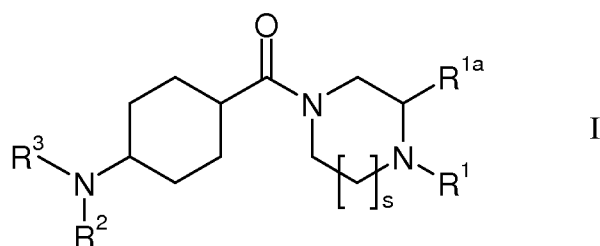


CYCLOHEXYL PIPERAZINYL METHANONE DERIVATIVES AND THEIR USE AS HISTAMINE H₃ RECEPTOR MODULATORS

The present invention is concerned with novel cyclohexyl piperazinyl methanone derivatives, their manufacture, pharmaceutical compositions containing them and their use as medicaments. The active compounds of the present invention are useful in treating obesity and other disorders.

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



wherein

s is 1 or 2;

10 R¹ is selected from the group consisting of lower alkyl, cycloalkyl, lower cycloalkylalkyl, lower cyanoalkyl, lower alkylsulfonylalkyl and tetrahydropyranyl;

R^{1a} is hydrogen or lower alkyl;

R² is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;

15 R³ is selected from the group consisting of
 -(CH₂)_m-aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl,
 20 -(CH₂)_n-heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl,

benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl,

indanyl, 1-oxo-indanyl,

-CO-(C₃-C₈)-alkyl,

5 -CO-(CH₂)_p-aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,

10 -CO-(CH₂)_q-heteroaryl, wherein q is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, and

-CO-NR⁴R⁵; or

15 R² and R³ together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring that is condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen;

R⁴ is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;

20 R⁵ is selected from the group consisting of lower alkyl, aryl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and 25 lower arylalkyl wherein the phenyl ring may be unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl;

or

30 R⁴ and R⁵ together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group, said heterocyclic ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano,

hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl, or
being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl,
5 lower alkoxy and halogen;
and pharmaceutically acceptable salts thereof.

The compounds of formula I are antagonists and/or inverse agonists at the histamine 3 receptor (H3 receptor).

Histamine (2-(4-imidazolyl) ethylamine) is one of the aminergic neurotransmitters
10 which is widely distributed throughout the body, e. g. the gastrointestinal tract (Burks 1994 in Johnson L.R. ed., Physiology of the Gastrointestinal Tract, Raven Press, NY, pp. 211 – 242). Histamine regulates a variety of digestive pathophysiological events like gastric acid secretion, intestinal motility (Leurs et al., Br J. Pharmacol. 1991, 102, pp 179-185), vasomotor responses, intestinal inflammatory responses and allergic reactions
15 (Raithel et al., Int. Arch. Allergy Immunol. 1995, 108, 127-133). In the mammalian brain, histamine is synthesized in histaminergic cell bodies which are found centrally in the tuberomammillary nucleus of the posterior basal hypothalamus. From there, the histaminergic cell bodies project to various brain regions (Panula et al., Proc. Natl. Acad. Sci. USA 1984, 81, 2572-2576; Inagaki et al., J. Comp. Neurol 1988, 273, 283 – 300).

20 According to current knowledge, histamine mediates all its actions in both the CNS and the periphery through four distinct histamine receptors, the histamine H1, H2 H3 and H4 receptors.

H3 receptors are predominantly localized in the central nervous system (CNS). As an autoreceptor H3 receptors constitutively inhibit the synthesis and secretion of
25 histamine from histaminergic neurons (Arrang et al., Nature 1983, 302, 832-837; Arrang et al., Neuroscience 1987, 23, 149-157). As heteroreceptors, H3 receptors also modulate the release of other neurotransmitters such as acetylcholine, dopamine, serotonin and norepinephrine among others in both the central nervous system and in peripheral organs, such as lungs, cardiovascular system and gastrointestinal tract (Clapham &
30 Kilpatrick, Br. J. Pharmacol. 1982, 107, 919- 923; Blandina et al. in The Histamine H3 Receptor (Leurs RL and Timmermann H eds, 1998, pp 27-40, Elsevier, Amsterdam, The Netherlands). H3 receptors are constitutively active, meaning that even without exogenous histamine, the receptor is tonically activated. In the case of an inhibitory receptor such as the H3 receptor, this inherent activity causes tonic inhibition of

neurotransmitter release. Therefore it may be important that a H3R antagonist would also have inverse agonist activity to both block exogenous histamine effects and to shift the receptor from its constitutively active (inhibitory) form to a neutral state.

The wide distribution of H3 receptors in the mammalian CNS indicates the
5 physiological role of this receptor. Therefore the therapeutic potential as a novel drug development target in various indications has been proposed.

The administration of H3R ligands - as antagonists, inverse agonists, agonists or partial agonists - may influence the histamine levels or the secretion of neurotransmitters in the brain and the periphery and thus may be useful in the treatment of several
10 disorders. Such disorders include obesity (Masaki et al; Endocrinol. 2003, 144, 2741-2748; Hancock et al., European J. of Pharmacol. 2004, 487, 183-197), cardiovascular disorders such as acute myocardial infarction, dementia and cognitive disorders such as attention deficit hyperactivity disorder (ADHD) and Alzheimer's disease, neurological disorders such as schizophrenia, depression, epilepsy, Parkinson's disease, and seizures or
15 convulsions, sleep disorders, narcolepsy, pain, gastrointestinal disorders, vestibular dysfunction such as Morbus Meniere, drug abuse and motion sickness (Timmermann, J. Med. Chem. 1990, 33, 4-11).

It is therefore an object of the present invention to provide selective, directly acting H3 receptor antagonists respectively inverse agonists. Such antagonists / inverse agonists
20 are useful as therapeutically active substances, particularly in the treatment and/or prevention of diseases which are associated with the modulation of H3 receptors.

In the present description the term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon
25 atoms, more preferably one to ten carbon atoms.

The term "lower alkyl" or "C₁-C₈-alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1 to 6 carbon atoms and particularly preferred a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of
30 straight-chain and branched C₁-C₈ alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl and ethyl and most preferred methyl.

The term "cycloalkyl" or "C₃-C₇-cycloalkyl" denotes a saturated carbocyclic group containing from 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Especially preferred is cyclopentyl.

5 The term "lower cyclolalkylalkyl" or "C₁-C₇-cycloalkyl-C₁-C₈-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by a cycloalkyl group. A preferred lower cycloalkylalkyl group is cyclopropylmethyl.

10 The term "alkoxy" refers to the group R'-O-, wherein R' is lower alkyl and the term "lower alkyl" has the previously given significance. Examples of lower alkoxy groups are e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec. butoxy and tert.-butoxy, preferably methoxy and ethoxy and most preferred methoxy.

15 The term "lower alkoxyalkyl" or "C₁-C₈-alkoxy-C₁-C₈-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl groups is replaced by an alkoxy group, preferably methoxy or ethoxy. Among the preferred lower alkoxyalkyl groups are 2-methoxyethyl or 3-methoxypropyl.

The term "lower cyclolalkylalkoxy" or "C₁-C₇-cycloalkyl-C₁-C₈-alkoxy" refers to lower alkoxy groups as defined above wherein at least one of the hydrogen atoms of the lower alkoxy group is replaced by a cycloalkyl group. A preferred lower cycloalkylalkoxy group is cyclopropylmethoxy.

20 The term "lower cyanoalkyl" or "cyano-C₁-C₈-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by a cyano group. Among the preferred lower cyanoalkyl groups are cyanomethyl or cyanoethyl.

25 The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

30 The term "lower halogenalkyl" or "halogen-C₁-C₈-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Among the preferred halogenated lower alkyl groups are trifluoromethyl, difluoromethyl, trifluoroethyl, fluoromethyl and chloromethyl, with trifluoromethyl being especially preferred.

The term "lower halogenalkoxy" or "halogen-C₁-C₈-alkoxy" refers to lower alkoxy

groups as defined above wherein at least one of the hydrogen atoms of the lower alkoxy group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Among the preferred halogenated lower alkyl groups are trifluoromethoxy, difluoromethoxy, fluoromethoxy and chloromethoxy, with trifluoromethoxy being
5 especially preferred.

The term "lower hydroxyalkyl" or "hydroxy-C₁-C₈-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the lower alkyl group is replaced by a hydroxy group. Examples of lower hydroxyalkyl groups are hydroxymethyl or hydroxyethyl.

10 The term "alkylsulfonyl" or "lower alkylsulfanyl" refers to the group R'-S(O)₂-, wherein R' is lower alkyl and the term "lower alkyl" has the previously given significance. Examples of alkylsulfonyl groups are e.g. methylsulfonyl or ethylsulfonyl.

The term "lower alkylsulfonylalkyl" or "C₁₋₈-alkylsulfonyl-C₁₋₈-alkyl" refers to lower alkyl groups as defined above wherein at least one of the hydrogen atoms of the
15 lower alkyl groups is replaced by an alkylsulfonyl group, preferably methylsulfonyl. An example for a preferred lower alkylsulfanylalkyl group is 2-methylsulfonylethyl.

The term "halogenalkylsulfonyl" or "lower halogenalkylsulfanyl" refers to the group R'-S(O)₂-, wherein R' is lower halogenalkyl and the term "lower halogenalkyl" has the previously given significance. An example of a halogenalkylsulfonyl group is
20 trifluoromethylsulfonyl.

The term "lower alkanoyl" refers to the group -CO-R', wherein R' is lower alkyl and the term "lower alkyl" has the previously given significance. Preferred is a group -CO-R', wherein R' is methyl, meaning an acetyl group.

The term "benzoyl" refers to the group -CO-phenyl, wherein the phenyl ring may
25 be optionally substituted by one, two or three groups independently selected from the group consisting of lower alkyl, lower alkoxy, halogen, lower halogenalkyl, lower halogenalkoxy and cyano.

The term "carbamoyl" refers to the group -CO-NH₂.

The term "aryl" refers to a monovalent aromatic carbocyclic radical consisting of
30 one individual ring, or one or more fused rings in which at least one ring is aromatic in nature. Preferred "aryl" groups are the phenyl or naphthyl group, more preferably "aryl" refers to the phenyl group.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring comprising one, two or three atoms selected from the group consisting of nitrogen, oxygen and sulphur. Examples of heteroaryl groups are furyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, isoxazolyl, thiazolyl, isothiazolyl, oxazolyl, imidazolyl and pyrrolyl.

5 Especially preferred are pyridyl, thiazolyl and oxazolyl.

The term "heterocyclyl" refers to a saturated or partly unsaturated 5- or 6-membered ring which can comprise one, two or three atoms selected from nitrogen, oxygen and/or sulphur. Examples of heterocyclyl rings include piperidinyl, piperazinyl, azepinyl, pyrrolidinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, thiadiazolidinyl, dihydrofuryl, tetrahydrofuryl, dihydropyranyl, tetrahydropyranyl, and thiomorpholinyl. A preferred heterocyclyl group is piperidinyl or tetrahydropyranyl.

The term "form a 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, oxygen or sulfur" refers to a N-heterocyclic ring, which may optionally contain a further nitrogen, oxygen or sulfur atom, such as azetidiny, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or azepanyl. A "4-, 5-, 6- or 7-membered heterocyclic ring containing a sulfinyl group or a sulfonyl group" means a N-heterocyclic ring that contains a -S(O)- group or a -SO₂- group, for example 1-oxothiomorpholinyl or 1,1-dioxothiomorpholinyl. The heterocyclic ring may be unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl. The heterocyclic ring may also be condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen. Examples for such condensed heterocyclic rings are 3,4-dihydro-1H-isoquinoline or 1,3-dihydroisoindole.

The term "oxo" means that a C-atom of the heterocyclic ring may be substituted by =O, thus meaning that the heterocyclic ring may contain one or more carbonyl (-CO-) groups.

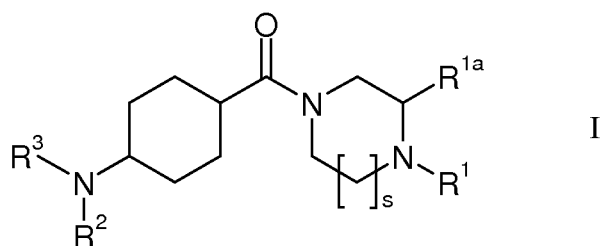
The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, preferably hydrochloric acid, and organic acids such as acetic acid, propionic acid,

glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, salicylic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the like. In addition these salts may be prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyamine resins and the like. The compound of formula I can also be present in the form of zwitterions. Particularly preferred pharmaceutically acceptable salts of compounds of formula I are the hydrochloride salts.

The compounds of formula I can also be solvated, e.g. hydrated. The solvation can be effected in the course of the manufacturing process or can take place e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of formula I (hydration). The term pharmaceutically acceptable salts also includes physiologically acceptable solvates.

“Isomers” are compounds that have identical molecular formulae but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereoisomers”, and stereoisomers that are non-superimposable mirror images are termed “enantiomers”, or sometimes optical isomers. A carbon atom bonded to four nonidentical substituents is termed a “chiral center”.

In detail, the present invention relates to compounds of the general formula



wherein

- s is 1 or 2;
- R^1 is selected from the group consisting of lower alkyl, cycloalkyl, lower cycloalkylalkyl, lower cyanoalkyl, lower alkylsulfonylalkyl and tetrahydropyranyl;
- R^{1a} is hydrogen or lower alkyl;
- 5 R^2 is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;
- R^3 is selected from the group consisting of
- 10 $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl,
- 15 $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl, indanyl, 1-oxo-indanyl,
- $-CO-(C_3-C_8)$ -alkyl,
- 20 $-CO-(CH_2)_p$ -aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,
- 25 $-CO-(CH_2)_q$ -heteroaryl, wherein q is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, and
- $-CO-NR^4R^5$; or
- 30 R^2 and R^3 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring that is condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen;

- R⁴ is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;
- R⁵ is selected from the group consisting of lower alkyl,
- 5 aryl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and lower arylalkyl wherein the phenyl ring may be unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower
- 10 halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl;
- or
- R⁴ and R⁵ together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing a further heteroatom selected
- 15 from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group, said heterocyclic ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl, or
- 20 being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen;

and pharmaceutically acceptable salts thereof.

- Preferred are compounds of formula I according to the present invention, wherein
- 25 R³ is selected from the group consisting of
- (CH₂)_m-aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower
- 30 cycloalkylalkoxy and lower hydroxyalkyl,
- (CH₂)_n-heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl,

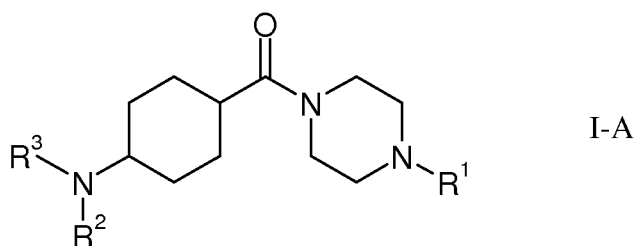
carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl, indanyl and 1-oxo-indanyl.

More preferred are compounds of formula I according to the invention, wherein R³ is $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl.

Also preferred are compounds of formula I, wherein R³ is $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl.

More preferred are compounds of formula I, wherein R³ is $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is pyridyl or isoxazolyl unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl.

