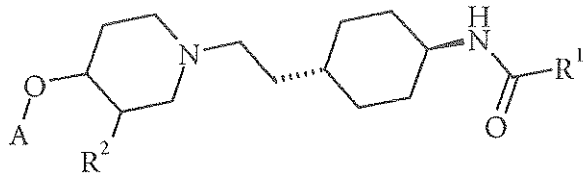
ETHER DERIVATIVES DUAL MODULATORS OF THE 5-HT2A AND D3 RECEPTORS

In particular, the present invention relates to compounds of the general formula I:



(I)

wherein:

A is aryl, or 5 to 12 membered heteroaryl which are optionally substituted by:
halogen,
cyano,
C_{1-6}-alkyl optionally substituted by cyano or C_{1-6}-alkoxy,
C_{1-6}-alkoxy,
$-S(O)_2-C_{1-6}$-alkyl;

R^1 is C_{1-6}-alkyl optionally substituted by:
one or more halogen, C_{1-6}-alkoxy or aryl optionally substituted by halogen,
or is C_{3-10}-cycloalkyl optionally substituted by one or more R^a,
or is 5 to 12 membered heterocycloalkyl optionally substituted by one or more R^a,
or is aryl optionally substituted by one or more R^a,
or is 5 to 12 membered heteroaryl optionally substituted by one or more R^a,
or is $-NR^bR^c$, wherein R^b is H or C_{1-6}-alkyl and wherein R^c is H, C_{1-6}-alkyl or aryl optionally substituted by one or more R^a,
wherein R^a is selected from:
halogen,
$-S(O)_2-C_{1-6}$-alkyl,
cyano,
oxo,
C_{1-6}-alkyl optionally substituted by aryl which is substituted by halogen,
C_{1-6}-haloalkyl,

C_{1-6}-haloalkoxy,

C_{1-6}-alkoxy optionally substituted by 5 to 6 membered heteroaryl which is optionally substituted by C_{1-6}-alkyl,

-NH(CO)-C_{1-6}-alkyl,

5 to 6 membered heterocycloalkyl, or

5 to 6 membered heteroaryl optionally substituted by C_{1-6}-alkyl or oxo;

R^2 is H or OH;

as well as pharmaceutically acceptable salts thereof.

It has been surprisingly found that the compounds of formula (I) according to the invention are dual modulators of the serotonin 5-HT_{2a} and dopamine D_3 receptors.

The compounds of the invention have high affinity for the dopamine D_3 and serotonin (5-Hydroxytryptamine; 5-HT) 5-HT_{2A} receptors and are believed to be effective in the treatment of psychotic disorders, as well as other diseases such as depression and anxiety, drug dependence, dementias and memory impairment. Psychotic disorders encompass a variety of diseases, which include schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, and other psychoses involving paranoia and delusions.

In particular schizophrenia is characterized by complex symptomatology including positive symptoms, (i.e. delusions and hallucinations), and negative symptoms, (i.e. anhedonia, restricted fluency and productivity of thought and speech). In addition it is now well recognized that cognitive impairment is the third major diagnostic category of schizophrenia, characterized by loss in working memory as well as other deficits. Other symptoms include aggressiveness, depression and anxiety (Stahl, S. M. (2000) Essential Psychopharmacology. Neuroscientific Basis and Practical Applications. Cambridge University Press, second edition, Cambridge, UK). The different categories and the clinical features of the disorder are defined in diagnostic schemes such as DSM-IV (Diagnostic and statistical manual of mental disorders, 4th edition) or ICD-10 (International classification of diseases, 10th edition). Currently medication used to treat schizophrenia, bipolar mania and other psychoses, include antipsychotics both typical (D_2/D_3 preferring) or the more recent atypicals, which exhibit polypharmacology interacting at multiple receptors (eg., D_1, D_2, D_3, D_4, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, H_1, M_1, M_2, M_4 etc ; Roth, B. L et al. (2004) Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat. Rev. Drug Discov. 3, 353-359). These antipsychotics, although relatively successful (some patients exhibit treatment resistance) at treating the positive symptoms of schizophrenia, are less effective

at treating negative symptoms, cognitive deficits, and associated depression and anxiety, all of which lead to reduced patient quality of life and socioeconomic problems (Lieberman J. A., et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353, 1209-1223). Furthermore, patient compliance is compromised by prevalent side effects such as weight gain, extrapyramidal symptoms (EPS), and cardiovascular effects (Lieberman J. A. et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353, 1209-1223). In the current invention, compounds with high affinity and greater selectivity for D_3 and 5-HT_{2A} receptors are described, and are proposed to treat psychoses and other diseases, with fewer associated side affects.

Dopamine, a major catecholamine neurotransmitter, is involved in the regulation of a variety of functions which include emotion, cognition, motor functions, and positive reinforcement, (Purves, D. et al. (2004) Neuroscience. Sinauer, third edition, Sunderland, Massachusetts). The biological activities of dopamine are mediated through G protein-coupled receptors (GPCRs) and in human, five different dopamine receptors D_1-D_5 have been identified, where the D_2-like receptors (D_2, D_3 and D_4) couple to the G-protein $G_{\alpha I}$ (Missale, C. et al.. (1998) Dopamine receptors: from structure to function. Physiol. Rev. 78, 189-225). The D_3 dopamine receptor is most highly expressed in the nucleus accumbens (Gurevich, E. V., Joyce, J. N. (1999) Distribution of dopamine D_3 receptor expressing neurons in the human forebrain: comparison with D_2 receptor expressing neurons. Neuropsychopharmacology 20, 60-80), and is proposed to modulate the mesolimbic pathway consisting of neuronal projections from the ventral tegmental area, hippocampus and amygdala to the nucleus accumbens, which projects to the prefrontal and cingulate cortices as well as various thalamic nuclei. The limbic circuit is thought to be important for emotional behavior and thus D_3 receptor antagonists are proposed to modulate psychotic symptoms such as hallucinations, delusions and thought disorder (Joyce, J. N. and Millan M. J., (2005) Dopamine D_3 receptor antagonists as therapeutic agents. Drug Discovery Today, {Drug-Discov-Today}, 1 Jul, Vol. 10, No. 13, P. 917-25, Issn: 1359-6446), while these antagonists spare the D_2 modulated striatal extrapyramidal system (associated with EPS induction). In addition, it has been reported that drug naive schizophrenic patients show altered levels of D_3 receptor expression (Gurevich, E. V. et al. (1997) Mesolimbic dopamine D_3 receptors and use of antipsychotics in patients with schizophrenia. A postmortem study. Arch. Gen. Psychiatry 54, 225-232) and dopamine release (Laruelle, M. (2000) Imaging dopamine dysregulation in schizophrenia:

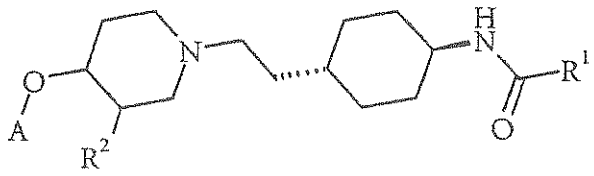
implication for treatment. Presented at Workshop Schizophr.: Pathol. Bases and Mech. Antipsychotic Action, Chicago), indicating that a disturbed homeostasis of dopamine plays an important role in the etiology of schizophrenic symptoms.

The neuro*trans*mitter serotonin is implicated in several psychiatric conditions including schizophrenia (Kandel, E. R. et al. (eds.; 2000) Principles of Neural Science, 3rd edition Appleton & Lange, Norwalk, CT). The involvement of serotonin in psychotic disorders is suggested by multiple studies which include treatment in humans with the psychotropic drug Lysergic acid (LSD; a serotonin agonist) which can induce schizophrenia-like symptoms such as hallucinations (Leikin, J. B. et al. (1989) Clinical features and management of intoxication due to hallucinogenic drugs. Med. Toxicol. Adverse Drug Exp. 4, 324-350). Furthermore, altered brain distribution of serotonin receptors as well as an altered serotonergic tone, have been detected in schizophrenic patients (Harrison, P. J. (1999) Neurochemical alterations in schizophrenia affecting the putative receptor targets of atypical antipsychotics. Focus on dopamine (D_1, D_3, D_4) and 5-HT_{2A} receptors. Br. J. Psychiatry Suppl. 38, 12-22). In mammals serotonin exerts its biological activities through a family of 14 5-HT GPCRs (Barnes, N. M., Sharp, T. (1999) A review of central 5-HT receptors and their function. Neuropharmacology 38, 1083-1152). The 5-HT_{2A} receptor is most prominently expressed in the prefrontal cortex and at lower levels in the basal ganglia and the hippocampus in human brain (Pompeiano, M. et al. (1994) Distribution of the serotonin 5-HT2 receptor family mRNAs: comparison between 5-HT_{2A} and 5-HT_{2C} receptors. Brain Res. Mol. Brain Res. 23, 163-178; Pazos, A., Probst, A., Palacios, J. M. (1987) Serotonin receptors in the human brain--IV. Autoradiographic mapping of serotonin-2 receptors. Neuroscience 21, 123-139), and is coupled predominantly to the G-protein $G_{\alpha q}$ (Roth, B. L. et al. (1998) 5-Hydroxytryptamine2-family receptors (5-hydroxytryptamine2A, 5-hydroxytryptamine2B, 5-hydroxytryptamine2C): where structure meets function. Pharmacol. Ther. 79, 231-257). Genetic linkage studies of a 5-HT_{2A} polymorphism to schizophrenia (Spurlock, G. et al. (1998) A family based association study of T102C polymorphism in 5HT_{2A} and schizophrenia plus identification of new polymorphisms in the promoter. Mol. Psychiatry 3, 42-49), as well as responsiveness to antipsychotic drugs (Arranz, M. J. et al. (2000) Pharmacogenetic prediction of clozapine response. Lancet 355, 1615-1616), further suggests a role for the 5-HT_{2A} receptor both in the treatment and pathology of psychosis. In addition, dopaminergic neuro*trans*mission appears to be under the afferent regulation of the 5-HT_{2A} receptor (Porras, G. et al. 5-HT_{2A} and 5-$HT_{2C/2B}$ receptor subtypes modulate dopamine release induced in vivo by amphetamine and morphine in both the rat nucleus accumbens and striatum.

Neuropsychopharmacology 26, 311-324 - 2002). Overall 5-HT_{2A} receptor antagonists are proposed to be suitable for the treatment of disorders associated with dysfunctional dopaminergic systems. Moreover, 5-HT_{2A} receptor antagonism has been recognized as beneficial for the treatment of psychosis (reviewed in de Angelis, L. (2002) 5-HT_{2A} antagonists in psychiatric disorders. Curr. Opin. Investig. Drugs 3, 106-112) and indeed is one of the defining features of so-called atypical antipsychotic drugs which are characterized by a relatively high affinity for the 5-HT_{2A}- relative to the D_2 receptor (Meltzer, H. Y. et al. (1989) Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. J. Pharmacol. Exp. Ther. 251, 238-246).

As mentioned hereinabove, the compounds of the invention have high affinity for the dopamine D_3 and serotonin 5-HT_{2A} receptors and are expected to be effective in the treatment of psychotic disorders which include schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, and other psychoses involving paranoia and delusions (Reavill-C , et al. (2000) Pharmacological actions of a novel, high-affinity, and selective human dopamine D_3 receptor antagonist, SB-277011-A. JPET 294:1154–1165; Harrison, P. J. (1999) Neurochemical alterations in schizophrenia affecting the putative receptor targets of atypical antipsychotics. Focus on dopamine (D_1, D_3, D_4) and 5-HT_{2A} receptors. Br. J. Psychiatry Suppl. 38, 12-22; de Angelis, L. (2002) 5-HT_{2A} antagonists in psychiatric disorders. Curr. Opin. Investig. Drugs 3, 106-112; Joyce, J. N. and Millan M. J., (2005) Dopamine D_3 receptor antagonists as therapeutic agents. Drug Discovery Today, {Drug-Discov-Today}, 1 Jul, Vol. 10, No. 13, P. 917-25, Issn: 1359-6446); drug dependency and abuse and withdrawal (Vorel, S. R. et al. E.L (2002) Dopamine D_3 receptor antagonism inhibits cocaine-seeking and cocaine-enhanced brain reward in rats. J. Neurosci., 22, 9595–9603; Campos, A. C. et al. (2003) The dopamine D_3 receptor antagonist SB277011A antagonizes nicotine-enhanced brain-stimulation reward in rat. Soc. Neurosci. Abstr., 322.8; Ashby, C. R., et al. (2003). Acute administration of the selective D_3 receptor antagonist SB-277011-A blocks the acquisition and expression of the conditioned place preference response to heroin in male rats. Synapse, 48, 154–156); anxiety, and depression (Reavill-C et al. (2000) Pharmacological actions of a novel, high-affinity, and selective human dopamine D_3 receptor antagonist, SB-277011-A. JPET 294:1154–1165; Drescher, K. et al. (2002) In vivo effects of the selective dopamine D_3 receptor antagonist A-437203. Am. Soc. Neurosci. 894.6).

In a first aspect, there is provided compounds of the general formula I:



(I)

wherein:

A is aryl, or 5 to 12 membered heteroaryl which are optionally substituted by:
halogen,
cyano,
C_{1-6}-alkyl optionally substituted by cyano or C_{1-6}-alkoxy,
C_{1-6}-alkoxy,
$-S(O)_2-C_{1-6}$-alkyl;

R^1 is C_{1-6}-alkyl optionally substituted by:
one or more halogen, C_{1-6}-alkoxy or aryl optionally substituted by halogen,
or is C_{3-10}-cycloalkyl optionally substituted by one or more R^a,
or is 5 to 12 membered heterocycloalkyl optionally substituted by one or more R^a,
or is aryl optionally substituted by one or more R^a,
or is 5 to 12 membered heteroaryl optionally substituted by one or more R^a,
or is $-NR^bR^c$, wherein R^b is H or C_{1-6}-alkyl and wherein R^c is H, C_{1-6}-alkyl or aryl optionally substituted by one or more R^a,
wherein R^a is selected from:
halogen,
$-S(O)_2-C_{1-6}$-alkyl,
cyano,
oxo,
C_{1-6}-alkyl optionally substituted by aryl which is substituted by halogen,
C_{1-6}-haloalkyl,
C_{1-6}-haloalkoxy,
C_{1-6}-alkoxy optionally substituted by 5 to 6 membered heteroaryl which is optionally substituted by C_{1-6}-alkyl,
$-NH(CO)-C_{1-6}$-alkyl,
5 to 6 membered heterocycloalkyl, or

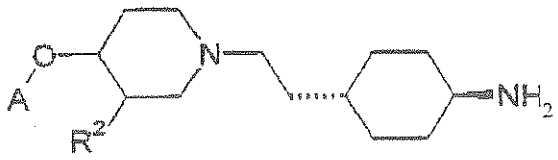
5 to 6 membered heteroaryl optionally substituted by C_{1-6}-alkyl or oxo;

R^2 is H or OH;

as well as pharmaceutically acceptable salts thereof.

