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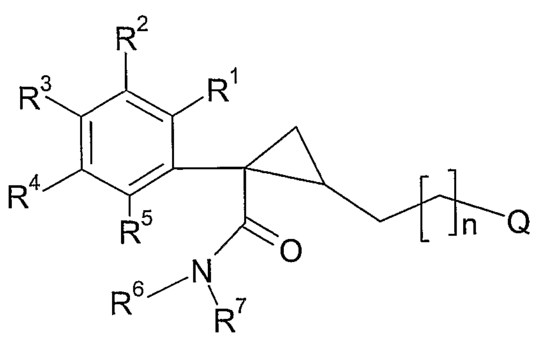
(54) Title: CYCLOPROPYL DERIVATIVES AS NK3 RECEPTOR ANTAGONISTS



(I)

(57) Abstract: The present invention relates to cyclopropyl derivatives of formula (I) and salt thereof. These compounds are NK3 receptor antagonists and may therefore be useful for treatment of diseases where the NK3 receptor is implicated, e.g. psychotic disorders.

CYCLOPROPYL DERIVATIVES AS NK3 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to novel compounds which are NK3 receptor antagonists and as such useful for treatment of diseases where the NK3 receptor is implicated.

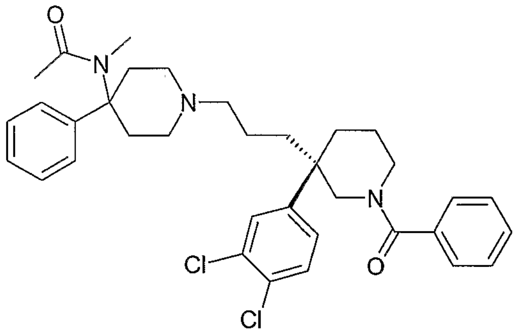
BACKGROUND OF THE INVENTION

Three tachykinins, Substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) are widely distributed throughout the peripheral and central nervous systems. The biological effects of these neuropeptides are primary mediated via binding to and subsequent activation of the three neurokinin receptors, NK1, NK2 and NK3. Substance P is considered to be the endogenous ligand for the NK1 receptor and likewise NKA and NKB for the NK2 and NK3 receptors, respectively. However, recent data indicates that there exist cross-reactivity within the tachykinin system, which might be of physiological relevance as both NKA and NKB potently are able to bind and activate the NK1 receptor (for review see Maggi, CA et al: Trends Pharmacol Sci. 1997, 18, p351-5). The three receptor subtypes belong to the G-protein-coupled receptor super family and have been cloned in various species including mice, rats and humans (Nakanishi S: Annu Rev Neurosci. 1991, 14, p123-36).

The three tachykinin receptors are expressed both centrally and in the periphery. The NK3 receptor is mainly expressed centrally in regions including cortex, striatum, substantia nigra compacta, ventral tegmental area, hypothalamus, amygdala and hippocampus (Stroessl AJ et al: Brain Res. 1990, 534, p1-7, Koutcherov Y et al: Neuroreport. 2000, 11, p3127-31). In the periphery, the NK3 receptor is expressed in regions including colon, kidney, lungs and the urinary bladder (Regoli D et al: Trends Pharmacol Sci. 1988 Aug;9(8): 290-5, Kamali F: Curr Opin Investig Drugs. 2001 Jul;2(7):950-6). Centrally, the NK3 receptor is expressed on cholinergic (Chen LW et al: Neuroscience. 2001;103(2):413-22), noradrenergic (references within Oury-Donat F et al: J Pharmacol Exp Ther. 1995, 274, p148-54) and dopaminergic neurons (Keegan KD et al: Br. J. Pharmacol. 1992, 105, p3-5). In agreement with these results, activation of the NK3 receptor has been reported to be implicated in the regulation of various monoamine transmitters, e.g. dopamine and acetylcholine (Marco N et al: Neuropeptides. 1998, 32, p481-8, Stoessl AJ et al: Brain Res. 1990, 517, p111-6), noradrenaline (Jung M et al: Neuroscience. 1996, 74, p403-14) and serotonine (Stoessl AJ et al: Brain Res. 1990, 517, p111-6).

The NK3 receptor-mediated regulation of monoamine systems supports that the NK3 receptor is involved in diverse functions including memory, learning, cortical processing and behavioral control (Yip J et al: Br J Pharmacol. 1997, 122, p715-25, Ding YQ et al: J Comp Neurol. 1996, 364, p290-310, Mileusnic D et al: Neurobiol Aging. 1999, 20, p19-35) and that it is target for various psychological and neurological disorders (Emonds-Alt X et al: Can J Physiol Pharmacol. 2002, 80, p482-8, Kamali F, Curr Opin Investig Drugs. 2001, 2, p950-6, Langlois X et al: J Pharmacol Exp Ther. 2001, 299, p712-7). Indeed, the NK3 receptor has been reported to be implicated in modulation of anxiety (Ribeiro SJ et al: Neuropeptides. 1999, 33, p181-8).

Further, it has been reported that the NK3 receptor antagonist SR142801 has effect against schizophrenia, in particular positive symptoms. SR142801 is described in, e.g., EP 673928. The structure of SR142801 is outlined below (Kamali F: Curr Opin Investig Drugs. 2001, Jul;2(7):950-6).



In vivo, NK3 receptor activation centrally has been reported to mediate hypertension and tachycardia (Nagashima A et al: Brain Res. 487, 1989, p392-396, Takano Y et al: Brain Res. 1990, 528, p231-7, Picard P et al: Br J Pharmacol. 1994, 112, p240-9) whereas NK3 receptor activation in the periphery mediates hypotension and bradycardia (Couture R et al: Naunyn Schmiedebergs Arch Pharmacol. 1989, 340, p547-57). Additional in vivo studies have indicated that NK3 receptor activation decrease water, salt and alcohol intake (Massi M et al: Brain Res Bull. 1991 26 p155-60, Massi M et al: Neurosci Lett. 1988, 92, p341-6 and Ciccocioppo R et al: Brain Res Bull. 1994, 33, p71-7) which together with the localization of the NK3 receptor on MCH neurons support a role of the NK3 receptor in the regulation of food intake (Griffond B et al: J Chem Neuroanat. 1997, 12, p183-9). Further in vivo studies have shown that the NK3 receptor is implicated in renal control of water and electrolyte homeostasis (Yuan YD: Br J Pharmacol. 1997, 120, p785-96). Activation of the NK3 receptor has been reported to inhibit gastric acid secretion (Improta G et al: Peptides. 1991, 12, p1433-4), induce oral dyskinesia (Liminga U et al: Pharmacol Biochem Behav. 1991, 38, p617-20) and oedema (Inoue H et al: Inflamm Res. 1996, 45, p316-23).

In vitro NK3 activation has been reported to have proconvulsive effect (Maubach KA et al: Neuroscience. 1998, 83, p1047-62) and to mediate hyperexcitability in ischemic injury (Stumm R et al: J Neurosci. 2001, 21, p798-811).

Selective high affinity non-peptide NK3 receptor antagonists have been shown to be antinociceptic (Fioramonti J et al: Neurogastroenterol Motil. 2003, 15, p363-9, Couture R et al: Life Sci. 2000, 66, p51-65, Julia V et al: Gastroenterology. 1999, 116, p1124-31, Coudore-Civiale MA: European Journal of Pharmacology 1998, 361, p175–184) and analgesic (Houghton AK et al: Neuropharmacology. 2000, 39, p133-40). In addition, studies demonstrate consistent effect of a NK3 receptor antagonist against visceral pain encouragingly precluding constipation (Mayer EA et al: Gastroenterology. 1999, 116, p1250-2, Julia V et al: Gastroenterology. 1999 116 p1124-31). Similarly inhibition of the NK3 receptor is stated to prevent gut inflammation highlighting effect against inflammatory bowel disease (Mazelin L et al: Life Sci. 1998, 63, p293-304), cough, airway hyperresponsiveness, microvascular hypersensitivity and reduction of bronchoconstriction (Daoui S et al: Am J Respir Crit Care Med. 1998, 158, p42-8 , Rumsey WL et al: J Pharmacol Exp Ther. 2001, 298, p307-15, Daoui S et al: Pulm Pharmacol Ther. 1997 10 p261-70). Inhibition of the NK3 receptor as therapeutic strategy for Parkinsons disease has been substantiated in several reports (Arenas E: J Neurosci. 1991, 11, p2332-8, Kemel ML et al: J Neurosci. 2002, 22, p1929-36).

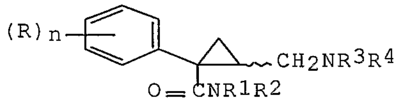
Accordingly, pre-clinical, in vivo and in vitro studies support that NK3 receptor antagonists are of relevance for the treatment or prevention of various disorders including: schizophrenia, depression, anxiety, Parkinson’s disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema and plasma extravasation.

Hence, there is a desire for NK3 receptor antagonists. The present inventors have now found such compounds with a strong affinity for the NK3 receptor.

