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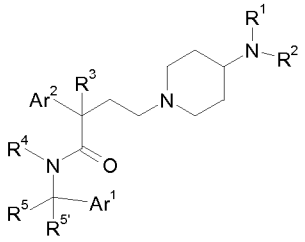
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(54) **Title:** PIPERIDINE DERIVATIVES AS NK3 RECEPTOR ANTAGONISTS



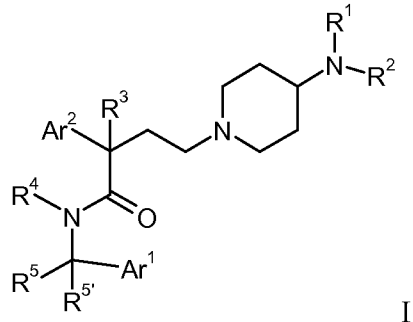
(I)

(57) **Abstract:** The invention relates to a compound of general formula (I) wherein Ar^1/Ar^2 are independently from each other phenyl or pyridinyl, which are optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen, lower alkyl substituted by alkoxy, lower alkyl substituted by cyano, lower di-alkyl amino, pyridinyl or cyano; R^1 is hydrogen, lower alkyl, $-(CH_2)_2O$-lower alkyl, or cycloalkyl: R^2 is $-S(O)_2$-lower alkyl or -C(O) -lower alkyl; or R^1 and R^2 form together with the N-atom to which they are attached a pyrrolidin-2- one or a piperidin-2-one group; R^3 is hydrogen, halogen or lower alkyl; R^4 is hydrogen or lower alkyl; $R^5/R^{5'}$ are independently from each other hydrogen, lower alkyl, lower alkyl substituted by halogen, lower alkyl substituted by hydroxy or cycloalkyl; or R^5 and $R^{5'}$ form together with the carbon-atom to which they are attached a cycloalkyl group; or to a pharmaceutically active salt 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).

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PIPERIDINE DERIVATIVES AS NK3 RECEPTOR ANTAGONISTS

The invention relates to a compound of general formula



I

wherein

Ar^1/Ar^2 are independently from each other phenyl or pyridinyl, which are optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen, lower alkyl substituted by alkoxy, lower alkyl substituted by cyano, lower di-alkyl amino, pyridinyl or cyano;

R^1 is hydrogen, lower alkyl, $-(CH_2)_2O$-lower alkyl or cycloalkyl:

R^2 is $-S(O)_2$-lower alkyl or $-C(O)$-lower alkyl;

or R^1 and R^2 form together with the N-atom to which they are attached a pyrrolidin-2-one or a piperidin-2-one group;

R^3 is hydrogen, halogen or lower alkyl;

R^4 is hydrogen or lower alkyl;

$R^5/R^{5'}$ are independently from each other hydrogen, lower alkyl, lower alkyl substituted by halogen, lower alkyl substituted by hydroxy or cycloalkyl;

or R^5 and $R^{5'}$ form together with the carbon-atom to which they are attached a cycloalkyl group;

or to a pharmaceutically active salt thereof.

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

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

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

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

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

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

would preferably have a low dosage allowing once-per-day dosage, due to the low adherence of schizophrenic patients.

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

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

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

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

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

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

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

The term "lower alkyl substituted by hydroxy" denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by a hydroxy , for example $-CH_2OH$, $-CH_2CH_2OH$, and the like.

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

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

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

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

The following groups of compounds of formula I are preferred:

Preferred are compounds of formula I, wherein Ar^1 and Ar^2 are both phenyl.

Especially preferred from this group are compounds, wherein
- R^1 is methyl and R^2 is $S(O)_2CH_3$, for example
2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide

N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide or
2-(3,4-dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyramide; diastereoisomer 1.

- R^1 is cyclopropyl and R^2 is $S(O)_2CH_3$, for example
4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
N-(4-chloro-3-trifluoromethyl-benzyl)-4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide or
4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide.

- R^1 is ethyl and R^2 is $S(O)_2CH_3$, for example
2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyramide
N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
N-(3-chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-

dimethyl-N-(4-trifluoromethyl-benzyl)-butyramide
2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-N-(4-methyl-benzyl)-butyramide
N-(2-chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide or
2-(3,4-dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyramide; diastereoisomer 1.

- R^1 and R^2 form together with the N-atom to which they are attached a pyrrolidin-2-one group, for example

2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(3-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-(4-trifluoromethyl-benzyl)-butyramide
2-(3,4-dichloro-phenyl)-2,N-dimethyl-N-(4-methyl-benzyl)-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(2-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
2-(3,4-dichloro-phenyl)-N-[-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide; diastereoisomer 1
2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-(2,2,2-trifluoro-1-phenyl-ethyl)-butyramide
2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-[2,2,2-trifluoro-1-(4-fluoro-phenyl)-ethyl]-butyramide
N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-

piperidin-1-yl]-butyramide
(R or S)-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
(R or S)-2-(3,4-dichloro-phenyl)-N-[(S or R)-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-*N*-((S)-1-phenyl-propyl)-butyramide
2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-(R or S) methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide or

2-(3,4-dichloro-phenyl)-*N*-(4-fluoro-3-trifluoromethyl-benzyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide.

- R^1 is lower alkyl and R^2 is $C(O)CH_3$, for example
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2-methyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2-methyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(3-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2,N-dimethyl-N-(4-trifluoromethyl-benzyl)-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide; diastereoisomer 1
(R or S)-4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide (diastereosisomer 1)
4-[4-(acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-

phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 1)
4-[4-(acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 2)
4-[4-(acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide
4-[4-(acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 1) or
4-[4-(acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide.

- R^1 is $-(CH_2)_2OCH_3$ and R^2 is $C(O)CH_3$, for example

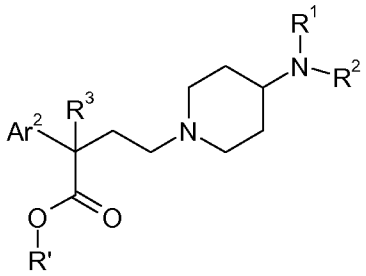
4-{4-[acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 1)
4-{4-[acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastreoisomer 1)
4-{4-[acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-(R or S) methyl-butyramide or
4-{4-[acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide.

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 1. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein before unless indicated to the contrary.

In more detail, the compounds of formula **I** can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in 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.

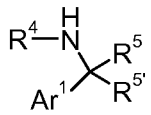
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by processes described below, which process comprises

a) cleaving off an O-protecting group under aqueous basic conditions from a compound of formula IV

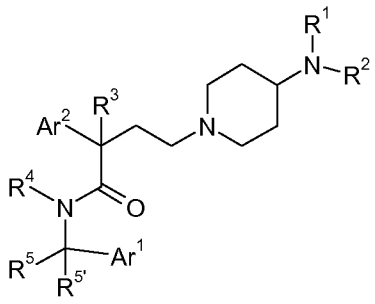


IV

and reacting a compound of formula IV under coupling conditions with an amine of formula



to a compound of formula



I

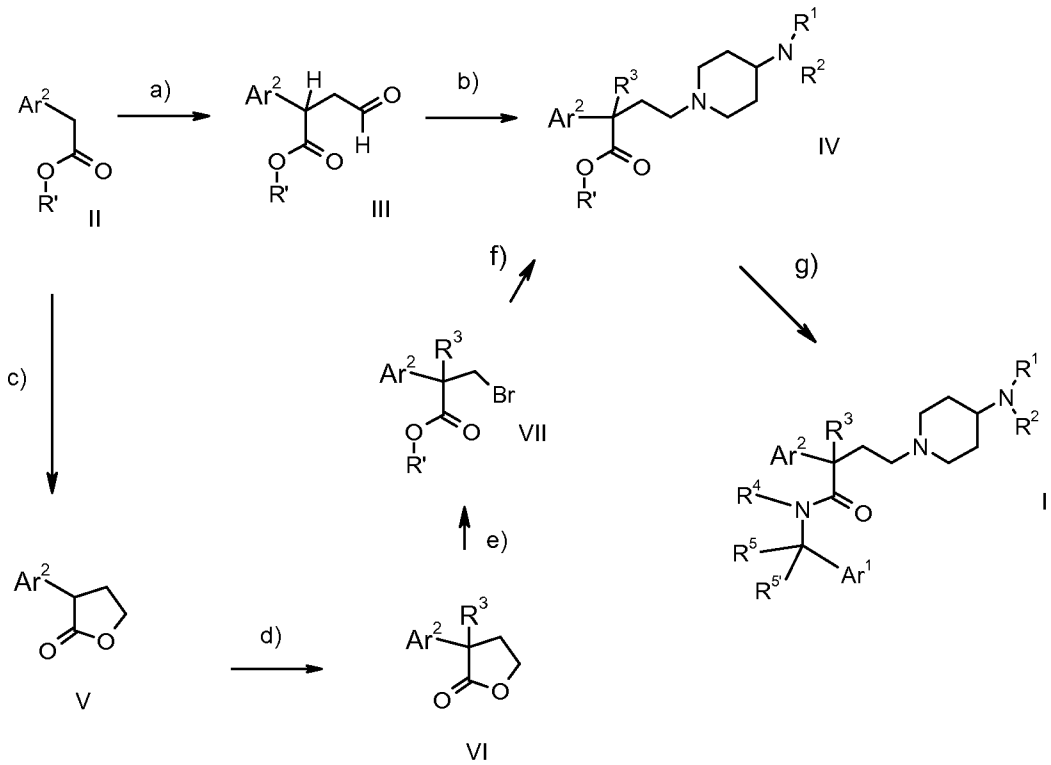
wherein the definitions have same meanings as described above, and

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

The process is described in scheme 1 in more detail.

General experimental part:

Scheme 1



R^1, R^2, R^3, R^4, R^5, $R^{5'}$, Ar^1 and Ar^2 are as described above and R' is an O-protecting group, such as benzyl.

Step a)

Phenylacetic acid ester derivatives **II** are commercially available or can be accessed by

methods described in literature. Reaction of ester derivatives **II** with protected bromo alkyl aldehydes (either commercially available or synthetically accessible by methods known in the art) under basic conditions lead to aldehyde derivatives **III** as described analogously in literature (for reaction conditions described in literature affecting such 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). However, it is convenient to react ester derivative **II** with the respective protected bromo alkyl aldehyde (commercially available or accessible by methods known) in the presence of a base and a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dimethylformamide (DMF), tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include NaH and the like. The reaction 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 reaction with heating from ambient temperature 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 aldehyde protected intermediate which can be subjected to acidic cleavage of the protecting group in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the acid used in this stage, and any acid commonly used in this type of reaction may equally be employed here. Examples of such acid include HCl and the like. The reaction 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 reaction with heating from ambient temperature 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 aldehyde derivatives **III**.

Step b)

Reductive aminations are widely described in literature (for reaction conditions described

in literature affecting such 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). However, we find it convenient to transform aldehyde derivative **III** with piperidine derivatives (Journal of Medicinal Chemistry (2006), 49(16), 4801-4804) under reductive conditions in the presence of a solvent to afford ester derivatives **IV**. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the reducing agent used in this stage, and any reducing agent commonly used in this type of reaction may equally be employed here. Examples of such reducing agents include sodium triacetoxyborohydride and the like. The reaction 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 reaction with heating from ambient temperature 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 ester derivatives **IV**.

Step c)

Reaction of ester derivatives **II** with hydroxy-protected alkyl halides (either commercially available or synthetically accessible by methods known in the art) under basic conditions lead upon cleavage of the hydroxyl protecting group to lactones **V** as described in literature (for reaction conditions described in literature affecting such 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). However, it is convenient to react ester derivative **II** with 2-(2-bromoethoxy) tetrahydro-2-H-pyrane (commercially available in the presence of a base and a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dimethylformamide (DMF), tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include NaH and the like. The reaction 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 reaction with heating from ambient temperature 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 hydroxy protected intermediate which can be subjected to acidic cleavage of the protecting group in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dimethylformamide (DMF), tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the acid used in this stage, and any acid commonly used in this type of reaction may equally be employed here. Examples of such acid include HCl and the like. The reaction 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 reaction with heating from ambient temperature 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 lactone derivatives **V**.

Step d)

Lactone derivatives **V** can conveniently be transferred into the respective substituted lactone derivatives **VI** by reaction of lactone **V** with an electrophile in the presence of a base in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dimethylformamide (DMF), tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include NaH and the like. The reaction 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 reaction with heating from ambient temperature 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 lactone derivatives **VI**.

Step e)

Lactone derivative **VI** can conveniently be transferred into the respective ester derivative

VII by a two step reaction sequence. Any commonly used synthetic sequence is applicable however, we find it convenient to open the lactone derivative **VII** with HBr in the presence of an acid. Any commonly used acid which in combination with HBr affects such a reaction can be used. Examples of such acids include acetic acid and the like. The reaction 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 reaction with heating from ambient temperature 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 intermediately built acid derivative which is subjected to esterification conditions. Common procedures are described in literature, however, we find it convenient to transform the intermediately built acid into the respective ester derivative **VII** by reaction with $SOCl_2$ in methanol. The reaction 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 reaction with heating from ambient temperature 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 ester derivative **VII**.

Step f)

Transformation of ester derivatives **VII** with piperidine derivatives to access piperidine derivatives **IV** can be done by any commonly used procedure. However, we find it convenient to react ester derivative **VII** with piperidine derivatives in the presence of a solvent and a base. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dimethylformamide (DMF), tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include DIPEA, NEt_3 and the like. The reaction 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 reaction with heating from ambient temperature 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 piperidine derivatives **IV**.

Step g)

Transformation of piperidine derivatives **IV** into the final amide derivatives can be done according to procedures described in literature. However, we find it convenient to employ a two step reaction sequence in which the ester functionality in **IV** is cleaved under aqueous basic conditions and the liberated acid functionality converted with the respective amines under coupling conditions and to the piperidine derivatives **I**. There is no particular restriction on the nature of the aqueous base to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable aqueous bases include NaOH, LiOH and the like. Any commonly used co-solvent can be employed. Examples include THF and the like. The coupling of carboxylic acids with amines is widely described in literature and the procedures are known to those in the art (For reaction conditions described in literature affecting such 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 intermediately built acid can conveniently be transformed to the respective amide through coupling with an amine (either commercially available or accessible by methods described in references or by methods known in the art; as appropriate) by employing the usage of coupling reagents. For example coupling reagents like N,N'-carbonyldiimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and the like can equally well be employed to affect such transformation. We find it convenient to carry out the reaction in a solvent like dimethylformamide (DMF) and in the presence of a base. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: DMF, dichloromethane (DCM), dioxane, THF, and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include triethylamine and diisopropylethylamine, and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary

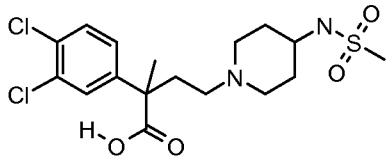
widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield piperidine derivatives **I**.

