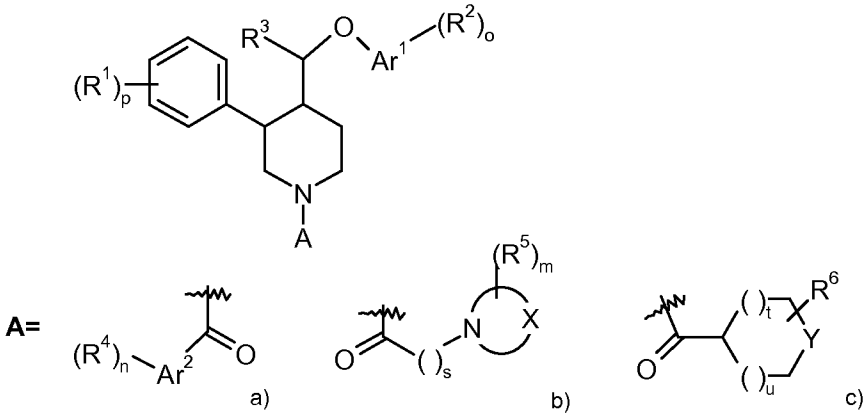
PIPERIDINE DERIVATIVES AS NK3 RECEPTOR ANTAGONISTS

The present invention relates to a compounds of formula I



wherein

Ar^1 is aryl or a six membered heteroaryl;

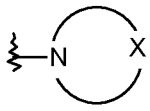
Ar^2 is aryl or a six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen or lower alkyl;

R^4 is hydrogen, lower alkyl, phenyl, optionally substituted by halogen, or is a five membered heteroaryl, optionally substituted by lower alkyl, or is aryl optionally substituted by halogen;

 is a six membered heterocyclic group, wherein X is $-N(SO_2CH_3)$;

R^6 is hydrogen;

Y is $-N(R^{7'})-$

$R^{7'}$ is a 6-membered heteroaryl group, optionally substituted by cyano or C(O)-cycloalkyl, wherein the cycloalkyl group is optionally substituted by lower alkyl,

n is 1;

m is 1;

o is 1;

p is 1;

s is 0;

t is 1;

u is 1;

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

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

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

The three main mammalian tachykinins, substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) belong to the family of neuropeptides sharing the common COOH-terminal pentapeptide sequence of Phe-X-Gly-Leu-Met-NH_2. As neurotransmitters, these peptides exert their biological activity via three distinct neurokinin (NK) receptors termed as NK-1, NK-2 and NK-3. SP binds preferentially to the NK-1 receptor, NKA to the NK-2 and NKB to the NK-3 receptor.

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

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

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

In recent years clinical studies with selective NK1 and NK2 receptor antagonists appeared in the literature showing results for the treatment of emesis, depression, anxiety, pain and migraine (NK1) and asthma (NK2 and NK1). The most exciting data were produced in the treatment of chemotherapy-induced emesis, nausea and depression with NK1 and in asthma with NK2- receptor antagonists. In contrast, no clinical data on NK3 receptor antagonists have appeared in the literature until 2000. Osanetant (SR 142,801) from Sanofi-Synthelabo was the first identified potent and selective non-peptide antagonist described for the NK3 tachykinin receptor for the potential treatment of schizophrenia, which was reported in the literature (*Current Opinion in Investigational Drugs, 2001,2(7), 950-956 and Psychiatric Disorders Study 4, Schizophrenia, June 2003, Decision Recources, Inc., Waltham, Massachusetts)*. The proposed drug SR 142,801 has been shown in a phase II trial as active on positive symptoms of schizophrenia, such as altered behaviour, delusion, hallucinations, extreme emotions, excited motor activity and incoherent speech, but inactive in the treatment of negative symptoms, which are depression, anhedonia, social isolation or memory and attention deficits.

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

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

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

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

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

The term "lower alkyl substituted by halogen" denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by halogen, for example $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CH_2CH_2CF_3$, $-CH_2CF_2CF_3$ and the like. Preferred lower alkyl substituted by halogen groups are groups having 1-4 carbon atoms.

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

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

The term "aryl" denotes a cyclic aromatic hydrocarbon radical consisting of one or more fused rings containing 6-14 carbon atoms in which at least one ring is aromatic in nature, for example phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl or indanyl. Preferred is the phenyl group.

The term "five or six membered heteroaryl" denotes a cyclic aromatic hydrocarbon radical consisting of one or more fused rings containing 5-14 ring atoms, preferably containing 5-10 ring atoms, in which at least one ring is aromatic in nature, and which contains at least one heteroatom, selected from N, O or S, for example quinoxalinyl, dihydroisoquinolinyl, pyrazin-2-yl, pyrazolyl, 2,4-dihydro-pyrazol-3-one, pyridinyl, pyridazinyl, isoxazolyl, benzo[1,3]dioxol, pyrimidin-4-yl, pyrimidin-5-yl, benzotriazol-5-yl, indolyl, benzoimidazol-5-yl, [1,3,4]-oxadiazolyl, [1,2.4]triazol-1-yl, [1,6]naphthyridin-2-yl, imidazo[4,5-b]pyridine-6-yl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, furyl, imidazol-1-yl, or benzofuranyl. Preferred five or six

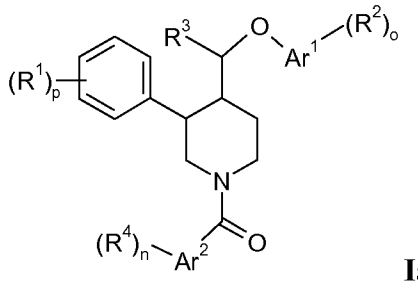
membered heteroaryl group are indolyl, pyridinyl, pirimidinyl, pyridazinyl or [1,2,4]oxadiazol-3 and 5-yl.

The term "six membered heterocyclic group" denotes a piperazinyl group.

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

The following structures are encompassed by formula I of the present invention:

Compounds of formula Ia:



Ia

wherein

Ar^1 is aryl or a six membered heteroaryl;

Ar^2 is aryl or a six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen or lower alkyl;

R^4 is hydrogen, lower alkyl, phenyl, optionally substituted by halogen, or is a five membered heteroaryl, optionally substituted by lower alkyl, or is aryl optionally substituted by halogen;

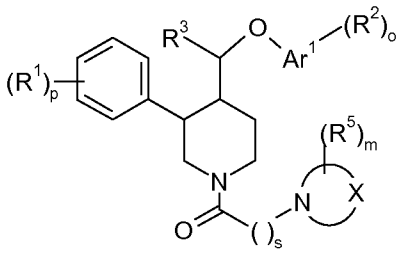
n is 1;

o is 1;

p is 1;

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

Compounds of formula Ib:



Ib

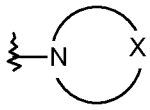
wherein

Ar^1 is aryl or a six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen or lower alkyl;



is a six membered heterocyclic group, wherein X is $-N(SO_2CH_3)$;

m is 1;

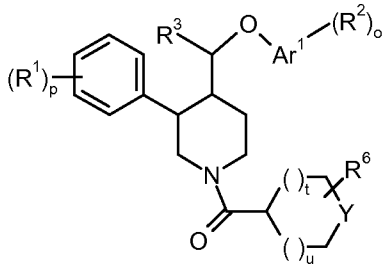
o is 1;

p is 1;

s is 0;

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

Compounds of formula Ic:



Ic

wherein

Ar^1 is aryl or a six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen or lower alkyl;

Y is $-N(R^{7'})-$;

$R^{7'}$ is a 6-membered heteroaryl group, optionally substituted by cyano or C(O)-cycloalkyl, wherein the cycloalkyl group is optionally substituted by lower alkyl;

R^6 is hydrogen;

p is 1;

o is 1;

t is 1;

u is 1;

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

Preferred compounds of formula Ia are those, wherein Ar^1 is a six membered heteroaryl and Ar^2 is aryl, for example the following compounds

[(3RS,4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

[(3RS,4RS)-3-(4-chloro-phenyl)-4-(5-trifluoromethyl-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanone

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanone

6-((S)-1-{(3S,4S)-3-(4-chloro-phenyl)-1-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile

6-((S)-1-{(3S,4S)-3-(4-chloro-phenyl)-1-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile

6-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-1-(4'-fluoro-biphenyl-4-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile or

[(3SR,4SR)-4-(5-chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone.

Preferred compounds of formula Ia are further those, wherein both Ar^1 and Ar^2 are six membered heteroaryl, for example the following compounds

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(6-methyl-pyridazin-4-yl)-methanone

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(6-methyl-pyridazin-4-yl)-methanone or

6-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-1-(6-methyl-pyridazine-4-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile.

Further preferred compounds are compounds of formula Ib, wherein Ar^1 is a six membered heteroaryl and X is $-N(SO_2CH_3)$, for example the following compounds

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone

6-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile

Preferred compounds of formula Ic are those, wherein Ar^1 is a six membered heteroaryl and Y is $NR^{7'}$, for example the following compounds

{4-[(3RS,4RS)-3-(4-chloro-phenyl)-4-(5-trifluoromethyl-pyridin-2-yloxymethyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone

{4-[(3RS,4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone

(4-{(3SR,4SR)-3-(4-chloro-phenyl)-4-[(SR)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

(4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

(4-{(3R,4R)-3-(4-chloro-phenyl)-4-[(R)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

6-((S)-1-{(3S,4S)-3-(4-chloro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-cyano-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

{4-[(3SR,4SR)-4-(5-chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone

4-[(3S,4S)-4-(5-chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-carbonitrile

4-[(3S,4S)-4-(5-chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(4-trifluoromethyl-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(4-cyano-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(4-fluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(3,4-difluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-[(3S,4S)-4-[(S)-1-(4-chloro-phenoxy)-ethyl]-3-(4-chloro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(3-fluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-[(3S,4S)-3-(4-chloro-phenyl)-4-((S)-1-p-tolyloxy-ethyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

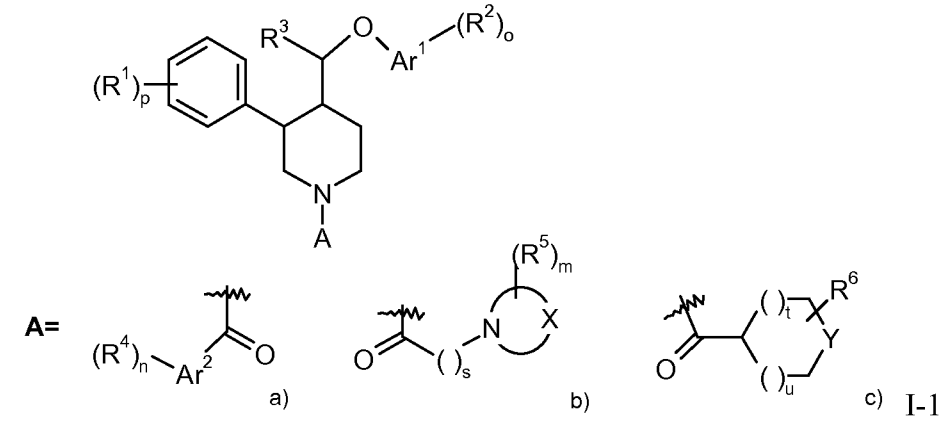
4-{(3S,4S)-3-(4-cloro-phenyl)-4-[(S)-1-(5-methyl-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-fluoro-pyrimidin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-[(3S,4S)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-

carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile
{4-[(3S,4S)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone
4-[(3S,4S)-4-[(S)-1-(5-cyano-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile
6-((S)-1-{(3S,4S)-3-(3,4-difluoro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile or
4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(SR)-1-(5-cyano-pyridin-2-ylamino)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile.

An embodiment of the invention are compounds of formula I-1



I-1

wherein

Ar^1 is aryl or a five or six membered heteroaryl;

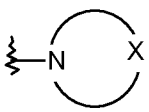
Ar^2 is aryl or a five or six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen, lower alkyl or CH_2OH;

R^4 is hydrogen, halogen, lower alkyl, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen, S-lower alkyl, $-S(O)_2$-lower alkyl, $-S(O)_2$-di-lower alkyl amino, $-(CH_2)_qR$, cyano, amino, mono or di-lower alkyl amino, NHC(O)-lower alkyl, cycloalkyl or is a five membered heteroaryl, optionally substituted by lower alkyl; wherein R is cyano, di-lower alkyl amino or pyrrolidin-1-yl;



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

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

R^5 is 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^5, then

R^5 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^6 is hydrogen, lower alkyl or hydroxy;

Y is $-CH(R^7)-$, $-N(R^{7'})-$ or –O-;

R^7 is hydrogen, hydroxy, =O, lower alkyl, $-S(O)_2$-lower alkyl, –C(O)-lower alkyl, $-C(O)CH_2O$-lower alkyl, $-CH_2CN$, $-C(O)CH_2CN$, -C(O)-cycloalkyl wherein the cycloalkyl group is optionally substituted by cyano, lower alkyl, one or two halogen atoms, =O or by amino, or is -C(O)O-lower alkyl, -NH-lower alkyl, $-NR^8C(O)O$-lower alkyl, $-NR^8C(O)$-lower alkyl or $-CH_2O$-lower alkyl; and

$R^{7'}$ is hydrogen, lower alkyl, $-S(O)_2$-lower alkyl, –C(O)-lower alkyl, $-C(O)CH_2$-O-lower alkyl, $-CH_2CN$, -C(O)CN, $-C(O)CH_2CN$, or C(O)-cycloalkyl, wherein the cycloalkyl group is optionally substituted by cyano, lower alkyl, one or two halogen atoms, =O or by amino, or is -C(O)O-lower alkyl or $-CH_2O$-lower alkyl;

R^8 is hydrogen or lower alkyl; or

R^6 and R^7 may form together with the carbon atoms to which they are attach a five or six-membered non aromatic ring or

R^6 and $R^{7'}$ may form together with the nitrogen and carbon atoms to which they are attach a five or six-membered non aromatic ring;

n is 1, 2 or 3; in case n is 2 or 3, R^4 may be the same or different;

m is 1 or 2; in case m is 2, R^5 may be the same or different;

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

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

q is 1, 2 or 3;

s is 0, 1, 2, 3 or 4

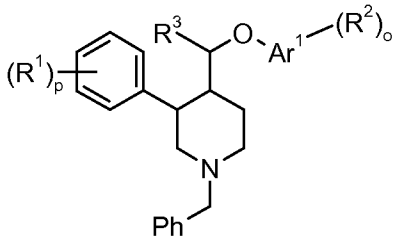
t is 0 or 1, or is 2 when u is 0; or

u is 0 or 1 when t is 1;

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

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

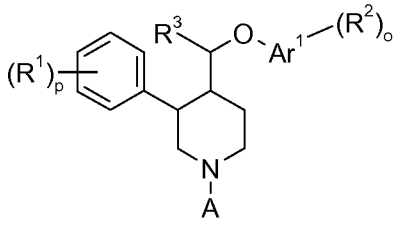
a) coupling a compound of formula



VIII

with a corresponding compound of formula A-Hal

to a compound of formula



I

wherein Hal is Cl, Br or I and the other definitions are as described above, and, if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