Several patent applications relate to compounds disclosed as NK receptor antagonist, e.g. EP 474561, EP 512901 and WO 03/051869. In particular, some patent applications relate to compounds disclosed as NK3 receptor antagonist, e.g. WO 9710211, US 5434158 and EP 673928. US 5750549 disclose cyclopentane derivatives as NK1 receptor antagonist.

The compounds of the present invention are all cyclopropyl derivates. As described in the following, some patent applications relate to different cyclopropane derivatives. However, none of these patent applications relates to the NK3 receptor or others of the NK receptors.

JP 03056415 describes cyclopropane derivatives of the following formula



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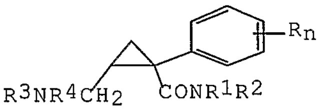
for treatment of cerebral ischemia.

EP 68999 describes cyclopropane derivatives of the following formula



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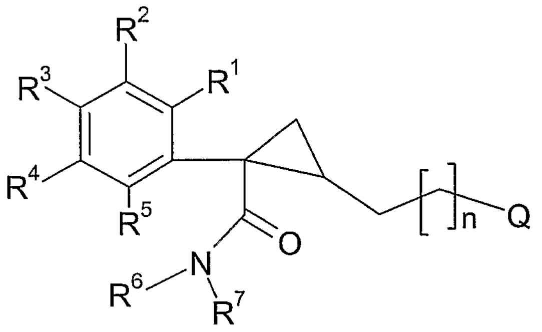
for treatment of depression.

SUMMARY OF THE INVENTION

The objective of the present invention is to provide compounds that are antagonists at the NK3 receptor. Some of the compounds may also have affinity for the NK1 and/or NK2 receptor.

Accordingly, in one aspect the present invention relates to a compound having the general formula I:



(I)

wherein the substituents are as defined herein, or a salt thereof, in particular a pharmaceutically acceptable acid addition salt thereof. The invention in particular provides the (1S,2R)-isomer of such compounds.

Moreover, the invention provides a pharmaceutical composition comprising a compound of formula I as defined herein or a pharmaceutically acceptable salt thereof. Accordingly, the invention provides a compound of formula I as defined herein or a pharmaceutically acceptable salt thereof for use in medicine.

The invention also provides the use of a compound of formula I as defined herein or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of diseases selected from the group consisting of: schizophrenia, psychotic disorders, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema and plasma extravasation.

Further, the invention also provides a method for the treatment of diseases selected from the group consisting of: schizophrenia, psychotic disorders, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema and plasma extravasation, comprising administering a therapeutically effective amount of a compound of formula I as defined herein or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term “halogen” means fluoro, chloro, bromo or iodo.

The expression “C_{1-6}-alk(en/yn)yl” means a C_{1-6}-alkyl, a C_{2-6}-alkenyl or a C_{2-6}-alkynyl group.

The term “C_{1-6} alkyl” refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

The term “C_{2-6} alkenyl” designates such groups having from two to six carbon atoms, including one double bond, including but not limited to ethenyl, propenyl, and butenyl.

The term “C_{2-6} alkynyl” designates such groups having from two to six carbon atoms, including one triple bond, including but not limited to ethynyl, propynyl and butynyl.

The expression “C_{3-8}-cycloalk(en)yl” means a C_{3-8}-cycloalkyl or a C_{3-8}-cycloalkenyl group.

The term “C_{3-8}-cycloalkyl” designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term “C_{3-8}-cycloalkenyl” designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and one double bond, including but not limited to cyclopropenyl, cyclopentenyl, cyclohexenyl, etc.

In the expression “C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl”, the terms “C_{3-8}-cycloalk(en)yl” and “C_{1-6}-alk(en/yn)yl” are as defined above.

The term “C_{1-6}-alk(en/yn)yloxy” refers to groups of the formula C_{1-6}-alk(en/yn)yl-O-, wherein C_{1-6}-alk(en/yn)yl is as defined above.

The terms “C_{1-6}-alk(en/yn)yl-carbonyl”, “C_{1-6}-alk(en/yn)yl-aminocarbonyl” and “di-(C_{1-6}-alkyl)aminocarbonyl” refer to groups of formula C_{1-6}-alk(en/yn)yl-CO-, C_{1-6}-alk(en/yn)yl-NH-CO- and (C_{1-6}-alk(en/yn)yl)$_2$-N-CO-, respectively, wherein C_{1-6}-alk(en/yn)yl is as defined above.

In the expressions “C_{1-6}-alk(en/yn)yl-amino”, “di-(C_{1-6}-alkyl)amino”, “C_{1-6}-alk(en/yn)ylthio”, “halo-C_{1-6}-alk(en/yn)yl”, “halo-C_{1-6}-alk(en/yn)yl-sulfonyl”, “halo-C_{1-6}-alk(en/yn)yl-sulfanyl”, “C_{1-6}-alk(en/yn)ylsulfonyl”, and “C_{1-6}-alk(en/yn)ylsulfanyl” etc., the terms “C_{1-6}-alk(en/yn)yl” and “halo” are as defined above.

As used herein, the term “acyl” refers to formyl, C_{1-6}-alk(en/yn)ylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)ylcarbonyl or a C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-carbonyl group, wherein C_{1-6}-alk(en/yn) and C_{3-8}-cycloalk(en)yl are as defined above and aryl is as defined below.

The term "thioacyl" is the corresponding acyl group, in which the carbonyl group is replaced with a thiocarbonyl group.

The term "aryl" refers to a carbocyclic aromatic group, such as phenyl or naphthyl, in particular phenyl and includes both substituted or unsubstituted carbocyclic aromatic groups. Thus, the aryl is optionally substituted with one or more substituents selected from the substituent list as defined below. Accordingly, the term aryl as used herein means an optionally substituted carbocyclic aromatic group, e.g. phenyl or naphthyl, such that said aromatic group is substituted with one or more substituents selected from the substituent list defined below, e.g., C_{1-6}-alkyl or halogen. The aryl is preferably mono- or bicyclic.

The term “heteroaryl” refers to an aromatic group containing at least one carbon atom and one or more heteroatoms selected from O, S or N. As used herein the term "heteroaryl" refers to a mono- or bicyclic heterocyclic group including but not limited to indolyl, thienyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzofuranyl, benzothienyl, pyridyl and furanyl, in particular pyrimidyl, indolyl, and thienyl. The term heteroaryl as used herein includes both substituted or unsubstituted heteroaryl. Thus, the heteroaryl is optionally substituted with one or more substituents selected from the substituent list as defined below, e.g., C_{1-6}-alkyl or halogen.

The term "monocyclic heteroaryl" as used herein refers to 5- to 6- membered aromatic systems containing 1 to 5 carbon atoms and one or more heteroatoms selected from O, S or N.

Accordingly, the term "heteroaryl" refers to 5-membered monocyclic rings such as, but not limited to, 1*H*-tetrazolyl, 3*H*-1,2,3-oxathiazolyl, 3*H*-1,2,4-oxathiazolyl, 3*H*-1,2,5-oxathiazolyl, 1,3,2-oxathiazolyl, 1,3,4-oxathiazolyl, 1,4,2-oxathiazolyl, 3*H*-1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,4,2-dioxazolyl, 3*H*-1,2,3-dithiazolyl, 3*H*-1,2,4-dithiazolyl, 1,3,2-dithiazolyl, 1,4,2-dithiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1*H*-1,2,3-triazolyl, 1*H*-1,2,4-triazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, 1*H*-imidazolyl, 1*H*-pyrazolyl, 1*H*-pyrrolyl, furanyl, thienyl, 1*H*-pentazole.

Further, the term "heteroaryl" refers to 6-membered monocyclic rings such as, but not limited to, 1,2,3-oxathiazinyl, 1,2,4-oxathiazinyl, 1,2,5-oxathiazinyl, 4*H*-1,3,5-oxathiazinyl, 1,4,2-oxathiazinyl, 1,4,3-oxathiazinyl, 1,2,3-dioxazinyl, 1,2,4-dioxazinyl, 4*H*-1,3,2-dioxazinyl, 4*H*-1,3,5-dioxazinyl, 1,4,2-dioxazinyl, 2*H*-1,5,2-dioxazinyl, 1,2,3-dithiazinyl, 1,2,4-dithiazinyl, 4*H*-1,3,2-dithiazinyl, 4*H*-1,3,5-dithiazinyl, 1,4,2-dithiazinyl, 2*H*-1,5,2-dithiazinyl, 2*H*-1,2,3-oxadiazinyl, 2*H*-1,2,4-oxadiazinyl, 2*H*-1,2,5-oxadiazinyl, 2*H*-1,2,6-oxadiazinyl, 2*H*-1,3,4-oxadiazinyl, 2*H*-1,3,5-oxadiazinyl, 2*H*-1,2,3-thiadiazinyl, 2*H*-1,2,4-thiadiazinyl, 2*H*-1,2,5-thiadiazinyl, 2*H*-1,2,6-thiadiazinyl, 2*H*-1,3,4-thiadiazinyl, 2*H*-1,3,5-thiadiazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 2*H*-1,2-oxazinyl, 2*H*-1,3-oxazinyl, 2*H*-1,4-oxazinyl, 2*H*-1,2-thiazinyl, 2*H*-1,3-thiazinyl, 2*H*-1,4-thiazinyl, pyrazinyl, pyridazinyl, pyrimidyl, pyridyl, 2*H*-pyranyl, 2*H*-thiinyl.