5

Examples

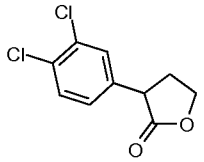
Intermediate 1

2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid



a) step 1:

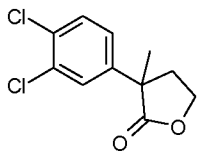
3-(3,4-Dichloro-phenyl)-dihydro-furan-2-one (commercially available)



A mixture of 30.00 g (137 mmol) (3,4-dichloro-phenyl)-acetic acid methyl ester (commercially available), 6.47 g (151 mmol) NaH (55%) and 35.80 g (171 mmol) 2-(2-bromo-ethoxy)-tetrahydro-pyran in 100 mL DMF was stirred at room temperature for 17h. The mixture was evaporated to dryness and partitioned between water and ethyl acetate. The combined organic phases were washed with NaCl aq., dried with Na_2SO_4 and evaporated. The residue was treated with 400 mL 4N HCl in dioxane and stirred for 16 h at room temperature. The mixture was evaporated to dryness and subjected to column chromatography on silica eluting with a gradient formed from ethyl acetate and heptane. The combined product fractions were evaporated to yield 18.5 g (58%) of the title compound as yellow oil.

b) step 2:

3-(3,4-Dichloro-phenyl)-3-methyl-dihydro-furan-2-one

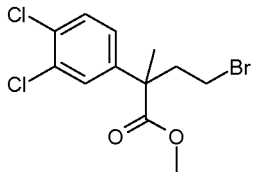


A mixture of 18.50 g (80 mmol) 3-(3,4-dichloro-phenyl)-dihydro-furan-2-one, 3.84 g (88 mmol) NaH (55% suspension) and 14.20 g (100 mmol) iodomethane in 300 mL THF was stirred for 64 h at room temperature. NH_4Cl aq. sat. was added and the mixture was extracted with ethyl acetate. The organic phases were washed with NaCl aq. sat. dried with Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash

column chromatography on silica eluting with a gradient formed from ethyl acetate and heptane. The product containing fractions were evaporated to yield 16 g (82 %) of the title compound as yellow oil. MS(m/e): 246.0 (MH^+).

c) step 3:

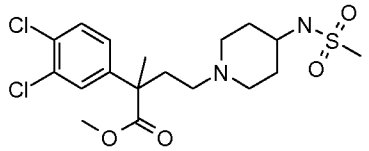
4-Bromo-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester



To a mixture of 3.30 g (13.5 mmol) 3-(3,4-dichloro-phenyl)-3-methyl-dihydro-furan-2-one in 15 mL acetic acid was added 48 mL HBr (33%) in acetic acid and after 63 h 20 mL HBr (33%) in acetic acid was added again and stirred for another 21 h at room temperature. The mixture was pored onto ice-water and extracted with ethyl ether. The combined organic phases were washed with NaCl aq. sat., dried with Na_2SO_4, filtered and evaporated to dryness, The residue was taken up in 150 mL toluene and 6.50 mL (89.0 mmol) thionylchloride were added. The mixture was heated to 75 °C for 4 h, cooled to 0 °C, treated with 20 mL methanol and allowed to stand for 16 h at room temperature. The mixture was evaporated to dryness and subjected to column chromatography on silica eluting with a gradient formed from ethyl acetate and heptane. The product containing fractions were evaporated to yield 4.32 g (94 %) of the title compound as light yellow oil. MS(m/e): 341.9 (MH^+).

d) step 4:

2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester



A mixture of 0.7 0g (2.05 mmol) 4-bromo-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester and 1.83 g (10.30 mmol) N-piperidin-4-yl-methanesulfonamide (commercially available) in 30 mL N,N-dimethylacetamide was stirred for 89 h at 60 °C. The mixture was evaporated to dryness and methanol, DCM and isolute was added and evaporated to dryness. The residue was subjected to column chromatography on silica eluting with a gradient formed from DCM, methanol and NH_3 aq.. The product

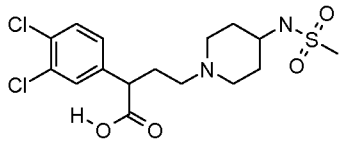
containing fractions were evaporated to yield 0.76 g (84 %) of the title compound as light brown waxy solid. MS(m/e): 437.3 (MH^+).

e) step 5:

A mixture of 0.76 g (1.7 mmol) 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester and 0.23 g (5.4 mmol) $LiOH \cdot H_2O$ in 15 mL water and 15 mL THF was stirred at room temperature for 18 h. The mixture was evaporated and treated with 4N HCl aq. and evaporated to dryness. The residue was used without further purification in the subsequent step. MS(m/e): 423.1 (MH^+).

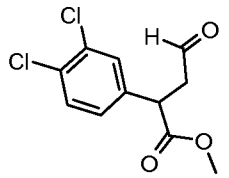
Intermediate 2

2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid



a) step 1:

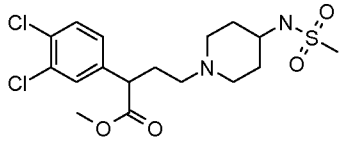
2-(3,4-Dichloro-phenyl)-4-oxo-butyric acid methyl ester



A mixture of 25.0 g (114 mmol) (3,4-dichloro-phenyl)-acetic acid methyl ester (commercially available), 5.7 g (131 mmol) NaH (55%) and 23.1 g (137 mmol) bromoacetaldehyde dimethylacetal in 80 mL DMF was stirred at room temperature for 3 h. The mixture was poured onto ice / water and extracted with ethyl acetate. The combined organic phases were washed with NaCl aq., dried with Na_2SO_4 and evaporated to dryness. The residue was dissolved in 250 mL THF and treated with 300 mL 1N HCl at room temperature for 20 h. Water was added and the mixture was extracted with ethyl acetate. The combined organic phases were washed with NaCl aq., dried with Na_2SO_4, evaporated to dryness and subjected to column chromatography on silica eluting with a gradient formed from heptane and ethyl acetate. The product containing fractions were evaporated to yield 9.7 g (32 %) of the title compound as light yellow oil. MS(m/e): 260.1 / 262.2 (MH^+)

b) step 2:

2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid methyl ester



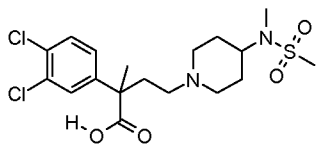
A mixture of 0.89 g (3.4 mmol) 2-(3,4-dichloro-phenyl)-4-oxo-butyric acid methyl ester, 0.67 g (3.7 mmol) N-Piperidin-4-yl-methanesulfonamide (commercially available), 1.08 g (5 .0 mmol) sodium triacteoxyborohydride and 0.30 g (5.0 mmol) acetic acid in 40 mL THF was stirred at room temperature for 64 h. Water and Na_2CO_3 aq. was added and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with NaCl sat. aq. dried with Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography on silica eluting with a gradient formed from DCM, methanol and NH_3 aq.. The product containing fractions were evaporated to yield 1.21 g (84 %) of the title compound as off-white solid. MS(m/e): 423.1 (MH^+).

c) step 3:

A mixture of 1.16 g (2.7 mmol) 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid methyl ester and 0.35 g (8.2 mmol) $LiOH \cdot H_2O$ in 20 mL water and 20 mL THF was stirred for 69 h at room temperature and evaporated. The residue was treated with 4N HCl aq. and evaporated to dryness and dried in vacuo. The residue was used without further purification in the subsequent step. MS(m/e): 409.4 (MH^+).

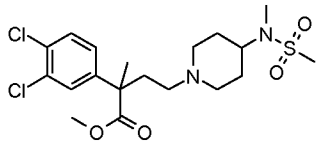
Intermediate 3

2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid



a) step 1:

2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid methyl ester



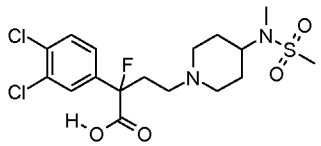
In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester (intermediate 1, step 4) the title compound was prepared from 4-bromo-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester and N-methyl-N-piperidin-4-yl-methanesulfonamide (DE 2824064) as light yellow viscous oil. MS(m/e): 451.2 (MH^+).

b) step 2:

In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1, step 5) the title compound was prepared from 2-(3,4-dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid methyl ester by saponification with $LiOH \cdot H_2O$ as off-white foam. MS(m/e): 437.1 (MH^+).

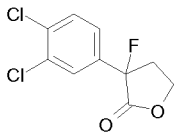
Intermediate 4

2-(3,4-Dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-butyric acid



a) step 1:

3-(3,4-Dichloro-phenyl)-3-fluoro-dihydro-furan-2-one

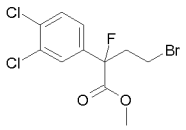


A mixture of 4.00 g (18.7 mmol) 3-(3,4-dichloro-phenyl)-dihydro-furan-2-one (commercially available), 0.83 g (19.0 mmol) NaH (55% suspension in oil) and 6.00 g (19.0 mmol) N-fluorobenzenesulfonimide (commercially available) in 100 mL THF stirred at room temperature for 1 h. The mixture was filtered and the filtrate evaporated to dryness. DCM and isolute was added and the mixture was evaporated to dryness. The residues was subjected to column chromatography on silica eluting with a gradient formed from heptane and toluene. The product containing fraction were evaporated to

yield 3.8 g (88 %) of the title compound as colourless oil. MS(m/e): 248.1/ 250.1 /251.1 (MH^+).

b) step 2:

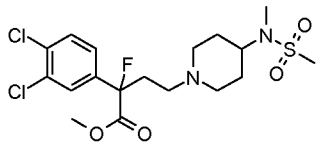
4-Bromo-2-(3,4-dichloro-phenyl)-2-fluoro-butyric acid methyl ester



In analogy to the procedure described for the preparation of 4-bromo-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester (intermediate 1, step 3) the title compound was synthesized from 3-(3,4-dichloro-phenyl)-3-fluoro-dihydro-furan-2-one by acidic bromination with acetic acid and HBr and subsequent esterification with $SOCl_2$ and methanol. The title compound was obtained as colourless oil. MS(m/e): 342/346/348 (MH^+).

c) step 3:

2-(3,4-Dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-butyric acid methyl ester



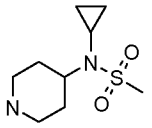
In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester (intermediate 1, step 4) the title compound was prepared from 4-bromo-2-(3,4-dichloro-phenyl)-2-fluoro-butyric acid methyl ester and N-methyl-N-piperidin-4-yl-methanesulfonamide (DE 2824064) as light brown waxy solid. MS(m/e): 455.1 (MH^+).

d) step 4:

In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1, step 5) the title compound was prepared from 2-(3,4-dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-butyric acid methyl ester by saponification with $LiOH \cdot H_2O$ as off-white solid. MS(m/e): 441.1 (MH^+).

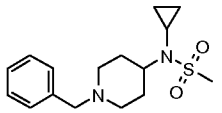
Intermediate 5

N-Cyclopropyl-N-piperidin-4-yl-methanesulfonamide



a) step 1:

N-(1-Benzyl-piperidin-4-yl)-N-cyclopropyl-methanesulfonamide



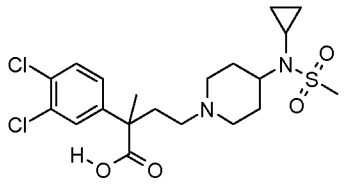
A mixture of 9.40 g (40.8 mmol) 1-benzyl-cyclopropylpiperidine-4-amine (commercially available), 5.14 g (44.8 mmol) methanesulfonyl chloride and 4.95 g (49.0 mmol) NEt_3 in 150 mL DCM was stirred for 17 h at room temperature. The mixture was evaporated to dryness and subjected to column chromatography on silica eluting with a gradient formed from DCM, methanol and NH_3 aq.. The product containing fractions were evaporated to yield 11.40 g (90 %) of the title compound as light yellow solid. MS(m/e): 309.3 (MH^+).

b) step 2:

A mixture of 11.3 g (36.6 mmol) N-(1-benzyl-piperidin-4-yl)-N-cyclopropyl methane sulfonamide and 5.1 g Pd/C (10 %) in 150 mL THF, 300 mL methanol and 31.7 mL formic acid was hydrogenated at room temperature. The mixture was filtered and evaporated to dryness. Water and Na_2CO_3 aq. was added and the mixture was extracted with THF/ethyl acetate. The combined organic phases were washed with NaCl aq. sat., dried with Na_2SO_4, filtered and evaporated to dryness. The residue was taken up in DCM and subjected to flash column chromatography on silica eluting with a gradient formed from DCM, methanol and NH_3 aq.. The product containing fractions were evaporated to yield 5 g (62 %) of the title compound as white solid. MS(m/e): 219.1 (MH^+).

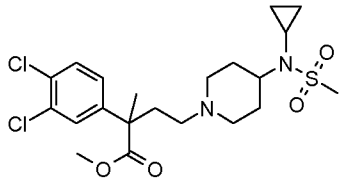
Intermediate 6

4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid



a) step 1:

4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester



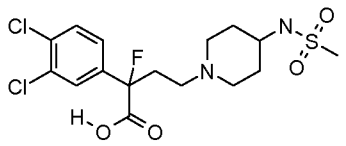
In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester (intermediate 1, step 4) the title compound was prepared from 4-bromo-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester and N-cyclopropyl-N-piperidin-4-yl-methanesulfonamide as viscous colourless oil. MS(m/e): 476.9 (MH^+).

b) step 2:

In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1, step 5) the title compound was prepared from 4-[4-cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester by saponification with $LiOH \cdot H_2O$ as white foam. MS(m/e): 446.1 (MH^+).

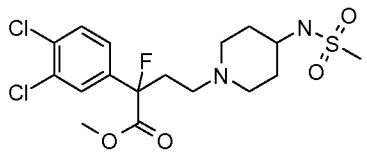
Intermediate 7

2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid



a) step 1:

2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid methyl ester



In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester (intermediate

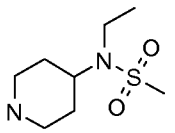
1, step 4) the title compound was prepared from 4-bromo-2-(3,4-dichloro-phenyl)-2-fluoro-butyric acid methyl ester and N-piperidin-4-yl-methanesulfonamide (commercially available) as light brown waxy solid. MS(m/e): 441.1 (MH^+).

b) step 2:

In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1, step 5) the title compound was prepared from 2-(3,4-dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid methyl ester by saponification with $LiOH \cdot H_2O$ and conversion with HCl into the respective salt as off-white solid. MS(m/e): 427.1 (MH^+).

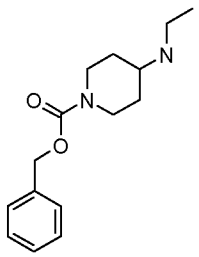
Intermediate 8

N-Ethyl-N-piperidin-4-yl-methanesulfonamide



a) step 1:

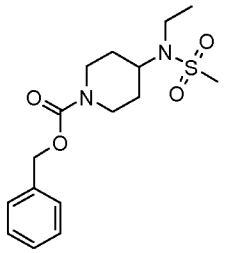
4-Ethylamino-piperidine-1-carboxylic acid benzyl ester



A mixture of 28.93 g (124 mmol) 1-(benzyloxycarbonyl)-4-piperidinone (commercially available, 8.30 g (186 mmol) ethylamine (2N in THF), 39.42 g (186 mmol) sodium triacetoxyborohydride and 11.10 g (186 mmol) acetic acid in 300 mL THF was stirred for 68 h at room temperature. Water and Na_2CO_3 aq. was added and extracted with ethyl acetate. The organic phases were washed with NaCl aq. sat., dried with Na_2SO_4, filtered and evaporated to dryness. The crude title compound was used in the consecutive step. MS(m/e): 263.0 (MH^+).

b) step 2:

4-(Ethyl-methanesulfonyl-amino)-piperidine-1-carboxylic acid benzyl ester



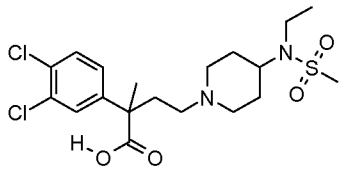
A mixture of 32.68 g (125 mmol) 4-ethylamino-piperidine-1-carboxylic acid benzyl ester, 16.00 g (140 mmol) methanesulfonyl chloride and 19.30 (149 mmol) DIPEA in 300 mL DCM was stirred for 80 min at room temperature. The mixture was concentrated, isolute was added and evaporated to dryness. The residue was subjected to flash column chromatography on silica eluting with a gradient formed from DCM, methanol and NH_3 aq.. The product containing fractions were evaporated and the residue was triturated with a mixture formed from heptane and diethyl ether. The precipitate was filtered and dried to yield 32.4 g (76 %) of the title compound as white solid. MS(m/e): 341.1 (MH^+).

c) step 3:

A solution of 32.4 g (95 mmol) 4-(ethyl-methanesulfonyl-amino)-piperidine-1-carboxylic acid benzyl ester in 400 mL THF and 300 mL methanol was hydrogenated at room temperature over 3.5 g Pd/ C (10%). The mixture was filtered and evaporated to dryness to yield the crude title compound which was used without further purification in the consecutive step. MS(m/e): 207.1 (MH^+).

