-ol (commercially available),
ES-MS m/e: 549.2 (M+H +).
Example 64

N-(l-{2-[(3SR,4RS)-3-[(RS)-l-(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-l-[(3SR,4RS)-3-[(RS)-l-(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-(l-{2-[(3SR,4RS)-3-[(RS)-l-(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-l-[(3SR,4RS)-3-[(RS)-l-(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)-l-[(3SR,4RS)-3-[(RS)-l-(4-chloro-phenoxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-ethanone
Coupling reaction according to general procedure IV:
- Pyrrolidine intermediate: 2-Bromo-l-[(3SR,4RS)-3-[(RS)-l-(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
l-[(3S,4R)-3-[(R)-l-(5-Chloro-pyridin-2-yloxy)-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-l-[(3SR,4RS)-3-[(RS)-l-(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
l-[(3S,4R)-3-[(R)-l-(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-l-[(3SR,4RS)-3-[RS]-l-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichlorophenyl)-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)-l-(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)-l-[(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-{(3SR,4SR)-1-[2-(4-Cyano-piperidin-1-yl)-acetyl]-4-(3,4-dichlorophenyl)-pyrrolidin-3-yl.ethoxy]-nicotinonitrile
Coupling reaction according to general procedure IV:
- **Pyrrolidine intermediate:** 6-{(SR)-l-[(3RS,4SR)-l-(2-Bromo-acetyl)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxyj-nicotinonitrile (XVI-B-4),
- **Amine:** Piperidine-4-carbonitrile (commercially available),

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

**Example 71**

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

![Chemical structure](image)

10 a) (3RS,4SR)-3-{(SR)-l-(5-Cvano-pyridin-2-yloxy)-ethyll-4-(3,4-dichloro-phenyl)-pyrrolidine-1-carbonyl氯化物

To a stirred solution of carbonic acid ditrichloromethyl ester (triphosgene) (67 mg, 0.22 mmol) in CH₂Cl₂ (14 mL) at -78 °C, was added a solution of 6-{(SR)-l-[(3RS,4SR)-4-(3,4-dichloro-phenyl)-pyrrolidin-3-yl]-ethoxyj-nicotinonitrile (intermediate XV-B-4) (210 mg, 0.56 mmol) and pyridine (0.10 mL, 1.23 mmol) in CH₂Cl₂ (7 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H₂O, dried over Na₂SO₄. 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]-ethoxyl-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 CH2Cl2 (4 mL) were added Et3N (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 (SiO2, EtOAc) to yield 24 mg (69%) of the title compound as a 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 CH2Cl2 (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 CH2Cl2 (1 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued overnight. The organic phase was washed with H2O, dried over Na2SO4. Concentration under vacuo yielded and column chromatography (SiO2, EtOAc/H2O, 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 13SR,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 CH2Cl2 (3 mL) were added Et3N (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$_2$CVMelOH 98/2) to yield 14 mg (40%) of 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)-l-(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 2-\{((SR)-l-[(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$_2$Cl$_2$ (1 mL) over 30 minutes. The temperature was raised to RT, and stirring was continued over night. The organic phase was washed with H$_2$O, dried over Na$_2$SO$_4$. Concentration under vacuo yielded and column chromatography (SiO$_2$, EtOAc/H$_2$O, 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)-l-(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 13SR,4RS)-3-(3,4-dichloro-phenyl)-4-[(SR)-l-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-pyrrolidin-1-carbonyl chloride (30 mg, 0.064 mmol) in CH$_2$Cl$_2$ (3 mL) were added Et$_3$N (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 of the title compound as a white solid. ES-MS m/e: 530.1 (M+H$^+$).
1. A compound of formula

\[
\begin{array}{c}
\text{(R}^3\text{)}_p \quad \text{N} \quad X \\
\quad \text{Ar)=(R}^2\text{)}_c \\
\quad \text{O} \quad \text{H} \\
\quad s \quad \text{N} \quad \text{X} \\
\quad \text{O} \quad \text{K} \quad (\text{R}^1\text{)}_n
\end{array}
\]

wherein

\( \text{Ar} \) is aryl or a five or six membered heteroaryl;

\( X \) is a six to nine membered mono or bi-heterocyclic group, wherein \( X \) may be a carbon atom, SO2 or a further hetero atom, selected from the group consisting of N or O;

if \( X \) is a carbon atom, O, SO2 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

\[
\begin{array}{c}
\text{N} \\
\text{N-R}^1 \\
\text{or N-R}^1 \\
\text{N} \\
\end{array}
\]

is

and Ar is phenyl.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5

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

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

N

5. A compound of formula I according to claim 2, wherein X 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]-(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

[(3RS,4SR)-3-(5-chloro-pyridin-2-yloxy)methyl]-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.

{(3RS,4SR)-3-(3,4-dichloro-phenyl)-4-[(SR)-1-(4-fluoro-phenoxy)-ethyl]-pyrrolidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone.
7. A compound of formula I according to claim 2, wherein

\[
\begin{align*}
\text{N} \equiv & \begin{array}{c}
\text{N} - R_1^2 \quad \text{or} \quad \text{N} - R_1^2
\end{array} \\
\text{Ar} & \text{ is pyrimidinyl}
\end{align*}
\]

and \( \text{Ar} \) is pyrimidinyl.