Finally the term "heteroaryl" also refers to bicyclic rings such as, but not limited to, 3*H*-1,2,3-benzoxathiazolyl, 1,3,2-benzodioxazolyl, 3*H*-1,2,3-benzodithiazolyl, 1,3,2-benzodithiazolyl, benzfurazanyl, 1,2,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, 1*H*-benzotriazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, benzoxazolyl, 1,2-benzisothiazolyl, 2,1-benzisothiazolyl, benzothiazolyl, 1*H*-

benzimidazolyl, 1*H*-indazolyl, 3*H*-1,2-benzoxathiolyl, 1,3-benzoxathiolyl, 3*H*-2,1-benzoxathiolyl, 3*H*-1,2-benzodioxolyl, 1,3-benzodioxolyl 3*H*-1,2-benzodithiolyl, 1,3-benzodithiolyl, 1*H*-indolyl, 2*H*-isoindolyl, benzofuranyl, isobenzofuranyl, 1-benzothienyl, 2-benzothienyl, 1*H*-2,1-benzoxazinyl, 1*H*-2,3-benzoxazinyl, 2*H*-1,2-benzoxazinyl, 2*H*-1,3-benzoxazinyl, , 2*H*-1,4-benzoxazinyl, 2*H*-3,1-benzoxazinyl, 1*H*-2,1-benzothiazinyl, 1*H*-2,3-benzothiazinyl, 2*H*-1,2-benzothiazinyl, 2*H*-1,3-benzothiazinyl, 2*H*-1,4-benzothiazinyl, 2*H*-3,1-benzothiazinyl, cinnolinyl, phtalazinyl, quinazolinyl, quinoxalinyl, isoquinolyl, quinolyl, 1*H*-2-benzopyranyl, 2*H*-1-benzopyranyl, 1*H*-2-benzothiopyranyl or 2*H*-1-benzothiopyranyl.

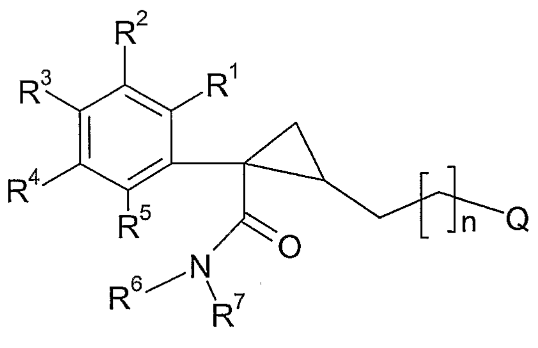
The expression "substituent list" means substituents selected from the group consisting of: halogen, cyano, nitro, C_{1-6}-alkyl (e.g methyl), C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, alkylsulphonyl, hydroxy, trifluoromethyl, trifluoromethylsulfonyl, C_{1-6}-alkylcarbonylamino and C_{1-6}-alkylcarbonylC_{1-6}-alkylamino".

The term "treatment" as used herein in connection with a disease or disorders includes also prevention as the case may be.

Compounds of the invention and salts thereof

The present invention relates to compounds of formula I which are antagonists at the NK3 receptor. These products may therefore be useful in the treatment of certain diseases such as, e.g., schizophrenia, psychotic disorders, depression, anxiety, or Parkinson's disease.

In one aspect, the invention relates to compounds of formula I,



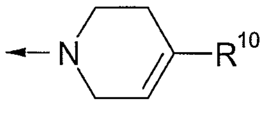
(I)

or a salt thereof, such as a pharmaceutically acceptable salt;

wherein

- R^1-R^5 are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl (e.g C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl; such as methyl), C_{3-8}-cycloalk(en)yl (e.g. C_{3-8}-cycloalkyl), C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl (e.g. C_{3-8}-cycloalkyl-C_{1-6}-alkyl), amino, C_{1-6}-alk(en/yn)ylamino (e.g. C_{1-6}-alkylamino), di-(C_{1-6}-alk(en/yn)yl)amino (.e.g. di-(C_{1-6}-alkyl)amino), C_{1-6}-alk(en/yn)ylcarbonyl (e.g C_{1-6}-alkylcarbonyl), aminocarbonyl, C_{1-6}-alk(en/yn)ylaminocarbonyl (e.g. C_{1-6}-alkylaminocarbonyl), di-(C_{1-6}-alk(en)yl)aminocarbonyl (e.g. di-(C_{1-6}-alkyl)aminocarbonyl)), hydroxy, C_{1-6}-alk(en/yn)yloxy (e.g. C_{1-6}-alkoxy; such as methoxy), C_{1-6}-alk(en/yn)ylthio (e.g. C_{1-6}-alkylthio, such as methylthio), halo-C_{1-6}-alk(en/yn)yl (e.g, halo-C_{1-6}-alkyl, such as trifluoromethyl), halo-C_{1-6}-alk(en/yn)ylsulfonyl (e.g trifluoromethylsulfonyl), halo-C_{1-6}-alk(en/yn)ylsulfanyl (.e.g trifluoromethylsulfanyl)), and C_{1-6}-alk(en/yn)ylsulfonyl (e.g. C_{1-6}-alkylsulfonyl);
- R^6 is selected from hydrogen, halo-C_{1-6}-alk(en/yn)yl (e.g. trifluoromethyl), C_{1-6}-alk(en/yn)yl (e.g. C_{1-6}-alkyl, such as methyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl), C_{3-8}-cycloalk(en)yl (e.g. C_{3-8}-cycloalkyl), and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl (e.g. C_{3-8}-cycloalkyl-C_{1-6}-alkyl);
- R^7 is an aryl or a heteroaryl; or R^7 is a group aryl-CR^8R^9-, wherein R^8 and R^9 are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl (e.g. C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl; such as methyl), C_{3-8}-cycloalk(en)yl (e.g. C_{3-8}-cycloalkyl), and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl (e.g. C_{3-8}-cycloalkyl-C_{1-6}-alkyl);
- n is 0, 1, or 2;

Q is selected from (i)-(vii), the arrow indicating the attachment point:



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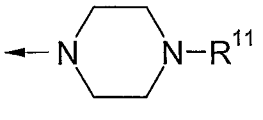

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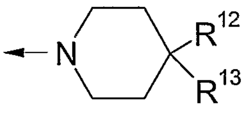

(iii)

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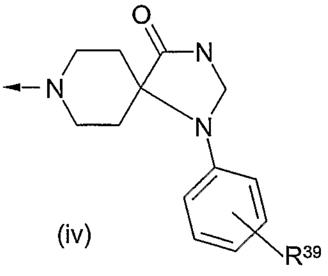

(iv)

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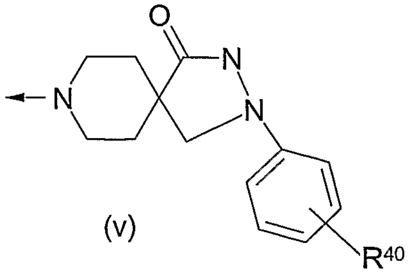

(v)

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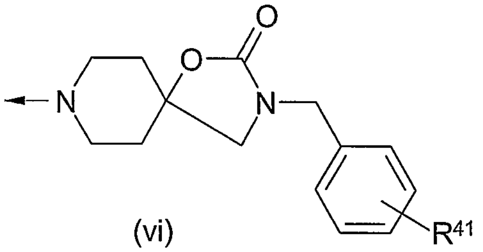

(vi)

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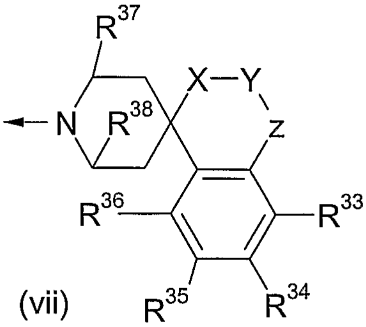


(vii)

wherein R^{10} is an optionally substituted aryl;

wherein R^{11} is selected from an optionally substituted aryl or optionally substituted benzyl, halo-C_{1-6}-alk(en/yn)ylsulfonyl (e.g. trifluoromethylsulfonyl), C_{1-6}-alk(en/yn)ylsulfonyl (e.g. C_{1-6}-alkylsulfonyl), arylsulphonyl, arylacyl, C_{1-6}-alk(en/yn)ylcarbonyl (e.g. C_{1-6}-alkylcarbonyl), aminocarbonyl, C_{1-6}-alk(en/yn)ylaminocarbonyl (e.g. C_{1-6}-alkylaminocarbonyl), and di-(C_{1-6}-alk(en)yl)aminocarbonyl (e.g. di-(C_{1-6}-alkyl)aminocarbonyl);

wherein R^{12} is an optionally substituted aryl;

wherein R^{13} is hydrogen, hydroxy, cyano, or amino, or one of the following groups:

-NHC_{1-6}-alk(en/yn)yl (e.g. -NHC_{1-6}-alkyl, -NHC_{2-6}-alkenyl, or -NHC_{2-6}-alkynyl; such as methyl);

-$N(C_{1-6}$-alk(en/yn)yl$)_2$ (e. g -$N(C_{1-6}$-alkyl$)_2$);

-$NR^{14}COR^{15}$, wherein R^{14} is hydrogen or C_{1-6}-alk(en/yn)yl and R^{15} is C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl;

-$NR^{16}COCONR^{17}R^{18}$, wherein R^{16} is hydrogen or C_{1-6}-alk(en/yn)yl and R^{17} and R^{18} are selected independently from hydrogen and C_{1-6}-alk(en/yn)yl (e.g. C_{1-6}-alkyl) or C_{3-8}-cycloalkyl; or R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl are optionally substituted (i.e. unsubstituted or substituted) with a C_{1-6}-alk(en/yn)yl.