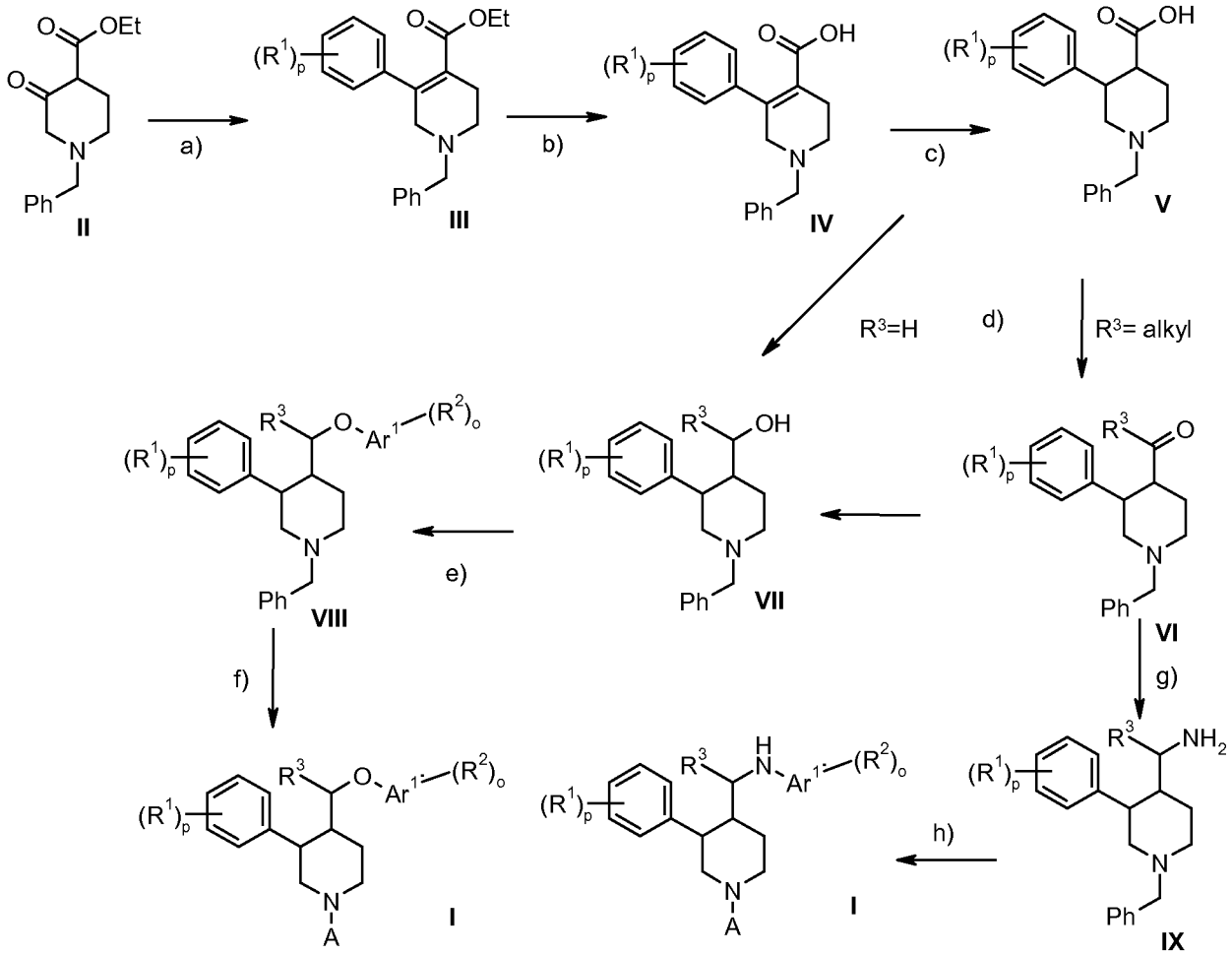
General synthetic scheme:

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 scheme. 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 given above. Appropriate

reaction conditions for the individual reaction steps are known to a person skilled in the art. Also, for reaction conditions described in literature affecting the described reactions see for example: *Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999*). The described reactions can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It is convenient to carry out the described reactions in a temperature range between -78 °C to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield the described intermediates and compounds.The reaction sequence is not limited to the one displayed in scheme 1, 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.

Scheme 1



a) It is convenient to react keto-ester **II** under basic conditions with triflic anhydride and subsequently under Palladium catalysis with boronic acid to access derivatives **III**.

b) The ester functionality in **III** is cleaved under basic aqueous conditions to access acid derivatives **IV**.

c) Reduction of the double bond in **IV** to access **V** can be done under various conditions with several metal catalysts and hydrogen under varying pressure. Chirality can be induced at this step.

d) Introduction of R_3 at this stage can be done in several ways. For R_3=H it is convenient to transform **V** to an intermediately built ester which optionally can be epimerised under basic conditions and subsequently reduced to the corresponding alcohol **VII**. In case R_3=alkyl acid **V** can optionally be transformed to the respective Weinreb amide which can be reacted with alkyl-

Grignard reagents to access ketone **VI**, which can optionally be epimerised at this stage. The resulting ketone can be reduced to the corresponding alcohol **VII**.

e) Alcohol **VII** can be transformed to ether derivatives **VIII** in various ways. We find it convenient to perform a nucleophilc substitution reaction or a Mitsunobu reaction.

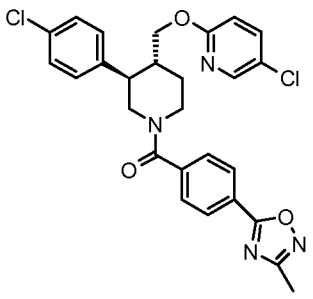
f) The transformation of derivatives **VIII** can be done by removal of the N-benzyl group under various ways and subsequent coupling with the appropriate A-X under various conditions to access the final compounds **I**.

g) Conversion of the ketone functionality in **VI** to access amine **IX** can be done under various conditions, however, we find it convenient to prepare the respective oxime from **VI** and subsequently reduce it.

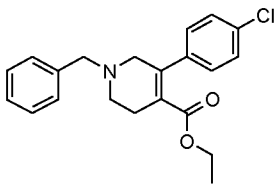
h) Amine **IX** can conveniently be coupled with aromatic electrophiles to introduce $Ar^1(R^2)o$. Subsequently, transformation of these derivatives can be done by removal of the N-benzyl group under various ways and subsequent coupling with the appropriate A-X under various conditions to access the final compounds **I**.

Example 1

[(3RS,4RS)-3-(4-Chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

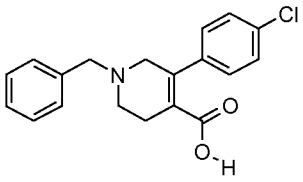


a) 1-Benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester



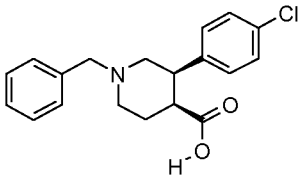
In a 1500 mL four necked flask (with mechanical stirrer) 22 g (84.2 mmol) ethyl N-benzyl-3-oxo-4-piperidine-carboxylate (from the HCl-salt by aq.Na_2CO_3/CH_2Cl_2-extraction) and 43.5 mL (252 mmol) DIPEA were dissolved in 300 mL DCM. The amber solution was cooled to -20 °C to -30 °C. 28.5 g (101 mmol) trifluoromethanesulfonic anhydride were added drop wise over a period of 45 min. The dark brown solution was stirred for 2 h at -20 °C/-30 °C. 300 mL water and 300 mL 10 % Na_2CO_3 aq. was added and the mixture was stirred for 15 min at 5-10 °C. The organic layer was separated and the aqueous layer was extracted twice with 150 mL DCM. The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was evaporated to dryness and dissolved in 500 mL dioxane. 15.8 g (101 mmol) 4-chlorophenylboronic acid, 93 mL Na_2CO_3 aq. (2M) and 3.8 g (3.36 mmol) tetrakis(triphenylphosphine)palladium(0) was added and the mixture was heated to reflux over night. After cooling to room temperature, the mixture was diluted with 400 g ice-water and extracted twice with 400 mL ethyl acetate. The organic layers were extracted once with 500 mL brine. After drying over Na_2SO_4 the filtrate was evaporated to dryness. The black oil was absorbed on 60 g isolute HM-N and purified by column chromatography to yield 14.6 g (48 %) of the title compound as viscous yellow oil. MS (m/e): 356.3 $[(M+H)^+]$.

b) 1-Benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid



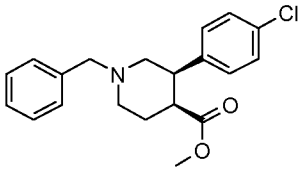
A mixture of 0.555 g (1.26 mmol) 1-benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester and 261 mg (6.2 mmol) $LiOH.H_2O$ in 15 mL THF and 5 mL water was stirred at room temperature over night. The mixture was evaporated to dryness, taken up in ethyl acetate, acidified with HCl to pH=1 and extracted with ethyl acetate. The combined organic layers were washed with water, evaporated to dryness and the residue was subjected to preparative HPLC chromatography on reversed phase eluting with a gradient formed from acetonitrile, water and formic acid to yield after evaporation of the product containing fractions 0.254 g (50 %) of the title compound as white solid. MS (m/e): 328.2 $[(M+H)^+]$.

c) (3RS, 4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid



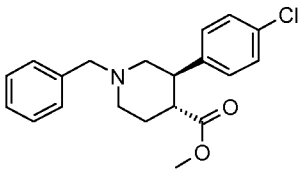
A 185-mL stainless steel autoclave was charged under argon in a glove box (O_2 content < 2 ppm) with the hydrochloride salt of 1-benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid (7.00 g, 21.36 mmol), [Ru(OAc)$_2$((*R*)- (6,6'-dimethoxybiphenyl-2,2'-diyl)bis(di-2-furylphosphine)] (81.30 mg, 0.11 mol), [Ru(OAc)$_2$((*S*)- (6,6'-dimethoxybiphenyl-2,2'-diyl)bis(di-2-furylphosphine)] (81.30 mg, 0.11 mol), triethylamine (3.00 mL, 21.42 mmol) and methanol (120 mL). The hydrogenation was run for 20 h at 30 °C under 40 bar of hydrogen. After the pressure was released, the white suspension was evaporated to dryness to yield 9.58 g of the crude title compound. The crude product was dissolved in 1 M NaOH (45 mL). TBME (50 mL) was added, the aqueous layer was separated and diluted with water (250 mL). Under stirring 2 M HCl (20.5 mL) was added (pH value = 6.0). The formed precipitate was filtered off and washed with water (50 mL). The filter cake was dissolved in methanol (100 mL) and the colourless solution evaporated to dryness to yield 5.13 g (70 %) of the title compound. MS (m/e): 330.2 [(M+H)$^+$].

d) (3RS, 4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methyl ester



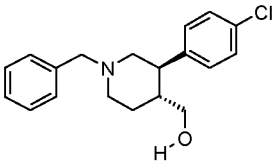
In a 500 ml round bottom flask with a magnetic stirring bar 3 g (9 mmol) (3RS, 4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid (SM050/4A) were suspended in 100 ml methanol. 50 mL 1.25 N HCl/MeOH was added and the mixture was stirred over night at reflux (76°C). Another 50 mL 1.25 N HCl/MeOH was added and the reaction mixture was continued to reflux for 24 h. The solvent was removed by evaporation and the brown residue was diluted with 200 mL Na_2CO_3 aq. sat. and 5 mL 4 N NaOH aq. The mixture was extracted with 3 portions of 200 mL ethyl acetate. The combined organic layers were washed with 150 mL brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica eluting with ethyl acetate / heptane to yield after evaporation of the product containing fractions 2.74 g (88 %) of the title compound as light yellow viscous oil. MS (m/e): 344.2 [(M+H)$^+$].

e) (3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methyl ester



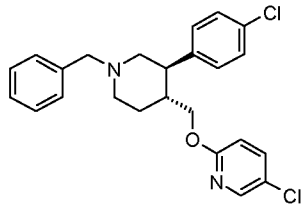
In a 250 ml round bottom flask under N_2 atmosphere and with a magnetic stirring bar, 1.5 g (4.3 mmol) ((3RS, 4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methyl ester were dissolved in 50 mL methanol and 0.7 mL NaOMe (5.4M in MeOH) was added. The solution was stirred for 4 h at reflux. Another 1mL NaOMe (5.4 M in MeOH) was added and refluxing was continued for 1 day. The solvent was evaporated and the residue dissolved in 40 mL water. The pH was adjusted to pH=12 with NaOH and the mixture was extracted with 2 portions of 50 mL ethyl acetate. The combined organic layers were washed with 30 mL brine, dried over Na_2SO_4, filtrated and evaporated to obtain 1.388 g (92 %) of the title compound. MS (m/e): 344.3 $[(M+H)^+]$.

f) [(3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-methanol



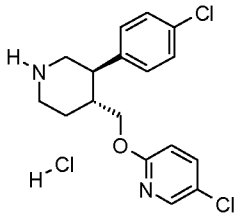
In a three necked 150 mL flushed round bottom flask under N_2 atmosphere and with a magnetic stirring bar, 1.388 g (4 mmol) (3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methyl ester were dissolved in 30 mL THF and at -5 °C five portions of 32 mg of $LiAlH_4$ was added. The reaction was stirred at 0 °C for 1 h and allowed to warm at room temperature during 1h. The light green solution was cooled to 0 °C and 50 mL water and 15 mL Na_2CO_3 aq. sat. was added drop wise. After 15 min the solution was warmed to room temperature and extracted with two portions of 75 mL ethyl acetate. The combined organic layers were washed with 30 mL of a brine, dried over Na_2SO_4, filtered and evaporated. The viscous oil obtained was filtered over silica eluting with ethyl acetate / heptane. 1.23 g (96 %) of the title compound was obtained as colourless viscous oil. MS (m/e): 316.1 $[(M+H)^+]$.

g) 2-[(3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-5-chloro-pyridine



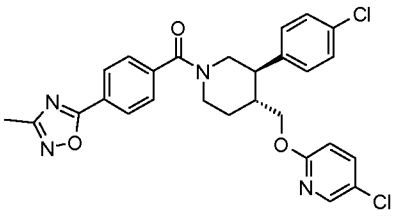
In a 100 mL four necked round bottom flask with a magnetic stirrer and inert atmosphere 1.3 g polymer bound triphenylphosphine was stirred in 15 mL THF. At 0-5 °C a solution of 514 mg (2.23 mmol) di-tert-butyl azodicarboxylate in 8 mL THF and a solution of 271 mg (2.1 mmol) 5-chloro-2-hydroxypyridine in 10 mL THF was added. The mixture was stirred for 20 min at 0 °C - 5 °C. 441 mg (1.4 mmol) [(3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-methanol in 8 mL THF was added. The ice bath was removed and the brownish mixture was stirred for 2 h at room temperature. The mixture was filtrated over decalite and washed with ethyl acetate. The solvents were evaporated and the residue purified by column chromatography on silica gel eluting with ethyl acetate / toluene to yield after evaporation of the product containing fractions 0.3 g (50 %) of the title compounds as white solid. MS (m/e): 298.3/427.1 [$(M+H)^+$].

h) 5-Chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride



In a 10 mL round bottom flask with a magnetic stirring bar and under N_2 atmosphere, 60 mg (0.14 mmol) 2-[(3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-5-chloro-pyridine were dissolved in 1 mL toluene. 23 uL 1-chloroethyl-chloroformate and 31 uL DIPEA was added. The solution was stirred at room temperature for 4 h. The solvent was removed under high vacuum and the residue dissolved in 1 mL methanol and stirred for 2 h at room temperature. The solvent was evaporated and the residue was purified over silica eluting with DCM/methanol/NH_3(2N) to yield after evaporation of the product containing fractions 35 mg (67 %) of the title compound as colourless viscous oil. MS (m/e): 208.0 / 337.1 [$(M+H)^+$].