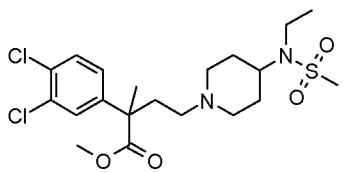
Intermediate 9

2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid



a) step 1:

2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid methyl ester



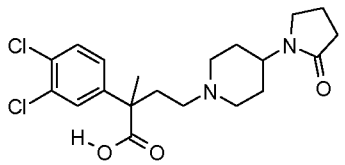
In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester (intermediate 1, step 4) the title compound was prepared from 4-bromo-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester and N-ethyl-N-piperidin-4-yl-methanesulfonamide (intermediate 8) as light yellow viscous oil. MS(m/e): 467.0 (MH^+).

b) step 2:

In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1, step 5) the title compound was prepared from 2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid methyl ester by saponification with $LiOH \cdot H_2O$ and conversion with HCl into the respective salt as white foam. MS(m/e): 451.0 (MH^+).

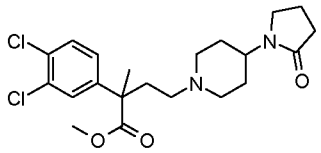
Intermediate 10

2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid



a) step 1:

2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid methyl ester



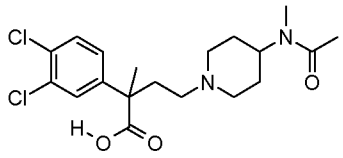
In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester (intermediate 1, step 4) the title compound was prepared from 4-bromo-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester and 1-piperidin-4-yl-pyrrolidin-2-one (commercially available) as light yellow viscous oil. MS(m/e): 427.1 (MH^+).

b) step 2:

In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1, step 5) the title compound was prepared from 2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid methyl ester by saponification with $LiOH \cdot H_2O$ and conversion with HCl into the respective salt as white foam. MS(m/e): 415.2 (MH^+).

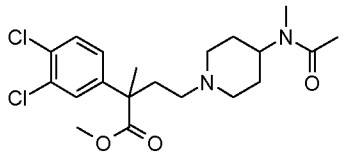
Intermediate 11

4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid



a) step 1:

4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester



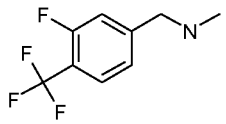
In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid methyl ester (intermediate 1, step 4) the title compound was prepared from 4-bromo-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester and N-methyl-N-piperidin-4-yl-acetamide (WO2005019194) as yellow viscous oil. MS(m/e): 415.3 (MH^+).

b) step 2:

In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1, step 5) the title compound was prepared from 4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid methyl ester by saponification with $LiOH \cdot H_2O$ and conversion with HCl into the respective salt as white foam. MS(m/e): 401.1 (MH^+).

Intermediate 12

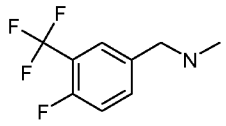
(3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amine, hydrochloride



A mixture of 7.65 g (39.8 mmol) 3-fluoro-4-trifluoro-benzaldehyde, 24.39 mL (49.0 mmol) methylamine (2M in THF), 3.60 mL acetic acid and 12.46 g (59.0 mmol) sodium triacetoxyborohydride in 200 mL THF was stirred for 22 h at room temperature. Water and Na_2CO_3 aq. was added and the mixture was extracted with ethyl acetate. The organic phases were washed with NaCl aq., dried with Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography on silica eluting with a gradient formed from DCM, methanol and NH_3 aq.. The combined product containing fractions were evaporated and treated with HCl in diethyl ether. The precipitate was filtered, washed with diethyl ether and dried to yield 4.00 g (42 %) of the title compound as white solid. MS(m/e): 208.1 (MH^+).

Intermediate 13

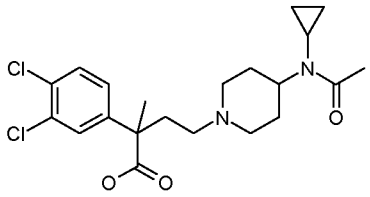
(4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride



In analogy to the procedure described for the synthesis of (3-fluoro-4-trifluoromethyl-benzyl)-methyl-amine, hydrochloride (intermediate 12) the title compound was prepared from 4-fluoro-3-trifluoro-benzaldehyde and methylamine under reductive conditions as white solid. MS(m/e): 208.3 (MH^+).

Intermediate 14

4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid

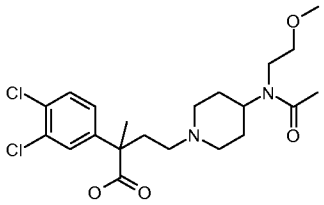


In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) the title compound was prepared from 2-(3,4-dichloro-phenyl)-4-oxo-butyric acid methyl ester,

N-Cyclopropyl-N-piperidin-4-yl-acetamide (intermediate 22) and subsequent saponification as exemplified in the synthesis of intermediate 2, c) step 3. MS(m/e): 427.2 (MH^+).

Intermediate 15

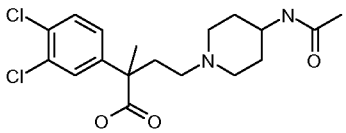
4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid



In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) the title compound was prepared from 2-(3,4-dichloro-phenyl)-4-oxo-butyric acid methyl ester, N-(2-Methoxy-ethyl)-N-piperidin-4-yl-acetamide, hydrochloride (intermediate 23) and subsequent saponification as exemplified in the synthesis of intermediate 2, c) step 3. MS(m/e): 445.1 (MH^+).

Intermediate 16

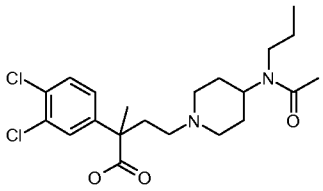
4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid



In analogy to the procedure described for the synthesis of 2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) the title compound was prepared from 2-(3,4-Dichloro-phenyl)-4-oxo-butyric acid methyl ester, 4-Acetylamino-piperidine (commercially available) and subsequent saponification as exemplified in the synthesis of intermediate 2, c) step 3. MS(m/e): 387.2 (MH^+).

Intermediate 17

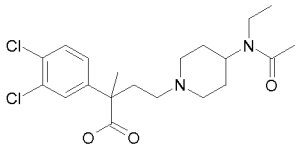
4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid



In analogy to the procedure described for the synthesis of 2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) the title compound was prepared from 2-(3,4-Dichloro-phenyl)-4-oxo-butyric acid methyl ester, N-Piperidin-4-yl-N-propyl-acetamide (WO 9410146) and subsequent saponification as exemplified in the synthesis of intermediate 2, c) step 3. MS(m/e): 429.2 (MH^+).

Intermediate 18

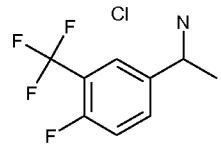
4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid



In analogy to the procedure described for the synthesis of 2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) the title compound was prepared from 2-(3,4-Dichloro-phenyl)-4-oxo-butyric acid methyl ester, N-Ethyl-N-piperidin-4-yl-acetamide (EP 457686) and subsequent saponification as exemplified in the synthesis of intermediate 2, c) step 3. MS(m/e): 415.2 (MH^+).

Intermediate 19

1-(4-Fluoro-3-trifluoromethyl-phenyl)-ethylamine; hydrochloride

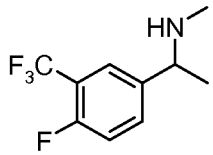


A mixture of 10g (49 mmol) 4-Fluoro-3-(trifluoromethyl) acetopheneone (commercially available), 27.5 g (97 mmol) titanium tetraisopropoxide and 34 mL (243 mmol) 7 N ammonia in MeOH at 0 °C was stirred over the weekend at 20 °C. Subsequently, 5.5 g (146 mmol) sodium borohydride was added and the mixture allowed to come from 0 °C to room temperature over night. Water and ammonia was added and the mixture was filtered through decalit and washed with ethyl acetate. The aqueous phase was separated washed with ethyl acetate and the combined organic phases washed with NaCL sat. aq.,

dried with Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography eluting with a gradient formed from DCM, methanol and ammonia. The product containing fractions were evaporated to dryness and transformed with HCl in diethyl ether to the respective hydrochloride salt. Yield: 4.4 g (37 %). MS(m/e): 207.9 (MH^+).

Intermediate 20

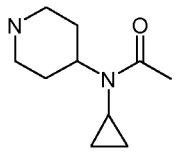
1-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl-methyl amine; hydrochloride



In analogy to the procedure described for the synthesis of Intermediate 20, 1-(4-Fluoro-3-trifluoromethyl-phenyl)-ethylamine; hydrochloride the title compound was prepared from 4-fluoro-3-(trifluoromethyl) acetopheneone (commercially available) and methylamine. MS(m/e): 191.2/222.1 (MH^+).

Intermediate 21

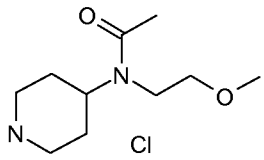
N-Cyclopropyl-N-piperidin-4-yl-acetamide



A mixture of 6.25 g (27 mmol) 1-(benzyloxycarbonyl)-4-piperidinone (commercially available, 1.83 g (32 mmol) cyclopropyl amine, 2.3 mL acetic acid and 8.51 g (40 mmol) sodium triacetoxyborohydride was stirred from 0 °C to room temperature over night. Water and Na_2CO_3 aq. was added and the mixture extracted with ethyl acetate. The organic phase was washed with NaCl sat. aq. , dried with Na_2SO_4 and evaporated to dryness. The residue was taken up in 100 mL DCM and 4.48 mL (32 mmol) NEt_3 and 2.09 mL acetyl chloride was added and allowed to stirr at 0 °C for 2 h. The mixture was evaporated and isolute was added and the residue was purified by column chromatography on silica eluting with a gradient formed from DCM, methanol and ammonia. The product containing fractions were evaporated and the residue taken up in methanol and hydrogenated over Pd/C with H_2. Filtration and evaporation yielded 4.5 g (92 %) of the title compound as light yellow solid. MS(m/e): 183.2 (MH^+).

Intermediate 22

N-(2-Methoxy-ethyl)-N-piperidin-4-yl-acetamide, hydrochloride

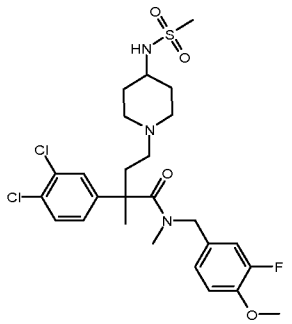


In analogy to the procedure described for the synthesis of N-cyclopropyl-N-piperidin-4-yl-acetamide (intermediate 22) the title compound was prepared from 1-(benzyloxycarbonyl)-4-piperidinone (commercially available and 2-methoxyethyloamine.

The title compound was obtained as hydrochloride salt by treatment of the free base with HCl. MS(m/e): 201.1 (MH^+).

Example 1

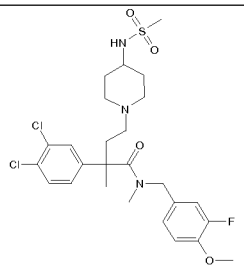
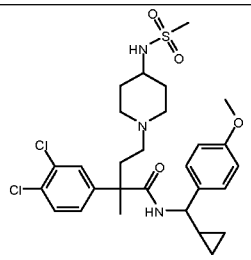
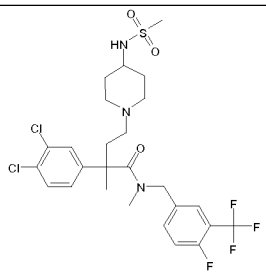
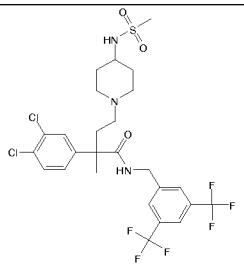
2-(3,4-Dichloro-phenyl)-N-(3-fluoro-4-methoxy-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide

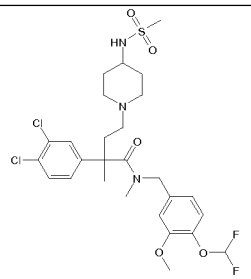
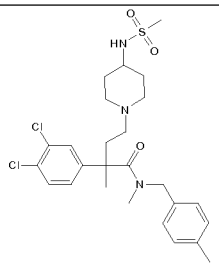
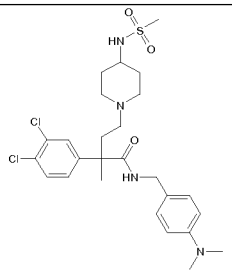
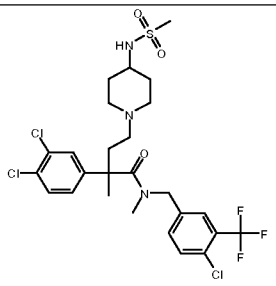


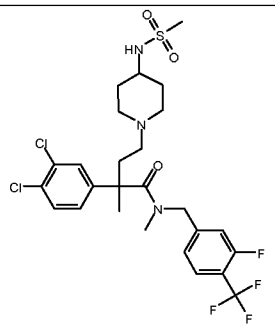
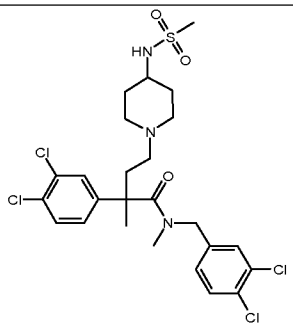
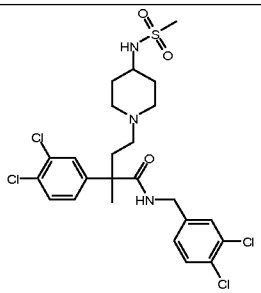
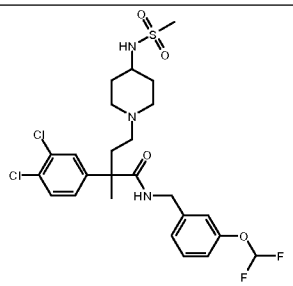
A mixture of 30 mg crude 2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid, 14 mg (0.068 mmol) (3-fluoro-4-methoxy-benzyl)-methyl-amine, hydrochloride, 0.33 mL TBTU/DMF (0.2N) and 50 uL DIPEA in 1.2 mL DMF was stirred at room temperature for 16 h. The mixture was subjected to purification by preparative HPLC on reversed phase eluting with a gradient formed from acetonitrile, water and NEt_3. The product containing fractions were evaporated to yield 6.5 mg of the title compound. MS(m/e): 574.3 (MH^+).