-$NR^{19}CONR^{20}R^{21}$, wherein R^{19} is hydrogen or C_{1-6}-alk(en/yn)yl and R^{20} and R^{21} are selected independently from hydrogen and C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalkyl; or R^{20} and R^{21} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl are optionally substituted (i.e. unsubstituted or substituted) with a C_{1-6}-alk(en/yn)yl;

-$NR^{22}SO_2R^{23}$, wherein R^{22} is hydrogen or C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalkyl and R^{23} is amino, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalkyl;

-COR^{24}, wherein R^{24} is C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalkyl;

-$CONR^{25}R^{26}$, wherein R^{25} and R^{26} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl and C_{3-8}-cycloalkyl, or R^{25} and R^{26} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl are optionally substituted (i.e. unsubstituted or substituted) with a C_{1-6}-alk(en/yn)yl, in particular C_{1-6}-alkyl;

-$NHCOOR^{42}$, wherein R^{42} is C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl;

wherein X, Y, and Z are selected independently from a bond; O; NR^{27}; $CR^{28}R^{29}$ and $S(O)_m$,

wherein m is 0, 1 or 2;

wherein R^{27} is selected from hydrogen, C_{1-6}-alk(en/yn)yl (such as C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl), C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, trifluoromethyl, acyl, thioacyl and trifluoromethylsulfonyl; or

R^{27} is a group $R^{30}SO_2$-, $R^{30}OCO$- or $R^{30}SCO$-, wherein R^{30} is C_{1-6}-alk(en/yn)yl (such as C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl), C_{3-8}-cycloalkyl, or C_{3-8}-cycloalkyl-C_{1-6}-alkyl; or

R^{27} is a group $R^{31}R^{32}NCO$- or $R^{31}R^{32}NCS$-, wherein R^{31} and R^{32} are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl (such as C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl), C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl and aryl, wherein said aryl is optionally substituted (i.e. unsubstituted or substituted), e.g. with one or more substituents selected from C_{1-6}-alkyl or halogen; or wherein R^{31} and R^{32} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group;

wherein R^{28} and R^{29} are independently selected from hydrogen, halo such as fluoro, C_{1-6}-alk(en/yn)yl (such as C_{1-6}-alkyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl), C_{3-8}-cycloalkyl, and C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

wherein R^{33}-R^{36} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl (such as C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl), C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, halo-C_{1-6}-alk(en/yn)yl, preferably trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl;

wherein R^{37}-R^{38} are either both hydrogen or are fused together in an ethylene chain CH^2-CH^2- forming an aza-bicyclo[3.2.1]octane-yl;

wherein R^{39}-R^{41} are independently selected from hydrogen and the substituent list as defined herein;

provided that no more than one of X, Y and Z may be a bond, and provided that two adjacent groups X, Y or Z may not at the same time be selected from O and S.

To further illustrate the invention, without limitation, the following embodiments of R^1-R^5 are within the scope of the invention, in particular for the compounds or salt thereof: R^1-R^5 are independently selected from hydrogen, halogen, cyano, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{1-6}-alkyloxy, C_{1-6}-alkylthio, and trifluoromethyl; R^1-R^5 are independently selected from a hydrogen and C_{1-6}-alkyl; R^1-R^5 are independently selected from hydrogen, Cl, F, cyano, methyl, methoxy, methylthio, and trifluoromethyl; R^1-R^5 are hydrogen; R^1-R^5 are independently selected from hydrogen and halogen; R^1-R^5 are independently selected from hydrogen, chloro and fluoro; R^1-R^5 are independently selected from hydrogen and chloro; R^1-R^5 are independently selected from hydrogen and fluoro; R^2 is chloro and R^3 is hydrogen, R^2 and R^3 are chloro, R^2 is fluoro and R^3 is hydrogen, or R^2 and R^3 is fluoro, where the rest of R^1-R^5 may, e.g., be hydrogen or they may also be substituted from the list above; at least one R^1-R^5 is F or Cl, such as a compound of the invention for which R^3 is F or Cl; R^1-R^5 is selected independently from H and cyano; R^1-R^5 are selected independently from H and C_{1-6}-alk(en/yn)yl; R^1-R^5 are selected independently from H and C_{1-6}-alkyl, such as methyl or ethyl; R^1-R^5 are selected independently from H and C_{1-6}-alk(en/yn)yloxy, preferably C_{1-6}-alkoxy, such as methoxy; R^1-R^5 are selected independently from H and C_{1-6}-alkylthio, such as methylthio; R^1-R^5 are selected independently from H and trifluoromethyl; at least 3 of R^1-R^5 are hydrogen, such as 3, 4 or all of R^1-R^5 are hydrogen; 1 of R^1-R^5 is substituted, such as in the positions R^2 or R^3, e.g. with a halogen (e.g. F or Cl), C_{1-6}-alkyl (e.g. methyl), C_{1-6}-alkoxy (e.g. methoxy) while the rest of R^1-R^5 being hydrogen; 2 of R^1-R^5 sre substituted, e.g. in the positions R^2 and R^3, e.g. selected independently from the group consisting of a halogen (e.g. F or Cl), C_{1-6}-alkyl (e.g. methyl), C_{1-6}-alkoxy (e.g. methoxy) while the rest of R^1-R^5 being hydrogen.

To further illustrate the invention, without limitation, the following embodiments of R^6 are within the scope of the invention, in particular for the compounds or salt thereof: R^6 is selected from hydrogen, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, and C_{3-8}-cycloalkyl-C_{1-6}-alkyl; R^6 is selected from hydrogen and C_{1-6}-alk(en/yn)yl; R^6 is hydrogen; R^6 is a C_{1-6}-alkyl; R^6 is methyl; R^6 is ethyl.

When R^7 is aryl or heteroaryl, it is understood that the aryl and heteroaryl are as defined herein and may be selected among these.

The invention in one aspect, relates to compounds of Formula (I) wherein R^7 is an aryl as defined herein. To further illustrate the invention, without limitation, the following embodiments of R^7, for which R^7 is an aryl, are within the scope of the invention, in particular for the compounds or salt thereof: R^7 is an unsubstituted phenyl; R^7 is phenyl substituted with one or more substituents, e.g. mono or disubstituted, selected independently from the substituent list as defined herein, including, e.g., halogen and C_{1-6}-alkyl; R^7 is an unsubstituted phenyl and R^6 is hydrogen; R^7 is an unsubstituted phenyl and R^6 is methyl.

To further illustrate the invention, without limitation, the following embodiments of R^7, for which R^7 is a group aryl-CR^8R^9-, are within the scope of the invention, in particular for the compounds or salt thereof: R^8 and R^9 are independently selected from hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl and C_{3-8}-cycloalkyl-C_{1-6}-alkyl; R^8 and R^9 are independently selected from hydrogen and C_{1-6}-alkyl; R^8 and R^9 are independently selected from hydrogen and methyl; R^8 and R^9 are hydrogen; R^8 is hydrogen and R^9 is methyl; R^8 and R^9 are methyl.

It is understood that for R^7 being "aryl-CR^8R^9", the aryl of aryl-CR^8R^9- is as defined herein, i.e. it may, e.g., have one or more of the following characteristic: the aryl is monocyclic or bicyclic; the aryl is unsubstituted; the aryl is phenyl; the aryl is naphthalene, the aryl is substituted with one or more substituents, preferably selected from the group consisting of halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylcarbonyl C_{1-6}-alkylamino, C_{1-6}-alkoxy (e.g. methoxy), C_{1-6}-alkylthio, hydroxy, trifluoromethyl , difluoromethyl, fluoromethyl and trifluoromethylsulfonyl; the aryl, e.g. phenyl, is an optionally substituted phenyl; the aryl, e.g. phenyl, is mono- or poly-substituted, e.g. di-substituted, e.g. with a halogen, such as fluoro or chloro, and/or e.g. with a C_{1-6}-alkoxy (e.g. methoxy).