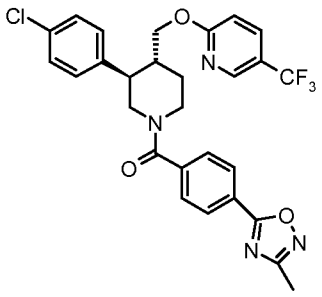
i) [(3RS, 4RS)-3-(4-Chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone



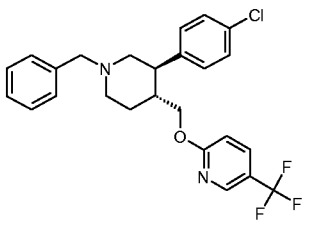
A mixture of 18 mg (0.08 mmol) 4-(3-methyl-1,2,4-oxadiazol-5-yl)benzoic acid, 43 mg (0.11 mmol) HATU, 0.1 mL DIPEA and 32 mg (0.09 mmol) 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride in 2 mL DMF was reacted at room temperature over night. The mixture was subjected to preparative HPLC purification on reversed phase eluting with a gradient formed from acetonitrile, water and NEt_3 to yield after evaporation of the product containing fractions 32 mg (64 %) of the title compound as white foam. MS (m/e): 523.3 $[(M+H)^+]$.

Example 2

[(3RS, 4RS)-3-(4-Chloro-phenyl)-4-(5-trifluoromethyl-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone



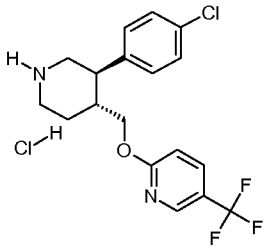
a) 2-[(3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-5-trifluoromethyl-pyridine



In analogy to the procedure described for the synthesis of 2-[(3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-5-chloro-pyridine (example 1, step g) the title compound was

prepared from [(3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-methanol and 5-trifluoromethyl-pyridin-2-ol (commercially available). MS (m/e): 298.3/461.2 [$(M+H)^+$].

b) 2-[(3RS, 4RS)-3-(4-Chloro-phenyl)-piperidin-4-ylmethoxy]-5-trifluoromethyl-pyridine; hydrochloride



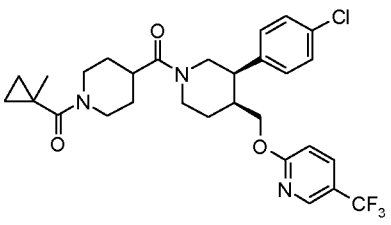
In analogy to the procedure described for the synthesis of 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride (example 1, step h) the title compound was prepared from 2-[(3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-5-trifluoromethyl-pyridine as light yellow viscous oil. MS (m/e): 208.0 / 371.2 [$(M+H)^+$].

c) [(3RS, 4RS)-3-(4-Chloro-phenyl)-4-(5-trifluoromethyl-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

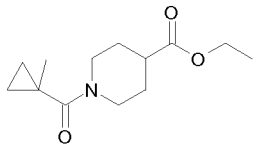
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-[(3RS, 4RS)-3-(4-Chloro-phenyl)-piperidin-4-ylmethoxy]-5-trifluoromethyl-pyridine; hydrochloride and 4-(3-methyl-1,2,4-oxadiazol-5-yl)benzoic acid (commercially available) as colourless viscous oil. MS (m/e): 557.0 [$(M+H)^+$].

Example 3

{4-[(3RS, 4RS)-3-(4-Chloro-phenyl)-4-(5-trifluoromethyl-pyridin-2-yloxymethyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone

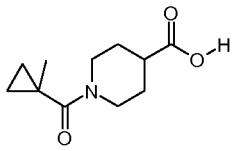


a) 1-(1-Methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid ethyl ester



To a stirred solution of 14.4 g (0.144 mol)1-methyl-cyclopropanecarboxylic acid in 200 mL DCM was added 27.1 g (0.141 mol) EDC, 19.10 g (0.141 g) HOBt and 35.93 mL (0.259 mol) Et_3N. After 1 h at room temperature 18.9 g (0.12 mol) piperidine-4-carboxylic acid ethyl ester was added and the mixture was stirred at room temperature over night. The mixture was poured onto water and extracted with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. Column chromatography (SiO_2, EtOAc/H, 1:1) yielded 26.1 g (92 %) of the title compound as a light yellow oil.

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



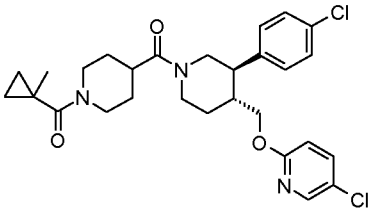
To a stirred solution of 26.09 g (0.109 mol) 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid ethyl ester in 500 mL THF, EtOH, water (1/1/1) was added 6.86 g (0.163 mol) $LiOH \cdot H_2O$. After 1 h at room temperature, the solvents were evaporated and the residue taken up in DCM and the organic phase was washed with aqueous HCl 1M. The organic phases were dried over Na_2SO_4 and evaporated under vacuum to give 19.8 g (86%) of the title compound as a white solid. MS (m/e): 212.1 $[(M+H)^+]$.

c) {4-[(3RS, 4RS)-3-(4-Chloro-phenyl)-4-(5-trifluoromethyl-pyridin-2-yloxymethyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-Chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-[(3RS, 4RS)-3-(4-Chloro-phenyl)-piperidin-4-ylmethoxy]-5-trifluoromethyl-pyridine; hydrochloride and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid as white solid. MS (m/e): 564.3 $[(M+H)^+]$.

Example 4

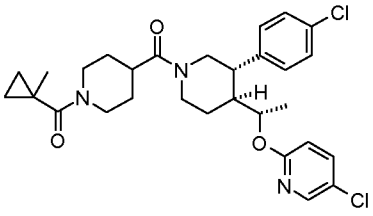
{4-[(3RS, 4RS)-3-(4-Chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone



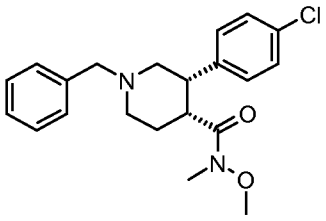
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-Chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid as white solid. MS (m/e): 530.2 [$(M+H)^+$].

Example 5

(4-{(3SR, 4SR)-3-(4-Chloro-phenyl)-4-[(SR)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone



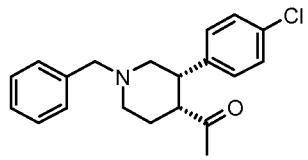
a) (3RS,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide



In a 100 mL round bottom flask with a magnetic stirrer 900 mg (2.72 mmol) (3RS,4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid and 1.14 g (3 mmol) HATU was

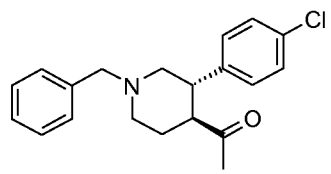
dissolved in 20 mL dry DMF. The greenish solution was stirred for 15 min, 320 mg (3.28 mmol) N,O-dimethylhydroxylamine hydrochlorideowed and 2.32 mL DIPEA was added. The mixture was stirred for 3 h at room temperature and concentrated under high vacuum. The green viscous oil was taken up in 60 mL ethyl acetate and 75 mL 5 % aqueous $NaHCO_3$-solution. The aqueous layer was separated and extracted once with 60 mL ethyl acetate. The combined organic layers were washed with 75 mL 1% AcOH/water-solution and once with 100 ml brine, dried over Na_2SO_4, filtered off and concentrated under vacuum. The residue was purified over silica eluting with a gradient formed from ethyl acetate / heptane to yield after evaporation of the product containing fractions 990 mg (97 %) of the title compound as colorless viscous oil. MS (m/e): 373.3 $[(M+H)^+]$.

b) 1-[(3SR,4RS)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone



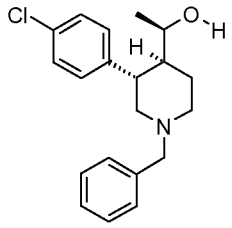
Under an inert atmosphere a 50 mL four necked flask (flame dried) with a magnetic stirrer was charged with 990 mg (2.65 mmol) (3SR,4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide in 15 ml THF. The light yellow solution was cooled to -40 °C and 2.2 mL methylmagnesium bromide (3M in diethyl ether) was added drop wise over 5 min. The reaction was slowly warmed up to 0 °C over 2 h. The reaction mixture was quenched slowly with 20 mL aqueous NH_4Cl-solution, diluted with 10 mL water and 10 mL ethyl acetate. The aqueous layer was separated and extracted once with 30 mL ethyl acetate. The combined organic layers were washed with 50 mL brine, dried over Na_2SO_4, filtered off and concentrated under vacuum and used without further purification in the consecutive step. MS (m/e): 327.2 $[(M+H)^+]$.

c) 1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone



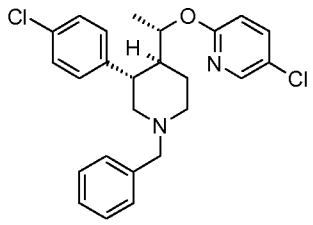
In analogy to the procedure described for the synthesis of (3RS, 4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methyl ester (example 1, step e) the title compound was prepared from1-[(3SR,4RS)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone through epimerisation with NaOMe. MS (m/e): 328.2/330.2 [$(M+H)^+$].

d) (RS)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol



Under an inert atmosphere a 100 mL four necked flask (flame dried) with a magnetic stirrer was charged with 835 mg (2.54 mmol)1-[(3SR,4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone in 25 mL THF. The yellow solution was cooled to 0 °C and 34 mg (0.89 mmol) $LiAlH_4$ was added. The mixture was stirred for 30 min at 0 °C and 30 min from 0 °C to 15 °C. At 0 °C 10 mL ethyl acetate was added drop-wise, followed by 5 mL THF:water 9:1 and 1 mL 4 N aqueous NaOH and 1 mL water. The mixture was stirred for 30 min at 40 - 50 °C and Na_2SO_4 was added. The mixture was filtered off and concentrated under vacuum. The residue was purified by chromatography on silica eluting with a gradient formed from DCM, methanol, NH_3aq. to yield after evaporation of the product containing fractions 466 mg (55 %) of the title compound as off-white foam. MS (m/e): 330.1 [$(M+H)^+$].

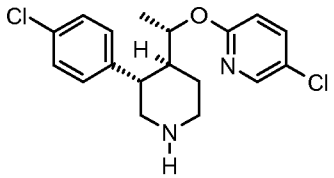
e) 2-{(SR)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine



In a 50 mL three-necked round bottom flask (flame dried) charged with a magnetic stirrer and under inert atmosphere to 1080 mg polymer bound triphenylphosphine (3 mmol/g) in 10 mL THF was added 502 mg (2.18 mmol) di-tert-butyl azodicarboxylate in 5 mL THF and 265 mg (2.04 mmol) 5-chloro-2-hydroxypyridine in 10 mL THF at 0 - 5 °C. The brownish suspension

was stirred for 20 min at 0 - 5 °C. 450 mg (1.36 mmol) (RS)-1-[(3SR,4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol in 5 mL THF was added and the ice bath was removed and the reaction was stirred for 63 h at room temperature. The suspension was filtered over a Dicalit-filter. The filtrate was concentrated under vacuum and the residue was purified by chromatography over silica eluting with a a gradient formed from i-propanol and heptane to yield after evaporation of the product containing fractions 480 mg (80 %) of the title compound as yellow viscous oil. MS (m/e): 441.2 $[(M+H)^+]$.

f) 5-Chloro-2-{(SR)-1-[(3SR,4SR)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine



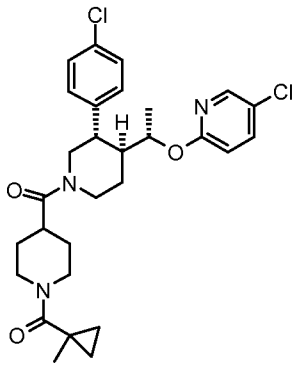
In analogy to the procedure described for the synthesis of 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride (example 1, step h) the title compound was prepared from 2-{(SR)-1-[(3SR,4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine as light yellow viscous oil. MS (m/e): 222.2 / 351.2 $[(M+H)^+]$.

g) (4-{(3SR, 4SR)-3-(4-Chloro-phenyl)-4-[(SR)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-chloro-2-{(SR)-1-[(3SR,4SR)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid as white solid. MS (m/e): 544.2 $[(M+H)^+]$.

Example 6

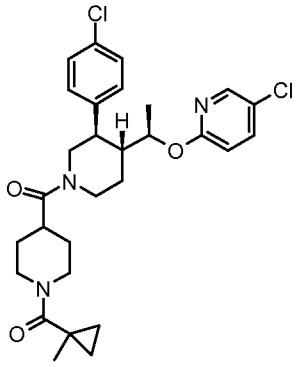
(4-{(3R,4R)-3-(4-Chloro-phenyl)-4-[(R)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone



The title compound was assessed through chromatography on Chiralpak AD eluting with ethanol/heptane from (4-{(3SR, 4SR)-3-(4-chloro-phenyl)-4-[(SR)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone (example 5) as off white foam. MS (m/e): 544.2 [$(M+H)^+$].

Example 7

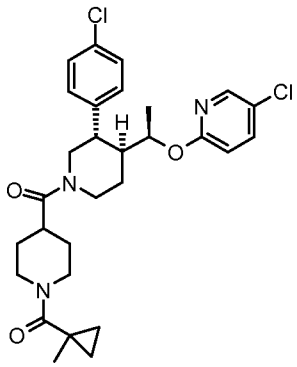
(4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone



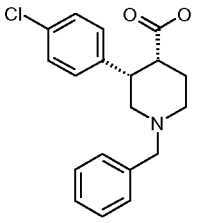
The title compound was assessed through chromatography on Chiralpak AD eluting with ethanol/heptane from (4-{(3SR, 4SR)-3-(4-chloro-phenyl)-4-[(SR)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone (example 5) as light yellow foam. MS (m/e): 544.2 [$(M+H)^+$].

Example 8

(4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(R)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

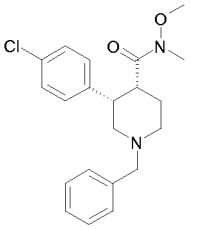


a) (3S,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid



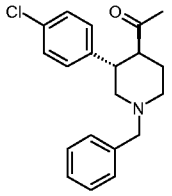
In analogy to the synthesis of (3RS, 4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid (example 1 (c)) the title compound was prepared through hydrogenation of 1-benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid under Ruthenium catalysis ([$Ru(OAc)_2$((*R*)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(di-2-furylphosphine)]). The title compound was used without further purification in the consecutive step.

b) (3S,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide



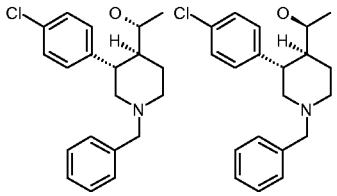
In analogy to the procedure described for the synthesis of (3RS,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide (example 5 (a)) the title compound was prepared from (3S,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid and methoxymethylamine. The title compound was obtained as brown viscous oil. MS (m/e): 373.2 [$(M+H)^+$].

c) 1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone



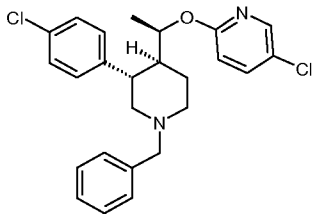
In analogy to the procedure described for the synthesis of 1-[(3SR,4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone (example 5 (c)) the title compound was prepared from (3S,4R)-1-benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide and methylmagnesium bromide with subsequent epimerisation with NaOMe in methanol. The title compound was obtained as off-white solid. MS (m/e): 328.2 $[(M+H)^+]$.

d) (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and (S)-1-[(3S,4S)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol



In analogy to the procedure described for the synthesis of (RS)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol (example 5 (d)) the title compounds were synthesized from 1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone through reduction with $LiAlH_4$. (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol was obtained as light yellow viscous oil. MS (m/e): 330.1 $[(M+H)^+]$ and (S)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol was obtained as colourless foam. MS (m/e): 330.1 $[(M+H)^+]$

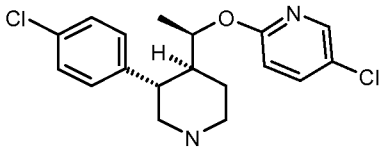
e) 2-{(R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine



A mixture of 69 mg (1.7 mmol) NaH (55% suspension in mineral oil), 359 mg (1.08 mmol) (S)-1-[(3S,4S)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 225 mg (1.52 mmol) 2,5-dichloropyridine in 2 mL DMF was stirred for 20 h at 40 °C. Further 0.2 eq. 2,5-dichloropyridine

was added and stirring was continued for 20 h at 60 °C. After evaporation the residue was purified by column chromatography on silica eluting with a gradient formed from ethyl acetate and heptane to afford after evaporation of the product containing fractions 205 mg (43 %) of the title compound as colorless viscous oil. MS (m/e): 441.1 [$(M+H)^+$]

f) 5-Chloro-2-{(R)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine



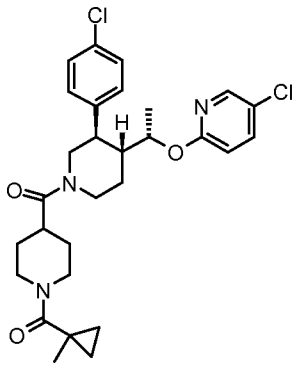
In analogy to the procedure described for the synthesis of 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride (example 1, step h) the title compound was prepared from 2-{(R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine as yellow oil. MS (m/e): 351.2 [$(M+H)^+$].

g) (4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(R)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

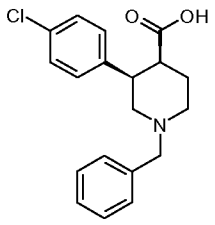
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(R)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid as white foam. MS (m/e): 544.2 [$(M+H)^+$].