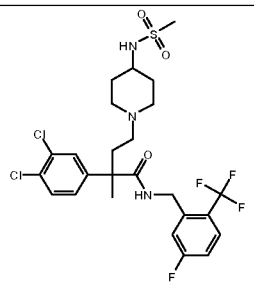
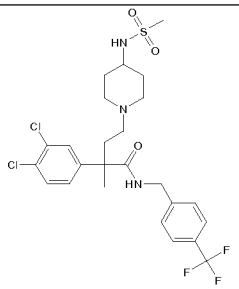
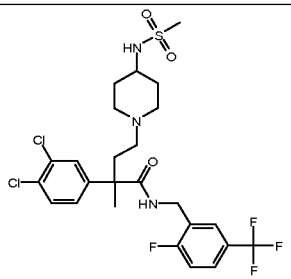
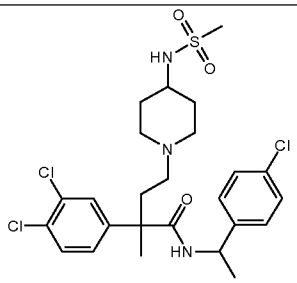
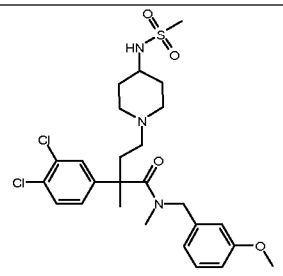
In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-methoxy-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide (example 1) further piperidine derivatives have been prepared from the starting materials listed in table 1. Optionally diastereoisomeric mixture have been separated by column chromatography. Table 1 comprises example 2- example 110.

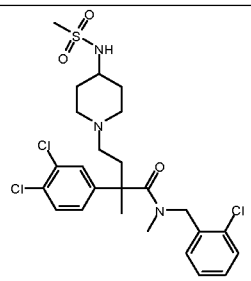
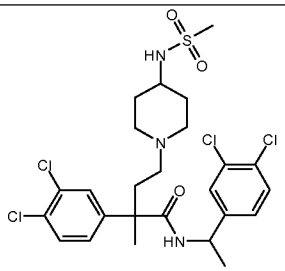
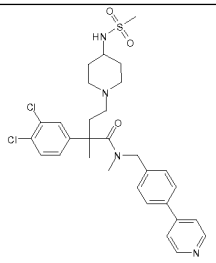
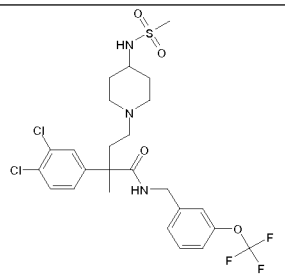
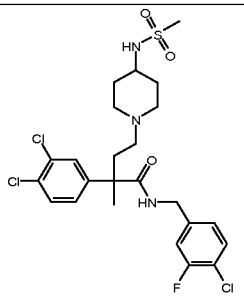
Table 1:

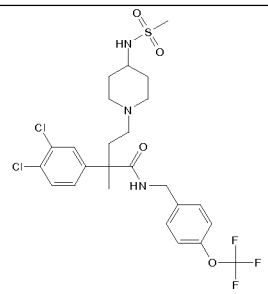
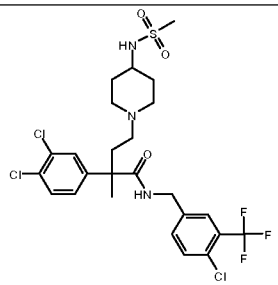
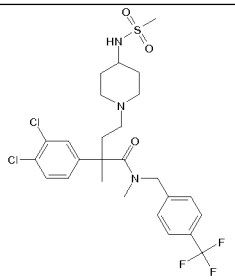
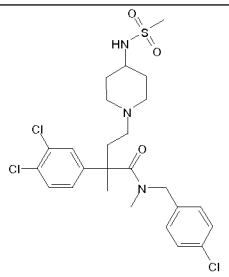
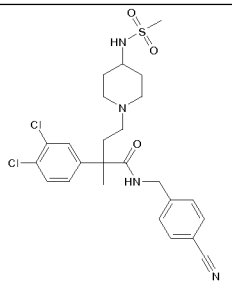
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
1		574.5	2-(3,4-Dichloro-phenyl)-N-(3-fluoro-4-methoxy-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (3-Fluoro-4-methoxy-benzyl)-methyl-amine (commercially available)	574.3	0.1872
2		582.6	N-[Cyclopropyl-(4-methoxy-phenyl)-methyl]-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and C-Cyclopropyl-C-(4-methoxy-phenyl)-methylamine (commercially available)	584.3	0.7035
3		612.5	2-(3,4-Dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	612.1	0.0232
4		648.5	N-(3,5-Bis-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 3,5-Bis-trifluoromethyl-benzylamine (commercially available)	648.3	0.1396

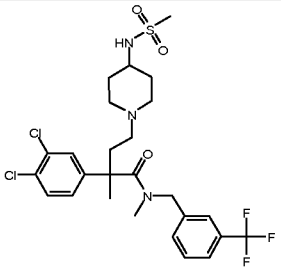
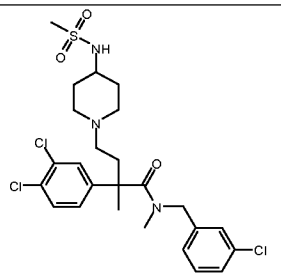
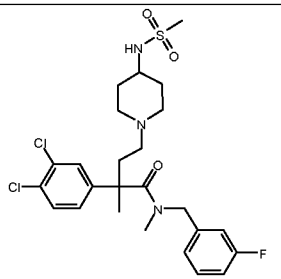
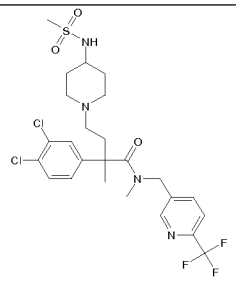
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
5		622.6	2-(3,4-Dichloro-phenyl)-N-(4-difluoromethoxy-3-methoxy-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (4-Difluoromethoxy-3-methoxy-benzyl)-methyl-amine (commercially available)	622.2	0.2716
6		540.6	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-N-(4-methyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and Methyl-(4-methyl-benzyl)-amine (commercially available)	540.4	0.0774
7		555.6	2-(3,4-Dichloro-phenyl)-N-(4-dimethylamino-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (4-Aminomethyl-phenyl)-dimethyl-amine (commercially available)	555.3	0.6205
8		629.0	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (4-Chloro-3-trifluoromethyl-benzyl)-methyl-amine (commercially available)	630.3	0.0226

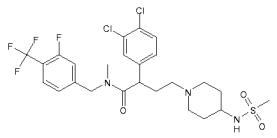
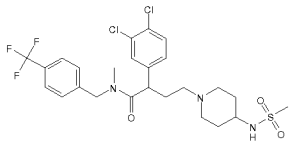
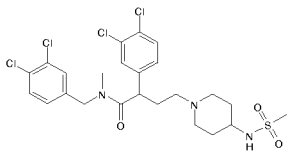
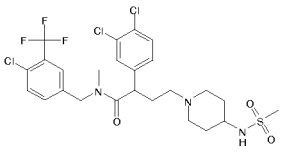
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
9		612.5	2-(3,4-Dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amine, hydrochloride (intermediate 12)	612.3	0.03
10		595.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (3,4-Dichloro-benzyl)-methyl-amine (commercially available)	596.1	0.024
11		581.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 3,4-Dichloro-benzylamine (commercially available)	582	0.0442
12		578.5	2-(3,4-Dichloro-phenyl)-N-(3-difluoromethoxy-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 3-Difluoromethoxy-benzylamine (commercially available)	578.1	0.3094

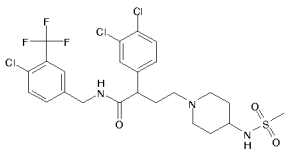
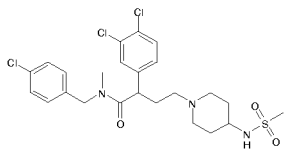
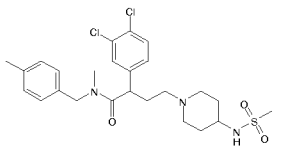
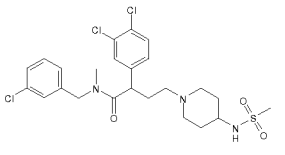
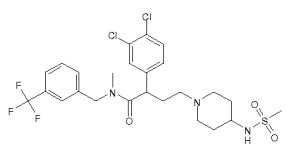
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
13		598.5	2-(3,4-Dichloro-phenyl)-N-(5-fluoro-2-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 5-Fluoro-2-trifluoromethyl-benzylamine (commercially available)	598.1	0.5804
14		580.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-N-(4-trifluoromethyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 4-Trifluoromethyl-benzylamine (commercially available)	580	0.058
15		598.5	2-(3,4-Dichloro-phenyl)-N-(2-fluoro-5-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 2-Fluoro-5-trifluoromethyl-benzylamine (commercially available)	598.3	0.1661
16		561.0	N-[1-(4-Chloro-phenyl)-ethyl]-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 1-(4-Chloro-phenyl)-ethylamine (commercially available)	562.5	0.1735
17		556.6	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-(3-methoxy-benzyl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (3-Methoxy-benzyl)-methyl-amine (commercially available)	556.1	0.2127

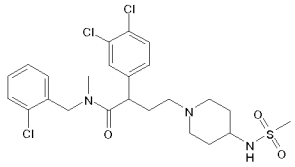
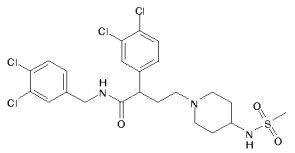
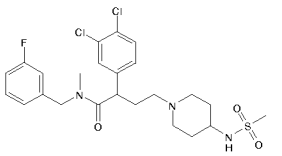
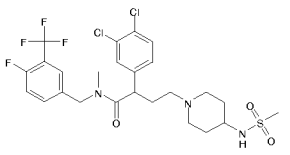
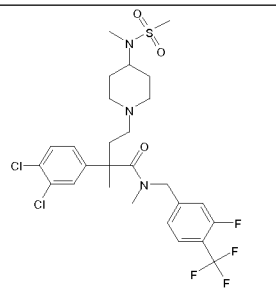
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
18		561.0	N-(2-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (2-Chloro-benzyl)-methyl-amine (commercially available)	560.2	0.0333
19		595.4	2-(3,4-Dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-ethyl]-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 1-(3,4-Dichloro-phenyl)-ethylamine (commercially available)	596.3	0.0599
20		603.6	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-N-(4-pyridin-4-yl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and Methyl-(4-pyridin-4-yl-benzyl)-amine (commercially available)	603.3	0.2032
21		596.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-N-(3-trifluoromethoxy-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 3-Trifluoromethoxy-benzylamine (commercially available)	596.2	0.1468
22		564.9	N-(4-Chloro-3-fluoro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 4-Chloro-3-fluoro-benzylamine (commercially available)	566.3	0.0708

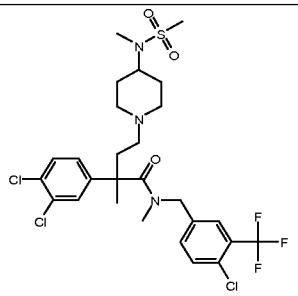
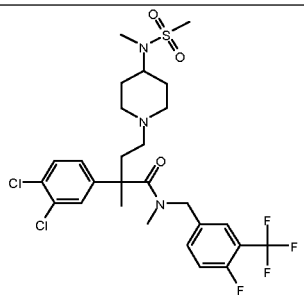
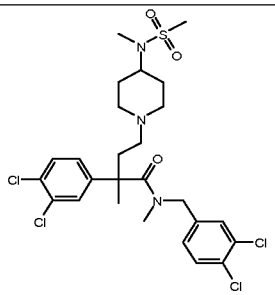
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
23		596.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-N-(4-trifluoromethoxy-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 4-Trifluoromethoxy-benzylamine (commercially available)	596.2	0.1403
24		614.9	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 4-Chloro-3-trifluoromethyl-benzylamine (commercially available)	616.3	0.0714
25		594.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-N-(4-trifluoromethyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and Methyl-(4-trifluoromethyl-benzyl)-amine (commercially available)	594.2	0.0287
26		561.0	N-(4-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (4-Chloro-benzyl)-methyl-amine (commercially available)	560.3	0.0265
27		537.5	N-(4-Cyano-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and 4-Aminomethyl-benzonitrile (commercially available)	537.3	0.2633

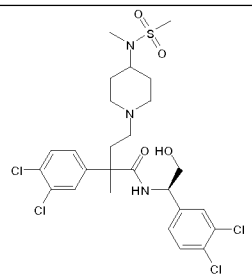
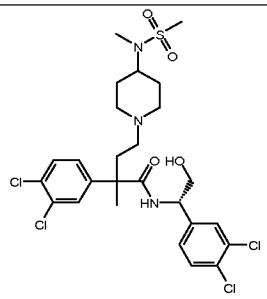
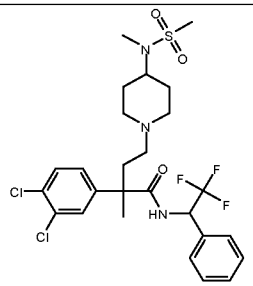
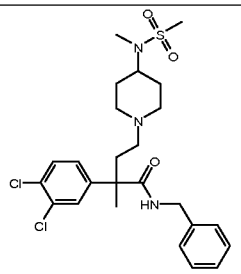
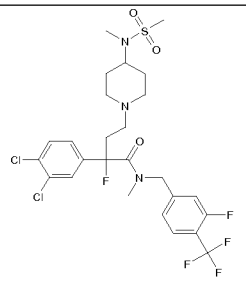
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
28		594.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-N-(3-trifluoromethyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and Methyl-(3-trifluoromethyl-benzyl)-amine (commercially available)	594.2	0.0217
29		561.0	N-(3-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (3-Chloro-benzyl)-methyl-amine (commercially available)	560.5	0.0485
30		544.5	2-(3,4-Dichloro-phenyl)-N-(3-fluoro-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and (3-Fluoro-benzyl)-methyl-amine (commercially available)	544.2	0.1233
31		595.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-N-(6-trifluoromethyl-pyridin-3-ylmethyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2-methyl-butyric acid (intermediate 1) and Methyl-(6-trifluoromethyl-pyridin-3-ylmethyl)-amine (commercially available)	595.2	0.5004

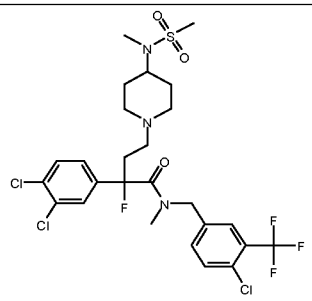
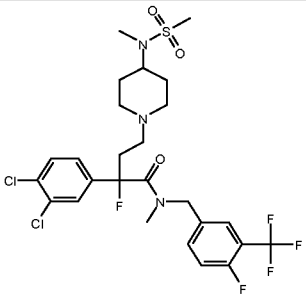
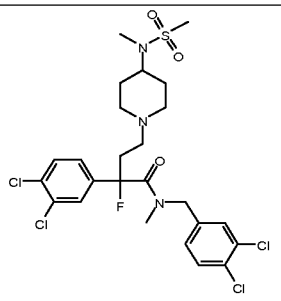
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
32		598.5	2-(3,4-Dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and (3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amine, hydrochloride (intermediate 12)	598.3	0.0617
33		580.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-N-(4-trifluoromethyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and Methyl-(4-trifluoromethyl-benzyl)-amine (commercially available)	580.3	0.0816
34		581.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and (3,4-Dichloro-benzyl)-methyl-amine (commercially available)	582.1	0.0775
35		614.9	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and (4-Chloro-3-trifluoromethyl-benzyl) -methyl-amine (commercially available)	616.1	0.1494