In a preferred embodiment, R^7 is an aryl-CR^8R^9- selected from benzyl or substituted benzyl, e.g. halogen substituted benzyl, e.g. 4-halo benzyl, such as 4-fluorobenzyl, or 2-halo-benzyl, such as 2-chloro-benzyl, or 3,4-dichloro-benzylamide, 3,4-dimethoxy-benzylamide methyl-1-phenyl-ethyl, methyl-1-(4-methoxyphenyl)-ethyl, or naphthalen-1-ylmethyl.

Further embodiments of the invention relates to compounds of formula I wherein R^6 is hydrogen or methyl.

Further aspects of the invention relate to compounds of formula I wherein Q is (i). One aspect of the invention relates to embodiments of the invention where Q is (i) and the aryl of R^{10} is selected from the aryls as defined herein.

In further embodiments, the invention relates to a compound or salt of the invention wherein Q is (ii). Preferably R^{11} is selected from an optionally substituted (i.e. substituted or not) aryl or optionally substituted (i.e. substituted or not) benzyl, trifluoromethylsulfonyl, C_{1-6}-alkylsulfonyl, arylsulphonyl, arylacyl, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl and di-(C_{1-6}-alkyl)aminocarbonyl), wherein said aryl is selected from the aryls as defined herein. The benzyl may be substituted with one ore more substituent selected from the substituent list as defined herein.

In further embodiments, the invention relates to a compound or salt of the invention wherein Q is (iii).

To further illustrate the invention, without limitation, the following embodiments of R^{12} are within the scope of the invention, in particular for the compounds or salt thereof: R^{12} is an aryl as defined herein; R^{12} is unsubstituted phenyl; R^{12} is a phenyl substituted with one or more substituents, e.g. mono or di-substituted, preferably selected from the substituent list as defined herein; the aryl, e.g. phenyl, in R^{12} is substituted with one or more, e.g. one or two substituents selected from a halogen and trifluoromehtyl; the aryl, e.g. phenyl, in R^{12} is substituted with at least one chloro or at least one fluoro and at least one trifluoromethyl; the aryl, e.g. phenyl, in R^{12} is substituted with one Cl and one trifluoromehtyl; R^{12} is 4-chloro-3-triflurometlyl-phenyl.

The following embodiments of the compound of the invention for which Q is (iii) are also within the scope of the invention: R^{12} is an aryl substituted with one or more substituents selected from a halogen and aminoacyl and R^{13} is hydrogen; R^{12} is phenyl substituted with one or more substituents, e.g. mono or di-substituted, selected from a halogen and aminoacyl and R^{13} is hydrogen.

In one embodiment when Q is (iii) the group R^{13} is hydroxy. In a preferred embodiment R^{12} is 4-chloro-3-triflurometlyl-phenyl and R^{13} is hydroxy.

In further embodiments of (iii) the R^{13} is -$NR^{14}COR^{15}$, where R^{14} and R^{15} are as defined herein. To further illustrate the invention, without limitation, the following embodiments of R^{13} are within the scope of the invention, in particular for the compounds or salt thereof: R^{14} is hydrogen; R^{14} is methyl; R^{15} is methyl; R^{14} is hydrogen or C_{1-6}-alkyl and R^{15} is C_{1-6}-alkyl or C_{3-8}-cycloalkyl; R^{14} is H or CH_3; R^{15} is CH_3; R^{14} is hydrogen and R^{15} is methyl; R^{14} and R^{15} are methyl.

In further embodiments of (iii), the R^{13} is -$NR^{16}CONR^{17}R^{18}$, wherein R^{16}, R^{17} and R^{18} is as defined herein. To further illustrate the invention, without limitation, the following embodiments of R^{13} are also within the scope of the invention, in particular for the compounds or salt thereof: R^{16} is hydrogen or C_{1-6}-alkyl and wherein R^{17} and R^{18} are selected independently from hydrogen, C_{1-6}-alkyl and C_{3-8}-cycloalkyl; R^{16} is hydrogen or C_{1-6}-alkyl and where R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, where said piperidinyl, piperazinyl and morpholinyl are optionally substituted with a C_{1-6}-alkyl, e.g. methyl; R^{16}, R^{17} and R^{18} are hydrogen(i.e. oxalamide, -NHCOCONH$_2$); R^{16} is C_{1-6}-alkyl, and R^{17} and R^{18} are hydrogen (i.e. *N*- C_{1-6}-alkyl oxalamide); R^{16} and R^{17} are hydrogen and R_{18} is C_{1-6}-alkyl (i.e. *N'*-C_{1-6}-alkyl-*N*-oxalamide); R^{16} and R^{17} are C_{1-6}-alkyl and R^{18} is hydrogen (i.e. *N'*-C_{1-6}-alkyl-*N*- C_{1-6}-alkyl oxalamide); R^{16} is hydrogen and R^{17} and R^{18} are C_{1-6}-alkyl, e.g. methyl, (i.e. *N',N'*-di-(C_{1-6}-alkyl)-*N*-oxalamide); R^{16} is hydrogen and R^{17} and R^{18} are methyl; R^{16}, R^{17} and R^{17} are C_{1-6}-alkyl (i.e. *N',N'*-di-(C_{1-6}-alkyl)-*N*- C_{1-6}-alkyl oxalamide).

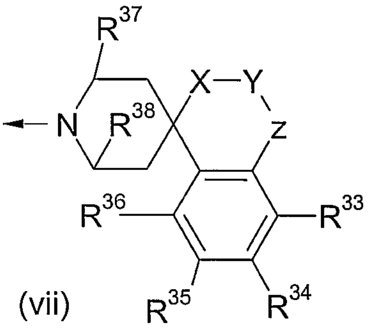
In further embodiments of (iii) the R^{13} is -NR^{19}CONR^{20}R^{21}, wherein R^{19}, R^{20} and R^{21} are as defined herein. To further illustrate the invention, without limitation, the following embodiments of R^{13} are also within the scope of the invention, in particular for the compounds or salt thereof: R^{19}, R^{20} and R^{21} are independently selected from hydrogen, C_{1-6}-alkyl and C_{3-8}-cycloalkyl; R^{19}, R^{20} and R^{21} are independently selected from hydrogen and C_{1-6}-alkyl; R^{19}, R_{20} and R_{21} are hydrogen; R^{19} is a C_{1-6}-alkyl and R^{20} and R^{21} are hydrogen; R_{19} and R_{20} are hydrogen and R^{21} is a C_{1-6}-alkyl; R^{19} and R^{20} are independently selected from a C_{1-6}-alkyl and R^{21} is H; R^{19} is H, and R^{20} and R^{21} are independently selected from a C_{1-6}-alkyl; or R^{19}, R^{20} and R^{21} are independently selected from a C_{1-6}-alkyl; R^{19} is H and R^{20} and R^{21} are independently selected from the group consisting of hydrogen, Me, Et, Bu, and i-Pr.

In further embodiments of (iii) the R^{13} is -NR^{22}SO$_2$R^{23}, wherein R^{22} and R^{23} are as defined herein. To further illustrate the invention, without limitation, the following embodiments of R^{13} are also within the scope of the invention, in particular for the compounds or salt thereof: R^{22} is hydrogen or a C_{1-6}-alkyl or C_{3-8}-cycloalkyl and R^{23} is amino, C_{1-6}-alkyl or C_{3-8}-cycloalkyl; R^{22} is hydrogen and R^{23} is a C_{1-6}-alkyl, e.g. methyl (i.e. *N*-(C_{1-6}-alkylsulphonamide) or R^{22} and R^{23} are independently selected from a C_{1-6}-alkyl, e.g. methyl i.e. *N*- C_{1-6}-alkyl (C_{1-6}-alkylsulphonamide); R^{22} is hydrogen; R^{23} is methyl; R^{22} and R^{23} are methyl; R^{22} is hydrogen and R^{23} is methyl.

In further embodiments of (iii) the R^{13} is -COR^{24}, wherein R^{24} is as defined herein. The following embodiments of R^{13} are also within the scope of the invention without limitation, in particular for the compounds or salt thereof: R^{24} is a C_{1-6}-alkyl; R^{24} is methyl.

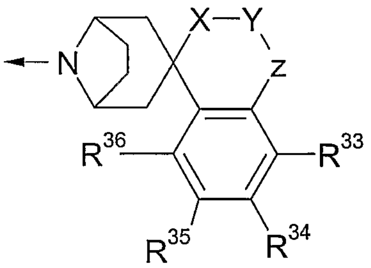
In further embodiments of (iii) the R^{13} is $-CONR^{25}R^{26}$, wherein R^{25} and R^{26} are as defined herein. To further illustrate the invention, without limitation, the following embodiments of R^{13} are also within the scope of the invention, in particular for the compounds or salt thereof: R^{25} and R^{26} are independently selected from hydrogen, C_{1-6}-alkyl and C_{3-8}-cycloalkyl; R^{25} and R^{26} are independently selected from hydrogen and methyl; R^{25} and R^{26} are hydrogen; R^{25} and R^{26} are methyl; R^{25} is methyl and R^{26} is hydrogen; R^{25} and R^{26} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl are optionally substituted with a C_{1-6}-alkyl, in a preferred embodiment the piperidinyl, piperazinyl and morpholinyl are not substituted; R^{25} and R^{26} together with the nitrogen to which they are attached form a piperidinyl, wherein the piperidinyl is optionally substituted with a C_{1-6}-alkyl, however preferably the piperidinyl is unsubstituted.