Example 9

(4-{(3R,4R)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

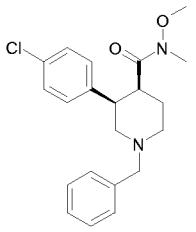


a) (3R,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid



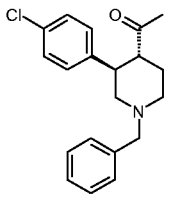
In analogy to the synthesis of (3RS, 4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid (example 1 (c)) the title compound was prepared through hydrogenation of 1-benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid under Ruthenium catalysis ([$Ru(OAc)_2$((*S*)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(di-2-furylphosphine)]). The title compound was used without further purification in the consecutive step.

b) (3R,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide



In analogy to the procedure described for the synthesis of (3RS,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide (example 5 (a)) the title compound was prepared from (3R,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid and methoxymethylamine. The title compound was obtained as yellow viscous oil. MS (m/e): 373.1 [$(M+H)^+$].

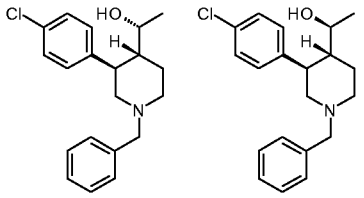
c) 1-[(3R,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone



In analogy to the procedure described for the synthesis of 1-[(3SR,4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone (example 5 (c)) the title compound was prepared from (3R,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide and

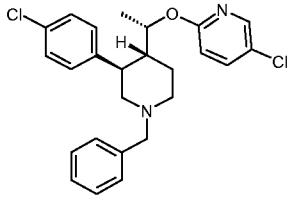
methylmagnesium bromide with subsequent epimerisation with NaOMe in methanol. The title compound was obtained as off-white solid. MS (m/e): 327.1 [$(M+H)^+$].

d) (R)-1-[(3R,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and (S)-1-[(3R,4R)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol



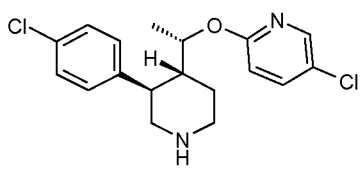
In analogy to the procedure described for the synthesis of (RS)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol (example 5 (d)) the title compounds were synthesized from 1-[(3R,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone through reduction with $LiAlH_4$. (R)-1-[(3R,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol was obtained as off-white solid. MS (m/e): 330.1 [$(M+H)^+$] and (S)-1-[(3R,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol was obtained as colourless viscous oil. MS (m/e): 330.1 [$(M+H)^+$]

e) 2-{(S)-1-[(3R,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine



In analogy to the procedure described for the synthesis of 2-{(R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine the title compound was prepared from (S)-1-[(3R,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 2,5-dichloropyridine as colourless viscous oil. MS (m/e): 441.1 [$(M+H)^+$].

f) 5-Chloro-2-{(S)-1-[(3R,4R)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine



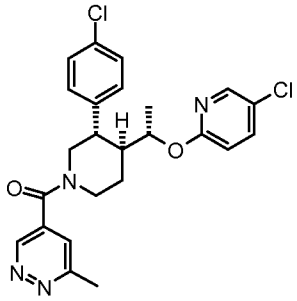
In analogy to the procedure described for the synthesis of 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride (example 1, step h) the title compound was prepared from 2-{(S)-1-[(3R,4R)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine as light yellow viscous oil. MS (m/e): 351.2 [$(M+H)^+$].

g) (4-{(3R,4R)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

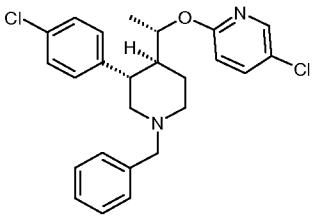
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3R,4R)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid as white foam. MS (m/e): 544.1 [$(M+H)^+$].

Example 10

{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(6-methyl-pyridazin-4-yl)-methanone

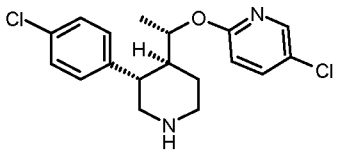


a) 2-{(S)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine



In analogy to the procedure described for the synthesis of 2-{(SR)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine the title compound was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 5-chloro-2-hydroxypyridine as viscous colourless oil. MS (m/e): 441.3 [$(M+H)^+$].

b) 5-Chloro-2-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine



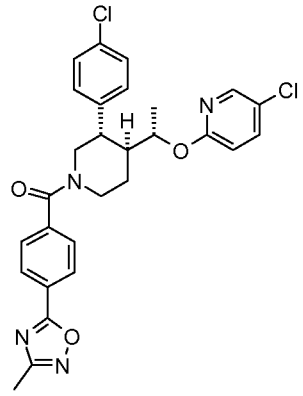
In analogy to the procedure described for the synthesis of 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride (example 1, step h) the title compound was prepared from 2-{(S)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine as light brown foam as the respective HCl salt. MS (m/e): 351.2 $[(M+H)^+]$.

c) {(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(6-methyl-pyridazin-4-yl)-methanone

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 6-Methyl-pyridazine-4-carboxylic acid (WO2009019163) as white solid. MS (m/e): 471.1 $[(M+H)^+]$.

Example 11

{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

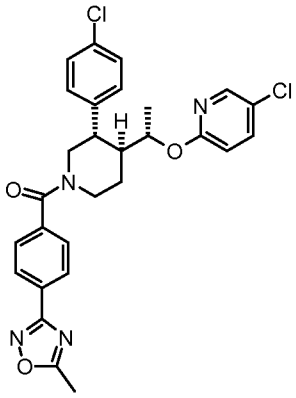


In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 4-(3-Methyl-

[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available) as white solid. MS (m/e): 537.2 [(M+H)$^+$].

Example 12

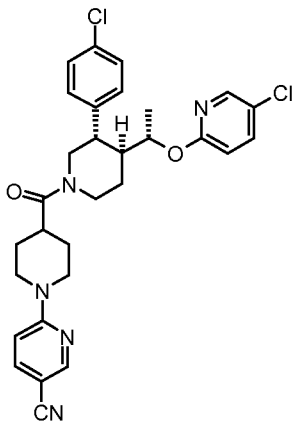
{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoic acid (commercially available) as white solid. MS (m/e): 537.3 [(M+H)$^+$].

Example 13

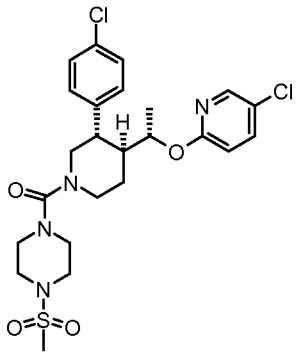
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) as white solid. MS (m/e): 564.2 [$(M+H)^+$].

Example 14

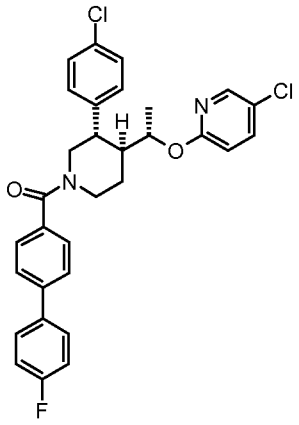
{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 4-Methanesulfonyl-piperazine-1-carbonyl chloride (WO 2009024502) as white solid. MS (m/e): 541.3 [$(M+H)^+$].

Example 15

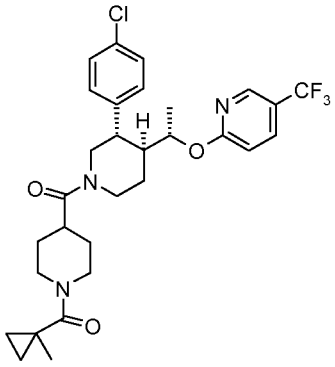
{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(4'-fluoro-biphenyl-4-yl)-methanone



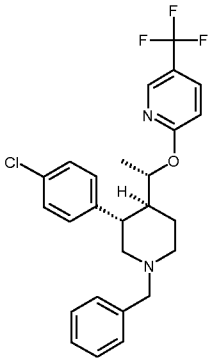
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 4'-Fluoro-biphenyl-4-carboxylic acid (commercially available) as white solid. MS (m/e): 551.3 [$(M+H)^+$].

Example 16

(4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

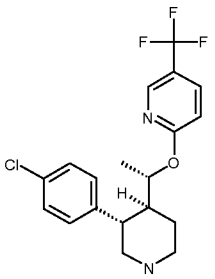


a) 2-{(S)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine



In analogy to the procedure described for the synthesis of 2-{(SR)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine the title compound was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 5-Trifluoromethyl-pyridin-2-ol as viscous colourless oil. MS (m/e): 475.2 $[(M+H)^+]$.

b) 2-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine



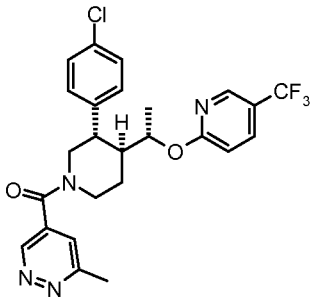
In analogy to the procedure described for the synthesis of 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride (example 1, step h) the title compound was prepared from 2-{(S)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine as off-white foam as the respective HCl salt. MS (m/e): 385.2 $[(M+H)^+]$.

c) (4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid as white solid. MS (m/e): 578.2 $[(M+H)^+]$.

Example 17

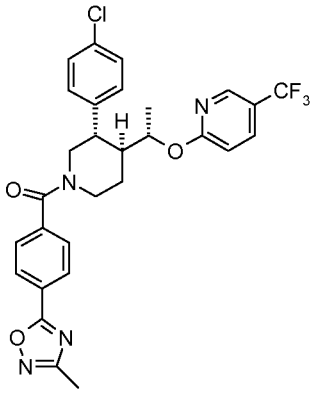
{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(6-methyl-pyridazin-4-yl)-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine and 6-Methyl-pyridazine-4-carboxylic acid (WO2009019163) as white solid. MS (m/e): 505.2 [$(M+H)^+$].

Example 18

{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

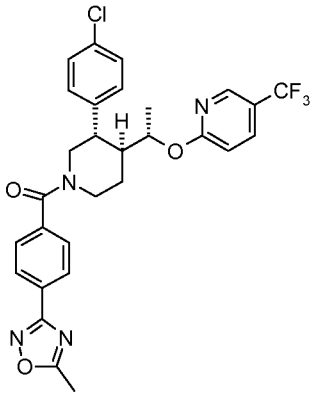


In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine and 4-(3-Methyl-

[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available) as white solid. MS (m/e): 571.3 [(M+H)$^+$].

Example 19

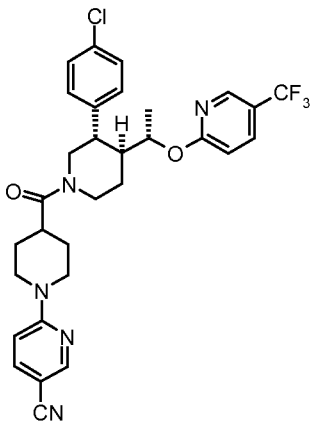
{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine and 4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoic acid (commercially available) as white solid. MS (m/e): 571.2 [(M+H)$^+$].

Example 20

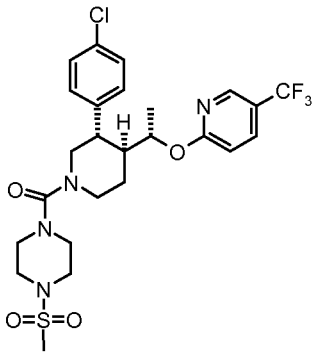
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine and 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) as white solid. MS (m/e): 598.3 $[(M+H)^+]$.

Example 21

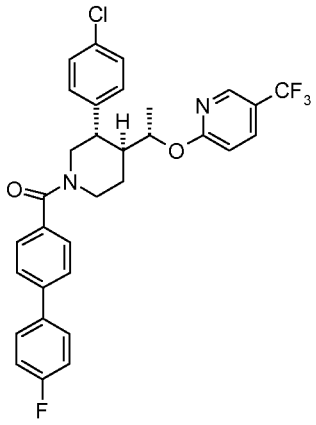
{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine and 4-Methanesulfonyl-piperazine-1-carbonyl chloride (WO 2009024502) as white solid. MS (m/e): 575.3 $[(M+H)^+]$.

Example 22

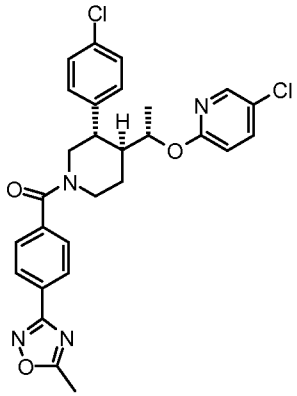
{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(4'-fluoro-biphenyl-4-yl)-methanone



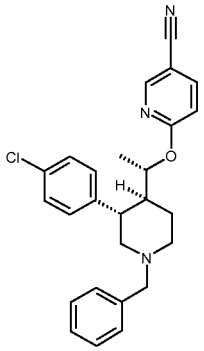
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 2-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine and 4'-Fluoro-biphenyl-4-carboxylic acid (commercially available) as white solid. MS (m/e): 583.2 [$(M+H)^+$].

Example 23

6-((S)-1-{(3S,4S)-3-(4-Chloro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile

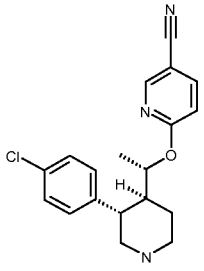


a) 6-{(S)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile



In analogy to the procedure described for the synthesis of 2-{(SR)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine the title compound was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 6-Hydroxy-nicotinonitrile. MS (m/e): 432.3 [$(M+H)^+$].

b) 6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile



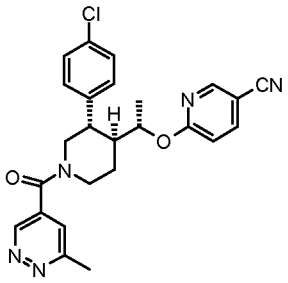
In analogy to the procedure described for the synthesis of 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride (example 1, step h) the title compound was prepared from 2-{(S)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-trifluoromethyl-pyridine as white foam as the respective HCl salt. MS (m/e): 342.1 [$(M+H)^+$].

c) 6-((S)-1-{(3S,4S)-3-(4-Chloro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid as white solid. MS (m/e): 535.4 [$(M+H)^+$].