Preferred are further compounds of formula I of the present invention having the formula



wherein

R¹ is lower alkyl or cycloalkyl;

- R^2 is selected from the group consisting of hydrogen,
lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;
- R^3 is selected from the group consisting of
- 5 $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,
- 10 $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, indanyl,
- $-CO-(C_3-C_8)$ -alkyl,
- 15 $-CO-(CH_2)_p$ -aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,
- 20 $-CO-(CH_2)_q$ -heteroaryl, wherein q is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, and
- $-CO-NR^4R^5$; or
- 25 R^2 and R^3 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring that is condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen;
- R^4 is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;
- 30 R^5 is selected from the group consisting of lower alkyl, aryl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and

lower arylalkyl wherein the phenyl ring may be unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl;

5 or

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group, said heterocyclic ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl, or being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen;

and pharmaceutically acceptable salts thereof.

Preferred compounds of formula I of the present invention are compounds of formula I-A, wherein R^3 is selected from the group consisting of

20 $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,

25 $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, and indanyl.

Especially preferred are those compounds of formula I-A, wherein R^3 is $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is phenyl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl.

Also preferred are compounds of formula I-A, wherein R^3 is $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, with those compounds, wherein the heteroaryl ring is pyridyl unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, being especially preferred.

A further group of preferred compounds of the present invention are the compounds of formula I, wherein R^3 is selected from the group consisting of

-CO-(C₃-C₈)-alkyl,

-CO-(CH₂)_p-aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, and

-CO-(CH₂)_q-heteroaryl, wherein q is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl.

In case, R^3 is -CO-(C₃-C₈)-alkyl, those compounds of formula I are more preferred, wherein (C₃-C₈)-alkyl signifies isopropyl.

Further preferred compounds are those compounds of formula I of the present invention, wherein R^3 is -CO-(CH₂)_p-aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is phenyl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl. Preferably, the phenyl ring is substituted with one, two or three groups independently selected from halogen or lower alkoxy.

Also preferred are compounds of formula I of the present invention, wherein R^3 is -CO-(CH₂)_q-heteroaryl, wherein q is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower

alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl

Another group of preferred compounds of formula I according to the present invention are those compounds of formula I, wherein R^3 is $-\text{CO}-\text{NR}^4\text{R}^5$ and wherein

- 5 R^4 is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;
- R^5 is selected from the group consisting of lower alkyl, aryl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and lower arylalkyl wherein the phenyl ring may be unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl;
- 10 or wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group, said heterocyclic ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl, or being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen.
- 15 20 25

More preferred are the compounds of formula I, wherein R^3 is $-\text{CO}-\text{NR}^4\text{R}^5$ and wherein

- R^4 is hydrogen or lower alkyl; and
- 30 R^5 is selected from the group consisting of lower alkyl, phenyl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and lower phenylalkyl wherein the phenyl ring may be unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower
- 35

halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl.

Especially preferred with this group are those compounds of formula I, wherein R⁵ is phenyl unsubstituted or substituted with one, two or three groups independently
5 selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, or wherein R⁵ is lower phenylalkyl wherein the phenyl ring may be unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl.

10 Furthermore, compounds of formula I according to the invention are preferred, wherein R³ is -CO-NR⁴R⁵ and wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group, said heterocyclic ring being unsubstituted or substituted by
15 one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl, or being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and
20 halogen.

More preferred are the compounds of formula I according to the invention, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from the group consisting of morpholine, piperidine, pyrrolidine, azepane, piperazine, azetidine and thiomorpholine, said heterocyclic ring
25 being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl, or being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen.

30 Especially preferred are the compounds of formula I of the invention, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a group selected from 2-methylpyrrolidine, piperidine, 4-methoxypiperidine, 4,4-difluoropiperidine, morpholine, 4-phenylpiperazine, 1,3-dihydro-isoindole and 3,4-dihydro-2H-quinoline.

Further preferred compounds of formula I according to the invention are those, wherein R¹ is lower alkyl, with those compounds wherein R¹ is isopropyl being especially preferred.

Also preferred are compounds of formula I, wherein R¹ is cycloalkyl, with those
5 compounds wherein R¹ is cyclopentyl being especially preferred.

Preferred are further compounds of formula I according to the invention, wherein R² is hydrogen or lower alkyl.

In addition, compounds of formula I according to the present invention are also preferred, wherein R² and R³ together with the nitrogen atom to which they are attached
10 form a 5- or 6-membered heterocyclic ring that is condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen.

Especially preferred are those compounds of formula I, wherein R² and R³ together with the nitrogen atom to which they are attached form a 1,3-dihydro-isoindole group or
15 a 3,4-dihydro-1H-isoquinoline group.

Preferred compounds of formula I of the present invention are the following:

- (4-isopropyl-piperazin-1-yl)-(4-p-tolylamino-cyclohexyl)-methanone,
[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
[4-(1,3-dihydro-isoindol-2-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
20 (4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
[4-(3,4-dihydro-1H-isoquinolin-2-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
[4-(indan-1-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
25 (4-isopropyl-piperazin-1-yl)-[4-(1-phenyl-propylamino)-cyclohexyl]-methanone,
(4-isopropyl-piperazin-1-yl)-{4-[2-(3-methoxy-phenyl)-ethylamino]-cyclohexyl}-methanone,
[4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
30 *N*-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-isobutyramide,

- N*-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-4-methoxy-benzamide,
2,4-difluoro-*N*-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-benzamide,
2,4-dichloro-*N*-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-benzamide,
1-benzyl-1-isopropyl-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
5 1,1-diethyl-3-[*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
4-phenyl-piperazine-1-carboxylic acid [*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-
cyclohexyl]-amide,
1-(4-chloro-phenyl)-3-[*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-
urea,
10 1-benzyl-1-ethyl-3-[*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
3,4-dihydro-2H-quinoline-1-carboxylic acid [*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-
cyclohexyl]-amide,
1-(3-fluoro-phenyl)-3-[*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-
urea,
15 2-methyl-pyrrolidine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-
cyclohexyl]-amide,
1-benzyl-1-isopropyl-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
1,1-diethyl-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
piperidine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-
20 amide,
morpholine-4-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-
amide,
4-methoxy-piperidine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-
cyclohexyl]-amide,
25 4-phenyl-piperazine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-
cyclohexyl]-amide,
1-(4-chloro-phenyl)-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-
methyl-urea,
1-benzyl-1-ethyl-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
30 3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-phenyl-1-propyl-urea,

- 3,4-dihydro-2H-quinoline-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 1-(3-fluoro-phenyl)-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-urea,
- 5 4,4-difluoro-piperidine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 1,3-dihydro-isoindole-2-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- (4-cyclopentyl-piperazin-1-yl)-[4-(2-fluoro-phenylamino)-cyclohexyl]-methanone,
- 10 (4-cyclopentyl-piperazin-1-yl)-[4-(3-fluoro-phenylamino)-cyclohexyl]-methanone,
- (4-cyclopentyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
- (4-cyclopentyl-piperazin-1-yl)-[4-(2,4-difluoro-phenylamino)-cyclohexyl]-methanone,
- 3-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
- (4-cyclopentyl-piperazin-1-yl)-[4-(2-methoxy-phenylamino)-cyclohexyl]-methanone,
- 15 (4-cyclopentyl-piperazin-1-yl)-[4-(4-methoxy-phenylamino)-cyclohexyl]-methanone,
- 1-{4-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone,
- [4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,
- (4-cyclopentyl-piperazin-1-yl)-[4-(pyrazin-2-ylamino)-cyclohexyl]-methanone,
- (4-cyclopentyl-piperazin-1-yl)-{4-[(3-fluoro-phenyl)-methyl-amino]-cyclohexyl}-
- 20 methanone,
- (4-cyclopentyl-piperazin-1-yl)-{4-[(4-fluoro-phenyl)-methyl-amino]-cyclohexyl}-methanone,
- [4-(2-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- [4-(2,4-difluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- 25 3-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
- (4-isopropyl-piperazin-1-yl)-[4-(4-methoxy-phenylamino)-cyclohexyl]-methanone,
- 1-{4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone,
- [4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- 2-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,

- cis*-[4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
[4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- 5 *trans*-1-{4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone,
cis-1-{4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone,
trans-(4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
cis-(4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
- 10 *trans*-[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
cis-[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
trans-(4-cyclobutyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
- 15 *cis*-(4-cyclobutyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
trans-[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone,
trans-(4-tert-butyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
- 20 *trans*-(4-sec-butyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
trans-(4-cyclohexyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
trans-[4-(4-fluoro-phenylamino)-cyclohexyl]-[4-(2-methanesulfonyl-ethyl)-piperazin-1-yl]-methanone,
trans-[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-propyl-piperazin-1-yl)-methanone,
- 25 *trans*-[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-methyl-[1,4]diazepan-1-yl)-methanone,
trans-(4-cyclopropylmethyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
trans-3-{4-[4-(4-fluoro-phenylamino)-cyclohexanecarbonyl]-piperazin-1-yl}-propionitrile,
- 30 3-chloro-4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,

- trans*-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- cis*-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- 5 *trans*-2-chloro-4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
- cis*-2-chloro-4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
- trans*-(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethanesulfonyl-phenylamino)-cyclohexyl]-methanone,
- cis*-(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethanesulfonyl-phenylamino)-cyclohexyl]-methanone,
- 10 *trans*-5-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-indan-1-one,
- cis*-5-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-indan-1-one,
- trans*-4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzamide,
- cis*-4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzamide,
- 15 *trans*-(4-cyclobutyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,
- cis*-(4-cyclobutyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,
- [4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone,
- 20 *trans*-(4-cyclopentyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- cis*-(4-cyclopentyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- 25 *trans*-(4-cyclopentyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,
- cis*-(4-cyclopentyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,
- [4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,
- 30

- [4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclopropyl-piperazin-1-yl)-methanone,
- trans*-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone,
- 5 *cis*-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone,
- trans*-(4-isopropyl-3-methyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,
- cis*-(4-isopropyl-3-methyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-
- 10 cyclohexyl]-methanone,
- trans*-(4-isopropyl-piperazin-1-yl)-[4-(6-trifluoromethyl-pyridin-3-ylamino)-cyclohexyl]-methanone
- trans*-(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- 15 *trans*-(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,
- trans*-[4-(4-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- trans*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- trans*-[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-
- 20 methanone,
- cis*-(4-isopropyl-piperazin-1-yl)-[4-(6-trifluoromethyl-pyridin-3-ylamino)-cyclohexyl]-methanone,
- cis*-(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- 25 *cis*-(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,
- cis*-[4-(4-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- cis*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- cis*-[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-
- 30 methanone,
- trans*-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,

- cis*-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- [4-(3,5-dimethyl-isoxazol-4-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- 5 *trans*-(4-cyclobutyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- trans*-(4-cyclobutyl-piperazin-1-yl)-[4-(6-trifluoromethyl-pyridin-3-ylamino)-cyclohexyl]-methanone,
- trans*-(4-cyclobutyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-
- 10 methanone,
- trans*-[4-(4-chloro-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone,
- trans*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone,
- trans*-[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone,
- 15 *cis*-(4-cyclobutyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- cis*-(4-cyclobutyl-piperazin-1-yl)-[4-(6-trifluoromethyl-pyridin-3-ylamino)-cyclohexyl]-methanone,
- cis*-(4-cyclobutyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-
- 20 methanone,
- cis*-[4-(4-chloro-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone,
- cis*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone,
- cis*-[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone,
- 25 *trans*-(4-cyclobutyl-piperazin-1-yl)-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-methanone,
- cis*-(4-cyclobutyl-piperazin-1-yl)-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-methanone,
- (4-cyclobutyl-piperazin-1-yl)-[4-(3,5-dimethyl-isoxazol-4-ylamino)-cyclohexyl]-
- 30 methanone,
- trans*-[4-(4-chloro-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,

- trans*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,
- trans*-[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,
- 5 *cis*-(4-cyclopentyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- cis*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,
- trans*-(4-cyclopentyl-piperazin-1-yl)-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-methanone,
- 10 *cis*-(4-cyclopentyl-piperazin-1-yl)-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-methanone,
- trans*-[4-(4-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone,
- trans*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-
- 15 methanone,
- cis*-[4-(4-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone,
- cis*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone,
- 20 *cis*-[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone,
- [4-(3,5-dimethyl-isoxazol-4-ylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone,
- cis*-[4-(4-chloro-phenylamino)-cyclohexyl]-(4-cyclopropylmethyl-piperazin-1-yl)-
- 25 methanone,
- cis*-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone,
- trans*-(4-sec-butyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- 30 *trans*-(4-sec-butyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,

- cis*-(4-*sec*-butyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone,
- cis*-(4-*sec*-butyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone,
- 5 *cis*-(4-*sec*-butyl-piperazin-1-yl)-[4-(3-chloro-phenylamino)-cyclohexyl]-methanone,
- trans*-(4-cycloheptyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
- trans*-[4-(4-fluoro-phenylamino)-cyclohexyl]-[4-(tetrahydro-pyran-4-yl)-piperazin-1-yl]-methanone,
- 10 *trans*-[4-(1-ethyl-propyl)-piperazin-1-yl]-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
- (4-cyclobutyl-piperazin-1-yl)-[4-(6-isopropoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
- (4-cyclobutyl-piperazin-1-yl)-[4-(6-cyclopropylmethoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
- 15 (4-cyclobutyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
- (4-cyclobutyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
- [4-(2,4-dichloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- [4-(6-chloro-pyridin-3-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- 20 6-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-nicotinonitrile,
- (4-isopropyl-piperazin-1-yl)-[4-(5-methanesulfonyl-pyridin-2-ylamino)-cyclohexyl]-methanone,
- and pharmaceutically acceptable salts thereof.

Especially preferred are the following compounds:

- 25 [4-(1,3-dihydro-isoindol-2-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- (4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
- [4-(indan-1-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- (4-isopropyl-piperazin-1-yl)-[4-(1-phenyl-propylamino)-cyclohexyl]-methanone,

- (4-isopropyl-piperazin-1-yl)-{4-[2-(3-methoxy-phenyl)-ethylamino]-cyclohexyl}-methanone,
[4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
5 (4-cyclopentyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
(4-cyclopentyl-piperazin-1-yl)-[4-(2,4-difluoro-phenylamino)-cyclohexyl]-methanone,
3-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
[4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,
(4-isopropyl-piperazin-1-yl)-[4-(4-methoxy-phenylamino)-cyclohexyl]-methanone,
10 [4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
and pharmaceutically acceptable salts thereof.

Further especially preferred compounds of formula I are the following:

- trans*-(4-cyclobutyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
[4-(2,4-dichloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
15 *trans*-[4-(6-chloro-pyridin-3-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
trans-6-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-nicotinonitrile,
trans-(4-isopropyl-piperazin-1-yl)-[4-(5-methanesulfonyl-pyridin-2-ylamino)-cyclohexyl]-methanone,
20 and pharmaceutically acceptable salts thereof.

Furthermore, the pharmaceutically acceptable salts of the compounds of formula I and the pharmaceutically acceptable esters of the compounds of formula I individually constitute preferred embodiments of the present invention.

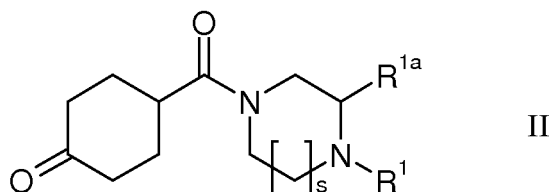
- Compounds of formula I may form acid addition salts with acids, such as
25 conventional pharmaceutically acceptable acids, for example hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, salicylate, sulphate, pyruvate, citrate, lactate, mandelate, tartarate, and methanesulphonate. Preferred 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
 5 active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). The invention embraces all of these forms.