In further embodiments, the invention relates to a compound or salt of the invention wherein Q is (vii) as described above.



(vii)

To further illustrate the invention, without limitation, the following embodiments of (vii) are within the scope of the invention: Y is a bond and X and Z are selected independently from O, NR^{27}, and $CR^{28}R^{29}$ and $S(O)_m$, provided that X and Z may not at the same time be selected from O and S; Y is a bond and X and Z are selected independently from $CR^{28}R^{29}$ and NR^{27}; X is $CR^{28}R^{29}$, Y is a bond and Z is NR^{27}; X is $CR^{28}R^{29}$, Y is a bond and Z is O; X is O, Y is a bond and Z is $CR^{28}R^{29}$; R^{28} and R^{29} are hydrogen; R^{27} is an acyl, e.g. C_{1-6}-alkylcarbonyl; Z is NR^{27} where R^{27} is a C_{1-6}-alkylcarbonyl, e.g. $-COCH_3$; X is $CR^{28}R^{29}$ where R^{28} and R^{29} are hydrogen, Y is a bond, and Z is $-NR^{27}$ where said R^{27} is $-COCH_3$; R^{27} is selected from the group $R^{30}SO_2$-, $R^{30}OCO$- and $R^{30}SCO$-; R^{27} is $R^{30}SO_2$; R^{30} is C_{1-6}-alkyl, e.g. methyl; X is $CR^{28}R^{29}$, Y is a bond and Z is NR^{27}, preferably R^{28} and R^{29} are hydrogen; R^{27} is the group $R^{31}R^{32}NCO$- or $R^{30}R^{31}NCS$-; Y is a bond; R^{33}-R^{36} are independently selected from hydrogen and halogen, e.g. chloro or fluoro; R^{33}-R^{36} are all hydrogen; R^{37} and ^{38} are both hydrogen; R^{37}-R^{38} are fused together in an ethylene chain CH2-CH2- forming an aza-bicyclo[3.2.1]octane-yl as shown in the figure below.



In further embodiments of Compound (I), Q is (iv). To further illustrate the invention, without limitation, the following embodiments of (iv) are within the scope of the invention: R^{39} is selected from the group consisting of hydrogen and halogen; R^{39} is hydrogen in all positions, i.e. the corresponding phenyl group is unsubstituted; the corresponding phenyl group is substituted in only one or two positions with a substituent R^{39} selected from the "substituent" list as defined herein, e.g. a halogen.

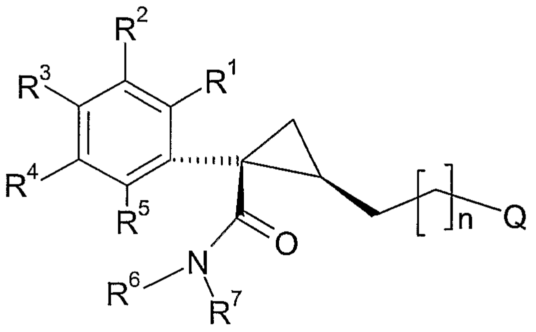
In further embodiments of Compound (I), Q is (v). To further illustrate the invention, without limitation, the following embodiments of (v) are within the scope of the invention: R^{40} is selected from the group consisting of hydrogen or halogen; R^{40} is hydrogen in all positions, i.e. the corresponding phenyl group is unsubstituted; the corresponding phenyl group is substituted in only one or two positions with a substituent R^{40} selected from the "substituent list" as defined herein, e.g. a halogen.

In further embodiments of Compound (I), Q is (vi). To further illustrate the invention, without limitation, the following embodiments of (vi) are within the scope of the invention: R^{41} is selected from the group consisting of hydrogen and halogen.; R^{41} is hydrogen in all positions, i.e. the corresponding benzyl group is unsubstituted; the corresponding benzyl group is substituted in only one or two positions with a substituent R^{41} selected from the substituent list as defined herein, e.g. with a halogen.

The compounds of the present invention may have one or more asymmetric centers and it is intended that any optical isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures, i.e. a mixture of stereoisomeres, are included within the scope of the invention.

The compounds of the general formula I exist as optical isomers thereof and such optical isomers are also embraced by the invention. In particular, the compounds of the invention possessing the absolute stereochemistry (1S,2R) are within the invention, either as enantiomers or as mixtures containing compounds of the invention possessing the absolute stereochemistry (1S,2R).

Accordingly, an important aspect of the invention is a compound or salt of the invention as described herein, wherein the compound of formula I is the (1S,2R)-isomer i.e. the compound with absolute configuration as shown in formula IA.



(IA)

The compound of the invention of formula I or the salt thereof may be part of a racemic mixtures comprising the (1S,2R)-isomer, i.e. the compound shown in formula IA or it may be present as the enantiomer, i.e. without the 3 others stereoisomers.

The invention in further embodiment relates to a compound of formula I which compound is the (1R,2R)-isomer.

The invention in further embodiment relates to a compound of formula I which compound is the (1R,2S)-isomer.

The invention in further embodiment relates to a compound of formula I which compound is the (1S,2S)-isomer.

In this context is understood that when specifying the enantiomeric form, then the compound is in a preferred embodiment in enantiomeric excess.

Accordingly, one embodiment of the invention relates to a compound of the invention having an enantiomeric excess of at least 60% (60% enantiomeric excess means that the ratio of Va to its enantiomer is 80:20 in the mixture in question), at least 70%, at least 80%, at least 85%, at least 90%, at least 96%, preferably at least 98%.

The expression "mixture of stereoisomeres comprising the (1S,2R)-isomer of formula 1" implies that in further embodiments, the compound of the invention, i.e. product, may be any one of the following mixture of stereoisomeres: a (1S,2R)-isomer and a (1R,2R)-isomer of formula 1; a (1S,2R)-isomer and a (1R,2S)-isomer of formula 1; a (1S,2R)-isomer and a (1S,2R)-isomer of formula 1; a (1S,2R)-isomer and a (1S,2S)-isomer of formula 1; a (1S,2R)-isomer and a (1R,2R)-isomer of formula 1, i.e. consisting of 2, 3 or 4 of the corresponding stereoisomers.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives. Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in “Enantiomers, Racemates, and Resolutions”, John Wiley and Sons, New York (1981). Optically active compounds can also be prepared from optically active starting materials.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

In further embodiments of formula I, the compound of the invention is any one of:

1. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
2. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
3. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
4. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
5. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
6. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
7. 1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
8. 2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
9. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
10. 2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
11. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
12. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

13. 1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
14. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
15. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
16. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
17. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
18. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;
19. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;
20. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
21. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
22. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
23. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
24. 2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
25. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
26. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
27. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
28. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

29. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
30. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
31. 1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
32. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
33. 1-(3,4-Difluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid -methyl-amide;
34. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
35. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
36. 1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
37. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
38. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
39. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;
40. 1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;
41. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;
42. 1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
43. 1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
44. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

45. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
46. 1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
47. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
48. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;
49. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
50. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
51. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
52. 1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
53. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
54. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;
55. 1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid benzyl-methyl-amide; and
56. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide;

57 2-(4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-ethyl-amide

58. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide -([R]-1-phenyl-ethyl) amide
59. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
60. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide; and

61. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
62. 1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]1-phenyl-ethyl)-amide;
63. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl)-amide;
64. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl) amide;
65. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl) amide;
66. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
67. 1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;
68. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;
69. 1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
70. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
71. 2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
72. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
73. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
74. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-flurophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
75. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
76. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

77. 1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]1-phenyl-ethyl)-amide;
78. 2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
79. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
80. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
81. 1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
82. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
83. 1-(3,4-Difluorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
84. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
85. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;
86. 1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid 3,4-dichloro-benzylamide;
87. 1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid 3,4-dimethoxy-benzylamide;
88. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid phenylamide;
89. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide;
90. 1-Phenyl-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
91. 2-(4-Benzyl-piperazin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
92. 1-(4-chlorophenyl)-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid 4-fluorobenzyl-methyl-amide;

93. 2-(4-Benzyl-piperazin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
94. 2-(4-Benzyl-piperazin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
95. 1-(4-chlorophenyl)-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;
96. 1-phenyl-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid 4-fluorobenzyl-methyl-amide;
97. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl amide;
98. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (2-fluoro-benzyl)-amide;
99. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-[1-(4-methoxyphenyl)-ethyl]-amide;
100. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl) amide;
101. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (3,4-dichlorobenzyl) amide;
102. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-phenyl-amide;
103. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
104. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-p-tolyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
105. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-m-tolyl-cyclopropanecarboxylic acid benzyl-methyl-amide;
106. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-m-tolyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
107. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-methoxy-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
108. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

109. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-p-tolyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

110. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-methoxy-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

111. 1-Phenyl-2-(4-phenyl-4-ureido-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

112. 1-(3,4-Dichlorophenyl)-2-(4-phenyl-4-ureido-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid -benzyl-methyl-amide;