Example 24

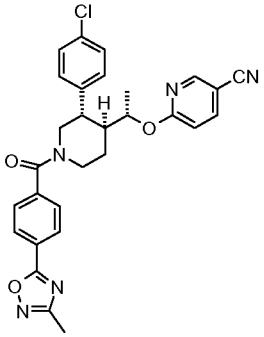
6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-1-(6-methyl-pyridazine-4-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 6-Methyl-pyridazine-4-carboxylic acid (WO2009019163) as white solid. MS (m/e): 462.1 $[(M+H)^+]$.

Example 25

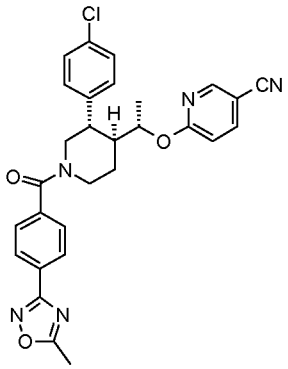
6-((S)-1-{(3S,4S)-3-(4-Chloro-phenyl)-1-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available) as white solid. MS (m/e): 528.3 $[(M+H)^+]$.

Example 26

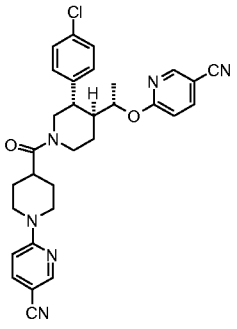
6-((S)-1-{(3S,4S)-3-(4-Chloro-phenyl)-1-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-benzoic acid (commercially available) as white solid. MS (m/e): 528.3 $[(M+H)^+]$.

Example 27

4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-cyano-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

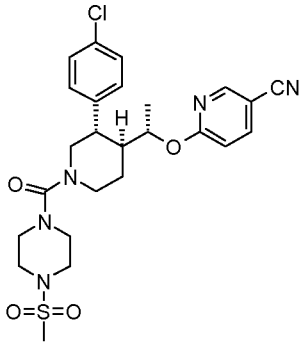


In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 5'-Cyano-3,4,5,6-tetrahydro-2H-

[1,2']bipyridinyl-4-carboxylic acid (commercially available) as white solid. MS (m/e): 555.3 [(M+H)$^+$].

Example 28

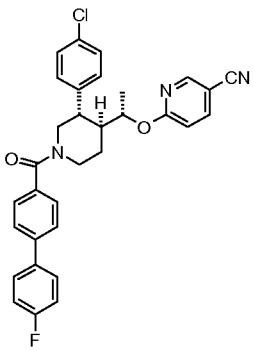
6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 4-Methanesulfonyl-piperazine-1-carbonyl chloride (WO 2009024502) as white solid. MS (m/e): 532.2 [(M+H)$^+$].

Example 29

6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-1-(4'-fluoro-biphenyl-4-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile

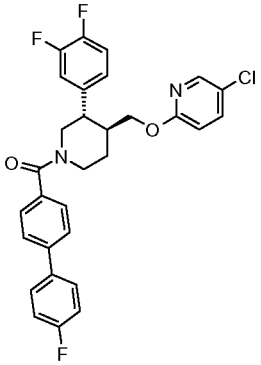


In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-

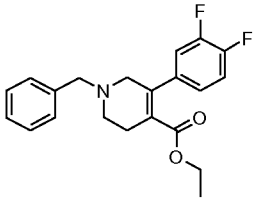
methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 4'-Fluoro-biphenyl-4-carboxylic acid (commercially available) as white solid. MS (m/e): 540.4 [$(M+H)^+$].

Example 30

[(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidin-1-yl]-(4'-fluoro-biphenyl-4-yl)-methanone

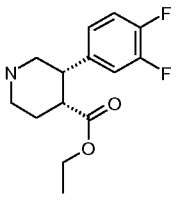


a) 1-Benzyl-5-(3,4-difluoro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester



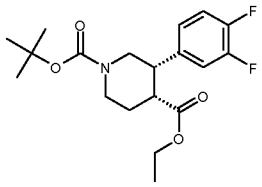
In analogy to the procedure described for the synthesis of 1-Benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester (example 1 a)) the title compound was obtained from ethyl N-benzyl-3-oxo-4-piperidine-carboxylate (commercially available) and 3,4-difluorophenylboronic acid as yellow viscous oil. MS (m/e): 358.2 [$(M+H)^+$].

b) (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-4-carboxylic acid ethyl ester



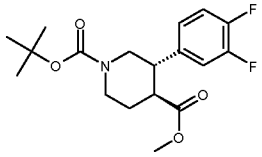
A solution of 2.73 g (7.6 mmol) 1-benzyl-5-(3,4-difluoro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester in 150 mL ethanol was hydrogenated over 600 mg Pd/C (10 %). The catalyst was filtered off and the filtrate was evaporated to dryness to yield 2 g (87%) of the title compound which was used without further purification in the subsequent step. MS (m/e): 270.3 [$(M+H)^+$].

c) (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester



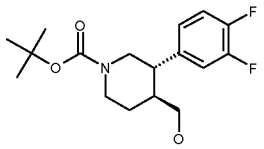
A mixture of 2 g (7.4 mmol) (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-4-carboxylic acid ethyl ester, 1.78 g (8.1 mmol) di-tert.-butyl-dicarbonat and catalytic amount DMAP in 60 mL THF was stirred at room temperature. After evaporation the residue was subjected to column chromatography on silica eluting with gradient formed from heptane and TBME to afford after evaporation of the product containing fractions 2.2 g (80 %) of the title compound as light yellow viscous oil. MS (m/e): 270.1 [$(M+H\text{-}Boc)^+$].

d) (3SR,4SR)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester



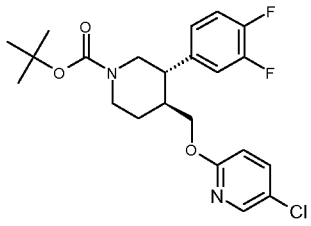
A mixture of 2.2 g (5.9 mmol) (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester and 0.18 mL NaOMe (5.4N in methanol) in 60 mL methanol was first stirred at room temperature and subsequently ar reflux until consumption of the starting material. The mixture was evaporated to dryness and the residue subjected to column chromatography on silica eluting with a gradient formed from ethyl acetate and heptane to afford after evaporation of the product containing fractions 1.5 g (71 %) of the title compound as colourless oil. MS (m/e): 256.1 [$(M+H\text{-}Boc)^+$].

e) (3SR,4SR)-3-(3,4-Difluoro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester



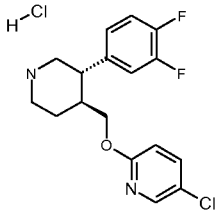
A mixture of 1.5 g (4.2 mmol) (3SR,4SR)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester and 0.16 g (4.2 mmol) LiAlH4 in 50 mL THF was stirred at room temperature for 1 h. Ethyl acetate, THF, water and NaOH aq.was added. Na_2SO_4 was added, the mixture was filtered off and evaporated to dryness. The residue was subjected to column chromatography on silica eluting with a gradient formed from ethyl acetate and heptane to afford after evaporation of the product containing fractions 1.06 g (77 %) of the title compound as viscous colourless oil. MS (m/e): 228.1 $[(M+H\text{-}Boc)^+]$.

f) (3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester



A mixture of 1 g (3 mmol) (3SR,4SR)-3-(3,4-Difluoro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester, 0.59 g (4.5 mmol) 5-chloro-2-hydroxy pyridine, 1.1 g (4.8 mmol) di-tert-butyl azodicarboxylate and 2.42 g (5 mmol) triphenylphosphine (polymer bound) in 70 mL THF was stirred at room temperature over night. the mixture was filtered through decalite and evaporated to dryness. The residue was subjected to column chromatography on silica eluting with a gradient formed from ethyl acetate and heptane to afford after evaporation of the product containing fractions 1.2 g (91 %) of the title compound as viscous colourless oil. MS (m/e): 439.1 $[(M+H)^+]$.

g) 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride



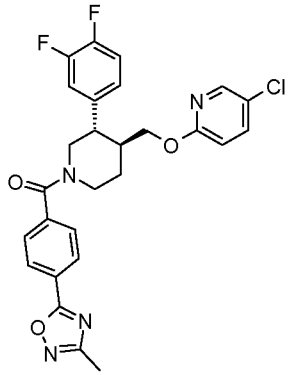
A solution of 1.2 g (2.7 mmol) (3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester in 15 mL methanol was treated with 6.8 mL HCl in dioxane (4N) and stirred for 4 h at room temperature. The mixture was evaporated to dryness and dried under high vacuum to afford the title compound which was used without further purification in the subsequent step. MS (m/e): 339.3 $[(M+H)^+]$.

h [(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidin-1-yl]-(4'-fluoro-biphenyl-4-yl)-methanone

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 4'-Fluoro-biphenyl-4-carboxylic acid (commercially available) as off-white solid. MS (m/e): 537.3 $[(M+H)^+]$.

Example 31

[(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

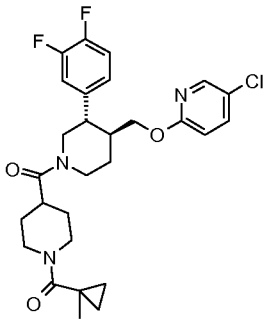


In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 4-(3-Methyl-

[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available) as off-white solid. MS (m/e): 525.3 [(M+H)$^+$].

Example 32

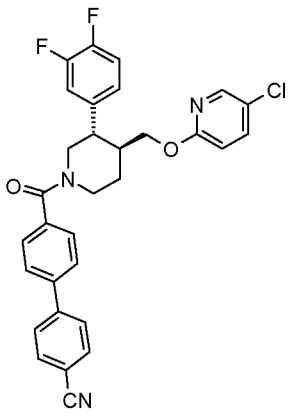
{4-[(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid (commercially available) as off-white solid. MS (m/e): 532.3 [(M+H)$^+$].

Example 33

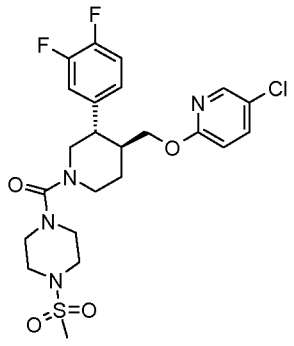
4-[(3S,4S)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-carbonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) as off-white solid. MS (m/e): 552.4 [$(M+H)^+$].

Example 34

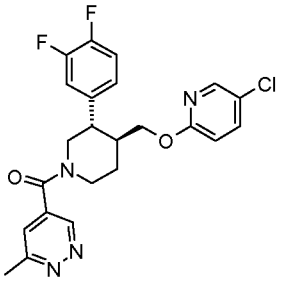
[(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 4-Methanesulfonyl-piperazine-1-carbonyl chloride (WO2009024502) as off-white solid. MS (m/e): 529.2 [$(M+H)^+$].

Example 35

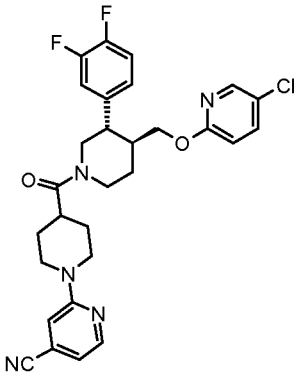
[(3S,4S)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidin-1-yl]-(6-methyl-pyridazin-4-yl)-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 6-Methyl-pyridazine-4-carboxylic acid (WO2009019163) as off-white solid. MS (m/e): 459.3 [$(M+H)^+$].

Example 36

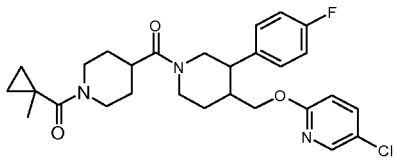
4-[(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4'-carbonitrile



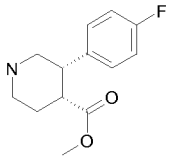
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 4'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) as off-white solid. MS (m/e): 552.1 [$(M+H)^+$].

Example 37

[4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone

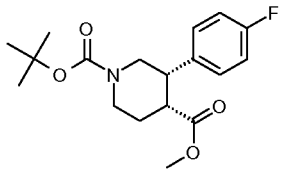


a) (3SR,4RS)-3-(4-Fluoro-phenyl)-piperidine-4-carboxylic acid methyl ester



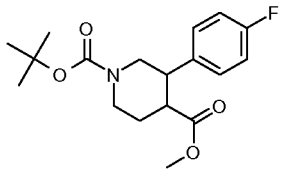
A mixture of 3.6 g (1.03 mmol) 1-Benzyl-5-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid (Bioorganic & Medicinal Chemistry Letters 2003, 2513-2518); hydrochloride, 16.6 mL HCl in methanol (1.25 N) in 250 mL methanol was stirred at room temperature over night. Further 16.6 mL HCl in methanol (1.25 N) was added and the mixture was stirred at 70 °C and subsequently hydrogenated with H_2 over 360 mg Pd/C (10%) for 44 h at room temperature. The mixture was filtered off and evaporated to dryness to yield 2.3 g (94 %) of the title compound as colourless oil. MS (m/e): 238.1 $[(M+H)^+]$.

b) (3SR,4RS)-3-(4-Fluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester



In analogy to the procedure described for the synthesis of (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester the title compound was prepared from (3SR,4RS)-3-(4-Fluoro-phenyl)-piperidine-4-carboxylic acid methyl ester and di-tert.-butyl-dicarbonat and catalytic amount DMAP as colourless viscous oil. MS (m/e): 238.1 $[(M+H\text{-}Boc)^+]$.

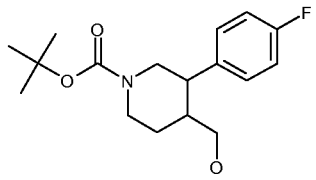
c) 3-(4-Fluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester



In analogy to the procedure described for the synthesis of (3SR,4SR)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester the title compound was prepared from (3SR,4RS)-3-(4-Fluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester

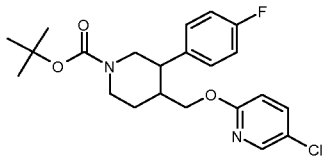
4-methyl ester through epimerization with NaOMe in methanol as a 7: 3 mixture cis:trans as colourless viscous oil. MS (m/e): 238.1 [(M+H-Boc)$^+$].

d) 3-(4-Fluoro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester



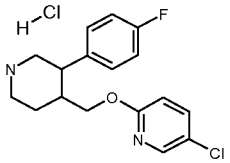
In analogy to the procedure described for the synthesis of (3SR,4SR)-3-(3,4-Difluoro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared from 3-(4-Fluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester through reduction as colourless viscous oil (7: 3 mixture cis:trans). MS (m/e): 210.1 [(M+H-Boc)$^+$].

e) 4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-fluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester



In analogy to the procedure described for the synthesis of (3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared through Mitsunobu reaction of 3-(4-Fluoro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester with 5-chloro-2-hydroxy pyridine as colourless viscous oil (7: 3 mixture cis:trans). MS (m/e): 421.2 [(M+H)$^+$].

f) 5-Chloro-2-[3-(4-fluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride



In analogy to the procedure described for the synthesis of 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride the title compound was

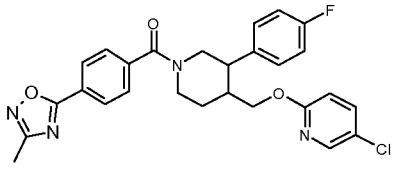
prepared from 4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-fluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester as off-white foam (7: 3 mixture cis:trans). MS (m/e): 421.2 [$(M+H)^+$].

g) [4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[3-(4-fluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid (commercially available) as off-white solid (7: 3 mixture cis:trans). MS (m/e): 514.4 [$(M+H)^+$].