In a second aspect, there is provided a process for the preparation of compounds of formula I as defined above, comprising the steps of:

a) reacting a compound of the formula II:

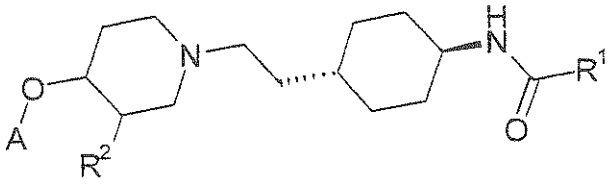


(II)

either with an acid of the formula III:

$$HOOCR^1 \qquad (III)$$

in the presence of a coupling reagent to obtain a compound of the formula I:



(I)

wherein A and R^2 are as defined above and,

wherein R^1 is C_{1-6}-alkyl optionally substituted by one or more halogen, C_{1-6}-alkoxy, aryl optionally substituted by halogen,

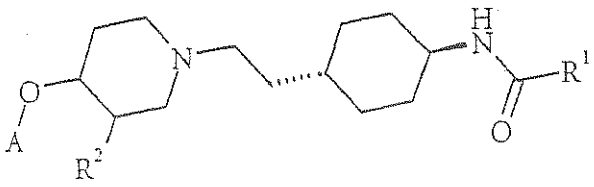
or is C_{3-10}-cycloalkyl optionally substituted by one or more R^a,

or is 5 to 12 membered heterocycloalkyl optionally substituted by one or more R^a,

or is aryl optionally substituted by one or more R^a,

or is 5 to 12 membered heteroaryl optionally substituted by one or more R^a;

or with and isocyanate or para nitro carbamate to obtain a compound of the formula I:



(I)

wherein R^1 is $-NR^bR^c$, wherein R^b is H or C_{1-6}-alkyl and wherein R^c is aryl optionally substituted by one or more R^a;

wherein R^a is as defined above,

and if desired,

converting the compound obtained into a pharmaceutically acceptable acid addition salt.

In a third aspect, there is provided a medicament containing one or more compounds as defined above and pharmaceutically acceptable excipients for the treatment and/or the prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, and psychoses comprising paranoia and delusions.

In a fourth aspect, there is provided a compound as defined above as well as its pharmaceutically acceptable salt for use in the treatment or prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, and psychoses comprising paranoia and delusions.

In a fifth aspect, there is provided the use of a compound as defined above as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and/or the prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, and psychoses comprising paranoia and delusions.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example hydrochloride,

hydrobromide, phosphate, acetate, fumarate, maleate, salicylate, sulphate, pyruvate, citrate, lactate, mandelate, tartarate, and methanesulphonate. Preferred are the hydrochloride salts. Also solvates and hydrates of compounds of formula I and their salts form part of the present invention.

Compounds of formula (I) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbens or eluent). The invention embraces all of these forms.

It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo. Physiologically acceptable and metabolically labile derivatives, which are capable of producing the parent compounds of general formula I in vivo are also within the scope of this invention.

"Aryl" means a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono-, bi- or tricyclic aromatic ring. Examples of aryl moieties include, but are not limited to, optionally substituted phenyl, naphthyl, phenanthryl, fluorenyl, indenyl, pentalenyl, azulenyl, oxydiphenyl, biphenyl, methylenediphenyl, aminodiphenyl, diphenylsulfidyl, diphenylsulfonyl, and diphenylisopropylidenyl, as well as those specifically illustrated by the examples herein below. Preferred aryl are phenyl and naphthyl, and still more preferably phenyl.

The aryl moieties of the invention further can be substituted by one, two or three substituents as those substituted which are specifically illustrated by the examples herein below. Preferably the additional ring is a 5- to 6- membered ring containing two oxygen atoms. Examples of such substituted aryl moieties include, but are not limited to, 2,3-dihydro-benzo[1,4]dioxinyl, 2,3-dihydro-benzofuranyl, benzodioxolyl, benzopyranyl, benzoxazinyl, benzoxazinonyl, benzopiperidinyl, benzopiperazinyl, benzopyrrolidinyl, benzomorpholinyl, as well as those specifically illustrated by the examples herein below.

"C_{1-6}-alkyl" denotes a straight- or branched-carbon chain group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl as well as those specifically illustrated by the examples herein below.

"C_{1-6}-haloalkyl" denotes a C_{1-6}-alkyl group as defined above which is substituted by one or more halogen. Examples of C_{1-6}-haloalkyl include but are not limited to methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl or n-hexyl substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred C_1-C_7-haloalkyl are difluoro- or trifluoro-methyl or ethyl.

"C_{1-6}-alkoxy" denotes a group wherein the alkyl group is as defined above and the alkyl group is connected via an oxygen atom.

"C_{1-6}-haloalkoxy" denotes a C_{1-6}-alkoxy group as defined above which is substituted by one or more halogen. Examples of C_{1-6}-haloalkoxy include but are not limited to methoxy or ethoxy, substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Prefered C_1-C_7 haloalkoxy are difluoro- or trifluoro-methoxy or ethoxy.

"Halogen" denotes chlorine, iodine, fluorine and bromine.

"C_{3-10}-cycloalkyl" denotes a monovalent saturated moiety, consisting of one, two or three carbon rings having 3 to 10 carbon atoms as ring members and includes but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and polyspiro groups such as bicyclo[3.2.1]octane or adamantane as well as those groups specifically illustrated by the examples herein below.

"5 to 12 membered heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, three or four ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point is on the aromatic ring moiety containing the heteroatom(s). The heteroaryl ring may be optionally substituted as defined herein. Examples of heteroaryl moieties include, but are not limited to, optionally substituted imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl, thienyl, benzothienyl, furanyl, pyridyl, pyrrolyl, pyrazolyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofurylbenzimidazolyl, benzooxazolyl, benzooxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzopyranyl, indolyl, isoindolyl, triazolyl, triazinyl, quinoxalinyl, purinyl, quinazolinyl, quinolizinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like, as well as those specifically illustrated by the examples herein below. Preferred 5 to 12 heteroaryls are 5 to 6 heteroaryls, for example [1,2,4]oxadiazolyl, indolyl, thiophenyl, pyridinyl as well as those specifically illustrated

by the examples herein below. Preferred 5 to 12 heteroaryls are 5 to 10 heteroaryls, for example [1,2,4]oxadiazolyl, thiophenyl, pyridinyl, quinolinyl as well as those specifically illustrated by the examples herein below.

"5 to 12 heterocycloalkyl" means a monovalent saturated or partially unsaturated moiety, consisting of one to three rings, incorporating one, two, or three or four heteroatoms (chosen from nitrogen, oxygen or sulfur), with the understanding that the attachment point is on the heterocyclic, saturated or partially saturated moiety. Preferably, the rings are three to seven membered. The heterocyclyl ring may be optionally substituted as defined herein. Examples of heterocyclyl moieties include, but are not limited to, optionally substituted piperidinyl, piperazinyl, homopiperazinyl, azepinyl, pyrrolidinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinuclidinyl, thiadiazolylidinyl, benzothiazolidinyl, benzoazolylidinyl, dihydrofuryl, tetrahydrofuryl, dihydropyranyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinylsulfoxide, thiamorpholinylsulfone, dihydroquinolinyl, dihydrisoquinolinyl, tetrahydroquinolinyl, tetrahydrisoquinolinyl, as well as those groups specifically illustrated by the examples herein below. Preferred 5 to 12 heterocycloalkyls are 5 to 10 heterocycloalkyls, for example tetrahydrofuranyl and tetrahydropyranyl.

"Oxo" denotes a group =O.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" of a compound means salts that are pharmaceutically acceptable, as defined herein, and that possess the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphtoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, tartaric acid, p-toluenesulfonic acid,

trimethylacetic acid, as well as those groups specifically illustrated by the examples herein below.

In the compounds of formula I according to the invention and independently from R^1 and R^2, A is preferably aryl optionally substituted by one or more of halogen, cyano or C_{1-6}-alkyl substituted by cyano or 5 or 6 membered heteroaryl, for example pyridinyl.

In a certain embodiment of the invention R^1 is C_{1-6}-alkyl optionally substituted by one or more halogen or C_{1-6}-alkoxy, for example the following compounds:
N-*trans*(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;
N-*trans*(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-*trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;
N-*trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-propionamide;
N-*trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-*trans*(4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-*trans*(4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;
N-*trans*(4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-*trans*(4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-2,2,2-trifluoro-acetamide;
trans N-(4-{2-[4-(2,3-Dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;
N-*trans* (4-{2-[4-(2,3-Dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-*trans*(4-{2-[4-(2,6-Dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;
N-*trans* (4-{2-[4-(2,6-Dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-*trans* (4-{2-[4-(2,4,5-Trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-*trans*(4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-*trans*(4-{2-[4-(4-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-*trans*(4-{2-[4-(3-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-*trans*(4-{2-[4-(3-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-*trans*(4-{2-[4-(2,3,4-Trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide; and

N-(*trans*-4-{2-[4-(Pyridin-3-yloxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

In another embodiment of the invention R^1 is C_{3-10}-cycloalkyl optionally substituted by one or more R^a, wherein R^a is C_{1-6}-alkyl, for example the following compounds:

Cyclopropanecarboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

2-Methyl-cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

2-Methyl-cyclopropanecarboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide; and

Cyclopropanecarboxylic acid *trans* (4-{2-[4-(4-chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide.

In another embodiment of the invention R^1 is 5 to 12 membered heterocycloalkyl, for example the following compounds:

Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-furan-2-carboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-furan-2-carboxylic acid trans (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide; and
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(4-chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide.

In another embodiment of the invention R^1 is aryl optionally substituted by one or more R^a, wherein R^a is selected from halogen, C_{1-6}-alkoxy, $-S(O)_2-C_{1-6}$-alkyl, 5 to 6 membered heteroaryl optionally substituted by C_{1-6}-alkyl, for example the following compounds:
4-Chloro-N-*trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;
N-*trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide;
N-*trans*(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methanesulfonyl-benzamide;
N-*trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methanesulfonyl-benzamide;
4-Chloro-N-*trans*(4-{2-[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;
N-*trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide;

4-Chloro-N-*trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

N-*trans* (4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methoxy-benzamide;

4-Methoxy-N-*trans*(4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

4-Chloro-N-*trans*(4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

4-Methoxy-N- *trans*(4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

4-Chloro-N-*trans*(4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide; and

N-*trans*(4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-ethoxy-benzamide.

In another embodiment of the invention R^1 is 5 to 12 membered heteroaryl, for example the following compounds:

1H-Indole-2-carboxylic acid *trans*(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-6-carboxylic acid *trans*(4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans*(4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans*(4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans*(4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans*(4-{2-[4-(4-cyano-2-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2-[4-(2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2-[4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2-[(3R,4R)-4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2-[(3S,4S)-4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans*(4-{2-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide; and

Quinoline-4-carboxylic acid *trans*(4-{2-[4-(pyridin-4-yloxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide.

In another embodiment of the invention R^1 is $-NR^bR^c$ wherein R^b is H and R^c is H, aryl optionally substituted by one or more R^a, wherein R^a is halogen or C_{1-6}-alkyl, for example the following compounds:

1-(4-Chloro-phenyl)-3-*trans*(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-urea;

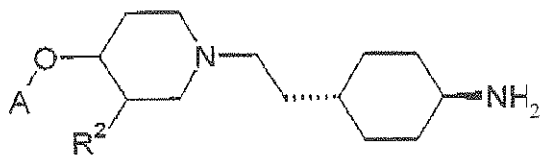
1-*trans*(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-p-tolyl-urea;

1-*trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-p-tolyl-urea; and

1-*trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(4-chloro-phenyl)-urea.

A further aspect of the present invention is the process for the manufacture of compounds of formula I as defined herein above, which process comprises:

a) reacting a compound of the formula II:



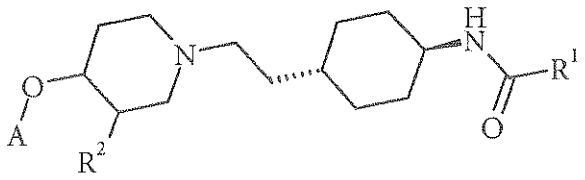
(II)

wherein A , R^1 and R^2 are as defined hereinabove,

either with an acid of the formula III:

$$HOOCR^1 \qquad (III)$$

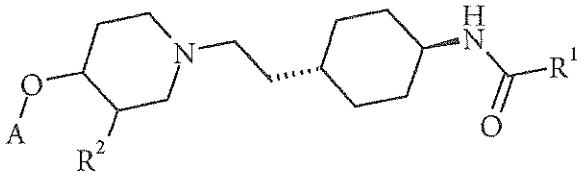
in the presence of a coupling reagent such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) in a suitable solvent like, e.g. dimethylformamide (DMF) or dioxane in the presence of a base (e.g. triethylamine or diisopropylethylamine) to obtain a compound of the formula (I):



(I)

wherein R^1 is C_{1-6}-alkyl optionally substituted by one or more halogen, C_{1-6}-alkoxy, aryl optionally substituted by halogen,
or is C_{3-10}-cycloalkyl optionally substituted by one or more R^a,
or is 5 to 12 membered heterocycloalkyl optionally substituted by one or more R^a,
or is aryl optionally substituted by one or more R^a,
or is 5 to 12 membered heteroaryl optionally substituted by one or more R^a;

or with an isocyanate or a reactive intermediate such as para nitro carbamate in a suitable solvent like, e.g. dimethylformamide (DMF) or acetonitrile in the presence of a base (e.g. triethylamine or diisopropylethylamine) to obtain a compound of the formula (I):



(I)

wherein R^1 is $-NR^bR^c$, wherein R^b is H or C_{1-6}-alkyl and wherein R^c is aryl optionally substituted by one or more R^a;

and if desired,
converting the compound obtained into a pharmaceutically acceptable acid addition salt.