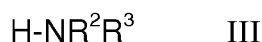
It will be appreciated, that the compounds of general formula I in this invention may be derivatised at functional groups to provide derivatives which are capable of
 10 conversion back to the parent compound in vivo. Physiologically acceptable and metabolically labile derivatives, which are capable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

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

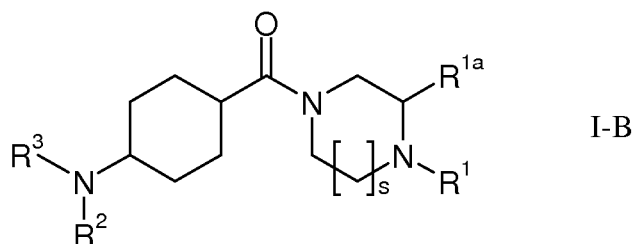
15 a) coupling a compound of formula II



wherein s , R^{1a} and R^1 is as defined herein before,
 with an amine of the formula III



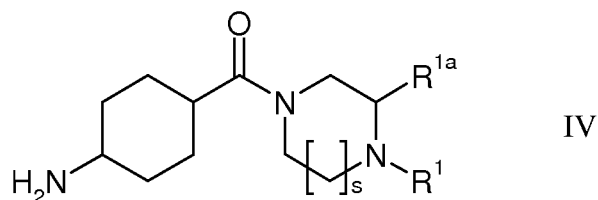
20 wherein R^2 and R^3 are as defined herein before with the proviso that R^3 does not contain a carbonyl group, in the presence of a coupling reagent under basic conditions to obtain a compound of the formula I-B



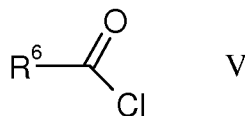
wherein s , R^{1a} , R^1 and R^2 are as defined herein before and R^3 is a group as defined herein before other than those groups containing a carbonyl group, ,
and if desired,

- 5 converting the compound obtained into a pharmaceutically acceptable acid addition salt,
or

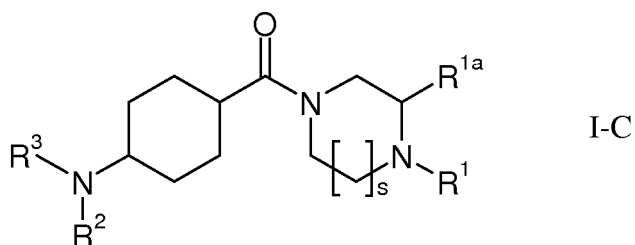
b) reacting a compound of formula IV



- wherein s , R^{1a} and R^1 are as defined herein before,
10 with an acid chloride of the formula V



wherein R^6 is selected from the group consisting of (C_3-C_8) -alkyl, $-(CH_2)_p$ -aryl and $-(CH_2)_q$ -heteroaryl, in the presence of a base
to obtain a compound of the formula I-C

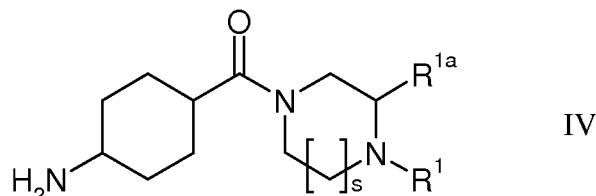


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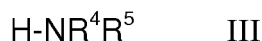
wherein R^2 is hydrogen and R^3 is selected from the group consisting of $-\text{CO}-(C_3-C_8)$ -alkyl, $-\text{CO}-(CH_2)_p$ -aryl and $-\text{CO}-(CH_2)_q$ -heteroaryl,
and if desired,

converting the compound obtained into a pharmaceutically acceptable acid addition salt,
or

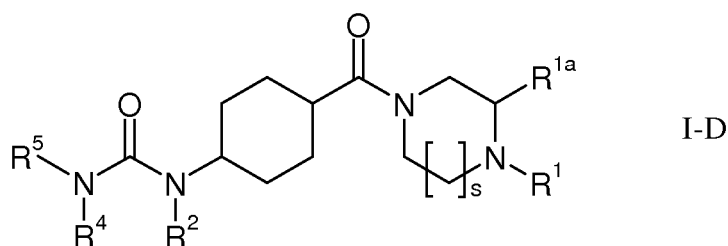
c) coupling a compound of formula IV



5 wherein s , R^{1a} and R^1 are as defined herein before,
after activation with phenylchloroformate with an amine of the formula VI



wherein R^4 and R^5 are as defined herein before,
to obtain a compound of the formula I-D



10

wherein s , R^{1a} , R^1 , R^2 , R^4 and R^5 are as defined herein before,
and if desired,
converting the compound obtained into a pharmaceutically acceptable acid addition salt.

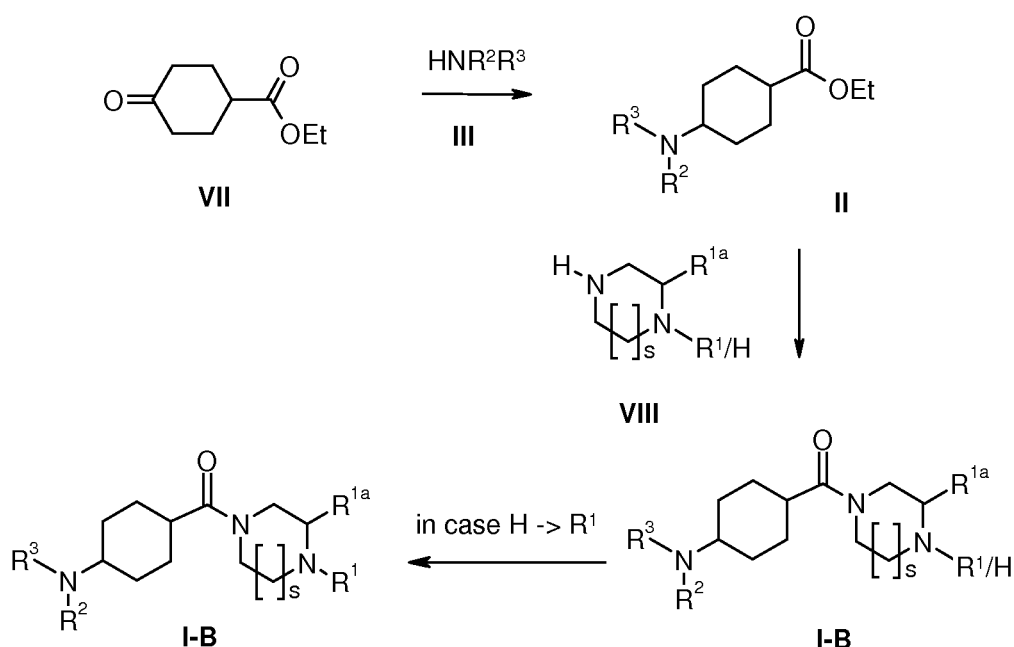
The preparation of compounds of formula I of the present invention may be
15 carried out in sequential or convergent synthetic routes. Syntheses of the invention are
shown in the following scheme. The skills required for carrying out the reaction and
purification of the resulting products are known to those skilled in the art. The
substituents and indices used in the following description of the processes have the
significance given herein before unless indicated to the contrary. In more detail, the
20 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 below, by methods described in references cited in the description or in the examples, or by methods known in the art.

Compounds of formula I-B, wherein R^3 is selected from $-(CH_2)_m$ -aryl, $-(CH_2)_n$ -heteroaryl and indanyl or wherein R^2 and R^3 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring that is condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen; can be prepared following the procedure as depicted in scheme 1.

10

Scheme 1

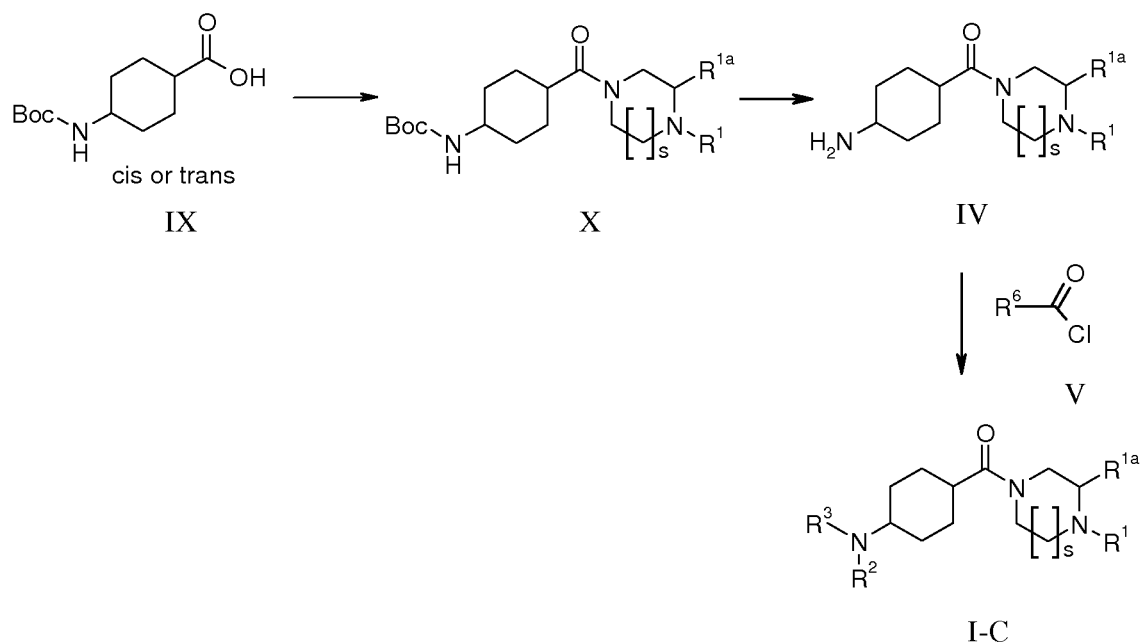


4-oxo-cyclohexanecarboxylic acid ethyl ester VII is commercially available and the ketone functionality can be modified according to methods described in literature and the procedures are known to those in the art (For reaction conditions described in literature affecting such reactions see for example: Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999). However, we find it convenient to transform the ketone functionality in VII through reductive amination with amines III (either commercially available or accessible by methods described in references or by methods known in the art; as appropriate) under reducing conditions. The reaction may be carried out in the presence or absence of a solvent and an acid. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse

effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: THF, methanol, and the like. There is no particular restriction on the nature of the acid used in this stage, and any acid commonly used in this type of reaction may equally be employed here. Examples of such acids include acetic acid, and the like. There is no particular restriction on the nature of the reducing agent used in this stage, and any reducing agent commonly used in this type of reaction may equally be employed here. Examples of such reducing agents include sodium triacetoxyborohydride, sodium borohydride, and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield the intermediately built esters which can be saponified by various methods known in literature. However, we find it convenient to cleave the ester functionality under basic conditions. The reaction may be carried out in the presence or absence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: THF, methanol, water and the like. There is no particular restriction on the nature of the base used in this stage, and any acid commonly used in this type of reaction may equally be employed here. Examples of such bases include lithium hydroxide, sodium hydroxide, and the like. The liberated acid functionality can be modified according to methods described in literature and the procedures are known to those in the art. However, we find it convenient to transform the acid functionality through amide coupling with substituted or unsubstituted piperazine(s) VIII (either commercially available or accessible by methods described in references or by methods known in the art; as appropriate) employing a coupling reagent. The reaction may be carried out in the presence or absence of a solvent and a base. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: DMF, THF, dioxane, and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include NEt_3 or diisopropylethylamide (DIPEA), and the like. There is no particular restriction on the nature of the coupling reagent used in this stage, and any coupling reagent commonly used in this type of reaction may equally be employed here.

Examples of such reducing agents include 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBT), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield compounds I-B. In the case when unsubstituted piperazine VII has been coupled the resulting compounds IA can be further functionalised at the free NH of the piperazine moiety by reductive amination with ketones or aldehydes respectively to access compounds I-B. The conditions as described above for a reductive amination apply at this reaction step similarly. Complementary to this procedure an alternative approach can be chosen reversing the order of steps i.e. cleavage of the ester functionality as described above in 4-oxo-cyclohexanecarboxylic acid ethyl ester VII (commercially available), amide coupling with suitable piperazines as described above and subsequent reductive amination as described above yielding the desired compounds of formula I-B. Access to the respective diastereoisomers is given through separation techniques as described in literature. We find it convenient to separate *cis* or *trans* isomers respectively from the diastereomeric mixture through silica gel chromatography or reversed phase HPLC techniques. The solvents for elution are chosen appropriately.

Compounds of formula I-C, wherein R^3 is selected from the group consisting of -CO-(C₃-C₈)-alkyl, -CO-(CH₂)_p-aryl and -CO-(CH₂)_q-heteroaryl, can be prepared following the procedure depicted in scheme 2.

Scheme 2

4-tert-Butoxycarbonylamino-cyclohexanecarboxylic acid IX (cis or trans) is commercially available and can subsequently be modified at the acid functionality according to methods described in literature and the procedures are known to those in the art (For reaction conditions described in literature affecting such reactions see for example: Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999). However, we find it convenient to transform the acid functionality in IX through amide coupling with substituted piperazines VIII (either commercially available or accessible by methods described in references or by methods known in the art; as appropriate) employing a coupling reagent. The reaction may be carried out in the presence or absence of a solvent and a base. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: DMF, THF, dioxane, and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include NEt_3 or DIPEA, and the like. There is no particular restriction on the nature of the coupling reagent used in this stage, and any coupling reagent commonly used in this type of reaction may equally be employed here. Examples of such reducing agents include TBTU, HATU, HOBT, and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We

find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield compounds X.

- 5 Removal of the protecting group in X can be affected under various conditions according to methods described in literature and the procedures are known to those in the art (For reaction conditions described in literature affecting such reactions see for example: *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999).
- 10 However, we find it convenient to cleave the Boc-protecting group under acidic conditions in the presence or the absence of a solvent to access the intermediate amine. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include:
- 15 dioxane, THF, water and the like. There is no particular restriction on the nature of the acid used in this stage, and any acid commonly used in this type of reaction may equally be employed here. Examples of such acids include HCl, acetic acid, and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the
- 20 reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield the intermediate amine. The coupling of the intermediate amines with acid chlorides is widely described in literature and the procedures are known
- 25 to those in the art (For reaction conditions described in literature affecting such reactions see for example: *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999). The respective amines IV can conveniently be transformed to the respective amides I-C through coupling with acid chlorides V (either commercially available or accessible by
- 30 methods described in references or by methods known in the art; as appropriate). We find it convenient to carry out the reaction in a solvent like DCM and in the presence of a base. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include:
- 35 dichloromethane (DCM), dioxane, THF, and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include triethylamine

and diisopropylethylamine, and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield amide derivatives I-C ($R^2 = H$). However, the resulting compound of formula I-C ($R^2 = H$) is a compound of the present invention and may be the desired product; alternatively it may be subjected to consecutive reactions like alkylation of the amide under suitable conditions. There are various reaction conditions known in literature to affect such transformations however we find it convenient to convert amides I-C ($R^2 = H$) to amides I-E ($R^2 = \text{alkyl}$) by reaction of I-C ($R^2 = H$) with suitable alcohols in the presence of a coupling reagent like a phosphorane (adapted from: THL 2002, 43, 2187-2190). The reaction can be carried out in the presence or absence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: toluene, and the like. There is no particular restriction on the nature of the phosphorane used in this stage provided it affects the reaction. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield amides I-E ($R^2 = \text{alkyl}$).