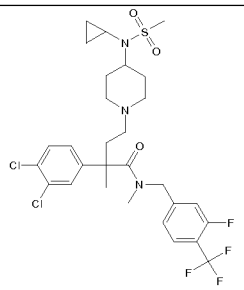
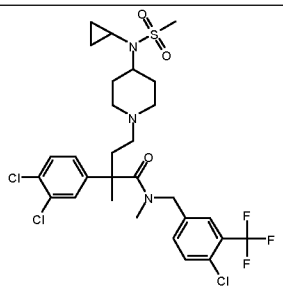
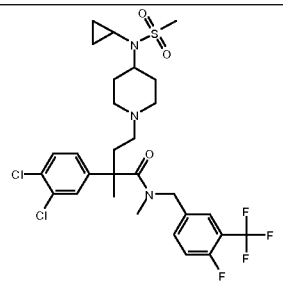
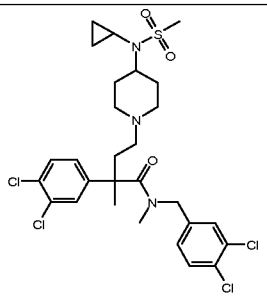
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
36		600.9	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and 4-Chloro-3-trifluoromethyl-benzylamine (commercially available)	600.2	0.3541
37		546.9	N-(4-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and (4-Chloro-benzyl)-methyl-amine (commercially available)	546.2	0.0787
38		526.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-N-(4-methyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and Methyl-(4-methyl-benzyl)-amine (commercially available)	526.4	0.0929
39		546.9	N-(3-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and (3-Chloro-benzyl)-methyl-amine (commercially available)	546.2	0.2126
40		580.5	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-N-(3-trifluoromethyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and Methyl-(3-trifluoromethyl-benzyl)-amine (commercially available)	580.3	0.2801

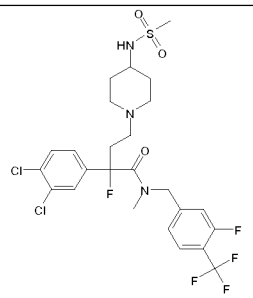
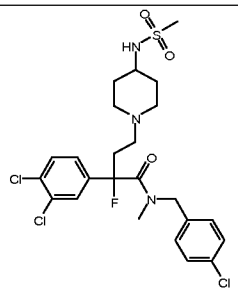
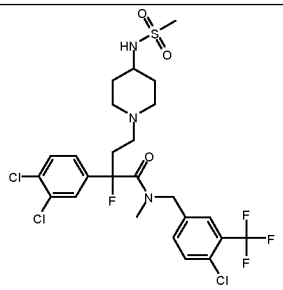
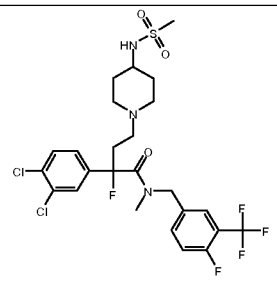
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
41		546.9	N-(2-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and (2-Chloro-benzyl)-methyl-amine (commercially available)	546.2	0.2588
42		567.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and 3,4-Dichloro-benzylamine (commercially available)	568.3	0.1919
43		530.5	2-(3,4-Dichloro-phenyl)-N-(3-fluoro-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and (3-Fluloro-benzyl)-methyl-amine (commercially available)	530.1	0.2544
44		598.5	2-(3,4-Dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 2) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	598.3	0.1323
45		626.5	2-(3,4-Dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 3) and (3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amine,	625.8	0.0085

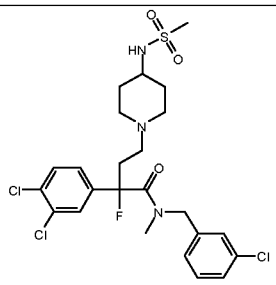
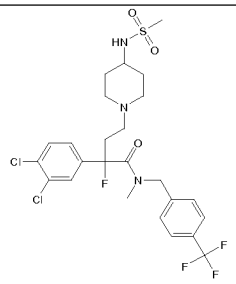
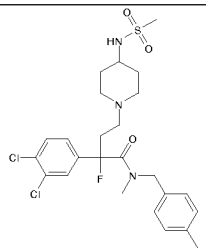
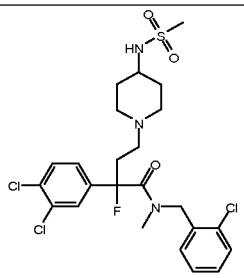
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
				hydrochloride (intermediate 12)		
46		643.0	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 3) and (4-Chloro-3-trifluoromethyl-benzyl) -methyl-amine (commercially available)	641.8	0.0024
47		626.5	2-(3,4-Dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 3) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	625.7	0.0021
48		609.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 3) and (3,4-Dichloro-benzyl)-methyl-amine (commercially available)	609.5	0.0036

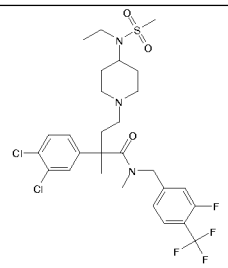
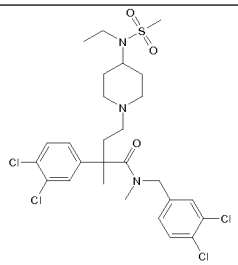
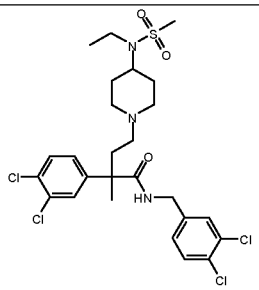
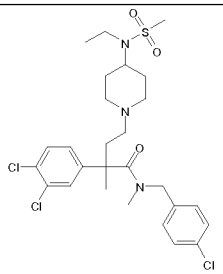
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
49		625.4	2-(3,4-Dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyramide; diastereoisomer 1	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 3) and 2-Amino-2-(3,4-dichloro-phenyl)-ethanol (WO 2005058892)	626.2	0.0055
50		625.4	2-(3,4-Dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyramide; diastereoisomer 2	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 3) and 2-Amino-2-(3,4-dichloro-phenyl)-ethanol (WO 2005058892)	626.2	0.0521
51		594.5	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-N-(2,2,2-trifluoro-1-phenyl-ethyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 3) and 2,2,2-Trifluoro-1-phenyl-ethylamine (commercially available)	594.3	0.0187
52		526.5	N-Benzyl-2-(3,4-dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 3) and benzylamine (commercially available)	525.8	0.0648
53		630.5	2-(3,4-Dichloro-phenyl)-2-fluoro-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-butyric acid (intermediate 4) and (3-Fluoro-4-trifluoromethyl-benzyl)-methyl-	629.8	0.0183

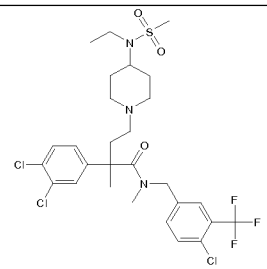
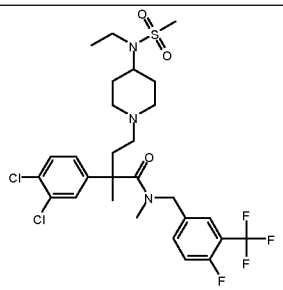
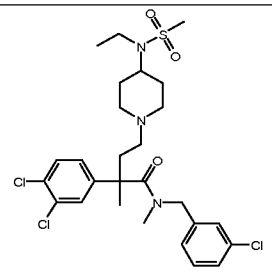
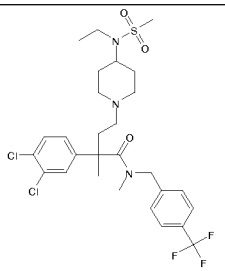
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
				amine, hydrochloride (intermediate 12)		
54		647.0	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-butyric acid (intermediate 4) and (4-Chloro-3-trifluoromethyl-benzyl)-methyl-amine (commercially available)	645.7	0.0245
55		630.5	2-(3,4-Dichloro-phenyl)-2-fluoro-N-(4-fluoro-3-trifluoromethyl-benzyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-butyric acid (intermediate 4) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	629.8	0.0234
56		613.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-butyric acid (intermediate 4) and (3,4-Dichloro-benzyl)-methyl-amine (commercially available)	613.7	0.0228

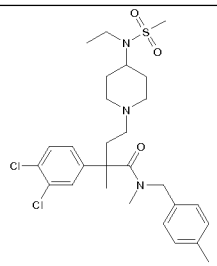
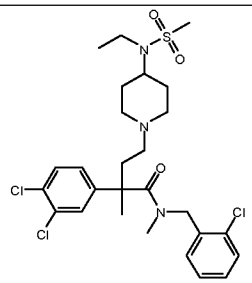
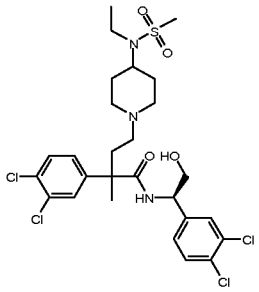
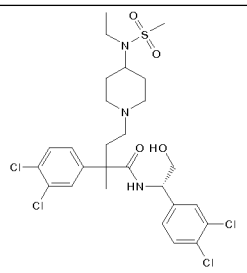
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
57		652.6	4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide	4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 6) and (3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amine, hydrochloride (intermediate 12)	653.8	0.0059
58		669.0	N-(4-Chloro-3-trifluoromethyl-benzyl)-4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide	4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 6) and (4-Chloro-3-trifluoromethyl-benzyl)-methyl-amine (commercially available)	669.8	0.0036
59		652.6	4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide	4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 6) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	653.7	0.0043
60		635.5	4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide	4-[4-(Cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 6) and (3,4-Dichloro-benzyl)-methyl-amine (commercially available)	635.5	0.0026

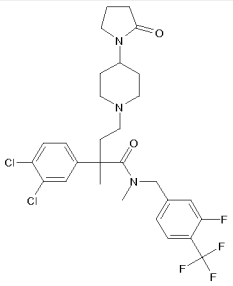
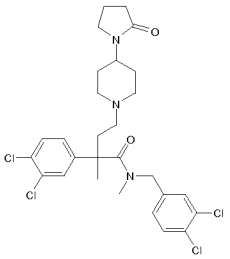
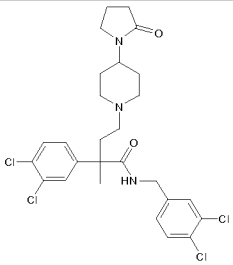
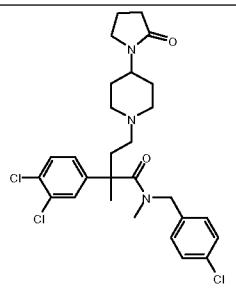
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
61		616.5	2-(3,4-Dichloro-phenyl)-2-fluoro-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 7) and (3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amine, hydrochloride (intermediate 12)	616.1	0.08
62		564.9	N-(4-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 7) and (4-Chloro-benzyl)-methyl-amine (commercially available)	564.2	0.1052
63		632.9	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 7) and (4-Chloro-3-trifluoromethyl-benzyl)-methyl-amine (commercially available)	632.2	0.1169
64		616.5	2-(3,4-Dichloro-phenyl)-2-fluoro-N-(4-fluoro-3-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 7) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	616.1	0.1219

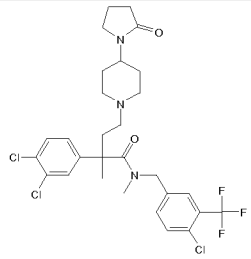
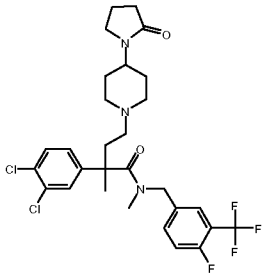
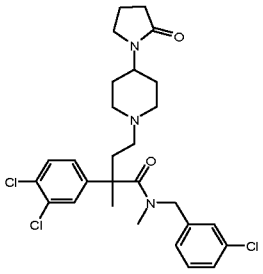
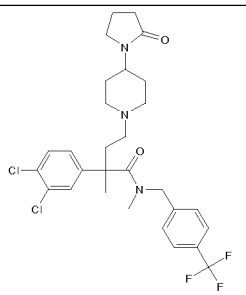
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
65		564.9	N-(3-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 7) and (3-Chloro-benzyl)-methyl-amine (commercially available)	564.2	0.3067
66		598.5	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-N-(4-trifluoromethyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 7) and Methyl-(4-trifluoromethyl-benzyl)-amine (commercially available)	598.3	0.0843
67		544.5	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-N-(4-methyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 7) and Methyl-(4-methyl-benzyl)-amine (commercially available)	546.2	0.3227
68		564.9	N-(2-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-N-methyl-butyramide	2-(3,4-Dichloro-phenyl)-2-fluoro-4-(4-methanesulfonylamino-piperidin-1-yl)-butyric acid (intermediate 7) and (2-Chloro-benzyl)-methyl-amine (commercially available)	564.2	0.1585

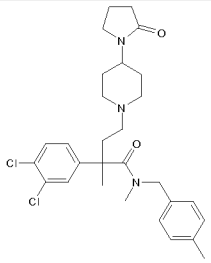
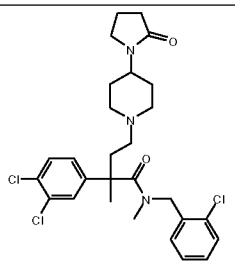
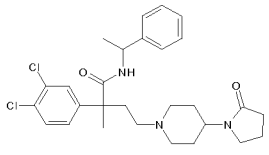
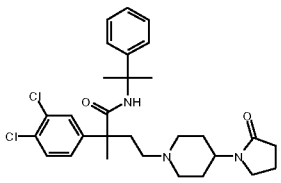
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
69		640.6	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and (3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amine, hydrochloride (intermediate 12)	640.3	0.0024
70		623.5	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and (3,4-Dichloro-benzyl)-methyl-amine (commercially available)	624.3	0.0012
71		609.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and 3,4-Dichloro-benzylamine (commercially available)	610.1	0.0028
72		589.0	N-(4-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and (4-Chloro-benzyl)-methyl-amine (commercially available)	590.2	0.0022

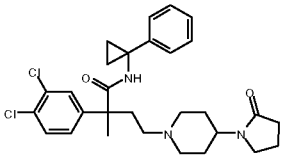
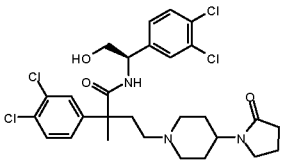
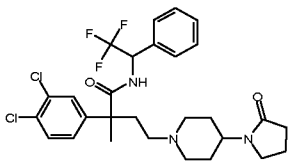
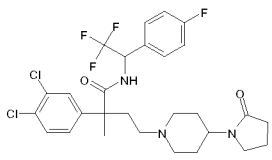
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
73		657.0	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and 4-Chloro-3-trifluoromethyl-benzylamine (commercially available)	658.3	0.0015
74		640.6	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	640.2	0.0013
75		589.0	N-(3-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and (3-Chloro-benzyl)-methyl-amine (commercially available)	590.2	0.0039
76		622.6	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-N-(4-trifluoromethyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and Methyl-(4-trifluoromethyl-benzyl)-amine (commercially available)	622.4	0.0017