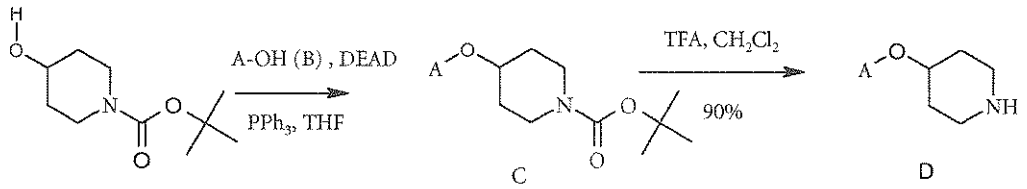
The preparation of compounds of formula (I) of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the invention are

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

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. Starting materials are either commercially available or can be prepared by methods analogous to the methods given herein below, by methods described in references cited in the description or in the examples, or by methods known in the art.

In the following schemes and unless stated otherwise, A, R^1 and R^2 are as described hereinabove.

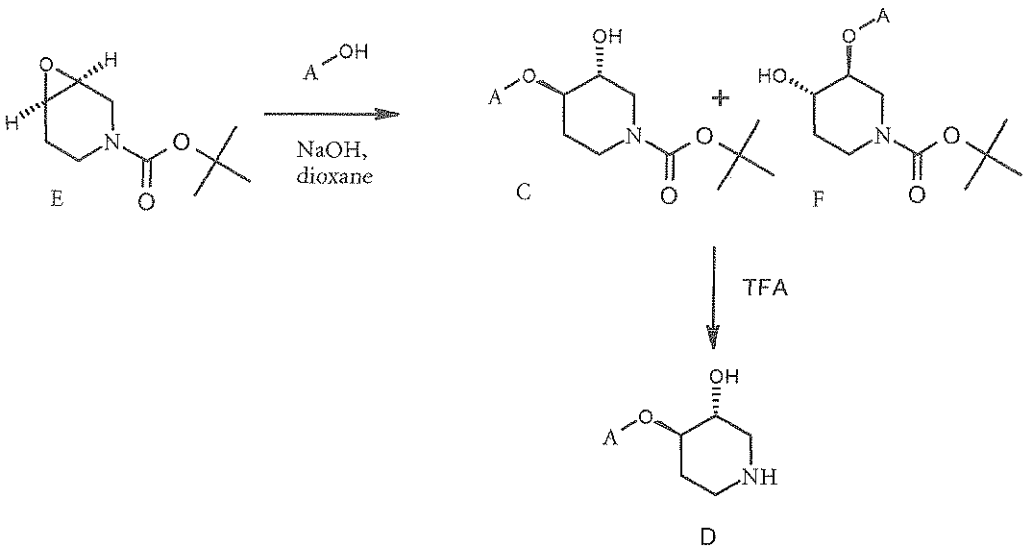
Scheme 1



The piperidin-4-yloxy-aryl or heteroaryl compound can be prepared according to scheme 1. The syntheses of ethers are 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, 1999). The transformation can be effected by employing reaction conditions which are commonly utilised in the so called "*Mitsunobu reaction*" which is known to those in the art and widely described (Hughes, David L. The Mitsunobu reaction. Organic Reactions, John Wiley & Sons, New York, 1992, 42, 335-656). It has been found convenient to couple the commercially available 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester with aryl or heteroaryl alcohols of formula B (either commercially available or accessible by methods described in references or by methods known in the art; as appropriate) under conditions employing a phosphine like a trialkylphosphine such as tributylphosphine ($(n\text{-}Bu)_3P$) or a triarylphosphine such as triphenylphosphine (Ph_3P) and the like and a diazo-compound like diethyl-azodicarboxylate (DEAD), diisopropyl-azodicarboxylate (DIAD) (optionally polymer bound), tetramethyl azodicarboxamide and the like in a solvent commonly used in such transformations like tetrahydrofurane (THF), toluene, dichloromethane and the like. There is no particular restriction on the nature of the

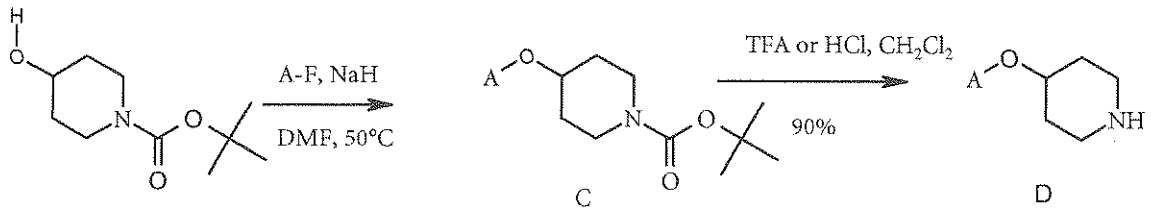
solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It has been found convenient to carry out the reaction at ambient temperature. 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 few hours to one day will usually suffice to yield the compounds of formula C. The protecting group can be removed under conditions known for those skilled in the art (e.g. treatment with an acid such as trifluoroacetic acid in a suitable solvent such as dichloromethane) as described on scheme 1.

Scheme 2



Aryl or heteroaryl piperidin-4-yloxy compounds with R^2 = OH can be prepared according to scheme 2 with opening of rac-cis-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester using the aryl or heteroaryl hydroxy derivative B in the presence of sodium hydroxide heating in a solvent like dioxane. Removal of the protecting group in conditions as the ones described on scheme 1 provides compounds of formula D were R^2 = OH

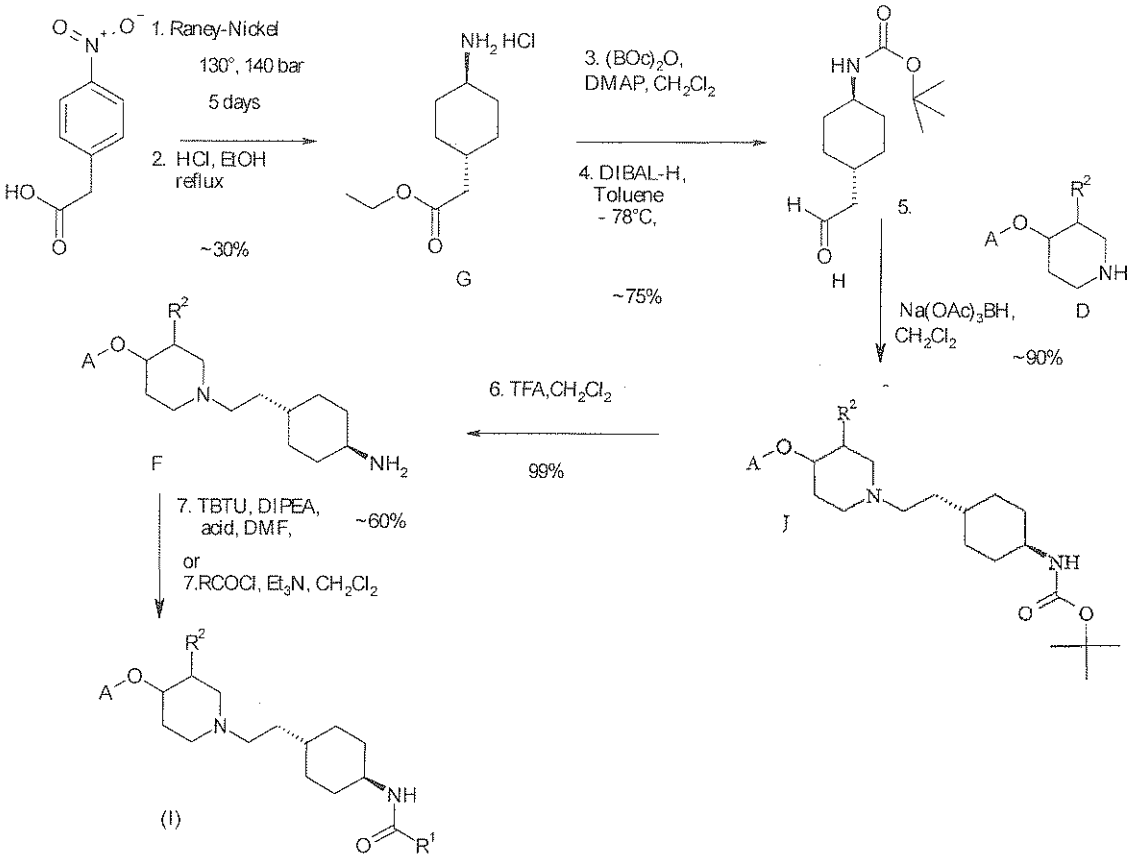
Scheme 3



Also aryl or heteroaryl piperidin-4-yloxy compounds of structure D containing an electron withdrawing group such as nitrile in *ortho* or *para* position can be prepared according to scheme 3 by an nucleophilic aromatic substitution of the corresponding fluoroaryl compound with 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester after deprotonation with a base such as NaH in a polar solvent such as DMF. Removal of the

protective group in conditions as the ones described in scheme 1 provides compounds of formula D.

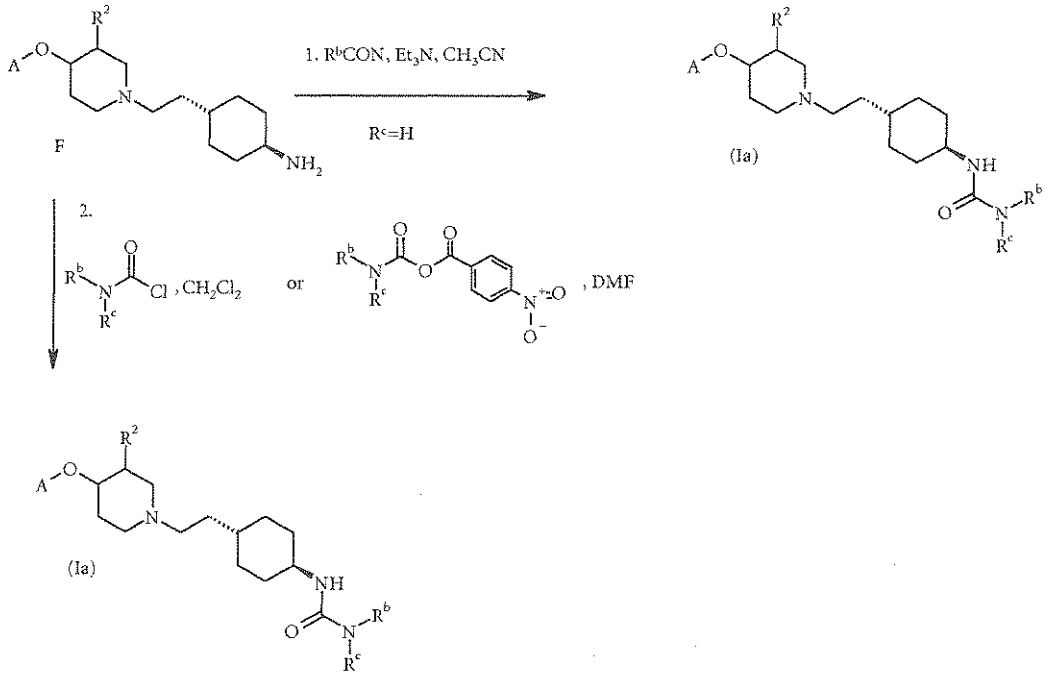
Scheme 4



(Heteroaryl or phenoxy-piperidin-1-yl) *trans*-ethyl-cyclohexyl-amides or *trans*-1,4-cyclohexyl ethyl derivates of formula (I) can be prepared as depicted in scheme 4 starting from 4-nitro-phenylacetic acid that by hydrogenation using raney nickel as catalyst. The hydrogenation with nickel leads preferentially to the desired *trans*-isomer (according to Wustrow et. al. J of Med. Chem., 1998, 41, 760-771). The ethyl ester can be prepared according to methods known to those skilled in the art and described in the mentioned literature (e.g by treatment with ethanol on the presence of an acid such as HCl) and the desired pure diastereoisomer can be resolved from the *cis*/*trans*mixture by crystallization as the HCl salt. *trans*-Amino ester chloride **G** is obtained. Reaction with tert-butyl dicarbonate in the presence of a base like triethylamine and a catalyst like