Urea derivatives of formula I-D (compounds wherein R^3 signifies $-\text{CO}-\text{NR}^4\text{R}^5$) can be prepared according to the following procedure:

The coupling of the intermediate amines (access to these intermediates as described above) with amines upon activation, respectively C1-fragment introduction, is widely described in literature and the procedures are known to those in the art (For reaction conditions described in literature affecting such reactions see for example: Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999). The respective intermediate amines can conveniently be transformed to the respective ureas through activation with phenylchloroformate to access the intermediately built phenylcarbamate and subsequent reaction with amines (either commercially available or accessible by methods described in references or by methods known in the art; as

appropriate). We find it convenient to carry out the reaction with phenyl chloroformate in a solvent like DCM and in the presence of a base. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: dichloromethane (DCM), dioxane, THF, and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include triethylamine and diisopropylethylamine, and the like.

Subsequently an amine (either commercially available or accessible by methods described in references or by methods known in the art; as appropriate) is added (either in one pot or after isolation of the respectively formed carbamate and separate reaction). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield urea derivatives I-D ($R^2=H$). In cases where R^2 is planned to be alkyl the intermediate X can be alkylated at the free NH under suitable reaction conditions known to those in the art preferably with suitable alkylating reagents under basic conditions. The reaction sequence will subsequently the route as outlined above. The resulting compound of formula I-F is a compound of the present invention and may be the desired product; alternatively it may be subjected to consecutive reactions like alkylation of the urea under suitable conditions. There are various reaction conditions known in literature to affect such transformations however we find it convenient to convert ureas I-F ($R^4=H$) to ureas I-G ($R^4=alkyl$) by reaction of I-F ($R^4=H$) with suitable alcohols in the presence of a coupling reagent like a phosphorane (adapted from: THL 2002, 43, 2187-2190). The reaction can be carried out in the presence or absence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include: toluene, and the like. There is no particular restriction on the nature of the phosphorane used in this stage provided it affects the reaction. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. We find it convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction

temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield urea derivatives I-G (R^4 =alkyl).

As described above, the compounds of formula I of the present invention can be used as medicaments for the treatment and/or prevention of diseases which are
5 associated with the modulation of H3 receptors.

In this context, the expression 'diseases associated with the modulation of H3 receptors' means diseases which can be treated and/or prevented by modulation of H3 receptors. Such diseases encompass, but are not limited to, obesity, metabolic syndrome (syndrome X), neurological diseases including Alzheimer's disease, dementia, age-related
10 memory dysfunction, mild cognitive impairment, cognitive deficit, attention deficit hyperactivity disorder, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke, dizziness, schizophrenia, depression, addiction, motion sickness and sleep disorders including narcolepsy, and other diseases including asthma, allergy, allergy-induced airway responses, congestion, chronic
15 obstructive pulmonary disease and gastro-intestinal disorders.

In a preferable aspect, the expression 'diseases associated with modulation of H3 receptors' relates to obesity, metabolic syndrome (syndrome X), and other eating disorders, with obesity being especially preferred.

The invention therefore also relates to pharmaceutical compositions comprising a
20 compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

Further, the invention relates to compounds as defined above for use as therapeutically active substances, particularly as therapeutic active substances for the treatment and/or prevention of diseases which are associated with the modulation of H3 receptors.

25 In another embodiment, the invention relates to a method for the treatment and/or prevention of diseases which are associated with the modulation of H3 receptors, which method comprises administering a therapeutically active amount of a compound of formula I to a human being or animal. A method for the treatment and/or prevention of obesity is preferred.

30 The invention further relates to the use of compounds of formula I as defined above for the treatment and/or prevention of diseases which are associated with the

modulation of H3 receptors.

In addition, the invention relates to the use of compounds of formula I as defined above for the preparation of medicaments for the treatment and/or prevention of diseases which are associated with the modulation of H3 receptors. The use of

5 compounds of formula I as defined above for the preparation of medicaments for the treatment and/or prevention of obesity is preferred.

Furthermore, the present invention relates to the use of a compound of formula I for the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor and particularly, wherein
10 the lipase inhibitor is orlistat.

It is a further preferred object of the present invention to provide a method for the treatment or prevention of obesity and obesity related disorders which comprises administration of a therapeutically effective amount of a compound according to formula I in combination or association with a therapeutically effective amount of other
15 drugs for the treatment of obesity or eating disorders so that together they give effective relief. Suitable other drugs include, but are not limited to, anorectic agents, lipase inhibitors, selective serotonin reuptake inhibitors (SSRI) and agents that stimulate metabolism of body fat. Combinations or associations of the above agents may be encompassing separate, sequential or simultaneous administration.

20 The term "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound
25 commonly referred to as panclicins. Panclicins are analogues of orlistat (Mutoh et al, 1994). The term "lipase inhibitor" refers also to polymer bound lipase inhibitors for example described in International Patent Application WO 99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterized in that they have been substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also
30 comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" preferably refers to tetrahydrolipstatin. Administration of a therapeutically effective amount of a compound according to formula I in combination or association with a therapeutically effective amount of tetrahydrolipstatin is especially preferred.

Tetrahydrolipstatin (orlistat) is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable
5 pharmaceutical compositions are described for example in International Patent Applications WO 00/09122 and WO 00/09123. Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 0 185 359, 0 189 577, 0 443 449, and 0 524 495.

Suitable anorectic agents of use in combination with a compound of the present
10 invention include, but are not limited to, APD356, aminorex, amphechloral, amphetamine, axokine, benzphetamine, bupropion, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, CP945598, cyclexedrine, CYT009-GhrQb, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex,
15 fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, metreleptin, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex, rimonabant, sibutramine, SLV319, SNAP 7941, SR147778 (Surinabant), steroidal plant extract (e.g. P57) and TM30338 and pharmaceutically acceptable salts
20 thereof.

Most preferable anorectic agents are sibutramine, rimonabant and phentermine.

Suitable selective serotonin reuptake inhibitors of use in combination with a compound of the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

25 Suitable agents that stimulate metabolism of body fat include, but are not limited to, growth hormone agonist (e.g. AOD-9604).

The use of a compound of formula I in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a compound selected from the group consisting of a lipase inhibitor, an anorectic agent, a
30 selective serotonin reuptake inhibitor, and an agent that stimulates metabolism of body fat, is also an object of the present invention.

The use of a compound of formula I in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a

lipase inhibitor, preferably with tetrahydrolipstatin, is also an object of the present invention.

It is a further preferred object to provide a method of treatment or prevention of Type II diabetes (non-insulin dependent diabetes mellitus (NIDDM)) in a human which
5 comprises administration of a therapeutically effective amount of a compound according to formula I in combination or association with a therapeutically effective amount of a lipase inhibitor, particularly, wherein the lipase inhibitor is tetrahydrolipstatin. Also an object of the invention is the method as described above for the simultaneous, separate or sequential administration of a compound according to formula I and a lipase
10 inhibitor, particularly tetrahydrolipstatin.

It is a further preferred object to provide a method of treatment or prevention of Type II diabetes (non-insulin dependent diabetes mellitus (NIDDM)) in a human which comprises administration of a therapeutically effective amount of a compound according to formula I in combination or association with a therapeutically effective amount of an
15 anti-diabetic agent.

The term "anti-diabetic agent" refers to compounds selected from the group consisting of 1) PPAR γ agonists such as pioglitazone (actos) or rosiglitazone (avandia), and the like; 2) biguanides such as metformin (glucophage), and the like; 3) sulfonylureas such as glibenclamide, glimepiride (amaryl), glipizide (glucotrol),
20 glyburide (DiaBeta), and the like; 4) nonsulfonylureas such as nateglinide (starlix), repaglinide (prandin), and the like; 5) PPAR α/γ agonists such as GW-2331, and the like 6) DPP-IV- inhibitors such as LAF-237 (vildagliptin), MK-0431, BMS-477118 (saxagliptin) or GSK23A and the like; 7) Glucokinase activators such as the compounds disclosed in e.g. WO 00/58293 A1, and the like; 8) α -Glucosidase inhibitors such as
25 acarbose (precose) or miglitol (glyset), and the like.

Also an object of the invention is the method as described above for the simultaneous, separate or sequential administration of a compound according to formula I and a therapeutically effective amount of an anti-diabetic agent.

The use of a compound of formula I in the manufacture of a medicament for the
30 treatment and prevention of Type II diabetes in a patient who is also receiving treatment with an anti-diabetic agent is also an object of the present invention.

It is a further preferred object to provide a method of treatment or prevention of dyslipidemias in a human which comprises administration of a therapeutically effective

amount of a compound according to formula I in combination or association with a therapeutically effective amount of a lipid lowering agent.

The term "lipid lowering agent" refers to compounds selected from the group consisting of 1) bile acid sequestrants such as cholestyramine (questran), colestipol (colestid), and the like; 2) HMG-CoA reductase inhibitors such as atorvastatin (lipitor), cerivastatin (baycol), fluvastatin (lescol), pravastatin (pravachol), simvastatin (zocor) and the like; 3) cholesterol absorption inhibitors such as ezetimibe, and the like; 4) CETP inhibitors such as torcetrapib, JTT 705, and the like; 5) PPAR α -agonists such as beclofibrate, gemfibrozil (lipid), fenofibrate (lipidil), bezafibrate (bezalip), and the like; 6) lipoprotein synthesis inhibitors such as niacin, and the like; and 7) niacin receptor agonists such as nicotinic acid, and the like.

Also an object of the invention is the method as described above for the simultaneous, separate or sequential administration of a compound according to formula I and a therapeutically effective amount of a lipid lowering agent.

The use of a compound of formula I in the manufacture of a medicament for the treatment and prevention of dyslipidemias in a patient who is also receiving treatment with a lipid lowering agent, is also an object of the present invention.

It is a further preferred object to provide a method of treatment or prevention of hypertension in a human which comprises administration of a therapeutically effective amount of a compound according to formula I in combination or association with a therapeutically effective amount of an anti-hypertensive agent.

The term "anti-hypertensive agent" or "blood-pressure lowering agent" refers to compounds selected from the group consisting of 1) Angiotensin-converting Enzyme (ACE) Inhibitors including benazepril (lotensin), captopril (capoten), enalapril (vasotec), fosinopril (monopril), lisinopril (prinivil, zestril), moexipril (univasc), perindopril (coversum), quinapril (accupril), ramipril (altace), trandolapril (mavik), and the like; 2) Angiotensin II Receptor Antagonists including candesartan (atacand), eprosartan (teveten), irbesartan (avapro), losartan (cozaar), telmisartan (micadisc), valsartan (diovan), and the like; 3) Adrenergic Blockers (peripheral or central) such as the beta-adrenergic blockers including acebutolol (sectrol), atenolol (tenormin), betaxolol (kerlone), bisoprolol (zebeta), carteolol (cartrol), metoprolol (lopressor; topol-XL), nadolol (corgard), penbutolol (levatol), pindolol (visken), propranolol (inderal), timolol (blockadren) and the like; alpha/beta adrenergic blockers including carvedilol (coreg), labetalol (normodyne), and the like; alpha-1 adrenergic blockers including

- prazosin (minipress), doxazosin (cardura), terazosin (hytrin), phenoxybenzamine (dibenzylamine), and the like; peripheral adrenergic-neuronal blockers including guanadrel (hylorel), guanethidine (ismelin), reserpine (serpasil), and the like; alpha-2 adrenergic blockers including a-methyldopa (aldomet), clonidine (catapres), guanabenz (wytensin),
- 5 guanfacine (tenex), and the like; 4) Blood Vessel Dilators (Vasodilators) including hydralazine (apresoline), minoxidil (lonitren), clonidine (catapres), and the like; 5) Calcium Channel Blockers including amlodipine (norvasc), felodipine (plendil), isradipine (dynacirc), nicardipine (cardine sr), nifedipine (procardia, adalat), nisoldipine (sular), diltiazem (cardizem), verapamil (isoptil), and the like; 6) Diuretics such as
- 10 thiazides and thiazides-like agents, including hydrochlorothiazide (hydrodiuril, microzide), chlorothiazide (diuril), chlorthalidone (hygroton), indapamide (lozol), metolazone (mykrox), and the like; loop diuretics, such as bumetanide (bumex) and furosemide (lasix), ethacrynic acid (edecrin), torsemide (demadex), and the like; potassium-sparing diuretics including amiloride (midamor), triamterene (dyrenium),
- 15 spironolactone (aldactone), and the like; 7) Tyrosine Hydroxylase Inhibitors, including metyrosine (demser), and the like; 8) Neutral Endopeptidase Inhibitors, including BMS-186716 (omapatrilat), UK-79300 (candoxatril), ecadotril (sinorphan), BP-1137 (fasidotril), UK-79300 (sapatrilat) and the like; and 9) Endothelin Antagonists including tezosentan (RO0610612), A308165, and the like.
- 20 Also an object of the invention is the method as described above for the simultaneous, separate or sequential administration of a compound according to formula I and a therapeutically effective amount of an anti-hypertensive agent.

The use of a compound of formula I in the manufacture of a medicament for the treatment and prevention of hypertension in a patient who is also receiving treatment

25 with an anti-hypertensive agent, is also an object of the present invention.

As described above, the compounds of formula I and their pharmaceutically acceptable salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention are good histamine 3 receptor (H3R) antagonists and/or inverse agonists.

30 The following test was carried out in order to determine the activity of the compounds of formula (I).

Binding assay with ^3H -(R) α -methylhistamine

Saturation binding experiments were performed using HR3-CHO membranes prepared as described in Takahashi, K, Tokita, S., Kotani, H. (2003) J. Pharmacol. Exp. Therapeutics 307, 213-218.

5 An appropriate amount of membrane (60 to 80 μg protein/well) was incubated with increasing concentrations of ^3H -(R) α -Methylhistamine di-hydrochloride (0.10 to 10 nM). Non specific binding was determined using a 200 fold excess of cold (R) α -Methylhistamine dihydrobromide (500 nM final concentration). The incubation was carried out at room temperature (in deep-well plates shaking for three hours). The final
10 volume in each well was 250 μl . The incubation was followed by rapid filtration on GF/B filters (pre-soaked with 100 μl of 0.5% PEI in Tris 50 mM shaking at 200 rpm for two hours). The filtration was made using a cell-harvester and the filter plates were then washed five times with ice cold washing buffer containing 0.5 M NaCl. After harvesting, the plates were dried at 55 $^{\circ}\text{C}$ for 60 min, then we added scintillation fluid (Microscint
15 40, 40 microl in each well) and the amount of radioactivity on the filter was determined in Packard top-counter after shaking the plates for two hours at 200 rpm at room temperature.

Binding Buffer: 50 mM Tris-HCl pH 7.4 and 5 mM $\text{MgCl}_2 \times 6\text{H}_2\text{O}$ pH 7.4. Washing Buffer: 50 mM Tris-HCl pH 7.4 and 5 mM $\text{MgCl}_2 \times 6\text{H}_2\text{O}$ and 0.5 M NaCl pH 7.4.