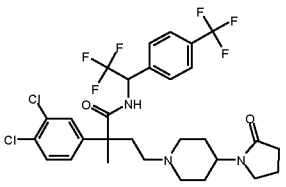
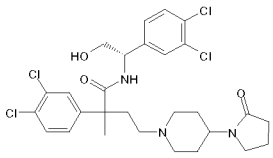
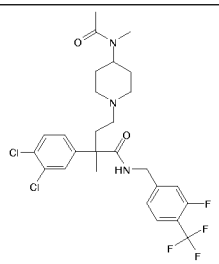
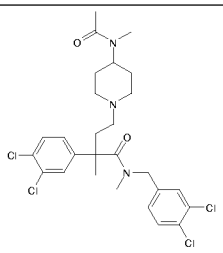
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
77		568.6	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-N-(4-methyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and Methyl-(4-methyl-benzyl)-amine (commercially available)	568.3	0.0031
78		589.0	N-(2-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and (2-Chloro-benzyl)-methyl-amine (commercially available)	590.2	0.0036
79		639.5	2-(3,4-Dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyramide; diastereoisomer 1	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and 2-Amino-2-(3,4-dichloro-phenyl)-ethanol (WO 2005058892)	640.3	0.0015
80		639.5	2-(3,4-Dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyramide; diastereoisomer 2	2-(3,4-Dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyric acid (intermediate 9) and 2-Amino-2-(3,4-dichloro-phenyl)-ethanol (WO 2005058892)	640.2	0.0133

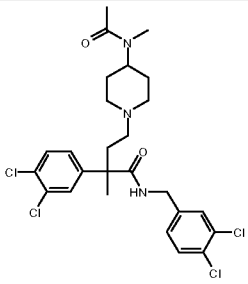
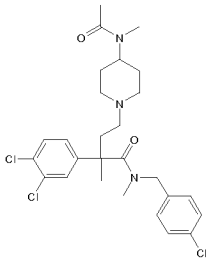
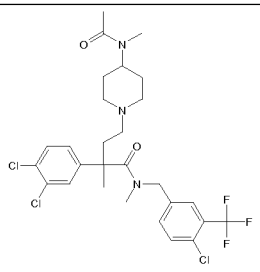
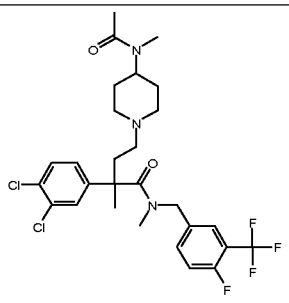
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
81		602.5	2-(3,4-Dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and (3-Fluoro-4-trifluoromethyl-benzyl)-methyl-amine, hydrochloride (intermediate 12)	601.9	0.003
82		585.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and (3,4-Dichloro-benzyl)-methyl-amine (commercially available)	585.7	0.0012
83		571.4	N-(3,4-Dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 3,4-Dichloro-benzylamine (commercially available)	569.7	0.0023
84		551.0	N-(4-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and (4-Chloro-benzyl)-methyl-amine (commercially available)	549.9	0.0021

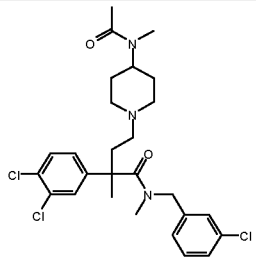
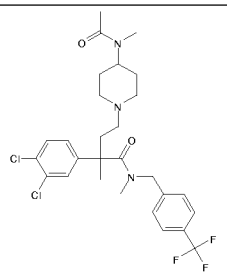
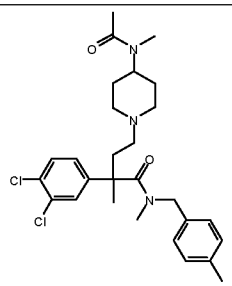
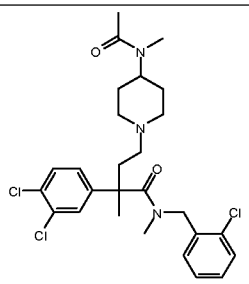
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
85		619.0	N-(4-Chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 4-Chloro-3-trifluoromethyl-benzylamine (commercially available)	619.7	0.0014
86		602.5	2-(3,4-Dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	601.9	0.0014
87		551.0	N-(3-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and (3-Chloro-benzyl)-methyl-amine (commercially available)	549.9	0.0046
88		584.5	2-(3,4-Dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-(4-trifluoromethyl-benzyl)-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and Methyl-(4-trifluoromethyl-benzyl)-amine (commercially available)	583.7	0.0018

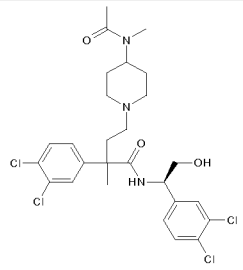
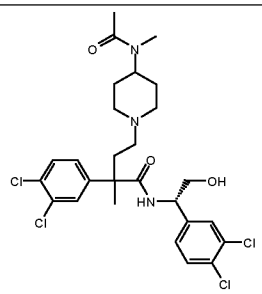
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
89		530.5	2-(3,4-Dichloro-phenyl)-2,N-dimethyl-N-(4-methyl-benzyl)-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and Methyl-(4-methyl-benzyl)-amine (commercially available)	529.9	0.0053
90		551.0	N-(2-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and (3-Chloro-benzyl)-methyl-amine (commercially available)	551.8	0.0025
91		516.5	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-(1-phenyl-ethyl)-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 1-Phenyl-ethylamine (commercially available)	516.2	0.0512
92		530.5	2-(3,4-Dichloro-phenyl)-2-methyl-N-(1-methyl-1-phenyl-ethyl)-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 1-Methyl-1-phenyl-ethylamine (commercially available)	530.2	0.9912

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
93		528.5	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-(1-phenyl-cyclopropyl)-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 1-Phenyl-cyclopropylamine (commercially available)	528.1	0.1842
94		601.4	2-(3,4-Dichloro-phenyl)-N-[-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide; diastereoisomer 1	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 2-Amino-2-(3,4-dichloro-phenyl)-ethanol (WO 2005058892)	602.1	0.003
95		570.5	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-(2,2,2-trifluoro-1-phenyl-ethyl)-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 2,2,2-Trifluoro-1-phenyl-ethylamine (commercially available)	572.2	0.0047
96		588.5	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-[2,2,2-trifluoro-1-(4-fluoro-phenyl)-ethyl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 2,2,2-Trifluoro-1-(4-fluoro-phenyl)-ethylamine (commercially available)	588.3	0.0072

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
97		638.5	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-[2,2,2-trifluoro-1-(4-trifluoromethyl-phenyl)-ethyl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 2,2,2-Trifluoro-1-(4-trifluoromethyl-phenyl)-ethylamine (commercially available)	638.2	0.0081
98		601.4	2-(3,4-Dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide; diastereoisomer 2	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 2-Amino-2-(3,4-dichloro-phenyl)-ethanol (WO 2005058892)	602.1	0.0499
99		590.5	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2-methyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 3-Fluoro-4-trifluoromethyl-benzylamine (commercially available)	590.3	0.0058
100		573.4	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and (3,4-Dichloro-benzyl)-methyl-amine (commercially available)	574.2	0.003

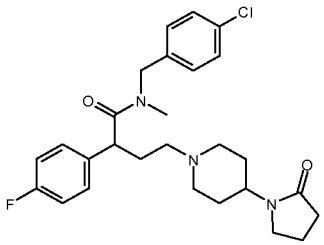
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
101		559.4	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2-methyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 3,4-Dichloro-benzylamine (commercially available)	560.2	0.0068
102		539.0	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and (4-Chloro-benzyl)-methyl-amine (commercially available)	538.3	0.0051
103		606.9	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and (4-Chloro-3-trifluoromethyl-benzyl) -methyl-amine (commercially available)	608.2	0.0022
104		590.5	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and (4-Fluoro-3-trifluoromethyl-benzyl)-methyl-amine, hyrdochloride (intermediate 13)	590.3	0.0023

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
105		539.0	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-N-(3-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and (3-Chloro-benzyl)-methyl-amine (commercially available)	538.3	0.0087
106		572.5	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2,N-dimethyl-N-(4-trifluoromethyl-benzyl)-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and Methyl-(4-trifluoromethyl-benzyl)-amine (commercially available)	572.2	0.0051
107		518.5	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2,N-dimethyl-N-(4-methyl-benzyl)-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and Methyl-(4-methyl-benzyl)-amine (commercially available)	518.4	0.0106
108		539.0	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-N-(2-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and (2-Chloro-benzyl)-methyl-amine (commercially available)	538.5	0.012

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
109		589.4	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide; diastereoisomer 1	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 2-Amino-2-(3,4-dichloro-phenyl)-ethanol (WO 2005058892)	590.2	0.0056
110		589.4	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide; diastereoisomer 2	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 2-Amino-2-(3,4-dichloro-phenyl)-ethanol (WO 2005058892)	590.2	0.1103

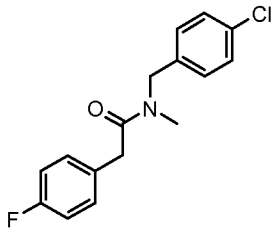
Example 111

N-(4-Chloro-benzyl)-2-(4-fluoro-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide



a) step 1:

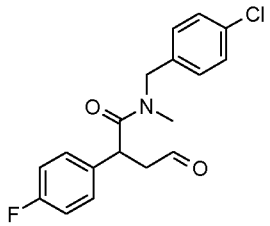
N-(4-Chloro-benzyl)-2-(4-fluoro-phenyl)-N-methyl-acetamide



A mixture of 1.09 g (7 mmol) 4-fluorophenylacetic acid, 1.37 g (9 mmol) (4-chloro-benzyl)-methyl-amine, 2.84 g (9 mmol) TBTU and 6 mL (35 mmol) DIPEA in 50 mL DMF was stirred at room temperature for 16 h. After evaporation of all volatiles Na_2CO_3 aq. was added and the mixture was extracted with ethyl acetate. The combined organic phases were washed with NaCl aq., dried with Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica eluting with a gradient formed from ethyl acetate and heptane. The product containing fractions were evaporated to yield 1.35 g (65 %) of the title compound as yellow oil. MS(m/e): 292.2 (MH^+).

b) step 2:

N-(4-Chloro-benzyl)-2-(4-fluoro-phenyl)-N-methyl-4-oxo-butyramide



A solution of 1.10 g (3.78 mmol) N-(4-chloro-benzyl)-2-(4-fluoro-phenyl)-N-methyl-acetamide in 10 mL DMF at 0 °C was treated with 0.18 g (4 mmol) NaH (55% in oil) and allowed to stir at 40-50 °C for 3 h. After cooling to 0 °C the mixture was treated with 0.80 g (5 mmol) bromoaetaldehyde dimethylacetal in 10 mL DMF and the mixture was stirred at room temperature for 16 h. After evaporation of all volatiles the residue was treated with water and THF and 1N HCl aq. was added. The mixture was stirred at room temperature for 2 h and extracted with ethyl acetate. The combined organic phases were washed with NaCl aq. sat., dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica eluting with a gradient formed from tert.-butylmethyl ether and heptane. The product containing fractions were evaporated to yield 0.90 g of the title compound which was used without further purification in the consecutive step. MS(m/e): 332.4 (MH^+).

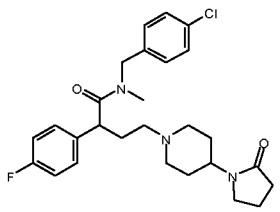
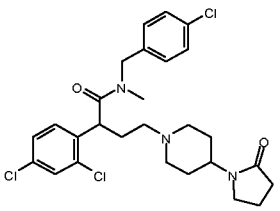
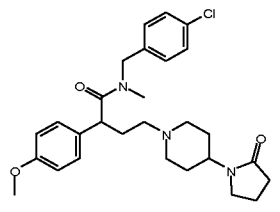
c) step 3:

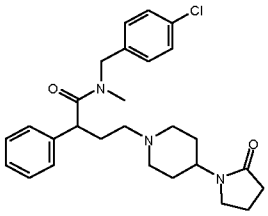
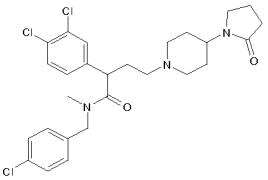
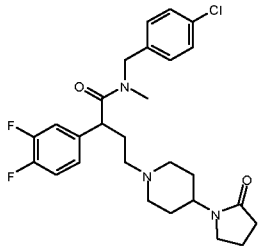
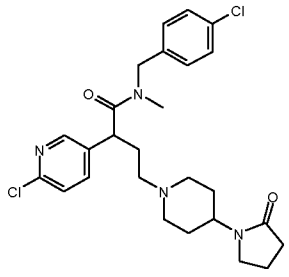
A mixture of 237 mg (0.71 mmol) N-(4-chloro-benzyl)-2-(4-fluoro-phenyl)-N-methyl-4-oxo-butyramide, 131 mg (0.77 mmol) 1-piperidin-4-yl-pyrrolidin-2-one, 0.226 (10.7 mmol) sodium triacetoxyborohydride and 64 mg acetic acid in 10 mL THF was stirred at room temperature for 17 h. Water and Na_2CO_3 aq. was added and the mixture was

extracted with ethyl acetate. The combined organic phases were washed with NaCl aq. sat., dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica eluting with a gradient formed from DCM, methanol and NH_3 aq.. The product containing fractions were evaporated to yield 277 mg (0.57 mmol) of the title compound as white foam. MS(m/e): 486.4 (MH^+).

In analogy to the procedure described for the synthesis of N-(4-chloro-benzyl)-2-(4-fluoro-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide (example 111) further piperidine derivatives have been synthesized from the starting materials listed in table 2. Table 2 comprises example 112 – 117.

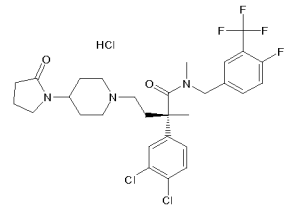
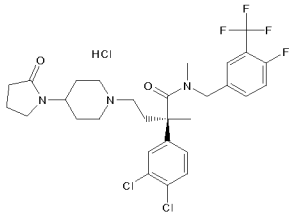
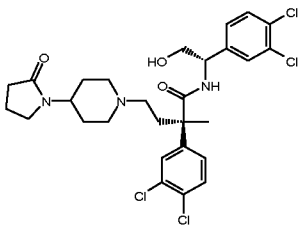
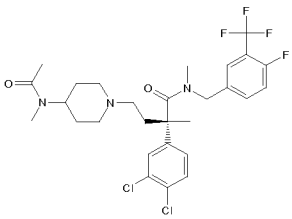
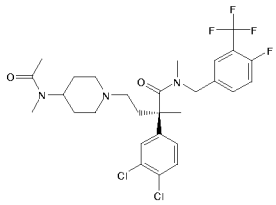
Table 2:

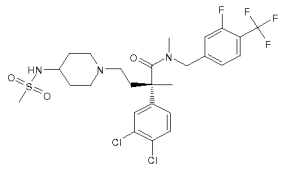
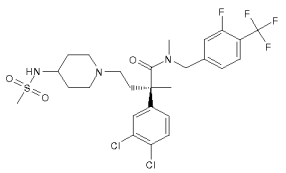
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
111		486.0	N-(4-Chloro-benzyl)-2-(4-fluoro-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	4-Fluorophenylacetic acid, (4-Chloro-benzyl)-methyl-amine, bromoaetaldehyde dimethylacetal and 1-Piperidin-4-yl-pyrrolidin-2-one	486.4	0.4084
112		536.9	N-(4-Chloro-benzyl)-2-(2,4-dichloro-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2,4-Dichlorophenylacetic acid, (4-Chloro-benzyl)-methyl-amine, bromoaetaldehyde dimethylacetal and 1-Piperidin-4-yl-pyrrolidin-2-one	536.2	0.1281
113		498.1	N-(4-Chloro-benzyl)-2-(4-methoxy-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	4-Methoxyphenylacetic acid, (4-Chloro-benzyl)-methyl-amine, bromoaetaldehyde dimethylacetal and 1-Piperidin-4-yl-pyrrolidin-2-one	498.1	0.7748

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
114		468.0	N-(4-Chloro-benzyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-2-phenyl-butyramide	Phenylacetic acid, (4-Chloro-benzyl)-methyl-amine, bromoaetaldehyde dimethylacetal and 1-Piperidin-4-yl-pyrrolidin-2-one	468.3	0.5603
115		536.9	N-(4-Chloro-benzyl)-2-(3,4-dichloro-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	3,4-Dichlorophenylacetic acid, (4-Chloro-benzyl)-methyl-amine, bromoaetaldehyde dimethylacetal and 1-Piperidin-4-yl-pyrrolidin-2-one	536.1	0.0081
116		504.0	N-(4-Chloro-benzyl)-2-(3,4-difluoro-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	3,4-Difluorophenylacetic acid, (4-Chloro-benzyl)-methyl-amine, bromoaetaldehyde dimethylacetal and 1-Piperidin-4-yl-pyrrolidin-2-one	504.2	0.1977
117		503.5	N-(4-Chloro-benzyl)-2-(6-chloro-pyridin-3-yl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	(6-Chloro-pyridin-3-yl)-acetic acid, (4-Chloro-benzyl)-methyl-amine, bromoaetaldehyde dimethylacetal and 1-Piperidin-4-yl-pyrrolidin-2-one	503.2	0.3872

Enantiomers were accessed from their respective starting materials (as listed in table 3) by column chromatography on appropriate chiral phase. Isolated compounds were optionally transferred into their respective salts by treatment with acid. Table 3 comprises example 118-124.