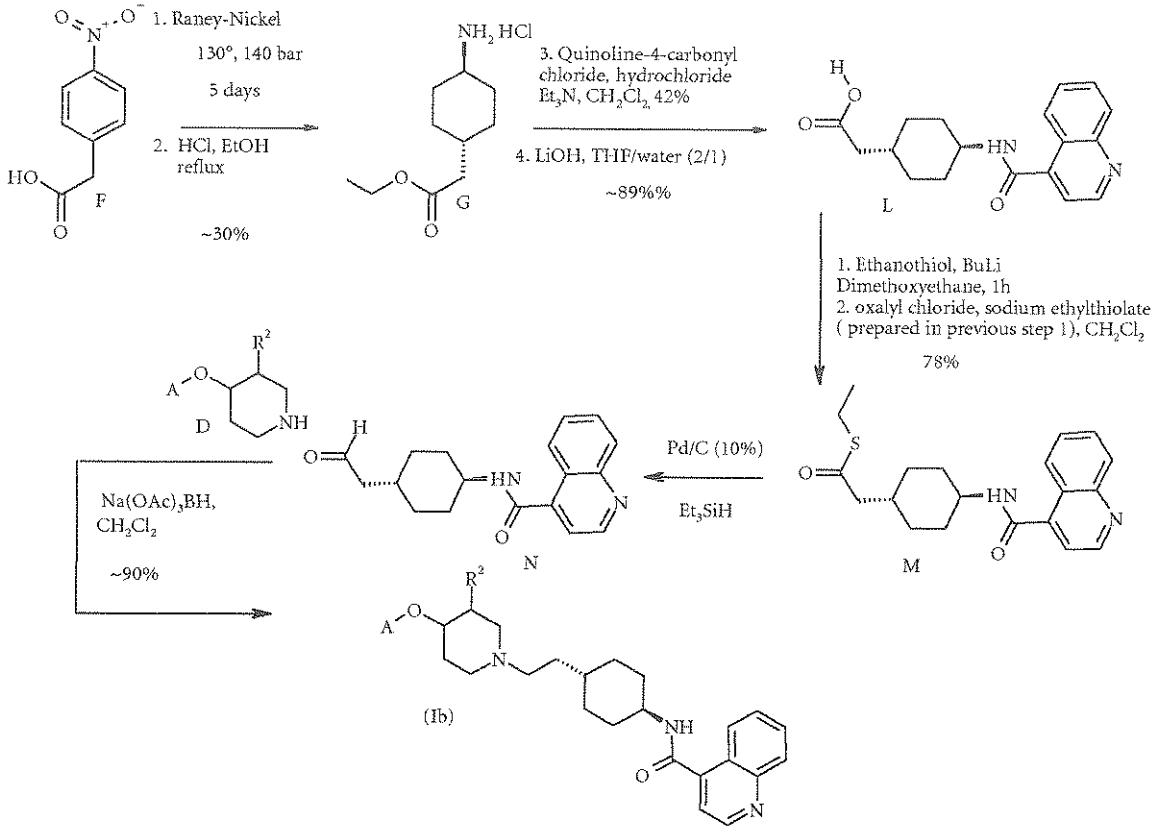
dimethylaminopyridine and reduction with diisobutylaluminium hydride (DIBAL-H) in an appropriate solvent such as e.g. toluene at -78 °C gives the aldehyde H which can be used without purification on the next step. Reductive amination of aldehyde H with aryl or heteroaryl piperidin-4-yloxy compounds of formula D either commercially available or accessible by methods described in references, by methods described in this patent or by methods known in the art, in the presence of a solvent like 1,2-dichloroethane and a reducing agent such as sodium triacetoxy borohydride yields intermediate J. Removal of the Boc protective group under acidic conditions such as trifluoroacetic acid in a suitable solvent such as e.g. THF yields the *trans*-amino cyclohexyl ethyl intermediate K (usually the TFA salt). The coupling of the amine intermediate K with carboxylic acids (either commercially available or accessible by methods described in references or by methods known in the art) is widely described in the literature (e.g. Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999) and can be accomplished by employing coupling reagents such as, e.g. N,N-carbonyldiimidazole (CDI) or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) in a suitable solvent like e.g. dimethylformamide (DMF) or dioxane in the presence of a base (e.g. triethylamine or diisopropylethylamine) to yield compounds of formula (I). In other cases an acid chloride can also be used in the presence of a base (e.g. triethylamine or diisopropylethylamine) in a solvent like dichloromethane.

Scheme 5



In other embodiments the intermediate K can also react with an isocyanate (when $R^c = H$) or a reactive intermediate ($R^c \neq H$) such as an appropriate acid chloride or a para nitro carbamate prepared by methods known in the art on the presence of a suitable solvent like, e.g. acetonitrile or dichloromethane in the presence of a base (e.g. triethylamine or diisopropylethylamine) to obtain a compound of the formula (Ia) as described on scheme 5 above.

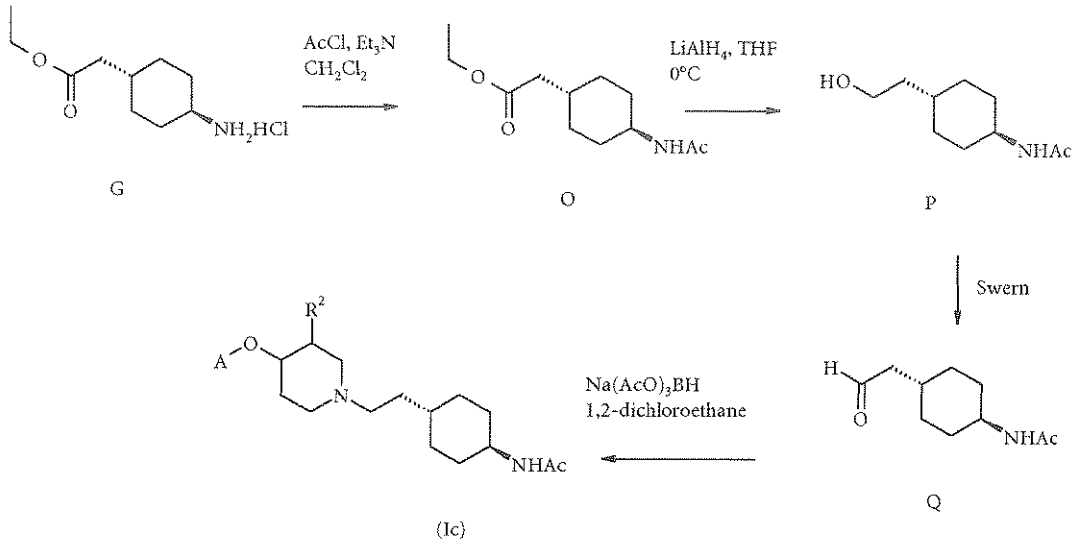
Scheme 6



In some embodiments the aryl or heteroaryl piperidin-4-yloxy compounds of formula D can be coupled in a reductive amination step with a more elaborated aldehyde N according to scheme 6. In some cases the quinoline-4-carboxylic acid [4-(2-oxo-ethyl)-cyclohexyl]-amide was used. The preparation of quinoline-4-carboxylic acid [4-(2-oxo-ethyl)-cyclohexyl]-amide N is described on scheme 6 starting from 4-nitro-phenylacetic acid F that is hydrogenated as already described on scheme 3 using raney nickel and preparing the *trans*-amino ethyl ester chloride G as already also described on scheme 3. In this case instead reacting G with tert-butyl dicarbonate, the amine hydrochloride can be reacted with quinoline-4-carbonyl chloride in the presence of a base such as triethylamine in a solvent such as dichloromethane to obtain *trans*-{4-[(quinoline-4-carbonyl)-amino]-cyclohexyl}-acetic acid ethyl ester. Hydrolysis of the ester function under acidic or basic conditions such as lithium hydroxide in a solvent mixture such as THF:water gives the corresponding carboxylic acid L. The preparation of acid derivatives in order to make reductions is known in literature (e.g. T. Fukuyama et. al., Synthesis 2000, 8, 1121-1123). In this case reaction of the carboxylic acid with sodium ethylthiolate prepared previously from ethanothiol and a base such as butyllithium in a solvent such as dimethoxyethane yields *trans*-{4-[(quinoline-4-carbonyl)-amino]-cyclohexyl}-thioacetic acid S-ethyl ester M that can be reduced with palladium on charcoal and triethylsilane in

a solvent mixture like acetone/methylenchloride (1:1) to obtain the desired *trans*-quinoline-4-carboxylic acid [4-(2-oxo-ethyl)-cyclohexyl]-amide N that can be used in a reductive amination using a reducing agent such as sodium triacetoxy borohydride in a solvent such as dichloromethane to obtain directly *trans*-quinoline-4-carboxylic acid (4-{2-[(heteroaryl or phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide (Ib).

Scheme 7



Acetic acid amide derivatives of structure (Ic) can be conveniently prepared according to scheme 7 starting from compound G. The reaction sequence involves in a first step the treatment of compound G with AcCl in presence of a base such as Et_3N in a solvent such as CH_2Cl_2 to obtain a compound of formula O. Reduction with a reagent such as $LiAlH_4$ in a solvent such as CH_2Cl_2 at 0 °C provides a compound of formula P. Among several oxidation conditions known in the literature, the *Swern* oxidation(A. Mancuso, D. Swern, *Synthesis* 1981, 165-185) of alcohol P provides intermediate Q. Reaction of aldehyde Q with an appropriate substituted piperidine in the presence of a reducing agent such as $Na(AcO)_3BH$ in a solvent such as 1,2-dichloroethane provides compounds of formula (Ic).

The ability of the compounds to bind to the 5-HT_{2A}, D_3 and D_2 receptors was determined using radioligand binding to cloned receptors selectively expressed in HEK-293 EBNA cells.

Membrane preparation for human D_2, human D_3 and human 5-HT_{2A} receptors

HEK-293 EBNA cells were transiently transfected with expression plasmids encoding for the human D_2 or D_3 dopamine- or for the human 5-HT_{2A} serotonin receptor, respectively. The cells were harvested 48 h post-transfection, washed three times

with cold PBS and stored at -80 °C prior to use. The pellet was suspended in cold 50 mM Tris-HCl buffer containing 10 mM EDTA (pH 7.4) and homogenized with a Polytron (Kinematica AG, Basel, Switzerland) for 20-30 sec at 12.000 rpm. After centrifugation at 48.000 X g for 30 min at 4 °C, the pellet was resuspended in cold 10 mM Tris-HCl buffer containing 0.1 mM EDTA (pH 7.4), homogenized, and centrifuged as above. This pellet was further resuspended in a smaller volume of ice cold 10 mM Tris-HCl buffer containing 0.1 mM EDTA (pH 7.4) and homogenized with a Polytron for 20-30 sec at 12.000 rpm. The protein content of this homogenate was determined with the Bio-Rad (Bradford) Protein Assay (Biorad Laboratories GmbH, München, Germany) according to the instructions of the manufacturer using gamma globulin as the standard. This homogenate was stored at -80 °C in aliquots and thawed immediately prior to use.

Radioligand binding assay conditions

Aliquots of membrane preparations were thawed at RT, resupended in assay buffer (D_2, D_3: 50 mM Tris-HCl, 120 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$, pH=7.4; 5-HT_{2A}: 50 mM Tris-HCl, 10 mM $MgCl_2$, 1 mM EGTA, pH=7.4), homogenized with a Polytron for 20-30 sec at 12.000 rpm and adjusted to a final concentration of approximately 7.5 µg protein / well (D_2, D_3) and 15 µg protein / well (5-HT_{2A}), respectively.

The binding affinity (Ki) of the compounds was determined using radioligand binding. Membranes were incubated in a total volume of 200 µl with a fixed concentration of radioligand (final concentration approximately 0.7 nM [^{3}H]-spiperone for D_2, 0.5 nM [^{3}H]-spiperone for D_3, and 1.1 nM [^{3}H]-ketanserin for 5-HT_{2A}) and ten concentrations of test compound in ranging between 10 µM –0.1 nM for 1 h at RT. At the end of the incubation, the reaction mixtures were filtered on to unifilter 96-well white microplates with bonded GF/C filters (Packard BioScience, Zürich, Switzerland; preincubated for 1 h in 0.1% polyethylenimine (PEI) in assay buffer) with a Filtermate 196 harvester (Packard BioScience) and washed 3 times with cold assay buffer. The nonspecific binding was determined with equally composed reaction mixtures in the presence of 10 µM unlabelled spiperone. Per well 45 µl of Microscint 40 (Perkin Elmer, Schwerzenbach, Switzerland) was added, plates for sealed, shaken for 20 min and counted for 3 min on a Topcount Microplate Scintillation Counter (Canberra Packard SA, Zürich, Switzerland) with quenching correction.

Data calculation

The CPM value for each duplicate of a concentration of competing compound was averaged (y1), then the % specific binding was calculated according to the equation (((y1 - non-specific)/(total binding-non-specific))x100). Graphs were plotted with the % specific binding using XLfit, a curve fitting program that iteratively plots the data using Levenburg Marquardt algorithm. The single site competition analysis equation used was $y = A + ((B-A)/(1+((x/C)^D)))$, where y is the % specific binding, A is the minimum y, B is the maximum y, C is the IC_{50}, x is the $\log_{10}$ of the concentration of the competing compound and D is the slope of the curve (the Hill Coefficient). From these curves the IC_{50} (inhibition concentration at which 50% specific binding of the radioligand was displaced) and Hill coefficient were determined. The affinity constant (Ki) was calculated using the Cheng-Prusoff equation $Ki = (IC_{50}/1+([L]/Kd)$, where [L] is the concentration of radioligand and Kd is the dissociation constant of the radioligand at the receptor as determined by the saturation isotherm.

The compounds of the present invention are selective dual modulators of the serotonin 5-HT_{2a} and dopamine D_3 receptors as this is shown with the activity table hereinafter which gives the Ki values in nM for the serotonin 5-HT_{2a}, dopamine D_3 and dopamine D_2 receptors for some examples of the compounds of the present invention:

Activity table

Example	3	11	18	51
Ki(nM) $D_3/5HT_{2A}/D_2$	48/22/1474	17/2/321	5/2/604	29/36/638
Example	8	13	19	62
Ki(nM) $D_3/5HT_{2A}/D_2$	50/31/843	14/3/790	12/3/683	100/43/3323
Example	9	15	21	72
Ki(nM) $D_3/5HT_{2A}/D_2$	14/13/574	17/2/556	3/2/697	5/9/319

Example	10	16	24	74
Ki(nM) $D_3/5HT_{2A}/D_2$	16/22/592	11/5/553	8/3/453	208/60/3004

The compounds of formula I and pharmaceutically acceptable salts thereof 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. However, the administration can 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 pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, 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.

As mentioned earlier, medicaments containing a compound of formula I or pharmaceutically acceptable salts thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable

substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The following examples are provided to further elucidate the invention:

Example 1

1H-Indole-2-carboxylic acid *trans*-(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Intermediate C

1.1 4-(4-Fluoro-phenoxy)-piperidine 1-carboxylic acid tert-butyl ester

To a solution of triphenyl phosphine (7.7 g, 29 mmol), in tetrahydrofuran (40 mL), diethylazodicarboxylate (5.12 g, 29 mmol) was added and the solution was stirred for 20 minutes. 4-Fluorophenole (3 g, 27 mmol) was added and the mixture was stirred for another 20 minutes at 0 °C. N-Boc-4-hydroxypiperidine (5.9 g, 29 mmol) was added dissolved in tetrahydrofuran (20 mL) and the mixture was stirred at room temperature overnight. Water was added and the solution was extracted three times with dichloromethane. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered and evaporated. The crude product was purified by flash-chromatography on silica gel with hexane:ethyl acetate (1:0 to 1:1) to give 4.8 g (60%) of the product as a white solid. MS (m/e): 296.3 ($M-H^+$).