113. 1-Phenyl-2-[4-(3-methyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluorobenzyl)-methyl-amide;

114. 2-[4-(3-Methyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

115. N-(1-{2-[(4-Fluoro-benzyl)-methyl-carbamoyl]-2-phenyl-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-oxalamide;

116. N-(1-{2-[benzyl-methyl-carbamoyl]-2-(3,4-dichlorophenyl)-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-oxalamide;

117. 1-Phenyl-2-(4-methanesulfonylamino-4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid -(4-fluorobenzyl)-methyl-amide;

118. 2-(4-Methanesulfonylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid -benzyl-methyl-amide;

119. {1-[2-((4-fluoro-benzyl)-methyl-carbamoyl)-2-phenyl-cyclopropylmethyl]-4-phenyl-piperidin-4-yl}-carbamic acid methyl ester;

120. (1-{2-benzyl-methyl-carbamoyl]-2-(3,4-dichlorophenyl)-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-carbamic acid methyl ester;

121. 1-(3,4-Dichloro-phenyl)-2-[4-(3,3-dimethyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

122. 1-phenyl-2-[4-(3,3-dimethyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluorobenzyl)-methyl-amide;

123. 2-[2-(4-Acetylamino-4-phenyl-piperidin-1-yl)-ethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

124. 2-[3-(4-Acetylamino-4-phenyl-piperidin-1-yl)-propyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

125. 2-[4-(2-Acetylamino-5-fluorophenyl)-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
126. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dimethylphenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
127. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
128. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
129. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;
130. 1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;
131. 1-(3,4-Dichlorophenyl)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;
132. 1-(3,4-Dichlorophenyl)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;

or a salt thereof, such as a pharmaceutically acceptable salt.

In an even more preferred embodiment of formula I, the compound is any one of the following compounds:

1a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
2a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
3a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
4a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;
5a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

6a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

7a. (1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

8a. (1S,2R)-2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

9a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

10a. (1S,2R)-2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

11a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

12a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

13a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

14a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

15a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

16a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

17a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

18a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

19a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

20a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

21a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

22a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

23a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

24a. (1S,2R)-2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

25a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

26a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

27a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

28a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

29a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

30a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

31a.(1S,2R)-1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

32a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

33a. (1S,2R)-1-(3,4-Difluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid -methyl-amide;

34a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

35a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

36a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

37a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

38a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

39a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

40a. (1S,2R)- (1S,2R)- 1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

41a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

42a. (1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

43a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

44a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

45a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

46a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

47a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

48a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;

49a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

50a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

51a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

52a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

53a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

54a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;

55a.(1S,2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

56a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide.

57a (1S,2R)- 2-(4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-ethyl-amide

58a. (1S,2R)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide -([R]-1-phenyl-ethyl) amide

59a. (1R,2S)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

60a. (1R,2R)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide; and

61a. (1S,2S)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

62a (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]1-phenyl-ethyl)-amide;

63a (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl)-amide;

64a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl) amide;

65a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl) amide;

66a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

67a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

68a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

69a. (1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

70a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

71a. (1S,2R)-2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

72a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

73a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

74a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-flurophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

75a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

76a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

77a. (1S,2R)-1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]1-phenyl-ethyl)-amide;

78a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

79a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

80a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

81a. (1S,2R)-1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

82a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

83a. (1S,2R)-1-(3,4-Difluorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

84a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

85a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

86a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid 3,4-dichloro-benzylamide;

87a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid 3,4-dimethoxy-benzylamide;

88a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid phenylamide;

89a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide;

90a. (1S,2R)-1-Phenyl-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

91a. (1S,2R)-2-(4-Benzyl-piperazin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

92a. (1S,2R)-1-(4-chlorophenyl)-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid 4-fluorobenzyl-methyl-amide;

93a. (1S,2R)-2-(4-Benzyl-piperazin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

94a. (1S,2R)-2-(4-Benzyl-piperazin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

95a. (1S,2R)-1-(4-chlorophenyl)-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

96a. (1S,2R)-1-phenyl-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid 4-fluorobenzyl-methyl-amide;

97a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl amide;

98a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (2-fluoro-benzyl)-amide;

99a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-[1-(4-methoxyphenyl)-ethyl]-amide;

100a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl) amide;

101a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (3,4-dichlorobenzyl) amide;

102a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-phenyl-amide;

103a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

104a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-p-tolyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

105a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-m-tolyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

106a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-m-tolyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

107a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-methoxy-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

108a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

109a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-p-tolyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

110a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-methoxy-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

111a. (1S,2R)-1-Phenyl-2-(4-phenyl-4-ureido-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

112a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-4-ureido-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid -benzyl-methyl-amide;

113a. (1S,2R)-1-Phenyl-2-[4-(3-methyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluorobenzyl)-methyl-amide;

114a. (1S,2R)-2-[4-(3-Methyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

115a. (1S,2R)-N-(1-{2-[(4-Fluoro-benzyl)-methyl-carbamoyl]-2-phenyl-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-oxalamide;

116a. (1S,2R)-N-(1-{2-[benzyl-methyl-carbamoyl]-2-(3,4-dichlorophenyl)-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-oxalamide;

117a. (1S,2R)-1-Phenyl-2-(4-methanesulfonylamino-4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid -(4-fluorobenzyl)-methyl-amide;

118a. (1S,2R)-2-(4-Methanesulfonylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid -benzyl-methyl-amide;

119a. (1S,2R)-{1-[2-((4-fluoro-benzyl)-methyl-carbamoyl)-2-phenyl-cyclopropylmethyl]-4-phenyl-piperidin-4-yl}-carbamic acid methyl ester;

120a. (1S,2R)-(1-{2-benzyl-methyl-carbamoyl]-2-(3,4-dichlorophenyl)-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-carbamic acid methyl ester;

121a. (1S,2R)-1-(3,4-Dichloro-phenyl)-2-[4-(3,3-dimethyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

122a. (1S,2R)-1-phenyl-2-[4-(3,3-dimethyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluorobenzyl)-methyl-amide;

123a. (1S,2R)-2-[2-(4-Acetylamino-4-phenyl-piperidin-1-yl)-ethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

124a. (1S,2R)-2-[3-(4-Acetylamino-4-phenyl-piperidin-1-yl)-propyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

125a. (1S,2R)-2-[4-(2-Acetylamino-5-fluorophenyl)-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

126a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dimethylphenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

127a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

128a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

129a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

130a. (1S, 2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;

131a. (1S, 2R)-1-(3,4-Dichlorophenyl)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;

132a. (1S, 2R)-1-(3,4-Dichlorophenyl)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;

or a salt thereof, such as a pharmaceutically acceptable salt.

In further embodiments of formula I, the compound is any one of:

5b. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl) amide;

6b. 2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl) amide;

19b.2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

20b.2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl) amide;

38b.2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl) amide;

40b.1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

41b.2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

58b. 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide -(1-phenyl-ethyl) amide

62b. 1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

63b. 2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

64b. 2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl) amide;

65b. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl) amide;

67b. 1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

68b. 2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl) amide;

77b. 1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

or a salt thereof, such as a pharmaceutically acceptable salt.

Within the invention is also a compound selected from the group consisting of 5b, 6b, 19b, 20b, 38b, 40b, 41b, 58b, 62b, 63b, 64b, 65b, 67b, 68b, 77b which is the (1S,2R)-isomer, i.e. having an absolute configuration as shown in formula IA; or a salt thereof, such as a pharmaceutically acceptable salt.

Other aspects of the invention relate to a compound of the invention of formula I which is the (1R,2R)-isomer (i.e. in contrast to formula IA which is the (1S,2R)-isomer).

Other aspects of the invention relate to a compound of the invention of formula I which is the (1S,2S)-isomer (i.e. in contrast to formula IA which is the (1S,2R)-isomer).

Other aspects of the invention relate to a compound of the invention of formula I which is the (1R,2S)-isomer (i.e. in contrast to formula IA which is the (1S,2R)-isomer).

The present invention also comprises salts of the compounds of the invention, typically, pharmaceutically acceptable salts. Such salts include pharmaceutical acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids.

Examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like.

Examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977,66,2, which is incorporated herein by reference.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutical acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

The compounds (including salts thereof) of the invention are NK3 receptor antagonists having a human NK3 binding affinity (K_i) of 5 μM or less, typically of 1 μM or less, and preferably of 200 nM or less, e.g. as measured by the method described in Example 20.

A further objective of the present invention is to provide compounds, including salts thereof, with such activities which have one or more of the following parameters which are improved: solubility, metabolic stability and bioavailability compared to prior art compounds.

Pharmaceutical use

As mentioned above the compounds of the invention are NK3 receptor antagonists and may thus be useful for treatment in a disorder or disease wherein the NK3 receptor is implicated.

Compounds of the invention and the salt thereof may be applicable for treatment, including prevention, of schizophrenia, psychotic disorders, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema or plasma extravasation. In a preferred embodiment, the compounds of the invention and the salt thereof can be used as an antipsychotic.