20 Indirect measurement of affinity of H3R inverse agonists: twelve increasing concentrations (ranging from 10 μM to 0.3 nM) of the selected compounds were always tested in competition binding experiments using membrane of the human HR3-CHO cell line. An appropriate amount of protein, e.g. approximately 500cpm binding of RAMH at K_d , were incubated for 1 hour at room temperature in 250 μl final volume in
25 96-well plates in presence of ^3H -(R) α -Methylhistamine (1 nM final concentration = K_d). Non-specific binding was determined using a 200 fold excess of cold (R) α - Methylhistamine dihydrobromide.

All compounds were tested at a single concentration in duplicates. Compounds that showed an inhibition of [^3H]-RAMH by more than 50% were tested again to determine
30 IC_{50} in a serial dilution experiment. K_i 's were calculated from IC_{50} based on Cheng-Prusoff equation (Cheng, Y, Prusoff, WH (1973) Biochem Pharmacol 22, 3099-3108).

The compounds of the present invention exhibit K_i values within the range of about 1 nM to about 1000 nM, preferably of about 1 nM to about 100 nM, and more

preferably of about 1 nM to about 30 nM. The following table shows measured values for some selected compounds of the present invention.

	K_i (nM)
Example 1	52.8
Example 13	88.1
Example 32	38.4

Demonstration of additional biological activities of the compounds of the present invention may be accomplished through in vitro, ex vivo, and in vivo assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent for the treatment of obesity-related disorders such as diabetes, Syndrome X, or atherosclerotic disease and related disorders such as hypertriglyceridemia and hypercholesteremia, the following assays may be used.

Method for Measuring Blood Glucose Levels

db/db mice (obtained from Jackson Laboratories, Bar Harbor, ME) are bled (by either eye or tail vein) and grouped according to equivalent mean blood glucose levels. They are dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 7 to 14 days. At this point, the animals are bled again by eye or tail vein and blood glucose levels are determined.

Method for Measuring Triglyceride Levels

hApoA1 mice (obtained from Jackson Laboratories, Bar Harbor, ME) are bled (by either eye or tail vein) and grouped according to equivalent mean serum triglyceride levels. They are dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 7 to 14 days. The animals are then bled again by eye or tail vein, and serum triglyceride levels are determined.

Method for Measuring HDL-Cholesterol Levels

To determine plasma HDL-cholesterol levels, hApoA1 mice are bled and grouped with equivalent mean plasma HDL-cholesterol levels. The mice are orally dosed once

daily with vehicle or test compound for 7 to 14 days, and then bled on the following day. Plasma is analyzed for HDL-cholesterol.

The compounds of formula (I) and their pharmaceutically acceptable salts and esters can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, 5 perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

10 The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and their pharmaceutically acceptable, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

15 Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the 20 nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or 25 hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency- 30 improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending

on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 1 mg to about 100 mg, comes into consideration. Depending
5 on the dosage it is convenient to administer the daily dosage in several dosage units.

The pharmaceutical preparations conveniently contain about 0.1-500 mg, preferably 0.5-100 mg, of a compound of formula (I).

The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

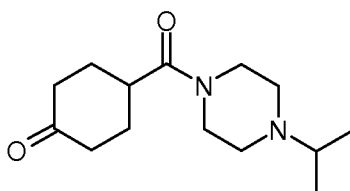
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Examples

Example 1

(4-Isopropyl-piperazin-1-yl)-(4-p-tolylamino-cyclohexyl)-methanone

a) Step 1: 4-(4-Isopropyl-piperazine-1-carbonyl)-cyclohexanone (Intermediate 1)



15 A mixture of 882 mg (6.2 mmol) 4-oxo-cyclohexanecarboxylic acid (commercially available), 875 mg (6.8 mmol) 1-(2-propyl)-piperazine, 2.98 g (9.3 mmol) TBTU and 3.2 g (24.8 mmol) DIPEA in 25 ml DMF was stirred for 3 h at room temperature. After removal of the volatiles the residue was extracted with ethyl acetate and evaporated. The residue was purified by column chromatography on silica eluting with a gradient formed
20 from n-heptane, and ethyl acetate (0.1 % NEt₃) and methanol. Evaporation of the combined product fractions yielded 830 mg (53 %) of the title compound as light brown oil. MS(m/e): 253.3 (MH⁺).

b) Step 2: (4-Isopropyl-piperazin-1-yl)-(4-p-tolylamino-cyclohexyl)-methanone

A mixture of 25 mg (0.1 mmol) 4-(4-isopropyl-piperazine-1-carbonyl)-
25 cyclohexanone, 27 mg (0.25 mmol) p-tolylamine, 60 mg acetic acid and 42 mg (0.2 mmol) sodium triacetoxyborohydride in 2 ml THF was shaken for 16 h at 70 °C. After evaporation methanol and DMF were added and the mixture was subjected to

preparative HPLC purification on reversed phase eluting with a gradient of acetonitrile / water (0.1 % NEt₃). The combined product fractions were evaporated to dryness to yield 5.1 mg (15 %) of the title compound. MS(m/e): 344.3 (MH⁺).

- According to the procedure described for example 1 further piperazinyl-carbonyl-
 5 cyclohexyl derivatives have been synthesized from their respective starting materials mentioned in table 1. Table 1 comprises example 2 to example 9.

Table 1

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
2	347.5	[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone (intermediate 1) and 4-fluoro-phenylamine (commercially available)	348.4
3	355.5	[4-(1,3-dihydro-isoindol-2-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone (intermediate 1) and 2,3-dihydro-1H-isoindole (commercially available)	356.3
4	360.5	(4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone	4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone (intermediate 1) and 6-methoxy-pyridin-3-ylamine (commercially available)	361.4

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
5	369.6	[4-(3,4-dihydro-1H-isoquinolin-2-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone (intermediate 1) and 1,2,3,4-tetrahydro-isoquinoline (commercially available)	370.4
6	369.6	[4-(indan-1-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone (intermediate 1) and indan-1-ylamine (commercially available)	370.3
7	371.6	(4-isopropyl-piperazin-1-yl)-[4-(1-phenyl-propylamino)-cyclohexyl]-methanone	4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone (intermediate 1) and 1-phenyl-propylamine (commercially available)	372.3
8	387.6	(4-isopropyl-piperazin-1-yl)-{4-[2-(3-methoxy-phenyl)-ethylamino]-cyclohexyl}-methanone	4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone (intermediate 1) and 2-(3-methoxy-phenyl)-ethylamine (commercially available)	388.3

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
9	395.5	[4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone (intermediate 1) and 4-difluoromethoxy-phenylamine (commercially available)	396.3

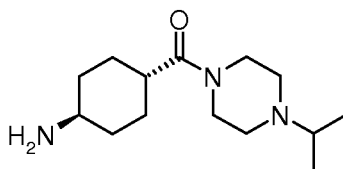
Example 10

N-[*trans*-4-(4-Isopropyl-piperazine-1-carbonyl)-cyclohexyl]-isobutyramide

- 5 a) Step 1: [*trans*-4-(4-Isopropyl-piperazine-1-carbonyl)-cyclohexyl]-carbamic acid tert-butyl ester

A mixture of 3 g (12 mmol) 4-tert-butoxycarbonylamino-*trans*-cyclohexane carboxylic acid (commercially available), 1.74 g (14 mmol) 1-(2-propyl)-piperazine (commercially available), 4.75 g (15 mmol) TBTU and 3.64 g (36 mmol) NEt₃ in 10 mL DMF was stirred for 3 h at room temperature. After evaporation the residue was washed
10 with 1N NaHCO₃ solution, extracted with DCM and the combined organic layers dried with MgSO₄ and evaporated to dryness to yield 4.56 g (94 %; 90% purity) of the title compound and was used in the consecutive step without further purification. MS(m/e): 354.3 (MH⁺).

- 15 b) Step 2: *trans*-(4-Amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride (Intermediate 2)



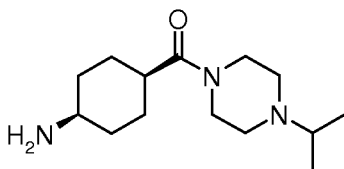
A mixture of 4.56 g (12 mmol) [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-carbamic acid tert-butyl ester and 29 mL 4N HCl in dioxane was stirred for 6

h at 50 °C evaporated to dryness and used without further purification in the consecutive step. MS(m/e): 254.1 (MH⁺).

c) Step 3: N-[*trans*-4-(4-Isopropyl-piperazine-1-carbonyl)-cyclohexyl]-isobutyramide

A mixture of 32 mg (0.1 mmol) *trans*-(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride, 21 mg (0.2 mmol) isobutyryl chloride and 101 mg (1 mmol) NEt₃ in 2 mL dichloromethane were shaken for 16 h at 40 °C. After evaporation methanol and DMF were added and the mixture was subjected to preparative HPLC purification on reversed phase eluting with a gradient of acetonitrile / water (0.1 % NEt₃). The combined product fractions were evaporated to dryness to yield 3.6 mg (11 %) of the title compound. MS(m/e): 324.4 (MH⁺).

cis-(4-Amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride (Intermediate 3)



a) Step 1: [*cis*-4-(4-Isopropyl-piperazine-1-carbonyl)- cyclohexyl]-carbamic acid tert-butyl ester

According to the procedure described for the synthesis of [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)- cyclohexyl]-carbamic acid tert-butyl ester the title compound was synthesised from 4-tert-butoxycarbonylamino-*cis*-cyclohexanecarboxylic acid (commercially available) and 1-(2-propyl)-piperazine (commercially available). MS(m/e): 354.3 (MH⁺).

b) Step 2: *cis*-(4-Amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride

According to the procedure described for the synthesis of *trans*-(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride the title compound was synthesised from [*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-carbamic acid tert-butyl ester. MS(m/e): 254.4 (MH⁺).

According to the procedure described for example 10 further piperazinyl-carbonyl-cyclohexyl derivatives have been synthesized from their respective starting materials mentioned in table 2. Table 2 comprises example 11 to example 13.

Table 2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
11	387.5	N-[<i>trans</i> -4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-4-methoxy-benzamide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride (intermediate 2) and 4-methoxy-benzoyl chloride (commercially available)	388.4
12	393.5	2,4-difluoro-N-[<i>trans</i> -4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-benzamide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and 2,4-difluoro-benzoyl chloride (commercially available)	394.4
13	426.4	2,4-dichloro-N-[<i>trans</i> -4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-benzamide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and 2,4-dichloro-benzoyl chloride (commercially available)	426.3

Example 14

1-Benzyl-1-isopropyl-3-[trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea

A mixture of 23 mg (0.07 mmol) *cis*-(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride, 13 mg (0.08 mmol) phenyl chloroformate and 36 mg (0.35 mmol) NEt₃ in 1.5 mL DCM were shaken for 2 h at room temperature. Afterwards 31 mg (0.21 mmol) benzyl-isopropyl-amine were added and the mixture was shaken for 16 h at room temperature. After evaporation methanol and DMF were added and the mixture was subjected to preparative HPLC purification on reversed phase eluting with a gradient of acetonitrile / water (0.1 % NEt₃). The combined product fractions were evaporated to dryness to yield 19 mg (62 %) of the title compound. MS(m/e): 429.5 (MH⁺).

According to the procedure described for example 14 further piperazinyl-carbonyl-cyclohexyl derivatives (examples 15 to 34) have been synthesized from their respective starting materials mentioned in table 3.

15

Table 3

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
15	352.5	1,1-diethyl-3-[<i>cis</i> -4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea	<i>cis</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 3) and diethylamine (commercially available)	353.5
16	441.6	4-phenyl-piperazine-1-carboxylic acid [<i>cis</i> -4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>cis</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 3) and 1-phenyl-piperazine (commercially available)	442.5

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
17	421	1-(4-chloro-phenyl)-3-[cis-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-urea	<i>cis</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 3) and (4-chloro-phenyl)-methyl-amine (commercially available)	421.3
18	414.6	1-benzyl-1-ethyl-3-[cis-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea	<i>cis</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 3) and benzyl-ethyl-amine (commercially available)	415.5
19	412.6	3,4-dihydro-2H-quinoline-1-carboxylic acid [cis-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>cis</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 3) and 1,2,3,4-tetrahydro-quinoline (commercially available)	413.4
20	404.5	1-(3-fluoro-phenyl)-3-[cis-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-urea	<i>cis</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 3) and (3-fluoro-phenyl)-methyl-amine (commercially available)	405.5

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
21	364.5	2-methyl-pyrrolidine-1-carboxylic acid [trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and 2-methyl-pyrrolidine (commercially available)	365.3
22	428.6	1-benzyl-1-isopropyl-3-[trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone dihydrochloride (intermediate 2) and benzyl-isopropyl-amine (commercially available)	429.5
23	352.5	1,1-diethyl-3-[trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and diethylamine (commercially available)	353.4
24	364.5	piperidine-1-carboxylic acid [trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and piperidine (commercially available)	365.3

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
25	366.5	morpholine-4-carboxylic acid [trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and morpholine (commercially available)	367.3
26	394.6	4-methoxy-piperidine-1-carboxylic acid [trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and 4-methoxy-piperidine (commercially available)	395.4
27	441.6	4-phenyl-piperazine-1-carboxylic acid [trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and 1-phenyl-piperazine (commercially available)	442.5
28	421	1-(4-chloro-phenyl)-3-[trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-urea	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and (4-chloro-phenyl)-methyl-amine (commercially available)	421.3

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
29	414.6	1-benzyl-1-ethyl-3-[trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and benzyl-ethyl-amine (commercially available)	415.5
30	414.6	3-[<i>trans</i> -4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-phenyl-1-propyl-urea	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and phenyl-propyl-amine (commercially available)	415.5
31	412.6	3,4-dihydro-2H-quinoline-1-carboxylic acid [trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and 1,2,3,4-tetrahydro-quinoline (commercially available)	413.4
32	404.5	1-(3-fluoro-phenyl)-3-[trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-urea	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and (3-fluoro-phenyl)-methyl-amine (commercially available)	405.5

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
33	400.5	4,4-difluoro-piperidine-1-carboxylic acid [trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and 4,4-difluoro-piperidine (commercially available)	401.4
34	398.6	1,3-dihydro-isoindole-2-carboxylic acid [trans-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide	<i>trans</i> -(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, dihydrochloride (intermediate 2) and 2,3-dihydro- <i>H</i> -isoindole (commercially available)	394.4

Example 35

(4-Cyclopentyl-piperazin-1-yl)-[4-(2-fluoro-phenylamino)-cyclohexyl]-methanone

A mixture of 86 mg (0.5 mmol) 4-oxo-cyclohexanecarboxylic acid ethyl ester
 5 (commercially available), 100 mg (0.6 mmol) 2-fluoro-phenylamine and 300 mg (5 mmol) acetic acid in 5 mL THF was stirred for 1 h at 60 °C. Afterwards 159 mg (0.75 mmol) sodium triacetoxyborohydride were added and the mixture was heated to 65 °C for 16 h. After evaporation of the volatiles 10 mL 1N NaHCO₃ aq. was added and the mixture was extracted with DCM. The combined organic layers were evaporated and
 10 methanol and DMF were added and the mixture was subjected to preparative HPLC purification on reversed phase eluting with a gradient of acetonitrile / water (0.1 % NEt₃). The combined product fractions were evaporated to dryness to yield the intermediate 3-(2-fluoro-phenylamino)-cyclohexanecarboxylic acid ethyl ester. MS(m/e): 266.2 (MH⁺). A mixture of 21 mg (0.08 mmol) 4-(2-fluoro-phenylamino)-
 15 cyclohexanecarboxylic acid ethyl ester, 17 mg (0.4 mmol) LiOH·H₂O in a mixture of 2mL THF/methanol/water was heated to 45 °C for 2 h and subsequently evaporated. The

intermediately built acid was dissolved in 2 mL DMF and treated with 30 mg (0.096 mmol) TBTU, 24 mg (0.24) NEt₃ and 13.5 mg (0.88 mmol) 1-cyclopentyl-piperazine (commercially available) and stirred for 16 h at room temperature. The mixture was directly subjected to preparative HPLC purification on reversed phase eluting with a
 5 gradient of acetonitrile / water (0.1 % NEt₃). The combined product fractions were evaporated to dryness to yield 6.4 mg (21 %) of the title compound. MS(m/e): 374.4 (MH⁺).