Intermediate D

1.2 4-(4-Fluoro-phenoxy)-piperidine

2 g (7 mmol) of 4-(4-fluoro-phenoxy)-piperidine 1-carboxylic acid tert-butyl ester was solved in dichloromethane (12 mL) and trifluoroacetic acidwas added at 0 °C (6.17 mL, 54 mmol) and the mixturewas stirred at room temperature overnight. $NaHCO_3$ was slowly added until pH 9 and the mixture extracted 3 times with dichloromethane and

ethyl acetate. The solvent was evaporated to yield 1.81 g (58.5 mmol, 85%) of a white solid that was used without purification on the next steps. MS (m/e): 196.3 ($M+H^+$).

1.3 *trans*-(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester

Intermediate G

trans-(4-Amino-cyclohexyl)-acetic acid ethyl ester

Step 1.

(4-Nitro-phenyl)-acetic acid (50 g, 276 mmol) was added to a stirred solution of 22.08 g of 50% sodium hydroxide solution in 450 mL deionizated water. The clear yellow solution was transferred into a high-pressure autoclave that it charged with 30 g (511 mmol) of water-wet sponge nickel catalyst. The autoclave was sealed, flushed with nitrogen and then pressurized to 115 bar with hydrogen. The reaction mixture was stirred and heated to 125 °C for 48 h. At that time the autoclavewas cooled, vented and charged under nitrogen with another 30 g (511 mmol) of the sponge nickel catalyst. The autoclave was flushed again with nitrogen and then pressurized to 115 bar and the vesselwas heated to 130 °C while stirring (a maximum pressure of 130 bars was observed). Hydrogenation was continued for 5 days to 130 °C. The autoclave was then cooled, vented and flushed with nitrogen and the contents are removed and filtered through filter aid to remove catalyst. After removal of the solvent 74 g of crude material was obtained. The intermediatedwas used directly in the next step without purification. MS (m/e): 158.3 ($M+H^+$).

step 2

A solution of *trans*-(4-amino-cyclohexyl)-acetic acid (74 g, 476 mmol) was adjusted to pH 5 with 25% HCl. The mixture was evaporated to dryness and dried under vacuum overnight. The residue was suspended in 146 mL of a 6.5 N ethanolic HCl solution and 0.6 L of ethanol was added to the mixture. After 4 h refluxing, the mixture was cooled and filtered and the filtrate was concentrated to dryness under vacuum. The residue was dissolved in ethanol, treated with ether and cooled overnight in the refrigerator to give *trans*-(4-amino-cyclohexyl)-acetic acid ethyl ester hydrochloride (19.7 g, 32% on the two steps) as a white solid which was filtered and dried under vacuum. MS (m/e): 186.1 ($M+H^+$).

Intermediate H

Step 1

trans-(4-tert-Butoxycarbonylamino-cyclohexyl)-acetic acid ethyl ester

To a solution of *trans*-(4-amino-cyclohexyl)-acetic acid ethyl ester (1.28 g, 7 mmol), in dichloromethane (15 mL), di-tert-butyl-dicarbonate (2,26 g, 10 mmol), triethylamine (0.699 mL, 7 mmol) and 4-dimethylaminopyridine (0.042 mL, 0.35 mmol) were added. The mixture was stirred for 8 h until TLC indicated completion of the reaction. Water was added and the solution was extracted three times with dichloromethane. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered and evaporated. The crude product was purified by flash-chromatography on silica gel with hexane:ethyl acetate (4:2 to 3:2) to give 1.2 g (60%) of the product as a white solid. MS (m/e): 284.4 ($M-H^+$).

Step 2

trans-[4-(2-Oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester

To a solution of *trans*-(4-tert-butoxycarbonylamino-cyclohexyl)-acetic acid ethyl ester (1.04 g, 4 mmol), in toluene (10 mL) at -78 °C a 1.2 M solution of DIBAL-H (5.1mL, 6 mmol) in toluene was added. The mixture was stirred at -78 °C until TLC after 0.5 h indicated completion of the reaction. Water was added and the solution was extracted three times with dichloromethane. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered and evaporated. The crude product was used without purification on the next step. MS (m/e): 242.3 ($M+H^+$).

Intermediate J

trans-(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester

A mixture of 4-(4-fluorophenoxy) piperidine (0.150 g, 0.485 mmol), *trans*-[4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester (0.117 g, 0.48 mmol), in 1, 2 dichloroethane (3 mL) and methanol (0.500 mL) was stirred for 4 h at room temperature and sodium triacetoxyborohydride (0.175 g, 0.829 mmol) was added and the resulting solution was stirred for 12 hours until the TLC indicated completion of the reaction. The mixture was filtrated and concentrated to dryness and purified with column chromatography on silica gel using CH_2Cl_2 –CH_2Cl_2 /MeOH (1-9:1). The product fractions were concentrated to give 0.176 g (0.45 mmol, 92.5% yield) of a light yellow solid. MS (m/e): 393.4 ($M+H^+$).

Intermediate K

1.4 *trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine trifluoroacetate

0.155 g (0.368 mmol) of *trans*-(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester was solved in dichloromethane (2 mL) and trifluoroacetic acidwas added at 0 °C (0.230 mL, 3 mmol) and the mixturewas stirred at room temperature overnight. $NaHCO_3$was slowly added until pH 9 and the mixture extracted 3 times with dichloromethane and ethyl acetate. The solvent was evaporated to yield 0.160 g (0.368 mmol, 100%) of a white solid that was used without purification on the next steps. MS (m/e): 321.4 ($M+H^+$).

1.5 1H-Indole-2-carboxylic acid trans-(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

1H-Indole-2-carboxylic acid (0.006 g, 0. 037 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate (0.011 g, 0.034 mmol) and (0.02 mL, 0.102 mmol) of N-ethyldiisopropylamine were stirred in 0.5 mL of DMF for 0.5 h at room temperature and *trans*-4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine trifluoro-acetic acid salt (0.015 g, 0.034 mmol) was added. The mixture was stirred for 12 hours at room temperature. The mixture was concentrated to dryness and the residue was taken up on methanol and purified with preparative HPLC on reversed phase eluting with acetonitrile/water. The combined product containing fractions were evaporated under reduced pressure to yield 0.009 g of a off-white solid (0.019 mmol, 52.4%). MS (m/e): 464.2 ($M+H^+$).

According to the procedure described for the synthesis of example 1 further derivatives have been synthesized from the respective *trans*-4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and the corresponding acid. They comprise examples 1 to 7.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
1	1H-Indole-2-carboxylic acid *trans*-(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-	463.5	*trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-	464.2

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
	cyclohexyl)-amide		cyclohexylamine and 1H-Indole-2-carboxylic acid	
2	Tetrahydro-pyran-4-carboxylic acid (*trans*-4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	432.6	*trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and tetrahydro-pyran-4-carboxylic acid	433.4
3	N-(*trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide	406.53	*trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 3-methoxy-propionic acid	407.4
4	4-Chloro-N-*trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide	459.0	*trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 4-chloro benzoic acid	459.4
5	N-*trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide	506. 6	*trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzoic acid	507.2
6	Cyclopropanecarboxylic acid (*trans*-4-{2-[4-(4-fluoro-phenoxy)-	388.5	*trans* 4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-	

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
	piperidin-1-yl]-ethyl}-cyclohexyl)-amide		cyclohexylamine and Cyclopropanecarboxylic acid	389.3
7	N-(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methanesulfonyl-benzamide	502.6	*Trans* 4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 4-methanesulfonyl-benzoic acid	503.1

Example 8

Trans N-(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

Trans-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine (intermediate K, example 1.4) (0.120 g, 0.276 mmol) was suspended in dichloromethane (2.4mL) and triethylaminewas added (0.964 mL, 0.690 mmol) followed by acetylchloride (0.021 mL, 0.303 mmol) and the mixture was stirred for 2 hours at room temperature until TLC indicated the end of the reaction. The solvent was removed and DMF (0.8 mL) was added and the solution was purified with preparative HPLC on reversed phase eluting with acetonitrile/water (0.05% Et_3N). The combined producted fractions were evaporated under reduced pressure to yield 0.016 g of a off-white solid (0.045 mmol, 16.3%). MS (m/e): 363.3 $(M+H^+)$

Example 9

*Trans*1-(4-Chloro-phenyl)-3-(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-urea

Trans-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine, trifluroacetic acid salt (intermediate K, example 1.4) (0.030g, 0.07 mmol) was suspended in acetonitrile (0.600mL) and 4-chlorophenyl isocyanate was added (0.012 g, 0077 mmol) and the mixture was stirred for 2 hours at room temperature until TLC indicated the end of the reaction. The solvent was removed and the crude was purified with chromatography eluting with dichloromethane/methanol (1/0 to 9/1). The combined

product fractions were evaporated under reduced pressure to yield 0.020g of a white solid (0.042 mmol, 60 %). MS (m/e): 474.1 ($M+H^+$)

According to the procedure described for the synthesis of example 9 further derivatives have been synthesized from the respective *Trans*-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yl}-(4-fluoro-phenyl)-methanone and the corresponding isocyanate. They comprise examples 9 to 10.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
9	1-(4-Chloro-phenyl)-3-*trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-urea	474.02	*Trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 4-chlorophenyl isocyanate	474.1
10	1-*Trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-p-tolyl-urea	453.6	*Trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and p-tolyl-isocyanate	454.5

Example 11

Quinoline-4-carboxylic acid trans (4-{2[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Intermediate J

11.3 *Trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester

According to the synthesis of intermediate J, example 1, the title compound was prepared from 4-(2,3-Dichloro-phenoxy)-piperidine (intermediate D, example 1.2) (0.600 g, 1. 7 mmol), *Trans*-[4-(2-Oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester (0.506g, 2 mmol) (intermediate H, example 1) and sodium triacetoxyborohydride

(0.666g, 3mmol) in 1,2-dichloroetane (8 mL).The mixture was filtrated and concentrated to dryness and purified with column chromatography on silica gel using CH_2Cl_2 –CH_2Cl_2 /MeOH (1-9:1). The product fractions were concentrated to give 0.696 g (1.53 mmol, 87.5% yield) of a light yellow solid. MS (m/e): 467.3 ($M+H^+$).

Intermediate K

11.4 *Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; trifluoro-acetic acid salt

According to the synthesis of intermediate K, example 1.4, the title compound was prepared from 0.695g (1.48 mmol) of *Trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester in dichloromethane (8 mL) and trifluoroacetic acid (1.05 mL, 14 mmol) to yield 0.603g (1.3 mmol, 84.1%) of the title compound as a white solid that was used without purification on the next steps. MS (m/e): 355.3 ($M+H^+$).

11.5 Quinoline-4-carboxylic acid *trans*(4-{2[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Quinoline-4-carboxylic acid (0.020 g, 0.115 mmol), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate (0.035 g, 0.106 mmol) and (0.05 mL, 0.318 mmol) of N-ethyldiisopropylamine were stirred in 0.5 mL of DMF for 0.5 h at room temperature and *Trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; trifluoro-acetic acid salt (0.050 g, 0.106 mmol) was added. The mixture was stirred for 12 hours at room temperature. The mixture was concentrated to dryness and the residue was taken up on methanol and purified with preparative HPLC on reversed phase eluting with acetonitrile/water. The combined producted fractions were evaporated under reduced pressure to yield 0.054 g of a off-white solid (0.101 mmol, 54.9%). MS (m/e): 510.2 ($M+H^+$).

According to the procedure described for the synthesis of example 11.5 further derivatives have been synthesized from the respective *Trans*4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; trifluoro-acetic acid salt and the corresponding acid. They comprise examples 11 to 18

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
11	Quinoline-4-carboxylic acid *trans*(4-{2[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	510.2	*Trans*4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and Quinoline-4-carboxylic acid	510.4
12	N-*trans*(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methanesulfonyl-benzamide	537.09	*Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 4-methanesulfonyl-benzoic acid	538.2
13	N- *trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide	440.9	*Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 3-Methoxy-propionic acid	441.0
14	4-Chloro-N-*trans* (4-{2-[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide	493.45	*Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 4-Chloro benzoic acid	493.1
15	Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2-chloro-4-fluoro-phenoxy)-	467.02	*Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-	467.0

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
	piperidin-1-yl]-ethyl}-cyclohexyl)-amide		cyclohexylamine and Tetrahydro-pyran-4-carboxylic acid	
16	N-*trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide	541.06	*Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzoic acid	541.1
17	Cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	422,9	*Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and Cyclopropanecarboxylic acid	423.3
18	N- *trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-propionamide	410.9	*Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and propionic acid	411.0

Example 19

N-trans (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

According to the synthesis of N-*Trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide (example 8), the title compound was prepared from *Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and acetylchloride MS (m/e): 397.0 $(M+H^+)$.

Example 20

Trans 1-(4- {2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(4-chloro-phenyl)-urea

According to the synthesis of *Trans* 1-(4-Chloro-phenyl)-3-(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-urea (example 9) the title compound was prepared from *Trans* 1-(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 4-chlorophenyl isocyanate . MS (m/e): 508.3 $(M+H^+)$.

According to the procedure described for the synthesis of example 20 further derivatives have been synthesized from the respective *Trans*-1-(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and the corresponding isocyanate. They comprise examples 20 to 21.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
20	1- *trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(4-chloro-phenyl)-urea	508.4	*Trans* 4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and 4-chlorophenyl isocyanate	508.3
21	1- *trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-p-tolyl-urea	488.05	*Trans*-4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and p-tolyl-isocyanate	488.2

Example 22

Tetrahydro-pyran-4-carboxylic acid trans (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Intermediate J

22.3 *Trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester

According to the synthesis of *Trans*-(4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester (intermediate J, example 1.3) the title compound was prepared from (2,4-Difluoro-phenoxy)-piperidine and *Trans*-[4-(2-Oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester with sodium triacetoxyborohydride in 1,2-dichloroetane. MS (m/e): 439.4 ($M+H^+$).

Intermediate K

22.4 *Trans* 4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; compound with trifluoro-acetic acid

According to the synthesis of *Trans* 4-{2-[4-(4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine (example 1.4) the title compound was prepared from *Trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester and trifluoroacetic acid . MS (m/e): 339.3 ($M+H^+$).

22.5 Tetrahydro-pyran-4-carboxylic acid trans (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

According to the synthesis of 1H-Indole-2-carboxylic acid *trans*-(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide (example 1) the title compound was prepared from *Trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; trifluoro-acetic acid salt and Tetrahydro-pyran-4-carboxylic acid using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate and N-ethyldiisopropylamine in DMF . The residue was taken up on methanol and purified with preparative HPLC on reversed phase eluting with acetonitrile/water. MS (m/e): 451.3. ($M+H^+$).