Example 38

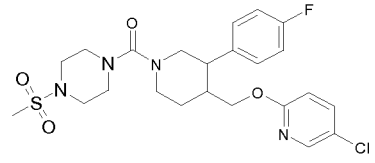
[4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from [4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone and 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available) as off-white solid (7: 3 mixture cis:trans). MS (m/e): 507.3 [$(M+H)^+$].

Example 39

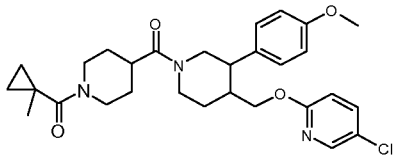
[4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



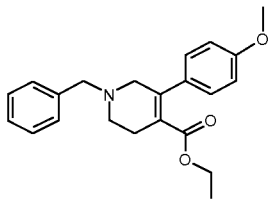
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from [4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone and 4-Methanesulfonyl-piperazine-1-carbonyl chloride (WO2009024502) as off-white solid (7: 3 mixture cis:trans). MS (m/e): 511.3 [$(M+H)^+$].

Example 40

[4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-methoxy-phenyl)-piperidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone

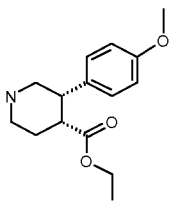


a) 1-Benzyl-5-(4-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester



In analogy to the procedure described for the synthesis of 1-Benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester the title compound was prepared from ethyl N-benzyl-3-oxo-4-piperidine-carboxylate and 4-methoxyphenylboronic acid as yellow viscous oil. MS (m/e): 352.3 [$(M+H)^+$].

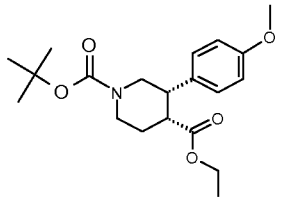
b) (3SR,4RS)-3-(4-Methoxy-phenyl)-piperidine-4-carboxylic acid ethyl ester



In analogy to the procedure described for the synthesis of (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-4-carboxylic acid ethyl ester the title compound was prepared from 1-Benzyl-5-(4-

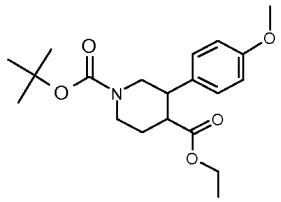
methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester through hydrogenation over Pd/C as colourless viscous oil. MS (m/e): 264.1 [$(M+H)^+$].

c) (3SR,4RS)-3-(4-Methoxy-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester



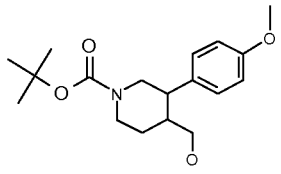
In analogy to the procedure described for the synthesis of (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester the title compound was prepared from (3SR,4RS)-3-(4-Methoxy-phenyl)-piperidine-4-carboxylic acid ethyl ester and di-tert.-butyl-dicarbonat and catalytic amount DMAP as colourless viscous oil. MS (m/e): 264.1 [(M+H-Boc)$^+$].

d) 3-(4-Methoxy-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester



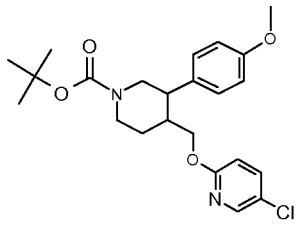
In analogy to the procedure described for the synthesis of (3SR,4SR)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester the title compound was prepared from (3SR,4RS)-3-(4-Methoxy-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester through epimerization with NaOEt in ethanol as a 1:1 mixture cis:trans as colourless viscous oil. MS (m/e): 264.1 [(M+H-Boc)$^+$].

e) 4-Hydroxymethyl-3-(4-methoxy-phenyl)-piperidine-1-carboxylic acid tert-butyl ester



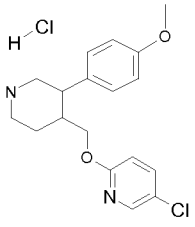
In analogy to the procedure described for the synthesis of (3SR,4SR)-3-(3,4-Difluoro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared from 3-(4-Methoxy-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester through reduction as colourless viscous oil (1:1 mixture cis:trans). MS (m/e): 222.1 [(M+H-Boc)$^+$].

f) 4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-methoxy-phenyl)-piperidine-1-carboxylic acid tert-butyl ester



In analogy to the procedure described for the synthesis of (3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared through Mitsunobu reaction of 4-Hydroxymethyl-3-(4-methoxy-phenyl)-piperidine-1-carboxylic acid tert-butyl ester with 5-chloro-2-hydroxy pyridine as colourless viscous oil (1:1 mixture cis:trans). MS (m/e): 433.2 [(M+H)$^+$].

g) 5-Chloro-2-[3-(4-methoxy-phenyl)-piperidin-4-ylmethoxy]-pyridine, hydrochloride



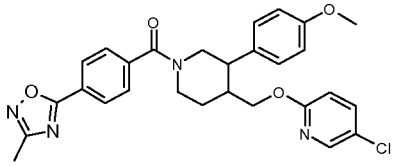
In analogy to the procedure described for the synthesis of 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride the title compound was prepared from 4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-methoxy-phenyl)-piperidine-1-carboxylic acid tert-butyl ester as off-white foam (1:1 mixture cis:trans). MS (m/e): 333.4 [(M+H)$^+$].

h) [4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-methoxy-phenyl)-piperidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[3-(4-methoxy-phenyl)-piperidin-4-ylmethoxy]-pyridine, hydrochloride and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid (commercially available) as off-white solid (1:1 mixture cis:trans). MS (m/e): 526.4 $[(M+H)^+]$.

Example 41

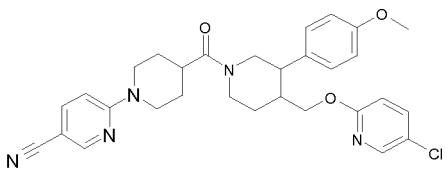
[4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-methoxy-phenyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[3-(4-methoxy-phenyl)-piperidin-4-ylmethoxy]-pyridine, hydrochloride and 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available) as off-white solid (1:1 mixture cis:trans). MS (m/e): 519.3 $[(M+H)^+]$.

Example 42

4-[4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-methoxy-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

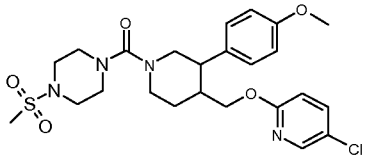


In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[3-(4-methoxy-phenyl)-piperidin-4-ylmethoxy]-pyridine, hydrochloride and 5'-Cyano-3,4,5,6-tetrahydro-2H-

[1,2']bipyridinyl-4-carboxylic acid (commercially available) as off-white solid (1:1 mixture cis:trans). MS (m/e): 546.2 [$(M+H)^+$].

Example 43

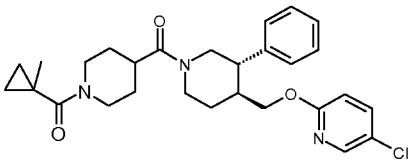
[4-(5-Chloro-pyridin-2-yloxymethyl)-3-(4-methoxy-phenyl)-piperidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



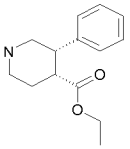
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-[3-(4-methoxy-phenyl)-piperidin-4-ylmethoxy]-pyridine, hydrochloride and 4-Methanesulfonyl-piperazine-1-carbonyl chloride (WO2009024502) as off-white solid (1:1 mixture cis:trans). MS (m/e): 523.5 [$(M+H)^+$].

Example 44

[(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone



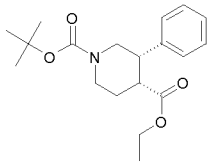
a) (3SR,4RS)-3-Phenyl-piperidine-4-carboxylic acid ethyl ester



In analogy to the procedure described for the synthesis of (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-4-carboxylic acid ethyl ester the title compound was prepared from 1-Benzyl-5-phenyl-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester ((Bioorganic & Medicinal

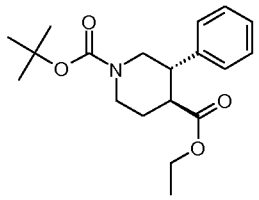
Chemistry Letters 2003, 2513-2518) through hydrogenation over Pd/C as colourless viscous oil. MS (m/e): 234.1 [$(M+H)^+$].

b) (3SR,4RS)-3-Phenyl-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester



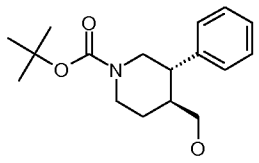
In analogy to the procedure described for the synthesis of (3SR,4RS)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester the title compound was prepared from (3SR,4RS)-3-Phenyl-piperidine-4-carboxylic acid ethyl ester and di-tert.-butyl-dicarbonat and catalytic amount DMAP as colourless viscous oil. MS (m/e): 234.1 [$(M+H\text{-}Boc)^+$].

c) (3SR,4SR)-3-Phenyl-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester



In analogy to the procedure described for the synthesis of (3SR,4SR)-3-(3,4-Difluoro-phenyl)-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-methyl ester the title compound was prepared from (3SR,4RS)-3-Phenyl-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester through epimerization with NaOEt in ethanol as white solid. MS (m/e): 234.1 [$(M+H\text{-}Boc)^+$].

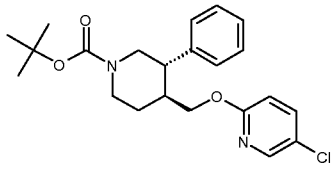
d) (3SR,4SR)-4-Hydroxymethyl-3-phenyl-piperidine-1-carboxylic acid tert-butyl ester



In analogy to the procedure described for the synthesis of (3SR,4SR)-3-(3,4-Difluoro-phenyl)-4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared

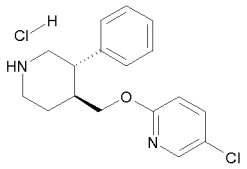
from) (3SR,4SR)-3-Phenyl-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester through reduction as colourless viscous oil. MS (m/e): 314.0 [(M+Na)$^+$].

e) (3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidine-1-carboxylic acid tert-butyl ester



In analogy to the procedure described for the synthesis of (3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carboxylic acid tert-butyl ester the title compound was prepared through Mitsunobu reaction of (3SR,4SR)-4-Hydroxymethyl-3-phenyl-piperidine-1-carboxylic acid tert-butyl ester with 5-chloro-2-hydroxy pyridine as colourless viscous oil. MS (m/e): 403.2 [(M+H)$^+$].

f) 5-Chloro-2-((3S,4S)-3-phenyl-piperidin-4-ylmethoxy)-pyridine, hydrochloride



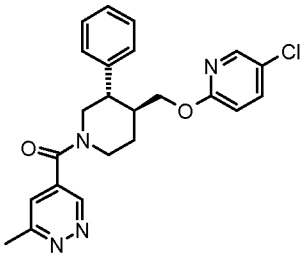
In analogy to the procedure described for the synthesis of 5-Chloro-2-[(3SR,4SR)-3-(3,4-difluoro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride the title compound was prepared from (3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidine-1-carboxylic acid tert-butyl ester as off-white foam. MS (m/e): 303.3 [(M+H)$^+$].

g) [(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidin-1-yl]-[1-(1-methyl-cyclopropanecarbonyl)-piperidin-4-yl]-methanone

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-((3S,4S)-3-phenyl-piperidin-4-ylmethoxy)-pyridine, hydrochloride and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid (commercially available) as off-white solid. MS (m/e): 496.4 [(M+H)$^+$].

Example 45

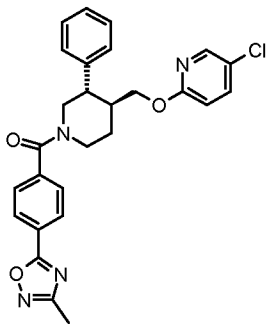
[(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidin-1-yl]-(6-methyl-pyridazin-4-yl)-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-((3S,4S)-3-phenyl-piperidin-4-ylmethoxy)-pyridine, hydrochloride and 6-Methyl-pyridazine-4-carboxylic acid (WO2009019163) as off-white solid. MS (m/e): 423.3 [$(M+H)^+$].

Example 46

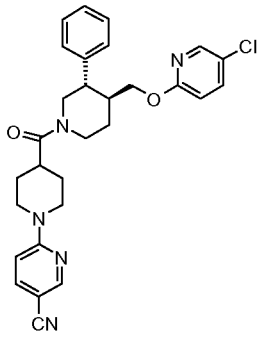
[(3SR,4SR)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-((3S,4S)-3-phenyl-piperidin-4-ylmethoxy)-pyridine, hydrochloride and 4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available) as off-white solid. MS (m/e): 489.3 [$(M+H)^+$].

Example 47

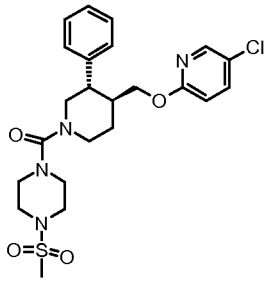
4-[(3S,4S)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-((3S,4S)-3-phenyl-piperidin-4-ylmethoxy)-pyridine, hydrochloride and 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) as off-white solid. MS (m/e): 516.4 [$(M+H)^+$].

Example 48

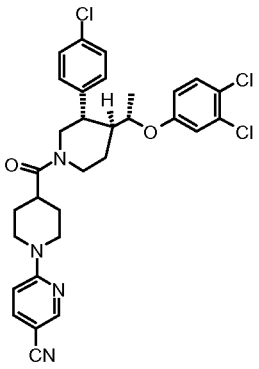
[(3S,4S)-4-(5-Chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidin-1-yl]-(4-methanesulfonyl-piperazin-1-yl)-methanone



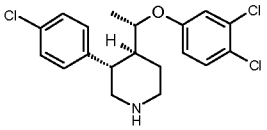
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-((3S,4S)-3-phenyl-piperidin-4-ylmethoxy)-pyridine, hydrochloride and 4-Methanesulfonyl-piperazine-1-carbonyl chloride (WO2009024502) as off-white solid. MS (m/e): 493.2 [$(M+H)^+$].

Example 49

4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



a) (3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine



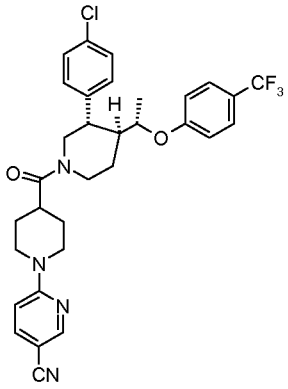
In analogy to the procedure described for the synthesis of 2-{(SR)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethoxy}-5-chloro-pyridine the title compound was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 3,4-Dichloro-phenol followed by removal of the benzyl protecting group by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol and used without further purification in the subsequent step.

b) 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from (3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine and 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) as viscous yellow oil. MS (m/e): 597.4 $[(M+H)^+]$.

Example 50

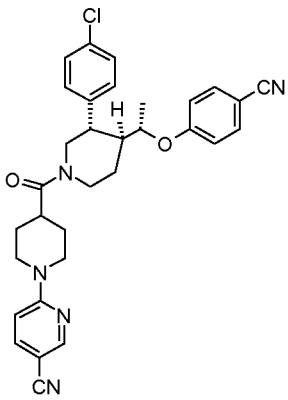
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(4-trifluoromethyl-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 4-trifluoromethyl-phenol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 597.4 [$(M+H)^+$].