According to the procedure described for example 35 further piperazinyl-carbonyl-cyclohexyl derivatives have been synthesized from their respective starting materials
 10 mentioned in table 4. *Cis* respectively *trans* isomers have been obtained through separation of the diastomeric reaction mixture by column chromatography on silica or preparative HPLC on reversed phase as appropriate. Table 4 comprises example 36 to example 146.

Table 4

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
36	373.5	(4-cyclopentyl-piperazin-1-yl)-[4-(3-fluoro-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	374.4
37	373.5	(4-cyclopentyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	374.4

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
38	391.5	(4-cyclopentyl-piperazin-1-yl)-[4-(2,4-difluorophenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 2,4-di-fluorophenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	392.2
39	380.5	3-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-cyanophenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	381.5
40	385.6	(4-cyclopentyl-piperazin-1-yl)-[4-(2-methoxyphenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 2-methoxyphenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	386.4
41	385.6	(4-cyclopentyl-piperazin-1-yl)-[4-(4-methoxyphenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-methoxyphenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	386.5

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
42	397.6	1-{4-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 1-(4-amino-phenyl)-ethanone (commercially available) and 1-cyclopentyl-piperazine (commercially available)	398.4
43	459.6	[4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), (4-amino-phenyl)-phenyl-methanone (commercially available) and 1-cyclopentyl-piperazine (commercially available)	460.4
44	357.5	(4-cyclopentyl-piperazin-1-yl)-[4-(pyrazin-2-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), pyrazin-2-ylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	358.5
45	387.5	(4-cyclopentyl-piperazin-1-yl)-{4-[(3-fluoro-phenyl)-methyl-amino]-cyclohexyl}-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), (3-fluoro-phenyl)-methyl-amine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	388.5

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
46	387.5	(4-cyclopentyl-piperazin-1-yl)-{4-[(4-fluoro-phenyl)-methyl-amino]-cyclohexyl}-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), (4-fluoro-phenyl)-methyl-amine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	388.5
47	347.5	[4-(2-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 2-fluoro-phenylamine (commercially available) and 1-(2-propyl)-piperazine (commercially available)	348.4
48	365.5	[4-(2,4-difluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 2,4-difluoro-phenylamine (commercially available) and 1-(2-propyl)-piperazine (commercially available)	366.3
49	354.5	3-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-cyano-phenylamine (commercially available) and 1-(2-propyl)-piperazine (commercially available)	355.5

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
50	359.5	(4-isopropyl-piperazin-1-yl)-[4-(4-methoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-methoxy-phenylamine (commercially available) and 1-(2-propyl)-piperazine (commercially available)	360.4
51	371.5	1-{4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 1-(4-amino-phenyl)-ethanone (commercially available) and 1-(2-propyl)-piperazine (commercially available)	372.3
52	433.6	[4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), (4-amino-phenyl)-phenyl-methanone (commercially available) and 1-(2-propyl)-piperazine (commercially available)	434.4
53	380.53	2-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 2-cyano-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	381.4

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
54	395.49	<i>cis</i> -[4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-difluoromethoxy-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	396.1
55	395.49	[4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-difluoromethoxy-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	396.1
56	371.52	<i>trans</i> -1-{4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 1-(4-amino-phenyl)-ethanone (commercially available) and 1-isopropyl-piperazine (commercially available)	372.2
57	371.52	<i>cis</i> -1-{4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 1-(4-amino-phenyl)-ethanone (commercially available) and 1-isopropyl-piperazine (commercially available)	372.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
58	360.5	<i>trans</i> -(4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-methoxy-pyridin-3-ylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	361.4
59	360.5	<i>cis</i> -(4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-methoxy-pyridin-3-ylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	361.4
60	347.48	<i>trans</i> -[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	348.3
61	347.48	<i>cis</i> -[4-(4-Fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-Methoxy-pyridin-3-ylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	348.3

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
62	372.51	<i>trans</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-methoxy-pyridin-3-ylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	373.2
63	372.51	<i>cis</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-methoxy-pyridin-3-ylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	373.2
64	361.5	<i>trans</i> -[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	362.5

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
65	361.5	<i>trans</i> -(4- <i>tert</i> -butyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1- <i>tert</i> -butyl-piperazine (commercially available)	362.4
66	361.5	<i>trans</i> -(4- <i>sec</i> -butyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1- <i>sec</i> -butyl-piperazine (commercially available)	362.4
67	387.5	<i>trans</i> -(4-cyclohexyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1-cyclohexyl-piperazine (commercially available)	388.4

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
68	411.5	<i>trans</i> -[4-(4-fluoro-phenylamino)-cyclohexyl]-[4-(2-methanesulfonyl-ethyl)-piperazin-1-yl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1-(2-methanesulfonyl-ethyl)-piperazine (commercially available)	412.3
69	347.5	<i>trans</i> -[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-propyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1-propyl-piperazine (commercially available)	348.5
70	333.5	<i>trans</i> -[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-methyl-[1,4]diazepan-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1-methyl-[1,4]diazepane (commercially available)	334.3

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
71	359.5	<i>trans</i> -(4-cyclopropylmethyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 1-cyclopropylmethyl-piperazine (commercially available)	360.2
72	358.5	<i>trans</i> -3-{4-[4-(4-fluoro-phenylamino)-cyclohexanecarbonyl]-piperazin-1-yl}-propionitrile	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-fluoro-phenylamine (commercially available) and 3-piperazin-1-yl-propionitrile (commercially available)	359.2
73	388.9	3-chloro-4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-amino-3-chloro-benzonitrile (commercially available) and 1-isopropyl-piperazine (commercially available)	389.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
74	415.5	<i>trans</i> -[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	416.2
75	415.5	<i>cis</i> -[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	416.2
76	388.9	<i>trans</i> -2-chloro-4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-amino-2-chloro-benzonitrile (commercially available) and 1-isopropyl-piperazine (commercially available)	389.2
77	388.9	<i>cis</i> -2-chloro-4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-amino-2-chloro-benzonitrile (commercially available) and 1-isopropyl-piperazine (commercially available)	389.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
78	461.5	<i>trans</i> -(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethanesulfonyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethanesulfonyl-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	462.3
79	461.5	<i>cis</i> -(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethanesulfonyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethanesulfonyl-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	462.3
80	383.5	<i>trans</i> -5-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-indan-1-one	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-amino-indan-1-one (commercially available) and 1-isopropyl-piperazine (commercially available)	384.3
81	383.5	<i>cis</i> -5-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-indan-1-one	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-amino-indan-1-one (commercially available) and 1-isopropyl-piperazine (commercially available)	384.3

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
82	372.5	<i>trans</i> -4-[4-(4-Isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzamide	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-amino-benzamide (commercially available) and 1-isopropyl-piperazine (commercially available)	373.3
83	372.5	<i>cis</i> -4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzamide	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-amino-benzamide (commercially available) and 1-isopropyl-piperazine (commercially available)	373.3
84	425.5	<i>trans</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	426.2
85	425.5	<i>cis</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	426.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
86	390	[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	390.2
87	441.5	<i>trans</i> -(4-cyclopentyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	442.3
88	441.5	<i>cis</i> -(4-cyclopentyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	442.3
89	439.5	<i>trans</i> -(4-cyclopentyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	440.3

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
90	439.5	cis-(4-cyclopentyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	440.3
91	404	[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	404.3
92	375.9	[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-cyclopropyl-piperazine (commercially available)	376.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
93	429.5	<i>trans</i> -[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	430.2
94	429.5	<i>cis</i> -[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	430.2
95	427.5	<i>trans</i> -(4-isopropyl-3-methyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	428.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
96	427.5	<i>cis</i> -(4-isopropyl-3-methyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	428.3
97	398.5	<i>trans</i> -(4-isopropyl-piperazin-1-yl)-[4-(6-trifluoromethyl-pyridin-3-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-trifluoromethyl-pyridin-3-ylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	399.2
98	397.5	<i>trans</i> -(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethyl-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	398.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
99	413.5	<i>trans</i> -(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	414.2
100	363.9	<i>trans</i> -[4-(4-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-chloro-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	364.2
101	363.9	<i>trans</i> -[4-(3-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	364.2
102	378	<i>trans</i> -[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	378.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
103	398.5	<i>cis</i> -(4-isopropyl-piperazin-1-yl)-[4-(6-trifluoromethyl-pyridin-3-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-trifluoromethyl-pyridin-3-ylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	399.2
104	397.5	<i>cis</i> -(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethyl-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	398.2
105	413.5	<i>cis</i> -(4-isopropyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	414.2
106	363.9	<i>cis</i> -[4-(4-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-chloro-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	364.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
107	363.9	<i>cis</i> -[4-(3-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	364.2
108	378	<i>cis</i> -[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	378.2
109	373.5	<i>trans</i> -[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-fluoro-2,3-dihydro-1H-indole (commercially available) and 1-isopropyl-piperazine (commercially available)	374.2
110	373.5	<i>cis</i> -[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-fluoro-2,3-dihydro-1H-indole (commercially available) and 1-isopropyl-piperazine (commercially available)	374.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
111	348.5	[4-(3,5-dimethyl-isoxazol-4-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3,5-dimethyl-isoxazol-4-ylamine (commercially available) and 1-isopropyl-piperazine (commercially available)	349.2
112	427.5	<i>trans</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	428.2
113	410.5	<i>trans</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(6-trifluoromethyl-pyridin-3-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-trifluoromethyl-pyridin-3-ylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	411.2
114	409.5	<i>trans</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethyl-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	410.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
115	375.9	<i>trans</i> -[4-(4-chloro-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-chloro-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	376.2
116	375.9	<i>trans</i> -[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	376.2
117	390	<i>trans</i> -[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	390.2
118	427.5	<i>cis</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	428.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
119	410.5	<i>cis</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(6-trifluoromethyl-pyridin-3-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 6-trifluoromethyl-pyridin-3-ylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	411.2
120	409.5	<i>cis</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethyl-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	401.2
121	375.9	<i>cis</i> -[4-(4-chloro-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-chloro-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	376.2
122	375.9	<i>cis</i> -[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	376.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
123	390	<i>cis</i> -[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclobutyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	390.2
124	385.5	<i>trans</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-fluoro-2,3-dihydro-1H-indole (commercially available) and 1-cyclobutyl-piperazine (commercially available)	386.2
125	385.5	<i>cis</i> -(4-cyclobutyl-piperazin-1-yl)-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-fluoro-2,3-dihydro-1H-indole (commercially available) and 1-cyclobutyl-piperazine (commercially available)	386.2
126	360.5	(4-cyclobutyl-piperazin-1-yl)-[4-(3,5-dimethyl-isoxazol-4-ylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3,5-dimethyl-isoxazol-4-ylamine (commercially available) and 1-cyclobutyl-piperazine (commercially available)	361.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
127	390	<i>trans</i> -[4-(4-chloro-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-chloro-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	391.2
128	390	<i>trans</i> -[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	390.2
129	404	<i>trans</i> -[4-(3-Chloro-4-methyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	404.2
130	423.5	<i>cis</i> -(4-cyclopentyl-piperazin-1-yl)-[4-(4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethyl-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	424.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
131	390	<i>cis</i> -[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-cyclopentyl-piperazine (commercially available)	390.2
132	399.6	<i>trans</i> -(4-cyclopentyl-piperazin-1-yl)-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-fluoro-2,3-dihydro-1H-indole (commercially available) and 1-cyclopentyl-piperazine (commercially available)	400.2
133	399.6	<i>cis</i> -(4-cyclopentyl-piperazin-1-yl)-[4-(5-fluoro-2,3-dihydro-indol-1-yl)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-fluoro-2,3-dihydro-1H-indole (commercially available) and 1-cyclopentyl-piperazine (commercially available)	400.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
134	378	<i>trans</i> -[4-(4-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-chloro-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	378.2
135	378	<i>trans</i> -[4-(3-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	378.2
136	378	<i>cis</i> -[4-(4-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-chloro-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	378.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
137	378	cis-[4-(3-chloro-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	378.2
138	392	cis-[4-(3-chloro-4-methyl-phenylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-4-methyl-phenylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	392.2
139	362.5	[4-(3,5-dimethyl-isoxazol-4-ylamino)-cyclohexyl]-(4-isopropyl-3-methyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3,5-dimethyl-isoxazol-4-ylamine (commercially available) and 1-isopropyl-2-methyl piperazine (commercially available)	363.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
140	375.9	<i>cis</i> -[4-(4-chloro-phenylamino)-cyclohexyl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-chloro-phenylamine (commercially available) and 1-cyclopropylmethyl-piperazine (commercially available)	376.2
141	375.9	<i>cis</i> -[4-(3-chloro-phenylamino)-cyclohexyl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1-cyclopropylmethyl-piperazine (commercially available)	376.2
142	429.5	<i>trans</i> -(4- <i>sec</i> -butyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1- <i>sec</i> -butyl-piperazine (commercially available)	430.2

Ex. No.	MW	Name	Starting materials	MW found (MH ⁺)
143	427.5	<i>trans</i> -(4- <i>sec</i> -butyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1- <i>sec</i> -butyl-piperazine (commercially available)	428.2
144	429.5	<i>cis</i> -(4- <i>sec</i> -butyl-piperazin-1-yl)-[4-(3-fluoro-4-trifluoromethyl-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-fluoro-4-trifluoromethyl-phenylamine (commercially available) and 1- <i>sec</i> -butyl-piperazine (commercially available)	430.2
145	427.5	<i>cis</i> -(4- <i>sec</i> -butyl-piperazin-1-yl)-[4-(4-trifluoromethoxy-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 4-trifluoromethoxy-phenylamine (commercially available) and 1- <i>sec</i> -butyl-piperazine (commercially available)	428.2
146	378	<i>cis</i> -(4- <i>sec</i> -butyl-piperazin-1-yl)-[4-(3-chloro-phenylamino)-cyclohexyl]-methanone	4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 3-chloro-phenylamine (commercially available) and 1- <i>sec</i> -butyl-piperazine (commercially available)	378.2

Example 147

trans-(4-Cycloheptyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone

a) Step 1: *trans*-[4-(4-fluoro-phenylamino)-cyclohexyl]-piperazin-1-yl-methanone

- 5 In analogy to the procedure described for the synthesis of 4-cyclopentyl-piperazin-1-yl)-[4-(2-fluoro-phenylamino)-cyclohexyl]-methanone (Example 35) the title compound was prepared from 4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 2-fluoro-phenylamine (commercially available) and piperazine. The intermediately built *trans*-4-(4-fluoro-phenylamino)-
10 cyclohexanecarboxylic acid was obtained from the racemic reaction mixture through separation by preparative HPLC on reversed phase.