According to the procedure described for the synthesis of example 39 further derivatives have been synthesized from the respective *Trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine and the corresponding acid.. They comprise examples 22 to 24.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
22	Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	450.5	*Trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; trifluoroacetic acid salt and Tetrahydro-pyran-4-carboxylic acid	451.3
23	Quinoline-6-carboxylic acid *trans* (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	493.6	*Trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; trifluoroacetic acid salt and Quinoline-6-carboxylic acid	494.5
24	Quinoline-4-carboxylic acid *trans* (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	493.5	*Trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; trifluoroacetic acid salt and Quinoline-4-carboxylic acid	494.4

Example 25

N-Trans (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

According to the synthesis of N-*Trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide (example 8), the title compound was prepared from *Trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexylamine; trifluoroacetic acid salt and acetylchloride MS (m/e): 381.3 $(M+H^+)$.

Example 26

Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Intermediate C

26.1 4-(2-Cyano-4-fluoro-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester

2-5-Difluorobenzonitrile (1.00 g, 7.2mmol) was added at room temperature to a stirred mixture under Argon of sodium hydride (55%, 207 mg, 9 mmol) in DMF (10 ml). 4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester (3.32 g, 17 mmol) was added in portions. The resulting mixture was stirred several hours at 50 °C before partitioning it between H_2O and EtOAc. The organic layer was washed with sat. aq. NH_4Cl sol. and brine and dried over $MgSO_4$. Evaporation of the solvent yielded 2.24 g (97.2%, 7 mmol) of a light brown solid. MS (m/z): 321.1 ($M+H^+$).

Intermediate D

26.2 5-Fluoro-2-(piperidin-4-yloxy)-benzonitrile; hydrochloride

A solution 4-(2-Cyano-4-fluoro-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester (2.2 g, 0.7 mmol) in CH_2Cl_2 (20 ml) was treated with sat. HCl sol. in Et_2O (10 ml). After 3 h the formed solid was collected by filtration and washed with Et_2O to yield 1.7 g (95%, 0.68 mmol) of a light brown solid. MS (m/z): 221.3 ($M+H^+$)

26.3 *Trans* (4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester

Prepared in analogy to example 1 (1.3) starting from 5-Fluoro-2-(piperidin-4-yloxy)-benzonitrile; hydrochloride and *Trans*-[4-(2-Oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester with sodium triacetoxyborohydride in 1,2-dichloroetane. MS (m/e): 446.3 ($M+H^+$).

26.4 *Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile; compound with trifluoro-acetic acid

Prepared in analogy to example 1 (1.4) starting from *Trans* (4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester and trifluoroacetic acid MS (m/e): 346.2 ($M+H^+$).

26.5 Cyclobutanecarboxylic acid (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Prepared in analogy to example 1 (1.5) from *Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile; trifluoro-acetic acid salt and Cyclobutanecarboxylic acid using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate and N-ethyldiisopropylamine in DMF. The residue was taken up on methanol and purified with preparative HPLC on reversed phase eluting with acetonitrile/water. MS (m/e): 428.0. $(M+H^+)$.

Using the same procedure further derivatives have been synthesized from the respective *Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and the corresponding acid.. They comprise examples 26 to 33.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
26	Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	427.5	*Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and Cyclobutanecarboxylic acid	428.0
27	Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	457.5	*Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and Tetrahydro-pyran-4-carboxylic acid	458.3
28	4-Chloro-N-trans (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide	484.0	*Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and 4-Chloro benzoic acid	484.3
29	N-*Trans* (4-{2-[4-(2-Cyano-4-fluoro-	479.6	*Trans* 2-{1-[2-(4-Amino-cyclohexyl)-	480.3

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
	phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methoxy-benzamide		ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and 4-Methoxy-benzoic acid	
30	N-*Trans* (4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide	413.5	*Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and 3-Methoxy-propionic acid	414.3
31	Cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	431.5	*Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and Cyclopropanecarboxylic acid	432.2
32	2-Methyl-cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	427.5	*Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and 2-Methyl-cyclopropanecarboxylic	428.4
33	Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	455.6	*Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile and Thiophene-2-carboxylic	456.3

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
			acid	

Example 34

Trans N-(4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

According to the synthesis of N-*Trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide (example 8), the title compound was prepared from *Trans* 2-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-fluoro-benzonitrile; trifluoroacetic acid salt and acetylchloride MS (m/e): 381.3 ($M+H^+$).

Example 35

Trans N-(4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-2,2,2-trifluoro-acetamide

The title compound was obtained as a by-product from the reaction of *Trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine; trifluoroacetic acid salt and acetylchloride (example 34) MS (m/e): 442.3 ($M+H^+$).

Example 36

Cyclobutanecarboxylic acid trans (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

According to the synthesis of 1H-Indole-2-carboxylic acid *trans*-(4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide (example 1) the title compound was prepared from *Trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Cyclobutanecarboxylic acid using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate and N-ethyldiisopropylamine in DMF . The residue was taken up on methanol and purified with preparative HPLC on reversed phase eluting with acetonitrile/water. MS (m/e): 453.0. ($M+H^+$).

Using the same procedure further derivatives have been synthesized from the respective *Trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and the corresponding acid. They comprise examples 36 to 39.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
36	Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	453.4	*Trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Cyclobutanecarboxylic acid	453.0
37	*Trans* N-(4-{2-[4-(2,3-Dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide	457.4	*Trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and 3-methoxy-propionic acid	457.2
38	Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	481.4	*Trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Thiophene-2-carboxylic acid	481.1
39	Tetrahydro-pyran-4-carboxylic acid trans (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	483.4	*Trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Tetrahydro-pyran-4-carboxylic acid	483.3

Example 40

N-Trans (4-{2-[4-(2,3-Dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

According to the synthesis of N-*Trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide (example 8), the title compound from the reaction of *Trans*

(4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and acetylchloride. MS (m/e): 415.3 ($M+H^+$).

Example 41

Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

According to the synthesis of example 1 the title compound was prepared from *Trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Cyclobutanecarboxylic acid. Preparative HPLC on reversed phase eluting with acetonitrile/water yielded the title compound. MS (m/e): 471.0 ($M+H^+$).

Using the same procedure further derivatives have been synthesized. They comprise examples 41 to 45.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
41	Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	471.4	*Trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Cyclobutanecarboxylic acid.	471.0
42	Tetrahydro-furan-2-carboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	487.4	*Trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Tetrahydro-furan-2-carboxylic acid	487.2
43	Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	501.4	*Trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Tetrahydro-pyran-4-carboxylic acid	501.4

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
44	N-*trans* (4-{2-[4-(2,6-Dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide	475.4	*Trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and 3-methoxy-propionic acid	475.1
45	Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	499.4	*Trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Thiophene-2-carboxylic acid	499.4

Example 46

N-Trans (4-{2-[4-(2,6-Dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

According to the synthesis of N-*Trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide (example 8), the title compound was prepared from *Trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and acetylchloride. MS (m/e): 432.3 $(M+H^+)$.

Example 47

Cyclobutanecarboxylic acid trans (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

According to the synthesis of example 19 the title compound was prepared from *Trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Cyclobutanecarboxylic acid. Preparative HPLC on reversed phase eluting with acetonitrile/water yielded the title compound. MS (m/e): 439.0 $(M+H^+)$.

Using the same procedure further derivatives have been synthesized. They comprise examples 47 to 50.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
47	Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	438.5	*Trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Cyclobutanecarboxylic acid	439.0
48	Tetrahydro-furan-2-carboxylic acid *trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	454.5	*Trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Tetrahydro-furan-2-carboxylic acid	455.4
49	4-Methoxy-N-*trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide	490.5	*Trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and 4-Methoxy benzoic acid	491.2
50	4-Chloro-N-*trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide	494.9	*Trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and 4-Chloro benzoic acid	495.2

Example 51

Tetrahydro-pyran-4-carboxylic acid trans (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

According to the synthesis of example 19 the title compound was prepared from *Trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and

Tetrahydro-pyran-4-carboxylic acid. Preparative HPLC on reversed phase eluting with acetonitrile/water yielded the title compound. MS (m/e): 469.5 ($M+H^+$).

Using the same procedure further derivatives have been synthesized. They comprise examples 51 to 56.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
51	Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	468.5	*Trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Tetrahydro-pyran-4-carboxylic acid	469.5
52	Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	438.5	*Trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Cyclobutanecarboxylic acid	439.0
53	2-Methyl-cyclopropanecarboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	438.5	*Trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and 2-Methyl-cyclopropanecarboxylic acid	439.5
54	4-Methoxy-N- *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide	490.5	*Trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and 4-Methoxy benzoic acid	491.2

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
55	4-Chloro-N-*trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide	494.9	*Trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and 4-Chloro benzoic acid	495.2
56	Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	466.5	*Trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and Thiophene-2-carboxylic acid	467.2

Example 57

N-trans (4-{2-[4-(2,4,5-Trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

According to the synthesis of N-*Trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide (example 8), the title compound was prepared from *Trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amine and acetylchloride. MS (m/e): 399.3 $(M+H^+)$.

Example 58

Thiophene-2-carboxylic acid trans (4-{2-[4-(4-cyano-2-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

According to the synthesis of example 1 the title compound was prepared from *Trans* 4-{1-[2-(4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-3-fluoro-benzonitrile and Thiophene-2-carboxylic acid. Preparative HPLC on reversed phase eluting with acetonitrile/water yielded the title compound. MS (m/e): 456.3 $(M+H^+)$.

Example 59

N-*trans* (4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

59.1 4-(2-Cyano-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester

2-Fluorobenzonitrile (2.00 g, 17 mmol) was added at room temperature to a stirred mixture under Ar of NaH (60%, 793 mg, 20 mmol) in DMF (20 ml). 4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester (3.32 g, 17 mmol) was added in portions. The resulting mixture was stirred several hours at 50 °C before partitioning it between H_2O and EtOAc. The organic layer was washed with sat. aq. NH_4Cl sol. and brine and dried over $MgSO_4$. Evaporation of the solvent yielded 5.65 g (quant., 0.17 mmol) of a yellow oil. MS (m/z): 303.1 ($M+H^+$).

59.2 2-(Piperidin-4-yloxy)-benzonitrile hydrochloride

A solution of 4-(2-cyano-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester (5.14 g, 17 mmol) in CH_2Cl_2 (40 ml) was treated with sat. HCl sol. in Et_2O (20 ml). After 2 h the formed solid was collected by filtration and washed with E_2O to yield 3.38 g (83%, 14 mmol) of a white powder. MS (m/z): 202.2 ($M+^+$).

59.3 *Trans*-4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester

A solution of 2-(piperidin-4-yloxy)-benzonitrile hydrochloride (255 mg, 1.07 mmol) and [*trans*-4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester (284 mg, 1.18 mmol) in 1,2-dichloroethane (5 ml) was stirred over night at room temperature. $Na(AcO)_3BH$ (340 mg, 1.60 mmol) was added and stirring continued for 24 h. The mixture was partitioned between H_2O and EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$ sol. and brine. After drying ($MgSO_4$) the solvent was evaporated and the product was purified by chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to yield 315 mg (69%, 0.74 mmol) of an off-white solid. MS (m/z): 428.4 ($M+H^+$).

59.4 2-{1-[2-(*trans*-4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-benzonitrile hydrochloride

A solution of Trans-4-{2-[4-(2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamicacid tert-butyl ester (305 mg, 0.71 mmol) in CH_2Cl_2 (3 ml) was treated with sat. HCl sol. in Et_2O (2 ml). After 2 h the formed solid was collected by filtration and washed with Et_2O to yield 249 mg (96%, 0.68 mmol) of a white powder. MS (m/z): 328.2 ($M+H^+$)

59.5 N-(*trans*-4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

To a solution of AcOH (21 mg, 0.34 mmol) in DMF (3 ml) were subsequently added TBTU (111 mg, 0.34 mmol) and Et_3N (100 mg, 0.98 mmol). After stirring 90 min at room temperature 2-{1-[2-(*trans*-4-amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-benzonitrile hydrochloride (120 mg, 0.33 mmol) was added. Stirring was continued over night, then the solvent was evaporated and the residue partitioned between H_2O and EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$ sol. and brine and dried over $MgSO_4$. Solvent evaporation afforded 102 mg (84%, 0.28 mmol) of an off-white solid. MS (m/z): 370.2 ($M+H^+$).

Using the same procedure further derivatives have been synthesized. They comprise examples 59 to 60.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
59	N-(*trans*-4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide	369.5	2-{1-[2-(*trans*-4-amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-benzonitrile hydrochloride and acetic acid	370.2
60	Quinoline-4-carboxylic acid (*trans*-4-{2-[4-(2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	482.6	2-{1-[2-(*trans*-4-amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-benzonitrile hydrochloride and quinoline-4-carboxylic acid	483.3
61	N-(*trans*-4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-ethoxy-benzamide	475.63	2-{1-[2-(*trans*-4-amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-benzonitrile hydrochloride and 4-ethoxy-benzoic acid	476.1

Example 62

N-trans-(4-{2-[4-(4-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

62.1 2-{1-[2-(*trans*-4-Amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-chloro-benzonitrile hydrochloride

Prepared in analogy to example 59.4 starting from 5-chloro-2-fluorobenzonitril. MS (m/z): 362.3 (M+H+).

62.1 N-(*trans*-4-{2-[4-(4-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

Prepared in analogy to example 59.5 from 2-{1-[2-(*trans*-4-amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-chloro-benzonitrile hydrochloride and acetic acid. MS (m/z): 404.5 (M+H+).

Using the same procedure further derivatives have been synthesized. They comprise examples 62 to 64.