Example 51

4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(4-cyano-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

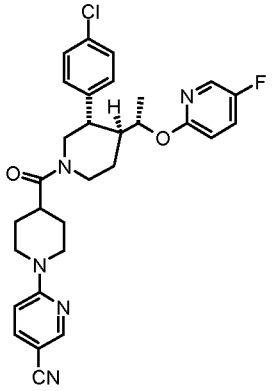


In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 4-cyano-phenol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-

chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 554.3 [$(M+H)^+$].

Example 52

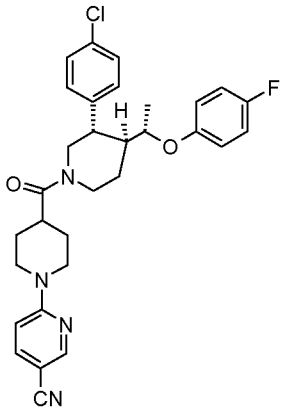
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 5-fluoro-2-hydroxy pyridine via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 548.4 [$(M+H)^+$].

Example 53

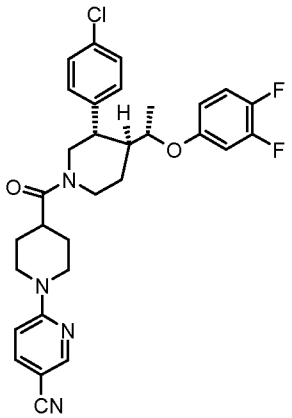
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(4-fluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 4-fluoro-phenol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as off-white foam. MS (m/e): 547.3 [$(M+H)^+$].

Example 54

4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-difluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

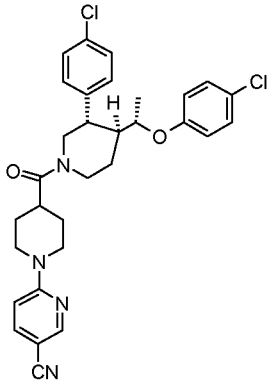


In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 3,4-difluoro-

phenol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as yellow foam. MS (m/e): 565.4 $[(M+H)^+]$.

Example 55

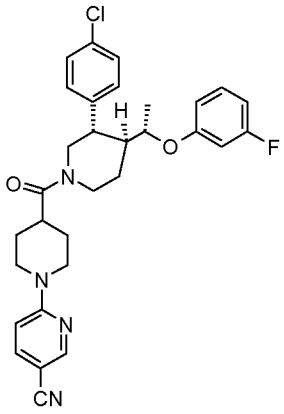
4-[(3S,4S)-4-[(S)-1-(4-Chloro-phenoxy)-ethyl]-3-(4-chloro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 4-chloro-phenol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 565.6 $[(M+H)^+]$.

Example 56

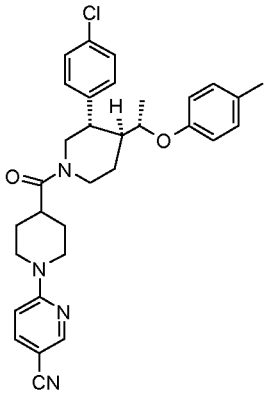
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3-fluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 3-fluoro-phenol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 547.4 [$(M+H)^+$].

Example 57

4-[(3S,4S)-3-(4-Chloro-phenyl)-4-((S)-1-p-tolyloxy-ethyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

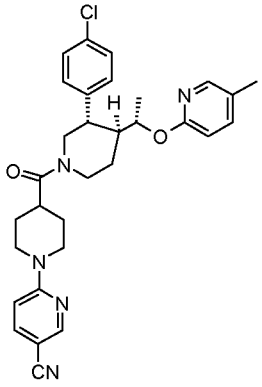


In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 4-methyl-phenol

via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 543.5 [$(M+H)^+$].

Example 58

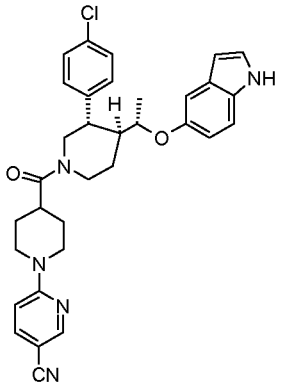
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-methyl-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 5-methyl-pyridin-2-ol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous light yellow oil. MS (m/e): 544.4 [$(M+H)^+$].

Example 59

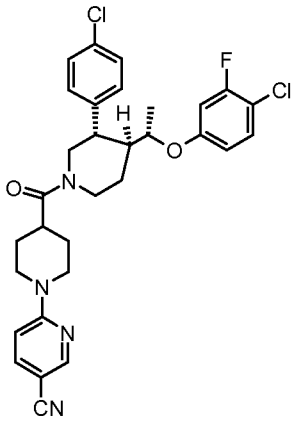
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(1H-indol-5-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 1H-indol-5-ol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 568.3 $[(M+H)^+]$.

Example 60

4-[(3S,4S)-4-[(S)-1-(4-Chloro-3-fluoro-phenoxy)-ethyl]-3-(4-chloro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

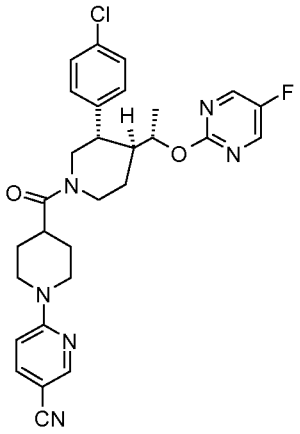


In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 4-Chloro-3-

fluoro-phenol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 581.5 $[(M+H)^+]$.

Example 61

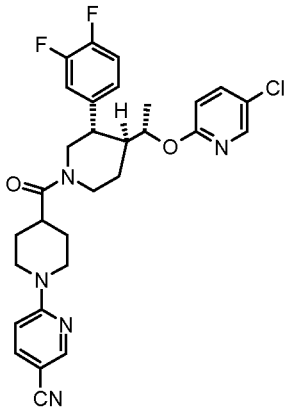
4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(5-fluoro-pyrimidin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile



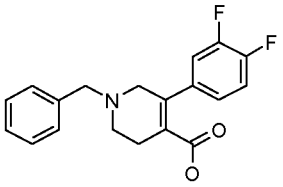
In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol and 5-fluoro-pyrimidin-2-ol via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as viscous yellow oil. MS (m/e): 549.4 $[(M+H)^+]$.

Example 62

4-[(3S,4S)-4-[(S)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

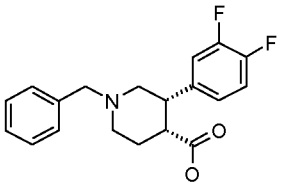


a) 1-Benzyl-5-(3,4-difluoro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid, hydrochloride



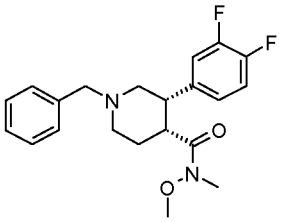
In analogy to the procedure described for the synthesis of 1-Benzyl-5-(4-chloro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid the title compound was prepared from 1-Benzyl-5-(3,4-difluoro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid ethyl ester through saponificatin with $LiOH \cdot H_2O$ and subsequent formation of the salt with HCl in diethyl ether. MS (m/e): 330.1 $[(M+H)^+]$.

b) (3S,4R)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidine-4-carboxylic acid



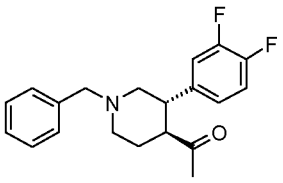
In analogy to the synthesis of (3RS, 4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid (example 1 (c)) the title compound was prepared through hydrogenation of 1-Benzyl-5-(3,4-difluoro-phenyl)-1,2,3,6-tetrahydro-pyridine-4-carboxylic acid, hydrochloride under Ruthenium catalysis ([$Ru(OAc)_2$((*R*)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(di-2-furylphosphine)]). The title compound was used without further purification in the consecutive step.

c) (3S,4R)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide



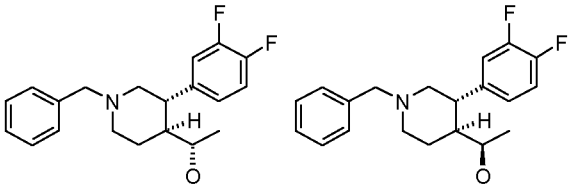
In analogy to the procedure described for the synthesis of (3RS,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide (example 5 (a)) the title compound was prepared from (3S,4R)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidine-4-carboxylic acid and methoxymethylamine. The title compound was obtained as light brown foam. MS (m/e): 375.4 [$(M+H)^+$].

d) 1-[(3S,4S)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethanone



In analogy to the procedure described for the synthesis of 1-[(3SR,4SR)-1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone (example 5 (c)) the title compound was prepared from (3S,4R)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidine-4-carboxylic acid methoxy-methyl-amide and methylmagnesium bromide with subsequent epimerisation with NaOMe in methanol. The title compound was obtained as light brown solid. MS (m/e): 330.3 [$(M+H)^+$].

e) (S)-1-[(3S,4S)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethanol and (R)-1-[(3S,4S)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethanol



In analogy to the procedure described for the synthesis of (RS)-1-[(3SR,4SR)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanol (example 5 (d)) the title compounds were synthesized

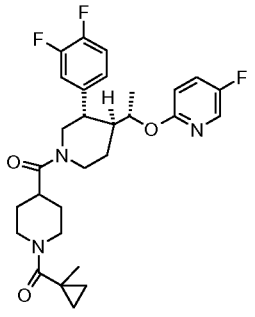
from 1-[(3S,4S)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethanone through reduction with $LiAlH_4$. (S)-1-[(3S,4S)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethanol was obtained as light yellow waxy solid. MS (m/e): 332.1 $[(M+H)^+]$ and (R)-1-[(3S,4S)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethanol was obtained as light yellow viscous oil. MS (m/e): 332.1 $[(M+H)^+]$.

f) 4-[(3S,4S)-4-[(S)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethanol and 5-Chloro-2-hydroxy-pyridine via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol to yield 5-Chloro-2-{(S)-1-[(3S,4S)-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as off-white solid. MS (m/e): 566.4 $[(M+H)^+]$.

Example 63

{4-[(3S,4S)-4-[(S)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone

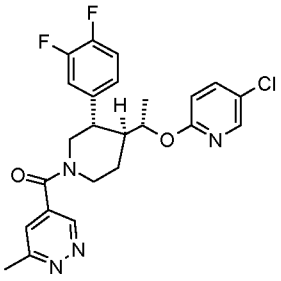


In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3S,4S)-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 1-(1-methyl-

cyclopropanecarbonyl)-piperidine-4-carboxylic acid (commercially available) as off-white solid. MS (m/e): 546.3 [(M+H)$^+$].

Example 64

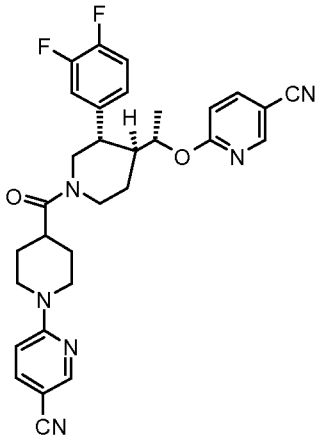
[(3S,4S)-4-[(S)-1-(5-Chloro-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidin-1-yl]-(6-methyl-pyridazin-4-yl)-methanone



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 5-Chloro-2-{(S)-1-[(3S,4S)-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethoxy}-pyridine and 6-Methyl-pyridazine-4-carboxylic acid (WO2009019163) as light brown solid. MS (m/e): 473.2 [(M+H)$^+$].

Example 65

4-[(3S,4S)-4-[(S)-1-(5-Cyano-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

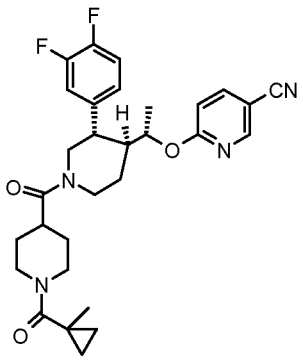


In analogy to the procedure described for the synthesis of 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-

[1,2']bipyridinyl-5'-carbonitrile (example 49) the respective piperidine derivative was prepared from (R)-1-[(3S,4S)-1-Benzyl-3-(3,4-difluoro-phenyl)-piperidin-4-yl]-ethanol and 3-cyano-6-hydroxy-pyridine via Mitsunobu reaction and subsequently the benzyl group was cleaved by treatment with 1-chloroethyl-chloroformate, DIPEA and methanol to yield 6-{(S)-1-[(3S,4S)-3-(3,4-Difluoro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile. Coupling with 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) yielded the title compound as off-white solid. MS (m/e): 557.3 [$(M+H)^+$].

Example 66

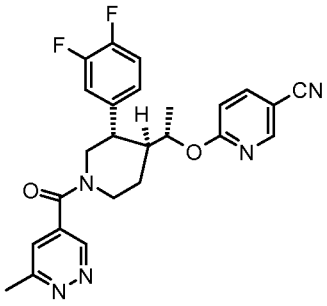
6-((S)-1-{(3S,4S)-3-(3,4-Difluoro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile



In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(3,4-Difluoro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carboxylic acid (commercially available) as light brown solid. MS (m/e): 537.4 [$(M+H)^+$].

Example 67

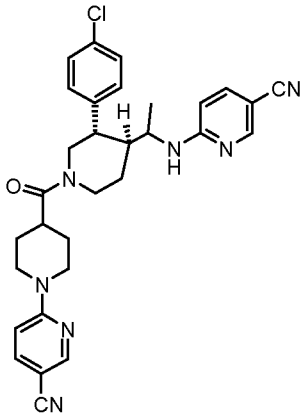
6-{(S)-1-[(3S,4S)-3-(3,4-Difluoro-phenyl)-1-(6-methyl-pyridazine-4-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile



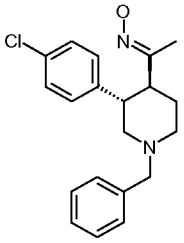
In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compound was prepared from 6-{(S)-1-[(3S,4S)-3-(3,4-Difluoro-phenyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile and 6-Methyl-pyridazine-4-carboxylic acid (WO2009019163) as light brown solid. MS (m/e): 464.3 [$(M+H)^+$].

Example 68 & Example 69

4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(SR)-1-(5-cyano-pyridin-2-ylamino)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile & 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(RS)-1-(5-cyano-pyridin-2-ylamino)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

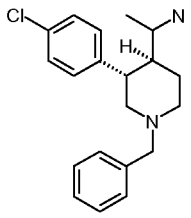


a) 1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone oxime



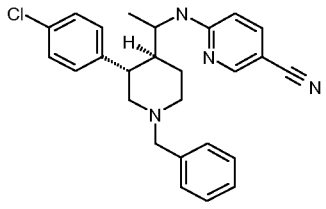
A mixture of 2 g (6.1 mmol) 1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone, 0.869 g (12.5 mmol) hydroxylamine, hydrochloride and 1.03 g (12.5mmol) sodium acetate in 25 mL ethanol was heated to reflux for 2 h. After cooling to room temperature water was added and the mixture was extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography on silica eluting with a ethyl acetate. The product containing fractions were evaporated to yield 1.6 g (77 %) of the title compound as colourless viscous oil. MS (m/e): 343.2 $[(M+H)^+]$.

b) 1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethylamine



A solution of 1.6 g (4.7 mmol) 1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethanone oxime in 300 mL methanol was hydrogenated over Raney Nickel (3.5 bar, 30°C, 23 h). The mixture was filtered and evaporated to dryness. The residue was purified by column chromatograpghy over silica eluting with a gradient formed from DCM, methanol and NH_3aq. to yield after evaporation of the product containing fractions 0.7 g (45 %) of the title compound as colourless viscous oil. MS (m/e): 329.4 $[(M+H)^+]$.