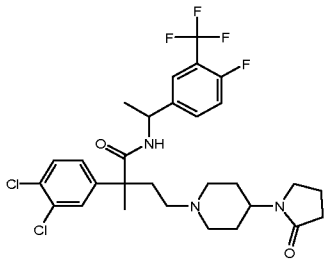
Table 3.

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
118		639.0	(S or R)-2-(3,4-Dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide; hydrochloride	chiral separation from example 86	602.4	0.1709
119		639.0	(R or S)-2-(3,4-Dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide; hydrochloride	chiral separation from example 86	602.4	0.0008
120		601.4	(R or S)-2-(3,4-Dichloro-phenyl)-N-[(S or R)-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	chiral separation from example 94	602.4	0.002
121		590.5	(S or R)-4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide	chiral separation from example 104	590.3	0.1735
122		590.5	(R or S)-4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide	chiral separation from example 104	590.3	0.0015

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
123		612.5	(S or R)-2-(3,4-Dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	chiral separation from example 45	612.2	0.8004
124		612.5	(R or S)-2-(3,4-Dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-(4-methanesulfonylamino-piperidin-1-yl)-2,N-dimethyl-butyramide	chiral separation from example 45	612.2	0.0188

Example 125

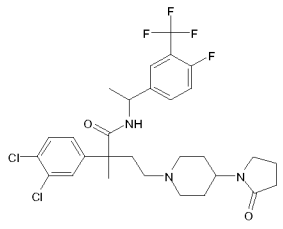
2-(3,4-Dichloro-phenyl)-*N*-[1-(4-fluoro-3-trifluoromethyl-phenyl)-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide

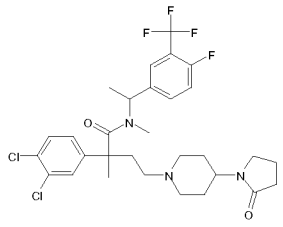
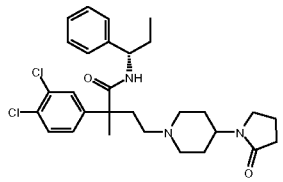
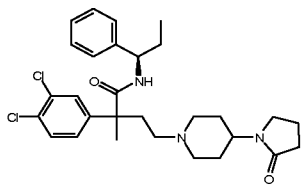
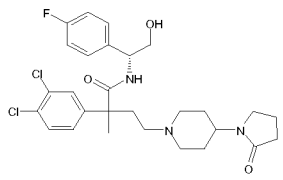


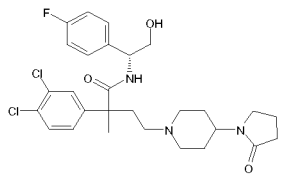
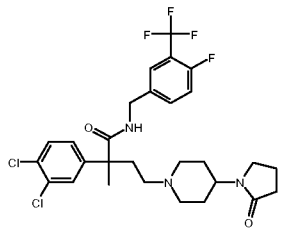
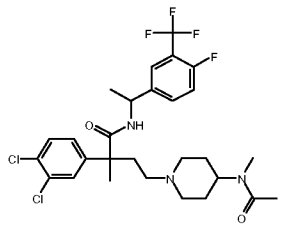
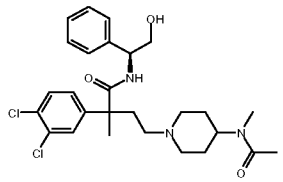
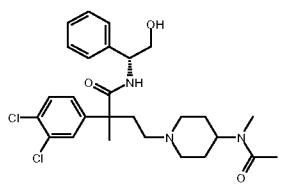
A mixture of 0.1 g (0.22 mmol) 2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10), 0.068 g (0.027 mmol) 1-(4-Fluoro-3-trifluoromethyl-phenyl)-ethylamine; hydrochloride (intermediate 20), 0.016 g (0.027 mmol) HATU and 0.23 mL DIPEA in 1.5 mL DMF was stirred at room temperature over night. The mixture was subjected to purification by reversed phase HPLC eluting with a gradient formed from acetonitrile, water and NEt3. the product containing fractions were evaporated to yield 0.079 g (59 %) of the title compound as light yellow viscous oil. MS(m/e): 601.9 (MH^+).

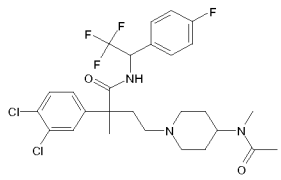
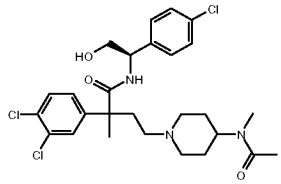
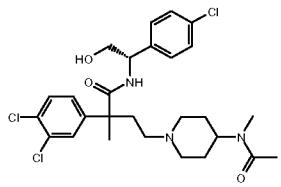
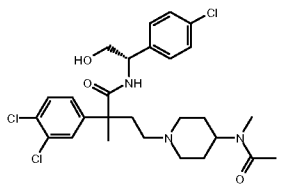
In analogy to the procedure described for the synthesis of 2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-3-trifluoromethyl-phenyl)-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide (example 125) further piperidine derivatives have been prepared from the starting materials listed in table 4. Optionally diastereoisomeric / epimeric mixture have been separated by column chromatography. Table 4 comprises example 125- example 169.

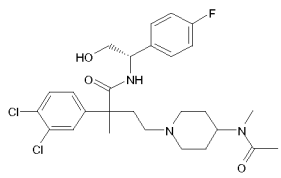
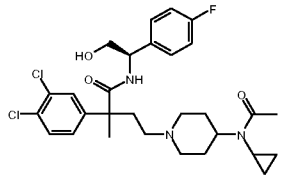
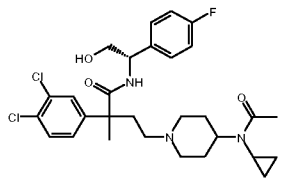
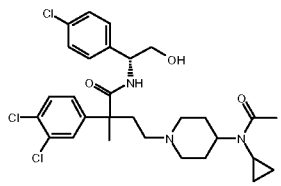
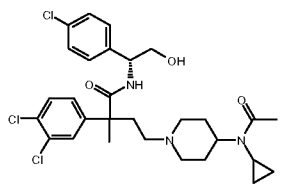
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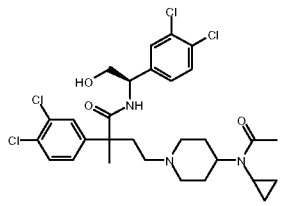
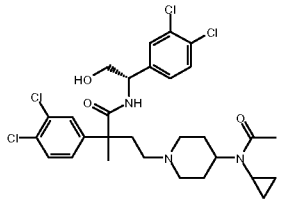
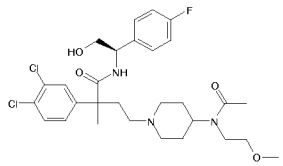
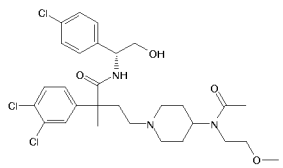
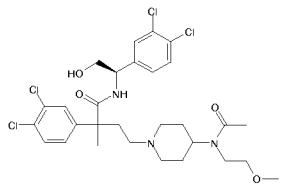
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
125		602.497	2-(3,4-Dichloro-phenyl)-*N*-[1-(4-fluoro-3-trifluoromethyl-phenyl)-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 1-(4-Fluoro-3-trifluoromethyl-phenyl)-ethylamine; hydrochloride (intermediate19)	601.9	0.0254

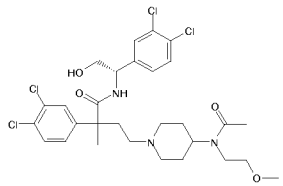
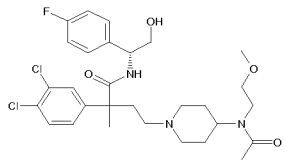
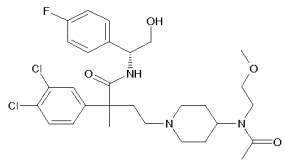
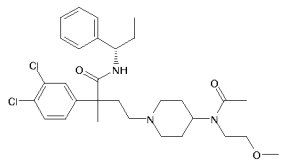
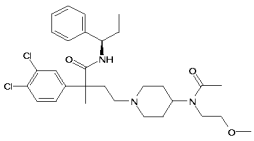
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
126		616.523	2-(3,4-Dichloro-phenyl)-*N*-[1-(4-fluoro-3-trifluoromethyl-phenyl)-ethyl]-2,*N*-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 1-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl-methyl amine; hydrochloride (Intermediate 20)	615.9	0.0303
127		530.536	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-*N*-((S)-1-phenyl-propyl)-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and (S)-(-)-1-phenylpropylamine (commercially available)	530.2	0.0052
128		530.536	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-*N*-((R)-1-phenyl-propyl)-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10)and (R)-(+)-1-phenylpropylamine (commercially available)	530.2	0.0902
129		550.499	2-(3,4-Dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-(R or S) methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and (R)-2-Amino-2-(4-fluoro-phenyl)-ethanol (commercially available)	550.4	0.0082

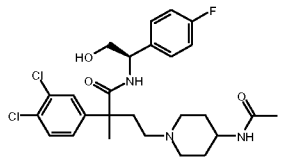
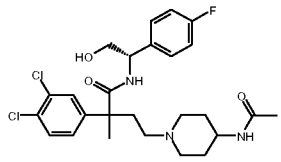
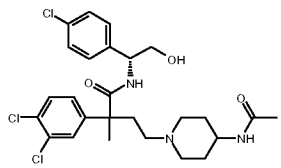
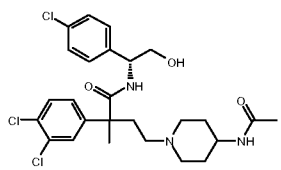
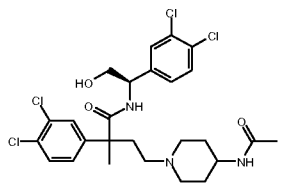
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
130		550.499	2-(3,4-Dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-(S or R) methyl -4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10)	550.4	0.1007
131		588.47	2-(3,4-Dichloro-phenyl)-*N*-(4-fluoro-3-trifluoromethyl-benzyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide	2-(3,4-Dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyric acid (intermediate 10) and 4-fluoro-3-(trifluoromethyl)benzylamine (commercially available	588.1	0.0034
132		590.486	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-3-trifluoromethyl-phenyl)-ethyl]-2-methyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 1-(4-Fluoro-3-trifluoromethyl-phenyl)-ethylamine; hydrochloride (intermediate19)	589.9	0.0462
133		520.497	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-((S)-2-hydroxy-1-phenyl-ethyl)-2-methyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and (S)-(-)-1-phenylpropylamine (commercially available)	520.2	0.5257
134		520.497	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-((R)-2-hydroxy-1-phenyl-ethyl)-2-methyl-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and (R)-(-)-1-phenylpropylamine (commercially available)	520.3	0.0356

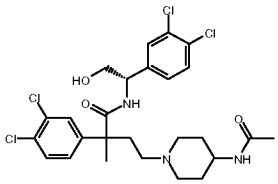
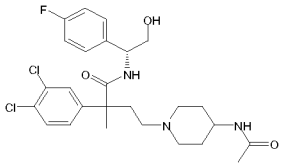
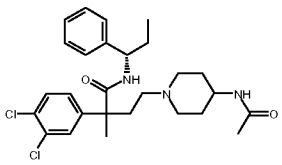
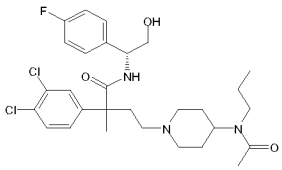
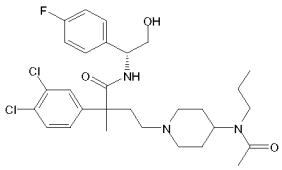
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
135		576.459	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-[2,2,2-trifluoro-1-(4-fluoro-phenyl)-ethyl]-butyramide	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 2,2,2-Trifluoro-1-(4-fluorophenyl)ethylamine (commercially available)	575.8	0.0126
136		554.943	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide (diastereosisomer 1)	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 4-Chlorophenylglycinol (commercially available)	553.7	0.0096
137		554.943	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide (diastereosisomer 2)	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 4-Chlorophenylglycinol (commercially available)	553.7	0.056
138		538.488	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 1)	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 4-Fluorophenylglycinol (commercially available)	538	0.0293

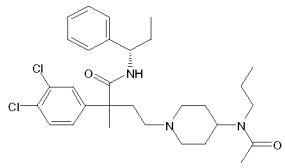
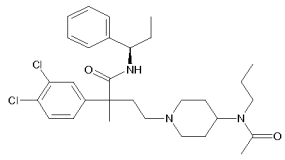
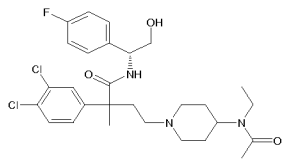
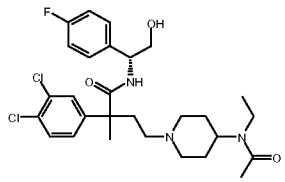
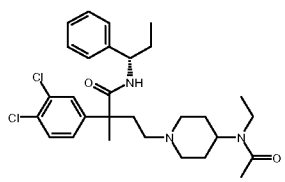
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
139		538.488	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 2)	4-[4-(Acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 11) and 4-Fluorophenylglycinol (commercially available)	538	0.1415
140		564.53	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 1)	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 14) and 4-Fluorophenylglycinol (commercially available)	564.4	0.0333
141		564.53	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 2)	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 14) and 4-Fluorophenylglycinol (commercially available)	564.4	0.1648
142		580.98	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide (diastereoisomer 1)	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 14) and 4-Chlorophenylglycinol (commercially available)	580.4	0.0109
143		580.98	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide (diastereoisomer 2)	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 14) and 4-Chlorophenylglycinol (commercially available)	580.4	0.0877