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
62	N-(*trans*-4-{2-[4-(4-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide		2-{1-[2-(*trans*-4-amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-chloro-benzonitrile hydrochloride and acetic acid	404.5
63	Cyclopropanecarboxylic acid *trans* (4-{2-[4-(4-chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide		2-{1-[2-(*trans*-4-amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-chloro-benzonitrile hydrochloride and Cyclopropanecarboxylic acid	430.5

Ex. No	Systematic name	MW	Starting materials	MW found $(M+H)^+$
64	Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(4-chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide		2-{1-[2-(*trans*-4-amino-cyclohexyl)-ethyl]-piperidin-4-yloxy}-5-chloro-benzonitrile hydrochloride and Tetrahydro-pyran-4-carboxylic acid	474.3

Example 65

N-*trans* 4-{2-[4-(3-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

Intermediate O

(*trans*-4-Acetylamino-cyclohexyl)-acetic acid ethyl ester

(*trans*-4-Amino-cyclohexyl)-acetic acid ethyl ester (10.0 g, 45 mmol) was dissolved in CH_2Cl_2 (150 ml) and Et_3N and AcCl (3.89 g, 50 mmol) were added. The reaction mixture was stirred 3 h at room temperature before washing it with H_2O and brine. After drying (Na_2SO_4) the solvent was evaporated to yield 8.42 g (82 %, 37 mmol) of a white solid. MS (m/z): 228.3 ($[M+H]^+$).

Intermediate P

N-[*trans*-4-(2-Hydroxy-ethyl)-cyclohexyl]-acetamide

$LiAlH_4$ (2.10 g, 55 mmol) and THF (150 ml) were placed in a dry ballon. After cooling this mixture to 0 °C a solution of (*trans*-4-acetylamino-cyclohexyl)-acetic acid ethyl ester (8.42 g, 37 mmol) in little THF was added dropwise. The reaction was stirred 1 h before careful neutralization with H_2O (5.6 ml), 1 N NaOH (3 x 5.6 ml) and more H_2O (5.6 ml). The resulting mixture was stirred over night before filtering off the solids. Evaporation of the solvent and drying under high vacuum afforded 5.25 g (76%, 28 mmol) of a light brown solid. MS (m/z): 186.4 ($[M+H^+]$).

Intermediate Q

N-[*trans*-4-(2-Oxo-ethyl)-cyclohexyl]-acetamide

DMSO (3.68 g, 47 mmol) in CH_2Cl_2 (20 ml) was added at -78 °C to a stirred solution of oxalylchloride (2.9 g, 23 mmol) in CH_2Cl_2 (100 ml). After 1 h stirring at -78 °C a solution of N-[*trans*-4-(2-hydroxy-ethyl)-cyclohexyl]-acetamide (2.18 g, 12 mmol) in CH_2Cl_2 (80 ml) was added followed after 2 h by Et_3N (7.14 g, 71 mmol). The mixture was allowed to reach room temperature and was then diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dryed (Na_2SO_4) and the solvent was evaporated to afford the crude product. Chromatography (CH_2Cl_2/MeOH 95:5) yielded 1.75 g (81 %, 9.5 mmol) of a light brown solid. MS (m/z): 184.3 ($[M+H]^+$).

65.1 2-Chloro-6-(piperidin-4-yloxy)-benzonitrile hydrochloride

2-Chloro-6-(piperidin-4-yloxy)-benzonitrile hydrochloride was prepared in analogy to example 59.2 from 2-chloro-6-fluoro-benzonitrile and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester. White solid. MS (m/z): 237.0 ($[M+H]^+$).

65.2 N-trans (4-{2-[4-(3-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

N-[*trans*-4-(2-Oxo-ethyl)-cyclohexyl]-acetamide (intermediate Q, 111 mg, 0.60 mmol) was added to a mixture of 2-chloro-6-(piperidin-4-yloxy)-benzonitrile hydrochloride (131 mg, 0.48 mmol) in 1,2-dichloroethane (5 ml). After stirring 8 h at room temperature $Na(AcO)_3BH$ (152 mg, 0.72 mmol) was added. The reaction mixture was stirred further 7 h before treatment with aq. sat. $NaHCO_3$ sol. Extraction with CH_2Cl_2, drying over Na_2SO_4, evaporation of the solvent and chromatography (amino modified silica gel, Hept to EtOAc) afforded 114 mg (59%, 0.28 mmol) of product as a white solid. MS (m/z): 404.5 ($[M+H]^+$).

Example 66

N-trans (4-{2-[4-(3-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

66.1 4-(3-Chloro-4-fluoro-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester

DEAD (214 mg, 1.2 mmol) was added dropwise to a cooled (0 °C) mixture of 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (206 mg, 1.0 mmol), 3-chloro-4-fluorophenol (150 mg, 1.0 mmol) and PPh_3 (332 mg, 1.3 mmol) in THF (5 ml). The yellow mixture was stirred overnight at room temperature. The solvent was evaporated

and the residue purified by chromatography (Hept to Hept:EtOAc 4:1) to yield 205 mg (61%, 0.62 mmol) of product. Yellowish viscous oil. MS (m/z): 330.3 ($[M+H]^+$).

66.2 N-trans (4-{2-[4-(3-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

The title compound was prepared in analogy to example 65.2 starting from 4-(3-chloro-4-fluoro-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester. White solid. MS (m/z): 397.1 ($[M+H]^+$).

Example 67

N-trans (4-{2-[4-(2,3,4-Trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

The title compound was prepared in analogy to example 66 starting from 2,3,4-trifluorophenol. White solid. MS (m/z): 399.3($[M+H]^+$).

Example 68

Quinoline-4-carboxylic acid (4-{2-[trans 4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Intermediate C

68.1 *Trans* 4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester

Rac-cis-7-Oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid tert-butyl ester (1g, 5 mmol)was solved in dioxane (5 mL), 2-Chloro-4-Fluorophenolwas added (1.471g, 10 mmol) and sodium hydroxide (0.401g, 10 mmol). After 20 h refluxing, the mixture was cooled, ammonium chloride was added and the mixture extracted three times with ethyl acetate, the combine organic phases were dried with magnesium sulfate and concentrated under vacuum. After a flash chromatography with heptane/AcOEt 1:1 to 1:2 heptane/AcOEt a solid the title compound was obtained as solid (0.778 g, 45% yield). MS (m/e): 404.5 ($M+AcO^-$).

Intermediate D

68.2 *Trans* 4-(2-Chloro-4-fluoro-phenoxy)-piperidin-3-ol; trifluoroacetic acid salt

0.126 g (0.36 mmol) of *trans* 4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester was solved in dichloromethane (1.5 mL) and trifluoroacetic acidwas added at 0°C (0.25 mL, 3 mmol) and the mixturewas stirred at

room temperature overnight. $NaHCO_3$was slowly added until pH 9 and the mixture extracted with 3 times with dichloromethane and ethyl acetate. The solvent was evaporated to yield 0.093 g (0.26 mmol, 71%) of a white solid that was used without purification on the next steps. MS (m/e): 246.2 ($M+H^+$).

Intermediate J

68.3 *Trans* (4-{2-[(4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester

According to the synthesis of example 1, the title compound was prepared from *Trans* 4-(2-Chloro-4-fluoro-phenoxy)-piperidin-3-ol; trifluoroacetic acid salt, *Trans*-[4-(2-Oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester and sodium triacetoxyborohydride. (MS (m/e): 471.4 ($M+H^+$).

Intermediate K

68.4 *Trans* 4-{2-[4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amine

According to the synthesis of intermediate K, example 1, the title compound was prepared from *Trans* (4-{2-[(4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester in dichloromethane and trifluoroacetic acid. MS (m/e): 371.3 ($M+H^+$).

68.5 Quinoline-4-carboxylic acid (4-{2-[*trans* 4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Prepared in analogy to example 1 from *Trans* 4-{2-[4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amine.and Quinoline-4-carboxylic acid with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate (0.035 g, 0.106 mmol) and N-ethyldiisopropylamine in DMF. MS (m/e): 527. 3 ($M+H^+$).

Example 69

Quinoline-4-carboxylic acid *trans* (4-{2-[(3R,4R)-4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

69.1 (3R,4R)- 4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester

0.700 g of *Trans* 4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (example 68.1) was separated in Chiralpak AD using 10% EtOH/heptane

to obtain 0.323g of (3R,4R)- 4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester. MS 405.4($M+AcO^-$).

Quinoline-4-carboxylic acid *trans* (4-{2-[(3R,4R)-4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Prepared in analogy to example 69 from (3R,4R)- 4-(2-Chloro-4-fluoro-phenoxy)- 3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amine.and Quinoline-4-carboxylic acid with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate (0.035 g, 0.106 mmol) and N-ethyldiisopropylamine in DMF. MS (m/e): 526.3 ($M+H^+$).

Example 70

Quinoline-4-carboxylic acid *trans* (4-{2-[(3S,4S)-4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

70.1 (3S,4S)-4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester

0.700 g of *Trans* 4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (example 69.1) was separated in Chiralpak AD using 10% EtOH/heptane to obtain 0.322g of (3S,4S)-4-(2-Chloro-4-fluoro-phenoxy)-3-hydroxy-piperidine-1-carboxylic acid tert-butyl ester. MS 405.4($M+AcO^-$).

Quinoline-4-carboxylic acid *trans* (4-{2-[(3S,4S)-4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Prepared in analogy to example 69 from (3S,4S)- 4-(2-Chloro-4-fluoro-phenoxy)- 3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amine.and Quinoline-4-carboxylic acid with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate (0.035 g, 0.106 mmol) and N-ethyldiisopropylamine in DMF. MS (m/e): 526.3 ($M+H^+$).

Example 71

Quinoline-4-carboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

Intermediate G

Trans-(4-Amino-cyclohexyl)-acetic acid ethyl ester

Step 1

(4-Nitro-phenyl)-acetic acid (0.005 g, 276mmol) was added to a stirred solution of 22.08g of 50% sodium hydroxide solution in 450mL deionizated water. The clear yellow solution was *trans*ferred into a high-pressure autoclave that it charged with 30g (511 mmol) of water-wet sponge nickel catalyst. The autoclave was sealed, flushed with nitrogen and then pressurized to 115 bar with hydrogen. The reaction mixture was stirred and heated to 125°C for 48h. At that time the autoclave was cooled, vented and charged under nitrogen with another 30g (511 mmol) of the sponge nickel catalyst. The autoclave was flushed again with nitrogen and then pressurized to 115 bar and the vesselwas heated to 130°C while stirring (a maximum pressure of 130 barswas observed). Hydrogenationwas continued for 5 days to 130°C. The autoclavewas then cooled, vented and flushed with nitrogen and the contents are removed and filtered through filter aid to remove catalyst. After removal of the solvent a crude was obtained. The intermediatewas used directly in the next step without purification. MS (m/e): 158.3 ($M+H^+$)

Step 2

A solution of the *Trans*-(4-amino-cyclohexyl)-acetic acid obtained (74g, 476mmol) was adjusted to pH 5 with 25% HCl. The mixture was evaporated to dryness and dried under vacuum overnight. The residue was suspended in 146mL of a 6.5N ethanolic HCl solution and 0.6L of ethanol was added to the mixture. After 4 h refluxing, the mixture was cooled, filtered and the filtrate was concentrated to dryness under vacuum. The residue was dissolved in ethanol, treated with ether and cooled overnight in the refrigerator.to give the *Trans*-(4-Amino-cyclohexyl)-acetic acid ethyl ester hydrochloride (19.7 g, 32% on the two steps) as a white solid which was filtered and dried under vacuum. MS (m/e): 186.1 ($M+H^+$)

Intermediate L

Trans-{4-[(Quinoline-4-carbonyl)-amino]-cyclohexyl}-acetic acid

Step 1

{*Trans* -4 -[(Quinoline-4-carbonyl)-amino]-cyclohexyl}-acetic acid ethyl ester hydrochloride salt

A mixture of *Trans*-(4-Amino-cyclohexyl)-acetic acid ethyl ester hydrochloride (3.63 g, 17 mmol)was solved in dichloromethane (115mL) and quinoline-4-carbonyl chloride hydrochloridewas added (4.184 g, 18mmol) followed by the slow addition of triethylamine (11.3mL, 81mmol) at 0°C. The mixturewas stirred at room temperature

overnight and the salts obtained are removed by filtration and the filtratewas extracted. The organic layerwas washed with $NaHCO_3$ and brine. The organic phases are dried and concentrated to obtain 3.8 g of a crude. After a flash chromatography with heptane/AcOEt 4:1 to AcOEt a solid was obtained that was recrystallized with EtOAc and n-heptane to obtain the title compound as a pink solid (2.72 g, 42% yield). MS (m/e): 341.3 ($M+H^+$).

Step 2

Trans-{4-[(Quinoline-4-carbonyl)-amino]-cyclohexyl}-acetic acid

4-[(Quinoline-4-carbonyl)-amino]-cyclohexyl}-acetic acid ethyl ester hydrochloride salt (2.7 g, 8 mmol) was reacted with lithium hydroxide monohydrate (3.33g, 79 mmol) in a mixture of water (65mL) and THF (130mL) and the mixture was heated at reflux for 5 hours. A 2/3 of the mixture was evaporated and HCl 37% was added until pH 7. The mixturewas then evaporated to dryness and 30 mL of waterwas added and the suspensionwas filtered to obtain a solid that was recrystallized on toluene (2.2 g, 88.6% yield). MS (m/e): 313.1 ($M+H^+$).

Intermediate M

Trans-{4-[(Quinoline-4-carbonyl)-amino]-cyclohexyl}-thioacetic acid S- ethyl ester

2.19 g of *Trans*-{4-[(Quinoline-4-carbonyl)-amino]-cyclohexyl}-acetic acid (7 mmol) was added in 1300 mL of dichloromethane. Then 1.8 mL of oxalyl chloridewas added (21 mmol). The suspension was heated to reflux for 3 hours and then the cloudy mixturewas concentrated under vacuum. The residuewas taken up in 500 mL of dichloromethane as a suspension and (1.28 g, 21 mmol) sodium ethylthiolate freshly prepared from 1.45 mL of ethanothiol and 12.07 mL of Butyl lithium (1.6 M in toluene) at 0°C and by stirring in dimethoxyethane (20mL) for 1 h at room temperature. The reaction mixture was stirred overnight. $NaHCO_3$ was added and the organic phase was extracted three times with dichloromethane. The organic phases were dried and concentrated and the residue was chromatographied with heptane/AcOEt 1:1 to AcOEt to yield the title compound as a solid (1.97 g, 78.9% yield). MS (m/e): 357.3 ($M+H^+$).