MS (m/e): 306.1 (MH⁺).

b) Step 2: *trans*-(4-cycloheptyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone

- 15 A mixture of 76.3 mg (0.25 mmol) (*trans*)-[4-(4-fluoro-phenylamino)-cyclohexyl]-piperazin-1-yl-methanone, 36.4 mg (0.325 mmol) cycloheptanone and 79.5 mg (0.375 mmol) sodium triacetoxyborohydride and 150 mg (2.5 mmol) acetic acid in 3 mL methanol was heated to 70 °C for 16h. The mixture was evaporated and NaHCO₃ aq. was added. The mixture was extracted with DCM and after evaporatioin purified by
20 preparative HPLC on reversed phase eluting with a gradient formed from acetonitrile, water and NEt₃. Evaporation of the product fraction yielded 7.8 mg (8%) of the title compound. MS (m/e): 402.5 (MH⁺).

Example 148

- trans*-[4-(4-Fluoro-phenylamino)-cyclohexyl]-[4-(tetrahydro-pyran-4-yl)-piperazin-1-yl]-methanone

- In analogy to the procedure described for the synthesis of *trans*-[4-(4-fluoro-phenylamino)-cyclohexyl]-piperazin-1-yl-methanone (example 147) the title compound was prepared from *trans*-[4-(4-fluoro-phenylamino)-cyclohexyl]-piperazin-1-yl-methanone and tetrahydro-pyran-4-one (commercially available).
30 MS (m/e): 390.4 (MH⁺).

Example 149

trans-[4-(1-Ethyl-propyl)-piperazin-1-yl]-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone

In analogy to the procedure described for the synthesis of *trans*-[4-(4-fluoro-phenylamino)-cyclohexyl]-piperazin-1-yl-methanone (example 147) the title compound
5 was prepared from *trans*-[4-(4-fluoro-phenylamino)-cyclohexyl]-piperazin-1-yl-methanone and pentan-3-one (commercially available).

MS (m/e): 376.4(MH⁺).

Example 150

10 (4-Cyclobutyl-piperazin-1-yl)-[4-(6-isopropoxy-pyridin-3-ylamino)-cyclohexyl]-methanone

a) Step 1: (4-Cyclobutyl-piperazin-1-yl)-[4-(6-hydroxy-pyridin-3-ylamino)-cyclohexyl]-methanone

In analogy the the procedure described for the synthesis of 4-cyclopentyl-piperazin-1-yl)-[4-(2-fluoro-phenylamino)-cyclohexyl]-methanone (Example 35) the
15 title compound was prepared from 4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 5-amino-pyridin-2-ol (commercially available) and 1-cyclobutyl-piperazine (commercially available).

MS (m/e): 359.2 (MH⁺).

20 b) Step 2: (4-Cyclobutyl-piperazin-1-yl)-[4-(6-isopropoxy-pyridin-3-ylamino)-cyclohexyl]-methanone

A mixture of 21 mg (0.058 mmol) (4-cyclobutyl-piperazin-1-yl)-[4-(6-hydroxy-pyridin-3-ylamino)-cyclohexyl]-methanone, 17.4 mg (0.29 mmol) isopropanol and 28 mg (0.11 mmol) cyanomethylene tri-*N*-butylphosphorane in 2 mL THF was heated to
25 80 °C for 2 h. The mixture was concentrated and purified by preparative HPLC on reversed phase eluting with a gradient formed from acetonitrile, water and NEt₃. Evaporation of the product fraction yielded 6.6 mg (28%) of the title compound.

MS (m/e): 401.4 (MH⁺).

Example 151

(4-Cyclobutyl-piperazin-1-yl)-[4-(6-cyclopropylmethoxy-pyridin-3-ylamino)-cyclohexyl]-methanone

In analogy to the procedure described for the synthesis of 4-cyclobutyl-piperazin-1-yl)-[4-(6-isopropoxy-pyridin-3-ylamino)-cyclohexyl]-methanone (example 150) the title
5 compound was prepared from (4-cyclobutyl-piperazin-1-yl)-[4-(6-hydroxy-pyridin-3-ylamino)-cyclohexyl]-methanone and cyclopropylmethanol (commercially available).

MS (m/e): 413.5 (MH⁺).

Example 152

10 trans-(4-Cyclobutyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone

a) Step 1:

A mixture of 500 mg (2.9 mmol) 4-oxo-cyclohexanecarboxylic acid ethyl ester (commercially available), 359 mg (0.6 mmol) 4-fluoro-phenylamine and 1.76 g (29 mmol) acetic acid in 5 mL THF was stirred for 1 h at room temperature. Afterwards 809
15 mg (3.8 mmol) sodium triacetoxymethylborohydride were added and the mixture was heated to 60 °C for 2 h. To the mixture, saturated NaHCO₃ aq. was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and evaporated. The mixture was purified with flash column chromatography (c-heptane-AcOEt 100:0 to 15:85). The combined product fractions were evaporated to dryness to
20 yield the intermediate 3-(4-fluoro-phenylamino)-cyclohexanecarboxylic acid ethyl ester (679 mg, 87 %). A mixture of 679 mg (2.6 mmol) of 4-(4-fluoro-phenylamino)-cyclohexanecarboxylic acid ethyl ester, 430 mg (10.5 mmol) of LiOH·H₂O in a mixture of THF (5mL)/methanol (1 mL)/water (1 mL) was stirred at room temperature for 72h. The mixture was filtrated and the filtrate was evaporated. The mixture was subjected to
25 preparative HPLC purification on reversed phase eluting with a gradient of acetonitrile / water (5 % HCOOH). The combined product fractions were evaporated to dryness to yield 122 mg of *trans*- 4-(4-fluoro-phenylamino)-cyclohexanecarboxylic acid (20 %) and 178 mg of *cis*-4-(4-fluoro-phenylamino)-cyclohexanecarboxylic acid (29 %).

trans-derivative: MS(m/e): 238.1 (MH⁺); *cis*-derivative MS(m/e): 238.1 (MH⁺).

b) Step 2:

44 mg (0.185 mmol) of *trans*-4-(4-fluoro-phenylamino)-cyclohexanecarboxylic acid was dissolved in 0.3 mL DMF and treated with 71 mg (0.223 mmol) TBTU (*O*-benzo-triazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate), 94 mg (0.927 mmol) NEt₃ and 43 mg (0.204 mmol) 1-cyclobutyl-piperazine and stirred for 12 h at room temperature. To the mixture, saturated NaHCO₃ aq. was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and evaporated. The mixture was purified with flash column chromatography (CH₂Cl₂-MeOH 9:1). The combined product fractions were evaporated to dryness to yield 45 mg (67%) of the title compound.

MS (m/e): 360.3 (MH⁺).

Example 153

cis-(4-Cyclobutyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone

According to the procedure described for step 2 in example 152, *cis*-(4-cyclobutyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone has been synthesized from *cis*-4-(4-fluoro-phenylamino)-cyclohexanecarboxylic acid.

MS (m/e): 360.3 (MH⁺).

Example 154

[4-(2,4-Dichloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone

According to the procedure described for step 2 in example 1, [4-(2,4-dichloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone has been synthesized from 2,4-dichloroaniline and 4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexanone.

MS (m/e): 398.2 (MH⁺).

Example 155

trans-[4-(6-Chloro-pyridin-3-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone

A mixture of 50 mg (0.197 mmol) of *trans*-(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, 47 mg (0.197 mmol) of 2-chloro-5-iodopyridine, 4 mg (0.02 mmol) of CuI, 84 mg (0.395 mmol) of K₃PO₄, 24 mg (0.395 mmol) of ethylene glycol

and 0.5 mL of 2-propanol was stirred at 160 °C for 30 min under microwave irradiation. To the mixture, saturated NaHCO₃ aq. was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and evaporated. The mixture was purified with preparative TLC (CH₂Cl₂-MeOH 20:1). The combined
5 product fractions were evaporated to dryness to yield 14 mg (19 %) of the title compound.

MS (m/e): 365.2 (MH⁺).

Example 156

trans-6-[4-(4-Isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-nicotinonitrile

10 A mixture of 214 mg (0.84 mmol) of *trans*-(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, 200 mg (1.44 mmol) of 6-chloronicotinonitrile (commercially available), 932 mg (7.22 mmol) of diisopropylethylamine and 5 mL of 1,4-dioxane was stirred at 170 °C for 20 min under microwave irradiation. The mixture was evaporated. The mixture was purified with flush column chromatography (CH₂Cl₂-
15 MeOH 95:5). The combined product fractions were evaporated to dryness to yield 26 mg (9 %) of the title compound.

MS (m/e): 356.1 (MH⁺).

Example 157

trans-(4-Isopropyl-piperazin-1-yl)-[4-(5-methanesulfonyl-pyridin-2-ylamino)-cyclohexyl]-methanone

20 A mixture of 215 mg (0.85 mmol) of *trans*-(4-amino-cyclohexyl)-(4-isopropyl-piperazin-1-yl)-methanone, 200 mg (0.85 mmol) of 2-bromo-5-methanesulfonyl-pyridine (Bioorg. Med. Chem. Lett. 16, 2076 (2006)), 547 mg (4.24 mmol) of diisopropylethylamine and 5 mL of 1,4-dioxane was stirred at 170 °C for 1 h under
25 microwave irradiation. The mixture was evaporated. The mixture was purified with flush column chromatography (CH₂Cl₂-MeOH 95:5). The combined product fractions were evaporated to dryness to yield the title compound.

MS (m/e): 409.1 (MH⁺).

Example A

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

<u>Ingredients</u>	<u>Per tablet</u>	
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

- 5 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:

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

- 5 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

- 5 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

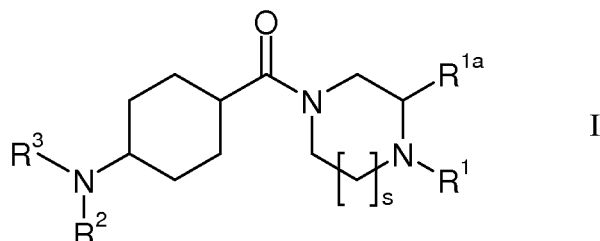
Sachets containing the following ingredients can be manufactured in a conventional manner:

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

- 5 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



wherein

5 s is 1 or 2;

R^1 is selected from the group consisting of lower alkyl, cycloalkyl, lower cycloalkylalkyl, lower cyanoalkyl, lower alkylsulfonylalkyl and tetrahydropyranyl;

R^{1a} is hydrogen or lower alkyl;

10 R^2 is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;

15 R^3 is selected from the group consisting of
 $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl,

20 $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl,

indanyl, 1-oxo-indanyl,

-CO-(C₃-C₈)-alkyl,

25 -CO-(CH₂)_p-aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower

alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,

5 $-\text{CO}-(\text{CH}_2)_q$ -heteroaryl, wherein q is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, and
 $-\text{CO}-\text{NR}^4\text{R}^5$; or

10 R^2 and R^3 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring that is condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen;

R^4 is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;

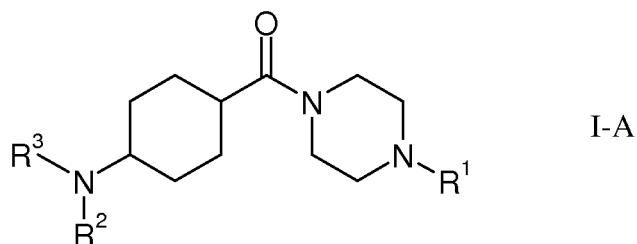
15 R^5 is selected from the group consisting of lower alkyl, aryl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and lower arylalkyl wherein the phenyl ring may be unsubstituted or substituted with
20 one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl;

or

25 R^4 and R^5 together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group, said heterocyclic ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and
30 carbamoyl, or being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen;

and pharmaceutically acceptable salts thereof.

2. Compounds of formula I according to claim 1 having the formula



wherein

R^1 is lower alkyl or cycloalkyl;

5 R^2 is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;

R^3 is selected from the group consisting of
 10 $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,

$-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is
 15 unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,

indanyl,

$-CO-(C_3-C_8)$ -alkyl,

$-CO-(CH_2)_p$ -aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is unsubstituted
 20 or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl,

$-CO-(CH_2)_q$ -heteroaryl, wherein q is 0, 1 or 2 and wherein the heteroaryl ring is
 25 unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, and

$-CO-NR^4R^5$; or

R^2 and R^3 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring that is condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen;

5 R^4 is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;

R^5 is selected from the group consisting of
lower alkyl,
aryl unsubstituted or substituted with one, two or three groups independently
10 selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy,
lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and
lower arylalkyl wherein the phenyl ring may be unsubstituted or substituted with
one or two groups independently selected from lower alkyl, halogen, lower
halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy
15 and lower hydroxyalkyl;
or

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or
7-membered heterocyclic ring optionally containing a further heteroatom selected
from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group,
20 said heterocyclic ring being unsubstituted or substituted by one, two or three
groups independently selected from lower alkyl, halogen, halogenalkyl, cyano,
hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and
carbamoyl, or
being condensed with a phenyl ring, said phenyl ring being unsubstituted or
25 substituted by one, two or three groups independently selected from lower alkyl,
lower alkoxy and halogen;

and pharmaceutically acceptable salts thereof.

3. Compounds of formula I according to claim 1, wherein R^3 is selected from the
group consisting of
30 $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or
substituted with one, two or three groups independently selected from lower alkyl,
halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl,
carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy,
lower cycloalkylalkoxy and lower hydroxyalkyl,

5 $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl, indanyl and 1-oxo-indanyl.

10 4. Compounds of formula I according to claims 1 or 3, wherein R^3 is $-(CH_2)_m$ -aryl, wherein m is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl.

15 5. Compounds of formula I according to claims 1 or 3, wherein R^3 is $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl.

20 6. Compounds of formula I according to any one of claims 1, 3 or 5, wherein R^3 is $-(CH_2)_n$ -heteroaryl, wherein n is 0, 1 or 2 and wherein the heteroaryl ring is pyridyl or isoxazolyl unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, carbamoyl, lower alkylsulfonyl, lower halogenalkylsulfonyl, lower halogenalkoxy, lower cycloalkylalkoxy and lower hydroxyalkyl.

25 7. Compounds of formula I according to claim 1, wherein R^3 is selected from the group consisting of

$-CO-(C_3-C_8)$ -alkyl,
 $-CO-(CH_2)_p$ -aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl, and

30

$-\text{CO}-(\text{CH}_2)_q$ -heteroaryl, wherein q is 0, 1 or 2 and wherein the heteroaryl ring is unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl.

5 8. Compounds of formula I according to claims 1 or 7, wherein R^3 is $-\text{CO}-(\text{CH}_2)_p$ -aryl, wherein p is 0, 1 or 2 and wherein the aryl ring is phenyl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl.