8. A compound of formula I according to claim 7, wherein the compounds are

\[
\begin{align*}
&\{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-\{(RS)-1-(4-chloro-phenoxy)-ethyl\}-pyrrolidin-1-yl\}\text{- methanone} \\
&\{(3SR,4SR)-3-(3,4-dichloro-phenyl)-4-\{(RS)-1-(5-fluoro-pyrimidin-2-yloxy)-ethyl\}-pyrrolidin-1-yl\}\text{- methanone} \\
&\{(3RS,4SR)-3-\{(RS)-1-(5-chloro-pyrimidin-2-yloxy)-ethyl\}-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl\}\text{- methanone}.
\end{align*}
\]

9. A compound of formula I according to claim 2, wherein

\[
\begin{align*}
\text{N} \equiv & \begin{array}{c}
(\text{R}_3^n) \\
\text{Ar} & \text{ is phenyl}
\end{array} \\
\text{N} & \text{ is}
\end{align*}
\]

and \( \text{Ar} \) is phenyl.

10. A compound of formula I according to claim 9, wherein the compounds are

\[
\begin{align*}
&\text{N-}\{(3SR,4SR)-3-(3,4-dichloro-phenyl)-4-{\{(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl\}}-pyrrolidin-1-yl\}\text{- methanone} \\
&\text{N-}\{(3SR,4SR)-3-(3,4-dichloro-phenyl)-4-{\{(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl\}}-piperidin-4-yl\}\text{- N-methyl-methanesulfonamide} \\
&\text{N-}\{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-{\{(RS)-1-(4-trifluoromethyl-phenoxy)-ethyl\}}-piperidin-4-yl\}\text{- N-methyl-methanesulfonamide} \\
&\text{N-}\{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-\{(RS)-1-(4-chloro-phenoxy)-ethyl\}\}-2-oxo-ethyl\}\text{- piperidin-4-yl\text{- acetamide}} \\
&\text{N-}\{(3SR,4RS)-3-(3,4-dichloro-phenyl)-4-\{(RS)-1-(4-chloro-phenoxy)-ethyl\}\}-2-oxo-ethyl\}\text{- piperidin-4-yl\text{- acetamide}} \\
&\text{N-}\{(3SR,4RS)-3-\{(RS)-1-(4-chloro-phenoxy)-ethyl\}\}\text{- methanone}.
\end{align*}
\]
11. A compound of formula I according to claim 2, wherein

\[ \text{is} \]

\[ \text{or} \]

and Ar is pyridyl.

12. A compound of formula I according to claim 11, wherein the compounds are

1-

\[([3S,4R]-3-[(R)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-4-(3,4-dichloro-phenyl)-pyrrolidin-1-yl]-5-morpholin-4-yl-pentanone \]

6-

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

10

6-

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

13. A compound of formula I according to claim 2, wherein

\[ \text{is} \]

\[ \text{or} \]

and Ar is pyridyl.

14. A compound of formula I according to claim 13, wherein the compounds are

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

2-

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

1\[

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-(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
with a compound of formula

\[
\text{HO-Ar-(R}^2)\text{)}
\]

to a compound of formula

\[
\text{I-C}
\]

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

b) reacting a compound of formula

\[
\text{XII-B}
\]

with a compound of formula

\[
(\text{RV} \quad \text{Ar} \quad \text{OH})
\]
to a compound of formula

(wherein the definitions are as in claim 1, or)
c) reacting a compound of formula

with a compound of formula

(wherein the definitions are as in claim 1,)
d) reacting a compound of formula

with a compound of formula
to a compound of formula

\[
\begin{align*}
\text{I-B}
\end{align*}
\]

wherein \(X^1\) is halogen, and the other definitions are as in claim 1.

e) reacting a compound of formula

\[
\begin{align*}
\text{XVI-B}
\end{align*}
\]

with a compound of formula

\[
\begin{align*}
\text{I-D}
\end{align*}
\]

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.

***
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

| INV. | C07D207/08 | C07D401/06 | C07D401/14 | C07D403/06 | C07D403/14 | C07D487/04 | C07D491/04 | C07D491/10 | A61K31/4468 | A61K31/496 | A61K31/506 | A61K31/5377 | A61P23/00 | A61P25/00 | A61P25/16 |
|------|------------|------------|------------|------------|------------|------------|------------|------------|-------------|-------------|------------|------------|------------|------------|------------|------------|

According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**EPO-Internal, WPI Data, BEILSTEIN Data**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>EP 0 714 891 A (LILLY CO ELI [US]) 5 June 1996 (1996-06-05) page 149, line 3 - line 45; claim 1</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

- **X** Special categories of cited documents
  - 'A' document defining the general state of the art which is not considered to be of particular relevance
  - 'E' earlier document but published on or after the international filing date
  - 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - 'O' document referring to an oral disclosure, use, exhibition or other means
  - 'P' document published prior to the international filing date but later than the priority date claimed
  - 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  - '*A' document member of the same patent family

Date of the actual completion of the international search: 30 October 2008

Date of mailing of the international search report: 06/11/2008

Name and mailing address of the ISA/Authorized officer

European Patent Office, P B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3018

Gettins, Marc

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