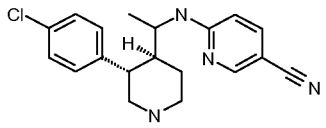
c) 6-{1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethylamino}-nicotinonitrile



A mixture of 610mg (1.8 mmol) 1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethylamine, 1.18g (2.8 mmol) 2-bromo-5-cyano-pyridine and 0.838 g (2.8 mmol) DIPEA in 3.5 mL DMF was heated to 60 °C for 3 days. The mixture was evaporated, Na_2CO_3aq. was added and the mixture was extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica eluting with a gradient formed from DCM, methanol and NH_3aq. to yield after evaporation

of the product containing fractions 0.526 g (66 %) of the title compound as off-white foam. MS (m/e): 431.4 [(M+H)$^+$].

d) 6-{1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethylamino}-nicotinonitrile



In analogy to the procedure described for the synthesis of 5-chloro-2-[(3RS, 4RS)-3-(4-chloro-phenyl)-piperidin-4-ylmethoxy]-pyridine; hydrochloride (example 1, step h) the title compound was prepared from 6-{1-[(3S,4S)-1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-ethylamino}-nicotinonitrile as light yellow viscous oil. MS (m/e): 341.2 [(M+H)$^+$].

e) 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(SR)-1-(5-cyano-pyridin-2-ylamino)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile & 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(RS)-1-(5-cyano-pyridin-2-ylamino)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

In analogy to the procedure described for the synthesis of [(3RS, 4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (example 1, step i) the title compounds were prepared from 6-{1-[(3S,4S)-3-(4-Chloro-phenyl)-piperidin-4-yl]-ethylamino}-nicotinonitrile and 5'-Cyano-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (commercially available) with subsequent separation via preparative HPLC on chiral pak AD eluting with heptane / ethanol to yield 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(SR)-1-(5-cyano-pyridin-2-ylamino)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile as off-white solid. MS (m/e): 554.4 [(M+H)$^+$] and 4-{(3S,4S)-3-(4-Chloro-phenyl)-4-[(RS)-1-(5-cyano-pyridin-2-ylamino)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile as off-white solid. MS (m/e): 554.4 [(M+H)$^+$]

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

Experimental procedure

The compounds were investigated in accordance with the tests given hereinafter

[^{3}H]SR142801 competition binding assay

hNK3 receptor binding experiment were performed using [^{3}H]SR142801 (Catalog No. TRK1035, specific activity: 74.0 Ci/mmol, Amersham, GE Healthcare UK limited, Buckinghamshire, UK) and membrane isolated from HEK293 cells transiently expressing recombinant human NK3 receptor. After thawing, the membrane homogenates were centrifuged at 48,000 X g for 10 min at 4 °C, the pellets were resuspended in the 50 mM Tris-HCl, 4 mM $MnCl_2$, 1 μM phosphoramidon, 0.1 % BSA binding buffer at pH 7.4 to a final assay concentration of 5 μg protein/well. For inhibition experiments, membranes were incubated with [^{3}H]SR142801 at a concentration equal to K_D value of radioligand and 10 concentrations of the inhibitory compound (0.0003 - 10 μM) (in a total reaction volume of 500 μl) for 75 min at room temperature (RT). At the end of the incubation, membranes were filtered onto unitfilter (96-well white microplate with bonded GF/C filter preincubated 1 h in 0.3 % PEI + 0.3 % BSA, Packard BioScience, Meriden, CT) with a Filtermate 196 harvester (Packard BioScience) and washed 4 times with ice-cold 50 mM Tris-HCl, pH 7.4 buffer. Nonspecific binding was measured in the presence of 10 μM SB222200 for both radioligands. The radioactivity on the filter was counted (5 min) on a Packard Top-count microplate scintillation counter with quenching correction after addition of 45 μl of microscint 40 (Canberra Packard S.A., Zürich, Switzerland) and shaking for 1 h. Inhibition curves were fitted according to the Hill equation: $y = 100/(1+(x/IC_{50})^{nH})$, where n_H = slope factor using Excel-fit 4 software (Microsoft). IC_{50} values were derived from the inhibition curve and the affinity constant (K_i) values were calculated using the Cheng-Prussoff equation $K_i = IC_{50}/(1+[L]/K_D)$ where [L] is the concentration of radioligand and K_D is its dissociation constant at the receptor, derived from the saturation isotherm. All experiments were performed in duplicate and the mean ± standard error (SEM) of the individual K_i values was calculated.

Some results of preferred compounds with a hNK-3 receptor affinity <0.010 μM were shown in the following table 1.

Table 1

Example	Data K_i [μM]	Example	Data K_i [μM]
5	0.0041	31	0.0083

7	0.0026	32	0.0058
10	0.0036	33	0.0013
11	0.0018	47	0.0099
12	0.0023	49	0.0055
13	0.0003	50	0.0013
14	0.0026	51	0.0019
16	0.0016	52	0.0006
17	0.0056	53	0.0006
18	0.0012	54	0.0017
19	0.0014	55	0.0009
20	0.0002	56	0.0038
21	0.0047	57	0.0014
23	0.0011	58	0.002
24	0.0087	61	0.0015
25	0.0015	62	0.0002
26	0.0051	63	0.0035
27	0.0003	65	0.0004
28	0.003	66	0.0046
29	0.0077	68	0.0014

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

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

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

Example A

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

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

Example B

Capsules of the following composition are manufactured:

	mg / capsule
Active substance	10
Lactose	155
Corn starch	30
Talc	5
Capsule fill weight	200

The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelantine capsules.

Example C

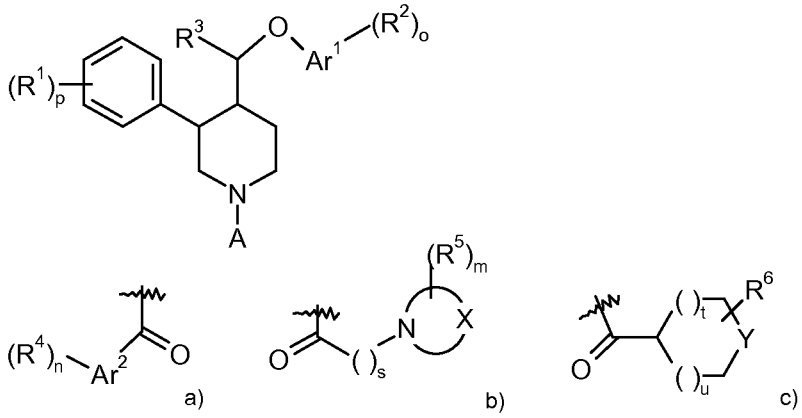
Suppositories of the following composition are manufactured:

	mg / supp.
Active substance	15
Suppository mass	1285
Total	1300

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45 °C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

Claims

1. A compound of formula I



wherein

Ar^1 is aryl or a six membered heteroaryl;

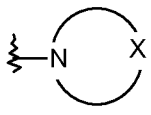
Ar^2 is aryl or a six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen or lower alkyl;

R^4 is hydrogen, lower alkyl, phenyl optionally substituted by halogen, or is a five membered heteroaryl, optionally substituted by lower alkyl, or is aryl optionally substituted by halogen;

 is a six membered heterocyclic group, wherein X is $-N(SO_2CH_3)$;

R^6 is hydrogen;

Y is $-N(R^{7'})-$

$R^{7'}$ is a 6-membered heteroaryl group, optionally substituted by cyano or C(O)-cycloalkyl, wherein the cycloalkyl group is optionally substituted by lower alkyl,

n is 1;

m is 1;

o is 1;

p is 1;

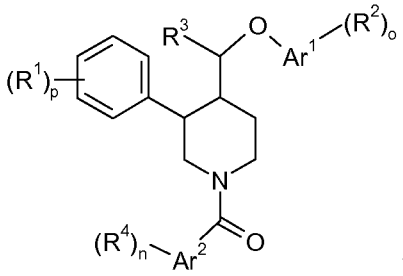
s is 0;

t is 1;

u is 1;

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

2. A compound of formula Ia according to claim 1,



Ia

wherein

Ar^1 is aryl or a six membered heteroaryl;

Ar^2 is aryl or a six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen or lower alkyl;

R^4 is hydrogen, lower alkyl, phenyl, optionally substituted by halogen, or is a five membered heteroaryl, optionally substituted by lower alkyl, or is aryl optionally substituted by halogen;

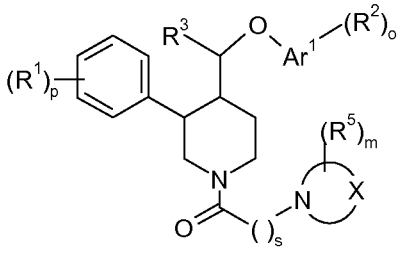
n is 1;

o is 1;

p is 1;

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

3. A compounds of formula Ib according to claim 1



Ib

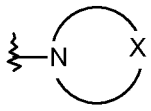
wherein

Ar^1 is aryl or a six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen or lower alkyl;



is a six membered heterocyclic group, wherein X is $-N(SO_2CH_3)$;

m is 1;

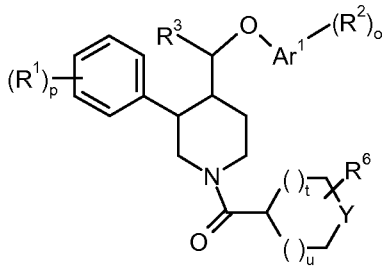
o is 1;

p is 1;

s is 0;

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

4. A compounds of formula Ic according to claim 1



Ic

wherein

Ar^1 is aryl or a six membered heteroaryl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy or lower alkyl substituted by halogen;

R^2 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or cyano;

R^3 is hydrogen or lower alkyl;

Y is $-N(R^{7'})-$;

$R^{7'}$ is a 6-membered heteroaryl group, optionally substituted by cyano or C(O)-cycloalkyl, wherein the cycloalkyl group is optionally substituted by lower alkyl;

R^6 is hydrogen;

p is 1;

o is 1;

t is 1;

u is 1;

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

5. A compound of formula Ia according to claim 2, wherein Ar^1 is a six membered heteroaryl and Ar^2 is aryl.

6. A compound of formula Ia according to claim 5, wherein the compounds are
[(3RS,4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
[(3RS,4RS)-3-(4-chloro-phenyl)-4-(5-trifluoromethyl-pyridin-2-yloxymethyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanone
{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone
{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-methanone
6-((S)-1-{(3S,4S)-3-(4-chloro-phenyl)-1-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-benzoyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile
6-((S)-1-{(3S,4S)-3-(4-chloro-phenyl)-1-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzoyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile
6-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-1-(4'-fluoro-biphenyl-4-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile or
[(3SR,4SR)-4-(5-chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidin-1-yl]-[4-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone.

7. A compound of formula Ia according to claim 2, wherein both Ar^1 and Ar^2 are six membered heteroaryl.

8. A compound of formula Ia according to claim 7, which compounds are

{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(6-methyl-pyridazin-4-yl)-methanone
{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(6-methyl-pyridazin-4-yl)-methanone or
6-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-1-(6-methyl-pyridazine-4-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile.

9. A compound of formula Ib according to claim 3, wherein Ar^1 is a six membered heteroaryl and X is $-N(SO_2CH_3)$.

10. A compound of formula Ib according to claim 9, which compounds are
{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidin-1-yl}-(4-methanesulfonyl-piperazin-1-yl)-methanone
6-{(S)-1-[(3S,4S)-3-(4-chloro-phenyl)-1-(4-methanesulfonyl-piperazine-1-carbonyl)-piperidin-4-yl]-ethoxy}-nicotinonitrile

11. A compound of formula Ic according to claim 4, wherein Ar^1 is a six membered heteroaryl and Y is $NR^{7'}$.

12. A compound of formula Ic according to claim 11, which compounds are
{4-[(3RS,4RS)-3-(4-chloro-phenyl)-4-(5-trifluoromethyl-pyridin-2-yloxymethyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone
{4-[(3RS,4RS)-3-(4-chloro-phenyl)-4-(5-chloro-pyridin-2-yloxymethyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone
(4-{(3SR,4SR)-3-(4-chloro-phenyl)-4-[(SR)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone
(4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone
(4-{(3R,4R)-3-(4-chloro-phenyl)-4-[(R)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-piperidin-1-yl)-(1-methyl-cyclopropyl)-methanone
4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-trifluoromethyl-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

6-((S)-1-{(3S,4S)-3-(4-chloro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-cyano-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

{4-[(3SR,4SR)-4-(5-chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone

4-[(3S,4S)-4-(5-chloro-pyridin-2-yloxymethyl)-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-6'-carbonitrile

4-[(3S,4S)-4-(5-chloro-pyridin-2-yloxymethyl)-3-phenyl-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(3,4-dichloro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(4-trifluoromethyl-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(4-cyano-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-fluoro-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(4-fluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(3,4-difluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-[(3S,4S)-4-[(S)-1-(4-chloro-phenoxy)-ethyl]-3-(4-chloro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(3-fluoro-phenoxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-[(3S,4S)-3-(4-chloro-phenyl)-4-((S)-1-p-tolyloxy-ethyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

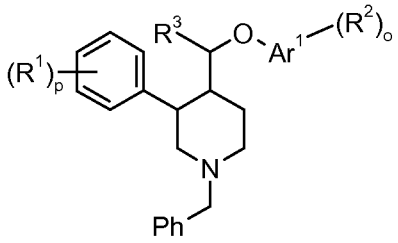
4-{(3S,4S)-3-(4-cloro-phenyl)-4-[(S)-1-(5-methyl-pyridin-2-yloxy)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile

4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(S)-1-(5-fluoro-pyrimidin-2-yloxy)-ethyl]-piperidine-1-

carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile
4-[(3S,4S)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile
{4-[(3S,4S)-4-[(S)-1-(5-chloro-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-piperidin-1-yl}-(1-methyl-cyclopropyl)-methanone
4-[(3S,4S)-4-[(S)-1-(5-cyano-pyridin-2-yloxy)-ethyl]-3-(3,4-difluoro-phenyl)-piperidine-1-carbonyl]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile
6-((S)-1-{(3S,4S)-3-(3,4-difluoro-phenyl)-1-[1-(1-methyl-cyclopropanecarbonyl)-piperidine-4-carbonyl]-piperidin-4-yl}-ethoxy)-nicotinonitrile or
4-{(3S,4S)-3-(4-chloro-phenyl)-4-[(SR)-1-(5-cyano-pyridin-2-ylamino)-ethyl]-piperidine-1-carbonyl}-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile.

13. A process for preparation of a compound of formula I as defined in claim 1, which process comprises

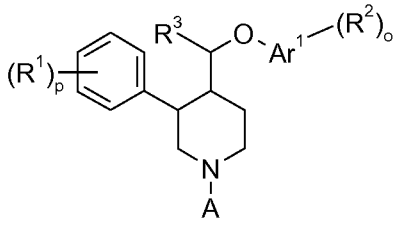
coupling a compound of formula



VIII

with a corresponding compound of formula A-Hal

to a compound of formula



I

wherein Hal is Cl, Br or I and the other definitions are as describedin claim 1, and, if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

14. A compound according to any on of claims 1 - 12, whenever prepared by a process as claimed in claim 13 or by an equivalent method.

15. A medicament containing one or more compounds as claimed in any one of claims 1 - 12 and pharmaceutically acceptable excipients.

16. A medicament according to claim 15 for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, anxiety and attention deficit hyperactivity disorder (ADHD).

17. The use of a compound as claimed in any one of claims 1 – 12 for the manufacture of medicaments for the treatment of depression, pain, psychosis, Parkinson's disease, schizophrenia, anxiety and attention deficit hyperactivity disorder (ADHD).

18. The invention as herein before described.

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