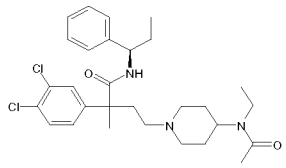
No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
144		615.43	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereosiomer 1)	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 14) and 3,4-di-Chlorophenylglycinol (commercially available)	616.2	0.0101
145		615.43	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 2)	4-[4-(Acetyl-cyclopropyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 14) and 3,4-di-Chlorophenylglycinol (commercially available)	616.2	0.0502
146		582.54	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 1)	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 15) and 4-Fluorophenylglycinol (commercially available)	582.2	0.0007
147		598.995	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 15) and 4-Chlorophenylglycinol (commercially available)	598.3	0.3824
148		633.44	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastreoisomer 1)	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 15) and 3,4-di-Chlorophenylglycinol (commercially available)	634.2	0.0038

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
149		633.44	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[(S)-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastreoisomer 2)	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 15) and 3,4-di-Chlorophenylglycinol (commercially available)	634.3	0.0194
150		582.54	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-(R or S) methyl-butyramide	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 15) and (R)-4-Fluorophenylglycinol (commercially available)	582.2	0.0017
151		582.54	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-(S or R) methyl-butyramide	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 15) and (R)-4-Fluorophenylglycinol (commercially available)	582.2	0.0211
152		562.578	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 15) and (S)-(-)-1-phenylpropylamine (commercially available)	562.2	0.0011
153		562.578	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((R)-1-phenyl-propyl)-butyramide	4-{4-[Acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 15) and (R)-(+)-1-phenylpropylamine (commercially available)	562.2	0.0609

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
154		524.46	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 1)	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid (intermediate 16) and 4-Fluorophenylglycinol (commercially available)	524.3	0.1703
155		524.46	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 2)	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid (intermediate 16) and 4-Fluorophenylglycinol (commercially available)	524.3	0.0138
156		540.916	4-(4-Acetylamino-piperidin-1-yl)-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide (diastereoisomer 1)	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid (intermediate 16) and 4-Chlorophenylglycinol (commercially available)	540.3	0.0505
157		540.916	4-(4-Acetylamino-piperidin-1-yl)-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide (diastereoisomer 2)	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid (intermediate 16) and 4-Chlorophenylglycinol (commercially available)	540.3	0.7727
158		575.36	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 1)	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid (intermediate 16) and 3,4-di-Chlorophenylglycinol (commercially available)	576.3	0.0346

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
159		575.36	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-*N*-[(S)-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 2)	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid (intermediate 16) and 3,4-di-Chlorophenylglycinol (commercially available)	576.3	0.2582
160		524.461	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid (intermediate 16) and (R)-4-Fluorophenylglycinol (commercially available)	524.4	0.1998
161		504.498	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide	4-(4-Acetylamino-piperidin-1-yl)-2-(3,4-dichloro-phenyl)-2-methylbutyric acid (intermediate 16) and (S)-(-)-1-phenylpropylamine (commercially available)	504.2	0.0442
162		566.541	4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 1)	4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 17) and (R)-4-Fluorophenylglycinol (commercially available)	566.4	0.0005
163		566.541	4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 2)	4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 17) and (R)-4-Fluorophenylglycinol (commercially available)	566.4	0.0056

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
164		546.579	4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide	4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 17) and (S)-(-)-1-phenylpropylamine (commercially available)	546.2	0.0008
165		546.579	4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((R)-1-phenyl-propyl)-butyramide	4-[4-(Acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 17) and (R)-(+)-1-phenylpropylamine (commercially available)	546.2	0.0145
166		552.514	4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 1)	4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 18) and (R)-4-Fluorophenylglycinol (commercially available)	552.4	0.0022
167		552.514	4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 2)	4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 18) and (R)-4-Fluorophenylglycinol (commercially available)	552.4	0.0349
168		532.552	4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide	4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 18) and (S)-(-)-1-phenylpropylamine (commercially available)	532.2	0.003

No	structure	MW	Systematic Name	starting materials	MW found (MH+)	hNK3 Ki (uM)
169		532.552	4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((R)-1-phenyl-propyl)-butyramide	4-[4-(Acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-butyric acid (intermediate 18) and (R)-(+)-1-phenylpropylamine (commercially available)	532.3	0.0576

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

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

[^{3}H]SR142801 competition binding assay

hNK3 receptor binding experiment were performed using [^{3}H]SR142801 (Catalog No. TRK1035, specific activity: 74.0 Ci/mmol, Amersham, GE Healthcare UK limited, Buckinghamshire, UK) and membrane isolated from HEK293 cells transiently expressing recombinant human NK3 receptor. After thawing, the membrane homogenates were centrifuged at 48,000 X g for 10 min at 4 °C, the pellets were resuspended in the 50 mM Tris-HCl, 4 mM $MnCl_2$, 1 μM phosphoramidon, 0.1 % BSA binding buffer at pH 7.4 to a final assay concentration of 5 μg protein/well. For inhibition experiments, membranes were incubated with [^{3}H]SR142801 at a concentration equal to K_D value of radioligand and 10 concentrations of the inhibitory compound (0.0003-10 μM) (in a total reaction volume of 500 μl) for 75 min at room temperature (RT). At the end of the incubation, membranes were filtered onto unitfilter (96-well white microplate with bonded GF/C

filter preincubated 1 h in 0.3% PEI + 0.3% BSA, Packard BioScience, Meriden, CT) with a Filtermate 196 harvester (Packard BioScience) and washed 4 times with ice-cold 50 mM Tris-HCl, pH 7.4 buffer. Nonspecific binding was measured in the presence of 10 µM SB222200 for both radioligands. The radioactivity on the filter was counted (5 min) on a Packard Top-count microplate scintillation counter with quenching correction after addition of 45 µl of microscint 40 (Canberra Packard S.A., Zürich, Switzerland) and shaking for 1 h. Inhibition curves were fitted according to the Hill equation: $y = 100/(1+(x/IC_{50})^{nH})$, where n_H = slope factor using Excel-fit 4 software (Microsoft). IC_{50} values were derived from the inhibition curve and the affinity constant (K_i) values were calculated using the Cheng-Prussoff equation $K_i = IC_{50}/(1+[L]/K_D)$ where [L] is the concentration of radioligand and K_D is its dissociation constant at the receptor, derived from the saturation isotherm. All experiments were performed in duplicate and the mean ± standard error (SEM) of the individual K_i values was calculated.

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

Example No.	K_i NK3 h (µM)	Example No.	K_i NK3 h (µM)
45	0.0085	94	0.003
46	0.0024	95	0.0047
47	0.0021	96	0.0072
48	0.0036	99	0.0058
49	0.0055	100	0.003
57	0.0059	101	0.0068
58	0.0036	102	0.0051
59	0.0043	103	0.0022
60	0.0026	104	0.0023
69	0.0024	105	0.0087
70	0.0012	106	0.0051
71	0.0028	109	0.0056
72	0.0022	115	0.0081
73	0.0015	119	0.0008
74	0.0013	120	0.002
75	0.0039	122	0.0015
76	0.0017	127	0.0052

77	0.0031	129	0.0082
78	0.0036	131	0.0034
79	0.0015	136	0.0096
81	0.003	146	0.0007
82	0.0012	148	0.0038
83	0.0023	150	0.0017
84	0.0021	152	0.0011
85	0.0014	162	0.0005
86	0.0014	163	0.0056
87	0.0046	164	0.0008
88	0.0018	166	0.0022
89	0.0053	168	0.003
90	0.0025		

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

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

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

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

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

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

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

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

Example A

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

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

Example B

Capsules of the following composition are manufactured:

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

The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added

thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

Example C

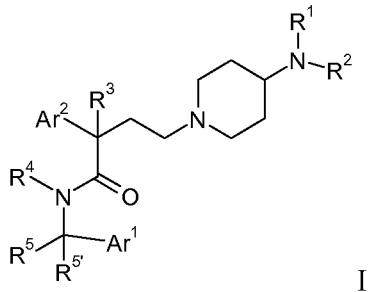
Suppositories of the following composition are manufactured:

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

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

Claims

1. A compound of formula



I

wherein

Ar^1/Ar^2 are independently from each other phenyl or pyridinyl, which are optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, lower alkoxy, lower alkyl substituted by halogen, lower alkoxy substituted by halogen, lower alkyl substituted by alkoxy, lower alkyl substituted by cyano, lower di-alkyl amino, pyridinyl or cyano;

R^1 is hydrogen, lower alkyl, $-(CH_2)_2O$-lower alkyl, or cycloalkyl:

R^2 is $-S(O)_2$-lower alkyl or $-C(O)$-lower alkyl;

or R^1 and R^2 form together with the N-atom to which they are attached a pyrrolidin-2-one or a piperidin-2-one group;

R^3 is hydrogen, halogen or lower alkyl;

R^4 is hydrogen or lower alkyl;

$R^5/R^{5'}$ are independently from each other hydrogen, lower alkyl, lower alkyl substituted by halogen, lower alkyl substituted by hydroxy or cycloalkyl;

or R^5 and $R^{5'}$ form together with the carbon-atom to which they are attached a cycloalkyl group;

or a pharmaceutically active salt thereof.

2. A compound of formula I according to claim 1, wherein Ar^1 and Ar^2 are both phenyl.

3. A compound of formula I according to claim 2, wherein R^1 is methyl and R^2 is $S(O)_2CH_3$.

4. A compound of formula I according to claim 3, which compounds are 2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-4-[4-(methanesulfonyl-

methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide or
2-(3,4-dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-4-[4-(methanesulfonyl-methyl-amino)-piperidin-1-yl]-2-methyl-butyramide; diastereoisomer 1.

5. A compound of formula I according to claim 2, wherein R^1 is cyclopropyl and R^2 is $S(O)_2CH_3$.

6. A compound of formula I according to claim 5, which compounds are
4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
N-(4-chloro-3-trifluoromethyl-benzyl)-4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide or
4-[4-(cyclopropyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide.

7. A compound of formula I according to claim 2, wherein R^1 is ethyl and R^2 is $S(O)_2CH_3$.

8. A compound of formula I according to claim 7, which compounds are
2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyramide
N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-

methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
N-(3-chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide
2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-N-(4-trifluoromethyl-benzyl)-butyramide
2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-N-(4-methyl-benzyl)-butyramide
N-(2-chloro-benzyl)-2-(3,4-dichloro-phenyl)-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2,N-dimethyl-butyramide or
2-(3,4-dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-4-[4-(ethyl-methanesulfonyl-amino)-piperidin-1-yl]-2-methyl-butyramide; diastereoisomer 1.

9. A compound of formula I according to claim 2, wherein R^1 and R^2 form together with the N-atom to which they are attached a pyrrolidin-2-one group.

10. A compound of formula I according to claim 9, which compounds are
2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(3-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-(4-trifluoromethyl-benzyl)-butyramide
2-(3,4-dichloro-phenyl)-2,N-dimethyl-N-(4-methyl-benzyl)-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
N-(2-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-

yl)-piperidin-1-yl]-butyramide
2-(3,4-dichloro-phenyl)-N-[-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide; diastereoisomer 1
2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-(2,2,2-trifluoro-1-phenyl-ethyl)-butyramide
2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-N-[2,2,2-trifluoro-1-(4-fluoro-phenyl)-ethyl]-butyramide
N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-N-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
(R or S)-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
(R or S)-2-(3,4-dichloro-phenyl)-N-[(S or R)-1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide
2-(3,4-dichloro-phenyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-*N*-((S)-1-phenyl-propyl)-butyramide
2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-(R or S) methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide or
2-(3,4-dichloro-phenyl)-*N*-(4-fluoro-3-trifluoromethyl-benzyl)-2-methyl-4-[4-(2-oxo-pyrrolidin-1-yl)-piperidin-1-yl]-butyramide.

11. A compound of formula I according to claim 2, wherein R^1 is lower alkyl and R^2 is $C(O)CH_3$.

12. A compound of formula I according to claim 11, wherein the compounds are
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(3-fluoro-4-trifluoromethyl-benzyl)-2-methyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(3,4-dichloro-benzyl)-2-(3,4-dichloro-phenyl)-2-methyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(4-chloro-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(4-chloro-3-trifluoromethyl-benzyl)-2-(3,4-dichloro-phenyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-N-(3-chloro-benzyl)-2-(3,4-dichloro-

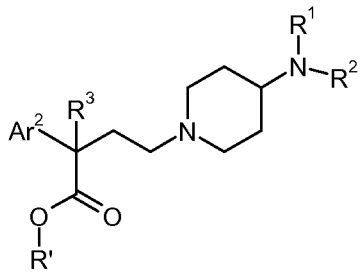
phenyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2,N-dimethyl-N-(4-trifluoromethyl-benzyl)-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide; diastereoisomer 1
(R or S)-4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-N-(4-fluoro-3-trifluoromethyl-benzyl)-2,N-dimethyl-butyramide
4-[4-(acetyl-methyl-amino)-piperidin-1-yl]-*N*-[1-(4-chloro-phenyl)-2-hydroxy-ethyl]-2-(3,4-dichloro-phenyl)-2-methyl-butyramide (diastereosisomer 1)
4-[4-(acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 1)
4-[4-(acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 2)
4-[4-(acetyl-propyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide
4-[4-(acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (epimer 1) or
4-[4-(acetyl-ethyl-amino)-piperidin-1-yl]-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide.

13. A compound of formula I according to claim 2, wherein R^1 is $-(CH_2)_2OCH_3$ and R^2 is $C(O)CH_3$.

14. A compound of formula I according to claim 13, wherein the compounds are
4-{4-[acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastereoisomer 1)
4-{4-[acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[1-(3,4-dichloro-phenyl)-2-hydroxy-ethyl]-2-methyl-butyramide (diastreoisomer 1)
4-{4-[acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-*N*-[(R)-1-(4-fluoro-phenyl)-2-hydroxy-ethyl]-2-(R or S) methyl-butyramide or
4-{4-[acetyl-(2-methoxy-ethyl)-amino]-piperidin-1-yl}-2-(3,4-dichloro-phenyl)-2-methyl-*N*-((S)-1-phenyl-propyl)-butyramide.

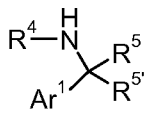
15. A process for preparation of the compound according to any one of claims 1-14, which process comprises

a) cleaving off an O-protecting group under aqueous basic conditions from a compound of formula IV

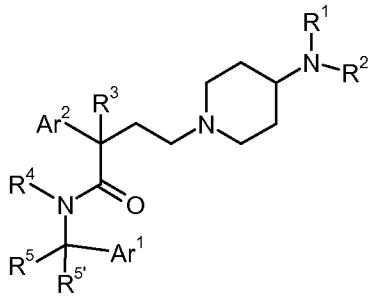


IV

and reacting a compound of formula IV under coupling conditions with an amine of formula



to a compound of formula



I

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

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

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

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

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

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

20. The invention as herein before described.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/061649

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/58 C07D401/04 A61K31/4468 A61P25/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/28931 A (MERCK & CO INC [US]; SHAH SHRENIK K [US]) 2 November 1995 (1995-11-02) page 1, line 6 - page 1, line 9; example 5	1-20
A	KAMALI F: "Osanetant Sanofi-Synthélabo" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 2, no. 7, 1 January 2001 (2001-01-01), pages 950-956, XP008060165 ISSN: 0967-8298 cited in the application page 1, right column, compound in box	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2008	29/12/2008

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/061649

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9528931 A	02-11-1995	AU 2391595 A	16-11-1995
		CA 2188031 A1	02-11-1995
		EP 0758238 A1	19-02-1997
		JP 9512272 T	09-12-1997
		US 5434158 A	18-07-1995