Intermediate N

Quinoline-4-carboxylic acid *trans*-[4-(2-oxo-ethyl)-cyclohexyl]-amide

Trans-{4-[(Quinoline-4-carbonyl)-amino]-cyclohexyl}-thioacetic acid S- ethyl ester (1.87g, 5 mmol) was solved in acetone / methylene chloride (40/40 mL), 0.8g of

molecular sieves were added to the mixture and the solution was stirred fo 0.5h. Then 0.558g (1mmol) of palladium on active charcoal 10% was added followed by 1.25 mL(8 mmol) of triethyl-silane. The reaction was stirred for 1.5h at room temperature and additional 0.558g (1 mmol) of palladium on active charcoal 10% and 1.25 mL (8 mmol) of triethyl-silane were added and the stirring was continued for another hour. The mixture was filtrated through celite and the mother liquid was concentrated to obtain after chromatography using heptane/AcOEt 1:1 to AcOEt 1.1 (37.1 mmol, 70.8 % yield) of the final compound. MS (m/e): 297.3 ($M+H^+$)

Quinoline-4-carboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

4-(4-Fluoro-phenoxy)-piperidine (intermediate D, example 1) (0.015g, 0.076 mmol) was solved in 1.2-dichloromethane (0.300 mL) and Quinoline-4-carboxylic acid *trans*-[4-(2-oxo-ethyl)-cyclohexyl]-amide (0.025 g, 0.084mmol) was added .Methanol (0.100 mL) was added to improve solubility and the mixture was stirred overnight. Sodium triacetoxyborohydride (0.029, 0.137 mmol) was added to the clear solution that was stirred 10 hours at room temperature. The mixture was concentrated to dryness and the residue was taken up on methanol and purified with preparative HPLC on reversed phase eluting with acetonitrile/water. The combined producted fractions were evaporated under reduced pressure to yield 0.034 g of a white solid (0.07 mmol, 93%). MS (m/e): 476.2 ($M+H^+$)

According to the procedure described for the synthesis of example 71 further derivatives have been synthesized from the respective Quinoline-4-carboxylic acid *trans*-[4-(2-oxo-ethyl)-cyclohexyl]-amide and the corresponding Piperidin-4-yloxy-phenyl or heteroaryl compound obtained by the methods explained on this patent.

Ex. No	Systematic name	MW	Starting materials	MW found (M+H)+
71	Quinoline-4-carboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	475.6	Quinoline-4-carboxylic acid *trans*-[4-(2-oxo-ethyl)-cyclohexyl]-amide and 4-(4-Fluoro-phenoxy)-	476.2

Ex. No	Systematic name	MW	Starting materials	MW found (M+H)+
			piperidine	
72	Quinoline-4-carboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	526.5	Quinoline-4-carboxylic acid *trans*-[4-(2-oxo-ethyl)-cyclohexyl]-amide and 4-(2,3-dichloro-phenoxy)-piperidine	526.5
73	Quinoline-4-carboxylic acid *trans* (4-{2-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide	505.06	Quinoline-4-carboxylic acid *trans*-[4-(2-oxo-ethyl)-cyclohexyl]-amide and 4-(3,4-dichloro-phenoxy)-piperidine	505.3

Example 74

Quinoline-4-carboxylic acid (*trans*-4-{2-[4-(pyridin-4-yloxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide

The title compound was prepared in analogy to example 59 starting from 4-(piperidin-4-yloxy)-pyridine (CAS# 224178-65-8) and performing the amide coupling reaction with quinoline-4-carboxylic acid. Orange crystals. MS (m/z): 459.3 ($[M+H]^+$).

Example 75

N-(*trans*-4-{2-[4-(Pyridin-3-yloxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

The title compound was prepared in analogy to example 59 starting from 3-(piperidin-4-yloxy)-pyridine (CAS# 310881-48-2) and performing the amide coupling reaction with acetic acid. Off-white solid. MS (m/z): 346.2 ($[M+H]^+$).

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxide (yellow)	0.8 mg	1.6 mg
Titanium dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesiumstearate and compressed to yield

kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Sodium carbonate	to obtain a final pH of 7
Water for injection solutions	ad 1.0 ml

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents

Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg

Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titanium dioxide	0.4 mg
Iron oxide yellow	1.1 mg

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

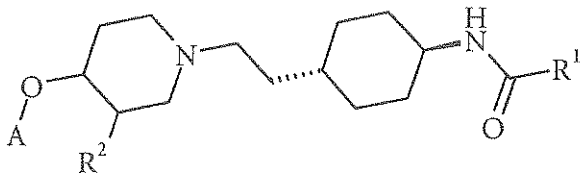
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcrystalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidone K 30	10.0 mg
Magnesium stearate	10.0 mg
Flavoring additives	1.0 mg

The active ingredient is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidone in water. The granulate is mixed with magnesium stearate and the flavoring additives and filled into sachets.

Claims

1. Compounds of the general formula I:



(I)

wherein:

A is aryl, or 5 to 12 membered heteroaryl which are optionally substituted by:
halogen,
cyano,
C_{1-6}-alkyl optionally substituted by cyano or C_{1-6}-alkoxy,
C_{1-6}-alkoxy,
$-S(O)_2-C_{1-6}$-alkyl;

R^1 is C_{1-6}-alkyl optionally substituted by:
one or more halogen, C_{1-6}-alkoxy or aryl optionally substituted by halogen,
or is C_{3-10}-cycloalkyl optionally substituted by one or more R^a,
or is 5 to 12 membered heterocycloalkyl optionally substituted by one or more R^a,
or is aryl optionally substituted by one or more R^a,
or is 5 to 12 membered heteroaryl optionally substituted by one or more R^a,
or is $-NR^bR^c$, wherein R^b is H or C_{1-6}-alkyl and wherein R^c is H, C_{1-6}-alkyl or aryl optionally substituted by one or more R^a,
wherein R^a is selected from:
halogen,
$-S(O)_2-C_{1-6}$-alkyl,
cyano,
oxo,
C_{1-6}-alkyl optionally substituted by aryl which is substituted by halogen,
C_{1-6}-haloalkyl,
C_{1-6}-haloalkoxy,
C_{1-6}-alkoxy optionally substituted by 5 to 6 membered heteroaryl which is optionally substituted by C_{1-6}-alkyl,
$-NH(CO)-C_{1-6}$-alkyl,
5 to 6 membered heterocycloalkyl, or

5 to 6 membered heteroaryl optionally substituted by C_{1-6}-alkyl or oxo;

R^2 is H or OH;

as well as pharmaceutically acceptable salts thereof.

2. The compounds of formula I according to claim 1 wherein A is aryl optionally substituted by one or more of halogen, cyano or C_{1-6}-alkyl substituted by cyano or A is 5 or 6 membered heteroaryl.

3. The compounds of formula I according to any one of claim 1 or 2, wherein R^1 is C_{1-6}-alkyl optionally substituted by one or more halogen or C_{1-6}-alkoxy.

4. The compounds of formula I according to claim 3, wherein they are selected from the group consisting of:

N- *trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;

N- *trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;

N- *trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-propionamide;

N- *trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N- *trans* (4-{2-[4-(2,4-Difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-*Trans* (4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;

N- *trans* (4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N- *trans* (4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-2,2,2-trifluoro-acetamide;

Trans N-(4-{2-[4-(2,3-Dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;

N-*Trans* (4-{2-[4-(2,3-Dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-*trans* (4-{2-[4-(2,6-Dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;

N-*Trans* (4-{2-[4-(2,6-Dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-*trans* (4-{2-[4-(2,4,5-Trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N- *trans* (4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N- *trans* (4-{2-[4-(4-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N- *trans* (4-{2-[4-(3-Chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N- *trans* (4-{2-[4-(3-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N- *trans* (4-{2-[4-(2,3,4-Trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide; and
N-(*trans*-4-{2-[4-(Pyridin-3-yloxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-acetamide

5. The compounds of formula I according to any one of claim 1 or 2, wherein R^1 is C_{3-10}-cycloalkyl optionally substituted by one or more R^a, wherein R^a is C_{1-6}-alkyl.

6. The compounds of formula I according to claim 5, wherein they are selected from the group consisting of:
Cyclopropanecarboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
2-Methyl-cyclopropanecarboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Cyclobutanecarboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
2-Methyl-cyclopropanecarboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide; and

Cyclopropanecarboxylic acid *trans* (4-{2-[4-(4-chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide.

7. The compounds of formula I according to any one of claim or 2, wherein R^1 is 5 to 12 membered heterocycloalkyl.

8. The compounds of formula I according to claim 7, wherein they are selected from the group consisting of:
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-furan-2-carboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-furan-2-carboxylic acid *trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide; and
Tetrahydro-pyran-4-carboxylic acid *trans* (4-{2-[4-(4-chloro-2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide.

9. The compounds of formula I according to any one of claim 1 or 2, wherein R^1 is aryl optionally substituted by one or more R^a, wherein R^a is selected from halogen, C_{1-6}-alkoxy, $-S(O)_2-C_{1-6}$-alkyl, 5 to 6 membered heteroaryl optionally substituted by C_{1-6}-alkyl.

10. The compounds of formula I according to claim 9, wherein they are selected from the group consisting of:

4-Chloro-N- *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

N- *trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide;

N- *trans* (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methanesulfonyl-benzamide;

N- *trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methanesulfonyl-benzamide;

4-Chloro-N- *trans* (4-{2-[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

N- *trans* (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(5-methyl-[1,2,4]oxadiazol-3-yl)-benzamide;

4-Chloro-N- *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

N-*trans* (4-{2-[4-(2-Cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-methoxy-benzamide;

4-Methoxy-N-*trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

4-Chloro-N-*trans* (4-{2-[4-(2,4,6-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

4-Methoxy-N- *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide;

4-Chloro-N-*trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-benzamide; and

N- *trans* (4-{2-[4-(2-Cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-4-ethoxy-benzamide.

11. The compounds of formula I according to any one of claim 1 or 2, wherein R^1 is 5 to 12 membered heteroaryl.

12. The compounds of formula I according to claim 11, wherein they are selected from the group consisting of:

1H-Indole-2-carboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans* (4-{2[4-(2-chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-6-carboxylic acid *trans* (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans* (4-{2-[4-(2,4-difluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2-cyano-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2,6-dichloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans* (4-{2-[4-(2,4,5-trifluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Thiophene-2-carboxylic acid *trans* (4-{2-[4-(4-cyano-2-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans* (4-{2-[4-(2-cyano-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid (4-{2-[*trans* 4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans* (4-{2-[(3R,4R)-4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans* (4-{2-[(3S,4S)-4-(2-chloro-4-fluoro-phenoxy)-3-hydroxy-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans* (4-{2-[4-(2,3-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide;

Quinoline-4-carboxylic acid *trans* (4-{2-[4-(3,4-dichloro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide; and

Quinoline-4-carboxylic acid (*trans*-4-{2-[4-(pyridin-4-yloxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-amide.

13. The compounds of formula I according to any one of claim 1 or 2, wherein R^1 is $-NR^bR^c$ wherein R^b is H and R^c is H, aryl optionally substituted by one or more R^a, wherein R^a is halogen or C_{1-6}-alkyl.

14. The compounds of formula I according to claim 13, wherein they are selected from the group consisting of:

Trans 1-(4-Chloro-phenyl)-3-*trans* (4-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-urea;

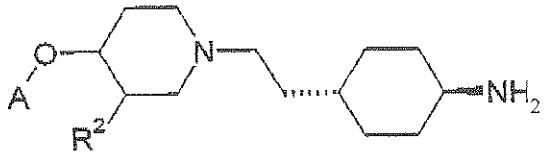
Trans 1- (4-{2-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-p-tolyl-urea;

Trans 1- (4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-p-tolyl-urea; and

Trans 1-(4-{2-[4-(2-Chloro-4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-cyclohexyl)-3-(4-chloro-phenyl)-urea.

15. A process for the preparation of compounds of formula I according to claim 1, comprising the steps of:

a) reacting a compound of the formula II:

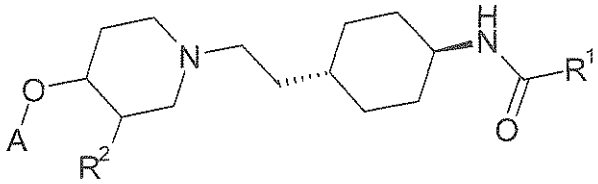


(II)

either with an acid of the formula III:

$$HOOCR^1 \qquad (III)$$

in the presence of a coupling reagent to obtain a compound of the formula I:



(I)

wherein A and R^2 are as defined in claim 1 and,

wherein R^1 is C_{1-6}-alkyl optionally substituted by one or more halogen, C_{1-6}-alkoxy, aryl optionally substituted by halogen,

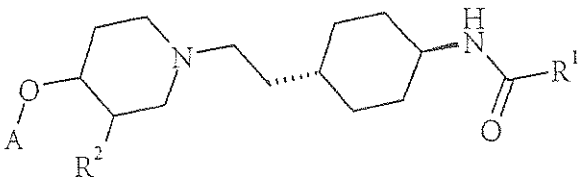
or is C_{3-10}-cycloalkyl optionally substituted by one or more R^a,

or is 5 to 12 membered heterocycloalkyl optionally substituted by one or more R^a,

or is aryl optionally substituted by one or more R^a,

or is 5 to 12 membered heteroaryl optionally substituted by one or more R^a;

or with and isocyanate or para nitro carbamate to obtain a compound of the formula I:



(I)

wherein R^1 is $-NR^bR^c$, wherein R^b is H or C_{1-6}-alkyl and wherein R^c is aryl optionally substituted by one or more R^a;

wherein R^a is as defined in claim 1,

and if desired,

converting the compound obtained into a pharmaceutically acceptable acid addition salt.

16. A medicament containing one or more compounds as claimed in any one of claims 1 to 14 and pharmaceutically acceptable excipients for the treatment and/or the prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, and psychoses comprising paranoia and delusions.

17. A compound in accordance with any one of claims 1 to 14 as well as its pharmaceutically acceptable salt for use in the treatment or prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, and psychoses comprising paranoia and delusions.

18. The use of a compound in accordance with any one of claims 1 to 14 as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and/or the prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, and psychoses comprising paranoia and delusions.

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