10 9. Compounds of formula I according to claim 1, wherein R^3 is $-\text{CO}-\text{NR}^4\text{R}^5$ and wherein

R^4 is selected from the group consisting of hydrogen, lower alkyl, lower halogenalkyl, lower alkoxyalkyl and lower cyanoalkyl;

R^5 is selected from the group consisting of
15 lower alkyl,
 aryl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and lower arylalkyl wherein the phenyl ring may be unsubstituted or substituted with
20 one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl;

or

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or
25 7-membered heterocyclic ring optionally containing a further heteroatom selected from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group, said heterocyclic ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl, or
30 being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen.

10. Compounds of formula I according to claims 1 or 9, wherein R^3 is $-\text{CO}-\text{NR}^4\text{R}^5$ and wherein
 R^4 is hydrogen or lower alkyl; and
 R^5 is selected from the group consisting of
5 lower alkyl,
phenyl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, and
10 lower phenylalkyl wherein the phenyl ring may be unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl.

11. Compounds of formula I according to any one of claims 1, 9 or 10, wherein R^5 is
15 phenyl unsubstituted or substituted with one, two or three groups independently selected from lower alkyl, halogen, lower halogenalkyl, cyano, lower alkoxy, lower alkanoyl, benzyoyl, lower halogenalkoxy and lower hydroxyalkyl, or lower phenylalkyl wherein the phenyl ring may be unsubstituted or substituted with one or two groups independently selected from lower alkyl, halogen, lower halogenalkyl,
20 cyano, lower alkoxy, lower alkanoyl, benzoyl, lower halogenalkoxy and lower hydroxyalkyl.

12. Compounds of formula I according to claim 1, wherein R^3 is $-\text{CO}-\text{NR}^4\text{R}^5$ and wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring optionally containing a further heteroatom
25 selected from nitrogen, oxygen or sulfur, a sulfinyl group or a sulfonyl group, said heterocyclic ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl, pyridyl and carbamoyl, or being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted
30 by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen.

13. Compounds of formula I according to claims 1 or 12, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring

selected from the group consisting of morpholine, piperidine, pyrrolidine, azepane, piperazine, azetidine and thiomorpholine, said heterocyclic ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, halogen, halogenalkyl, cyano, hydroxy, lower hydroxyalkyl, lower alkoxy, oxo, phenyl, benzyl,
5 pyridyl and carbamoyl, or being condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen.

14. Compounds of formula I according to any one of claims 1, 12 or 13, wherein R⁴ and R⁵ together with the nitrogen atom to which they are attached form a group selected
10 from 2-methylpyrrolidine, piperidine, 4-methoxypiperidine, 4,4-difluoropiperidine, morpholine, 4-phenylpiperazine, 1,3-dihydro-isoindole and 3,4-dihydro-2H-quinoline.

15. Compounds of formula I according to any one of claims 1 to 14, wherein R¹ is lower alkyl.

16. Compounds of formula I according to any one of claims 1 to 14, wherein R¹ is
15 cycloalkyl.

17. Compounds of formula I according to any one of claims 1 to 16, wherein R² is hydrogen or lower alkyl.

18. Compounds of formula I according to claim 1, wherein R² and R³ together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring
20 that is condensed with a phenyl ring, said phenyl ring being unsubstituted or substituted by one, two or three groups independently selected from lower alkyl, lower alkoxy and halogen.

19. Compounds of formula I according to claim 1, selected from the group consisting of

25 (4-isopropyl-piperazin-1-yl)-(4-p-tolylamino-cyclohexyl)-methanone,
[4-(4-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
[4-(1,3-dihydro-isoindol-2-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,

- (4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-methanone,
- [4-(3,4-dihydro-1H-isoquinolin-2-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- 5 [4-(indan-1-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
- (4-isopropyl-piperazin-1-yl)-[4-(1-phenyl-propylamino)-cyclohexyl]-methanone,
- (4-isopropyl-piperazin-1-yl)-{4-[2-(3-methoxy-phenyl)-ethylamino]-cyclohexyl}-methanone,
- [4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-
- 10 methanone,
- N*-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-isobutyramide,
- N*-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-4-methoxy-benzamide,
- 2,4-difluoro-*N*-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-benzamide,
- 2,4-dichloro-*N*-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-benzamide,
- 15 1-benzyl-1-isopropyl-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
- 1,1-diethyl-3-[*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
- 4-phenyl-piperazine-1-carboxylic acid [*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 1-(4-chloro-phenyl)-3-[*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-
- 20 urea,
- 1-benzyl-1-ethyl-3-[*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
- 3,4-dihydro-2H-quinoline-1-carboxylic acid [*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 1-(3-fluoro-phenyl)-3-[*cis*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-
- 25 urea,
- 2-methyl-pyrrolidine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 1-benzyl-1-isopropyl-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
- 1,1-diethyl-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
- 30 piperidine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,

- morpholine-4-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 4-methoxy-piperidine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 5 4-phenyl-piperazine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 1-(4-chloro-phenyl)-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-urea,
- 1-benzyl-1-ethyl-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-urea,
- 10 3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-phenyl-1-propyl-urea,
- 3,4-dihydro-2H-quinoline-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 1-(3-fluoro-phenyl)-3-[*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-1-methyl-urea,
- 15 4,4-difluoro-piperidine-1-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- 1,3-dihydro-isoindole-2-carboxylic acid [*trans*-4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexyl]-amide,
- (4-cyclopentyl-piperazin-1-yl)-[4-(2-fluoro-phenylamino)-cyclohexyl]-methanone,
- 20 (4-cyclopentyl-piperazin-1-yl)-[4-(3-fluoro-phenylamino)-cyclohexyl]-methanone,
- (4-cyclopentyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
- (4-cyclopentyl-piperazin-1-yl)-[4-(2,4-difluoro-phenylamino)-cyclohexyl]-methanone,
- 3-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
- (4-cyclopentyl-piperazin-1-yl)-[4-(2-methoxy-phenylamino)-cyclohexyl]-methanone,
- 25 (4-cyclopentyl-piperazin-1-yl)-[4-(4-methoxy-phenylamino)-cyclohexyl]-methanone,
- 1-{4-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone,
- [4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,
- (4-cyclopentyl-piperazin-1-yl)-[4-(pyrazin-2-ylamino)-cyclohexyl]-methanone,
- (4-cyclopentyl-piperazin-1-yl)-{4-[(3-fluoro-phenyl)-methyl-amino]-cyclohexyl}-
- 30 methanone,

- (4-cyclopentyl-piperazin-1-yl)-{4-[(4-fluoro-phenyl)-methyl-amino]-cyclohexyl}-methanone,
[4-(2-fluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
[4-(2,4-difluoro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
5 3-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
(4-isopropyl-piperazin-1-yl)-[4-(4-methoxy-phenylamino)-cyclohexyl]-methanone,
1-{4-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-phenyl}-ethanone,
[4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
2-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
10 and pharmaceutically acceptable salts thereof.

20. Compounds of formula I according to claim 1, selected from the group consisting of
[4-(1,3-dihydro-isoindol-2-yl)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
(4-isopropyl-piperazin-1-yl)-[4-(6-methoxy-pyridin-3-ylamino)-cyclohexyl]-
15 methanone,
[4-(indan-1-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
(4-isopropyl-piperazin-1-yl)-[4-(1-phenyl-propylamino)-cyclohexyl]-methanone,
(4-isopropyl-piperazin-1-yl)-{4-[2-(3-methoxy-phenyl)-ethylamino]-cyclohexyl}-methanone,
20 [4-(4-difluoromethoxy-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
(4-cyclopentyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
(4-cyclopentyl-piperazin-1-yl)-[4-(2,4-difluoro-phenylamino)-cyclohexyl]-methanone,
3-[4-(4-cyclopentyl-piperazine-1-carbonyl)-cyclohexylamino]-benzonitrile,
25 [4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-cyclopentyl-piperazin-1-yl)-methanone,
(4-isopropyl-piperazin-1-yl)-[4-(4-methoxy-phenylamino)-cyclohexyl]-methanone,
[4-(4-benzoyl-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,
trans-(4-cyclobutyl-piperazin-1-yl)-[4-(4-fluoro-phenylamino)-cyclohexyl]-methanone,
[4-(2,4-dichloro-phenylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,

trans-[4-(6-chloro-pyridin-3-ylamino)-cyclohexyl]-(4-isopropyl-piperazin-1-yl)-methanone,

trans-6-[4-(4-isopropyl-piperazine-1-carbonyl)-cyclohexylamino]-nicotinonitrile,

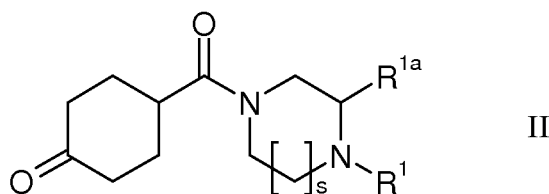
trans-(4-isopropyl-piperazin-1-yl)-[4-(5-methanesulfonyl-pyridin-2-ylamino)-

5 cyclohexyl]-methanone,

and pharmaceutically acceptable salts thereof.

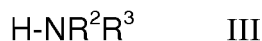
21. A process for the manufacture of compounds according to any one of claims 1 to 20, which process comprises

a) coupling a compound of formula II

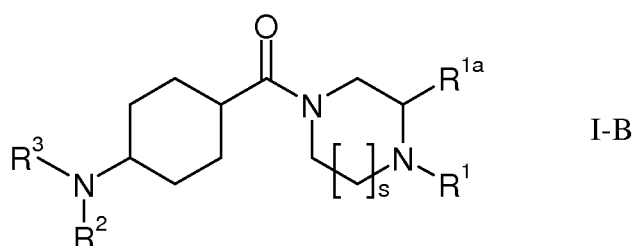


10

wherein s , R^{1a} and R^1 is as defined in claim 1, with an amine of the formula III

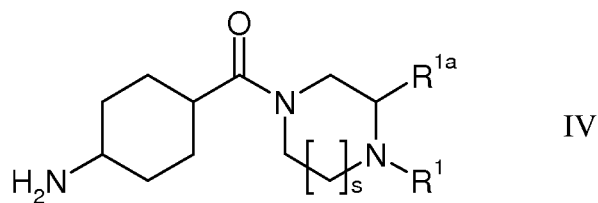


15 wherein R^2 and R^3 are as defined in claim 1 with the proviso that R^3 does not contain a carbonyl group, in the presence of a coupling reagent under basic conditions to obtain a compound of the formula I-B

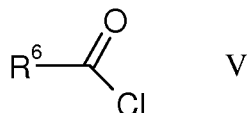


20 wherein s , R^{1a} , R^1 and R^2 are as defined in claim 1 and R^3 is a group as defined in claim 1 other than those groups containing a carbonyl group, , and if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt, or

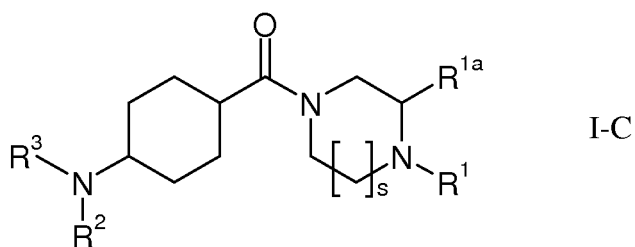
b) reacting a compound of formula IV



wherein s , R^{1a} and R^1 are as defined in claim 1,
with an acid chloride of the formula V

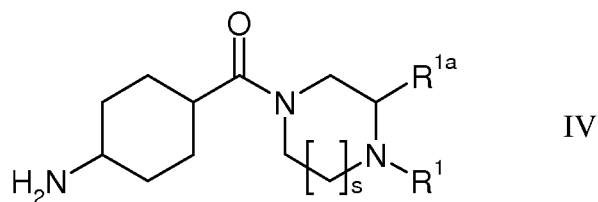


- 5 wherein R^6 is selected from the group consisting of (C_3-C_8) -alkyl, $-(CH_2)_p$ -aryl and $-(CH_2)_q$ -heteroaryl, in the presence of a base
to obtain a compound of the formula I-C



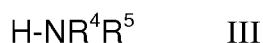
- 10 wherein R^2 is hydrogen and R^3 is selected from the group consisting of $-CO-(C_3-C_8)$ -alkyl, $-CO-(CH_2)_p$ -aryl and $-CO-(CH_2)_q$ -heteroaryl,
and if desired,
converting the compound obtained into a pharmaceutically acceptable acid addition salt,
or

c) coupling a compound of formula IV

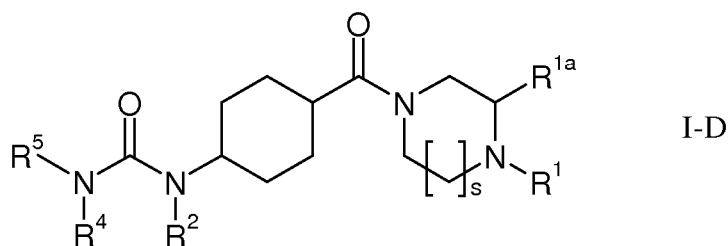


15

wherein s , R^{1a} and R^1 are as defined in claim 1,
after activation with phenylchloroformate with an amine of the formula VI



wherein R^4 and R^5 are as defined in claim 1,
to obtain a compound of the formula I-D



- wherein s , R^{1a} , R^1 , R^2 , R^4 and R^5 are as defined in claim 1,
5 and if desired,
converting the compound obtained into a pharmaceutically acceptable acid addition salt.

22. Compounds according to any one of claims 1 to 20 when manufactured by a process according to claim 21.

23. Pharmaceutical compositions comprising a compound according to any one of
10 claims 1 to 20 as well as a pharmaceutically acceptable carrier and/or adjuvant.

24. Pharmaceutical compositions according to claim 23 for the treatment and/or prevention of diseases which are associated with the modulation of H3 receptors.

25. Compounds according to any one of claims 1 to 20 for use as therapeutically active substances.

- 15 26. Compounds according to any one of claims 1 to 20 for use as therapeutically active substances for the treatment and/or prevention of diseases which are associated with the modulation of H3 receptors.

27. A method for the treatment and/or prevention of diseases which are associated with the modulation of H3 receptors, comprising the step of administering a
20 therapeutically active amount of a compound according to any one of claims 1 to 20 to a human being or animal in need thereof.

28. The use of compounds according to any one of claims 1 to 20 for the preparation of medicaments for the treatment and/or prevention of diseases which are associated with the modulation of H3 receptors.

29. The use according to claim 28 for the treatment and/or prevention of obesity.

5 30. A method for the treatment or prevention of obesity in a human being or animal, which method comprises administering a therapeutically effective amount of a compound of formula I according to any one of claims 1 to 20 in combination or association with a therapeutically effective amount of a compound selected from the group consisting of a lipase inhibitor, an anorectic agent, a selective serotonin reuptake
10 inhibitor, and an agent that stimulates metabolism of body fat.

31. A method of treatment or prevention of type II diabetes in a human being or animal, which comprises administration of a therapeutically effective amount of a compound of formula I according to any one of claims 1 to 20 in combination or association with a therapeutically effective amount of an anti-diabetic agent.

15 32. The use of a compound of formula I according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment or prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor.

33. The use of a compound of formula I according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment or prevention of type II diabetes in a
20 patient who is also receiving treatment with an anti-diabetic agent.

34. The use of a compound of formula I according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment or prevention of dyslipidemia in a patient who is also receiving treatment with a lipid lowering agent.

35. The novel compounds, processes and methods as well as the use of such
25 compounds substantially as described herein before.