Thus, a compound of the invention may be useful for the treatment of a disease or disorder in the central nervous system.

In further embodiments, the compound of the invention or salt thereof may also have some NK1 and/or NK2 activity in addition to the NK3 activity as described herein. Accordingly, the compound of the invention and the salts thereof may also be useful for the treatment, including prevention, of diseases where the NK1 receptor and/or the NK2 receptor is implicated, especially emesis, depression or anxiety.

In a further aspect, the invention relates to a compound of the invention or salts thereof for use as a medicament.

The present invention also relates to a pharmaceutical composition comprising a compound of the invention or a salt thereof and a pharmaceutically acceptable carrier or a diluent. The composition may comprise any one of the embodiments of formula I described herein.

The present invention also relates to use of a compound of the invention or a salt thereof, for the preparation of a medicament for the treatment of a disease or disorder, wherein an NK receptor antagonist, in particular an NK3 receptor antagonist is beneficial. The medicament may comprise any one of the embodiments of formula I described herein.

In particular the present invention relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment of any of the diseases indicated herein, including psychotic disorders, in particular schizophrenia.

In one aspect, the present invention relates to use of a compound of the invention or a salt thereof treatment of the positive symptoms of schizophrenia.

Further, the invention also relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment or prevention of depression or anxiety. The invention also relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment or prevention of Parkinson's disease. Further, the invention also relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment or prevention of convulsions.

A further aspect of the invention relates to a method for the treatment or prevention of schizophrenia, psychotic disorders, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema or plasma extravasation, in a living animal body, including a human, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable acid addition salt thereof. In general the invention also relates to use of a compound of the invention or a salt thereof for the preparation of a medicament for the treatment or prevention of these diseases/disorders.

The compounds of the invention or the salt thereof may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants, etc.

In an embodiment of the pharmaceutical composition, the compound of the invention administered in an amount of from about 0.001 to about 100 mg/kg body weight per day.

Conveniently, the compounds of the invention are administered in a unit dosage form containing said compounds in an amount of about 0.01 to 100 mg. The total daily dose is usually in the range of about 0.05 - 500 mg.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.01 to about 1000 mg, preferably from about 0.05 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a

Magnesium stearate	0.84 mg

2) Tablets containing 0.5 mg of a compound of the invention calculated as the free base:

Compound	0.5 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3) Syrup containing per millilitre:

Compound	25 mg
Sorbitol	500 mg
Hydroxypropylcellulose	15 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 mL
Flavour	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

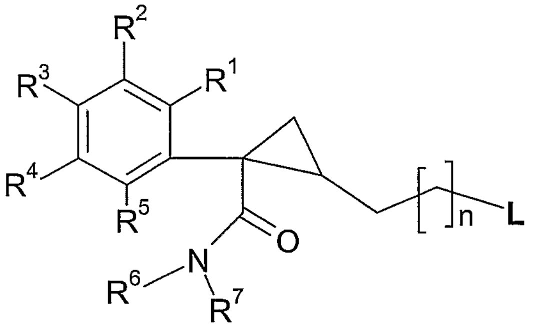
4) Solution for injection containing per millilitre:

Compound	0.5 mg
Sorbitol	5.1 mg
Acetic Acid	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

Methods of preparation of the compounds of the invention

The compounds of the invention may be prepared as follows:

Method 1 Alkylating an amine of formula III with an alkylating derivative of formula II:

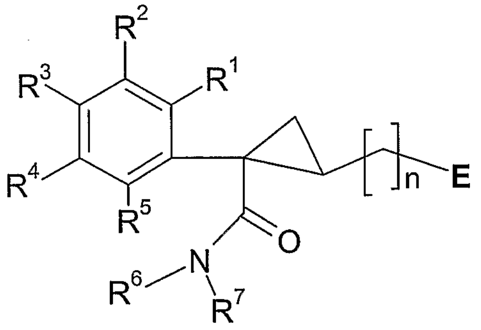


HQ

(II) (III)

where R^1-R^{36}, n and Q are as defined herein, and L is a leaving group such as e.g. halogen, mesylate or tosylate;

Method 2 Reductive alkylation of an amine of formula III with a reagent of formula IV:

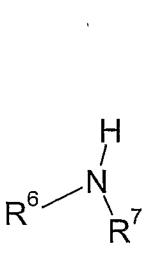


HQ

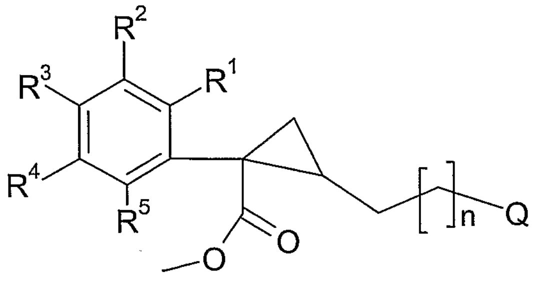
(IV) (III)

where R^1-R^{36}, n and Q are as defined herein, and E is an aldehyde or an activated carboxylic acid;

Method 3 Reacting an amine of formula VI with an methyl ester of formula VII by the use of Lewis acid catalyst:



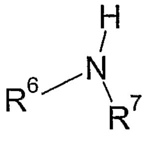
(VI)



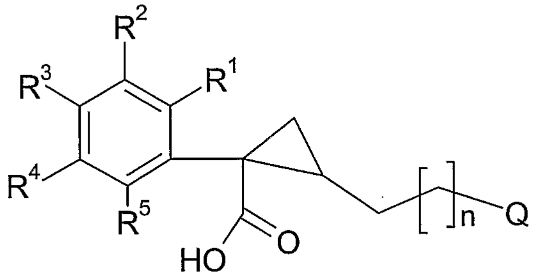
(VII)

where R^1-R^{36}, n and Q are as defined herein,

Method 4 Reacting an amine of formula VI with an acid of formula VIII by the use of an activating reagent or a coupling reagent:



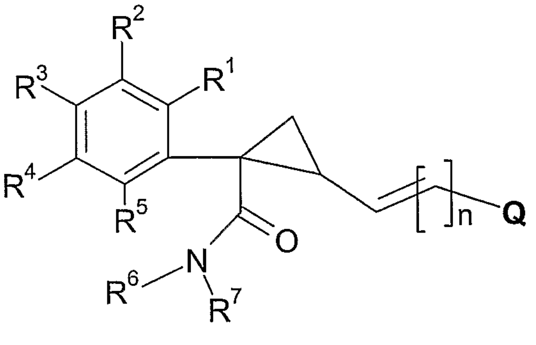
(VI)



(VIII)

wherein R^1-R^{36}, n and Q are as defined herein,

Method 5 Reducing an amine of formula IX:



(IX)

wherein R^1-R^{36}, n and Q are as defined herein, whereupon the compound of formula I is isolated as the free base or a pharmaceutically acceptable acid addition salt thereof.

The alkylation according to **method 1** is conveniently performed in an organic solvent such as a suitably boiling alcohol or ketone, preferably in the presence of an organic or inorganic base (potassium carbonate, diisopropylethylamine or triethylamine) at reflux temperature. Alternatively, the alkylation can be performed at a fixed temperature, which is different from the boiling point, in one of the above-mentioned solvents or in dimethyl formamide (DMF), dimethylsulfoxide (DMSO), or N-methylpyrrolidin-2-one (NMP), preferably in the presence of a base. The alkylating derivatives of formula II with n=0 have been described in the literature or can be prepared in an analogues manner e.g. Shuto *et al. J. Org. Chem.* 1996, 61, 915 and Ronsisvalle *et al. Biorg. Med. Chem.* 2000, 8, 1503 and Bonnaud *et al. J. Med. Chem.* 1987, 30, 318. The alkylating derivatives of formula II with n=1 and n=2 can be prepared from alkylating derivatives of formula II with n=0 by standard chain elongation methods e.g. by substitution of an bromide of formula II with n=0 with cyanide followed by hydrolysis, reduction to the alcohol and conversion to a leaving group L resulting in alkylating derivatives of formula II with n=1. Correspondingly, alkylating derivatives of formula II with n=2 can be prepared by substitution of an bromide of formula II with n=0 with a malonic ester derivative, followed by hydrolysis, decarboxylation, reduction to the alcohol and conversion to a leaving group L. Standard chain elongation methods are described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; or Organic Reactions, John Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions.

The amines of formula III are either commercially available or can be prepared by methods analogues to those described in the literature e.g. Marxer et al. *J. Org. Chem.* 1975, *4*0, 1427, by Parham et al. *J. Org. Chem.* 1976, *4*1, 2628 and by Bauer et al. *J. Med. Chem.* 1976, *19*, 1315, Maligres et al. *Tetrahedron* 1997, 53, 10983, and by Cheng et al. *Tet. Lett.* 1997, 38, 1497, Chen, Meng-Hsin; Abraham, John A. *Tetrahedron Lett.* 1996, *3*7, 5233-5234 and Slade, P.D. et al. *J. Med. Chem.* 1998, *4*1, 1218-1235 or as described by the methods used in the examples or analogues methods.

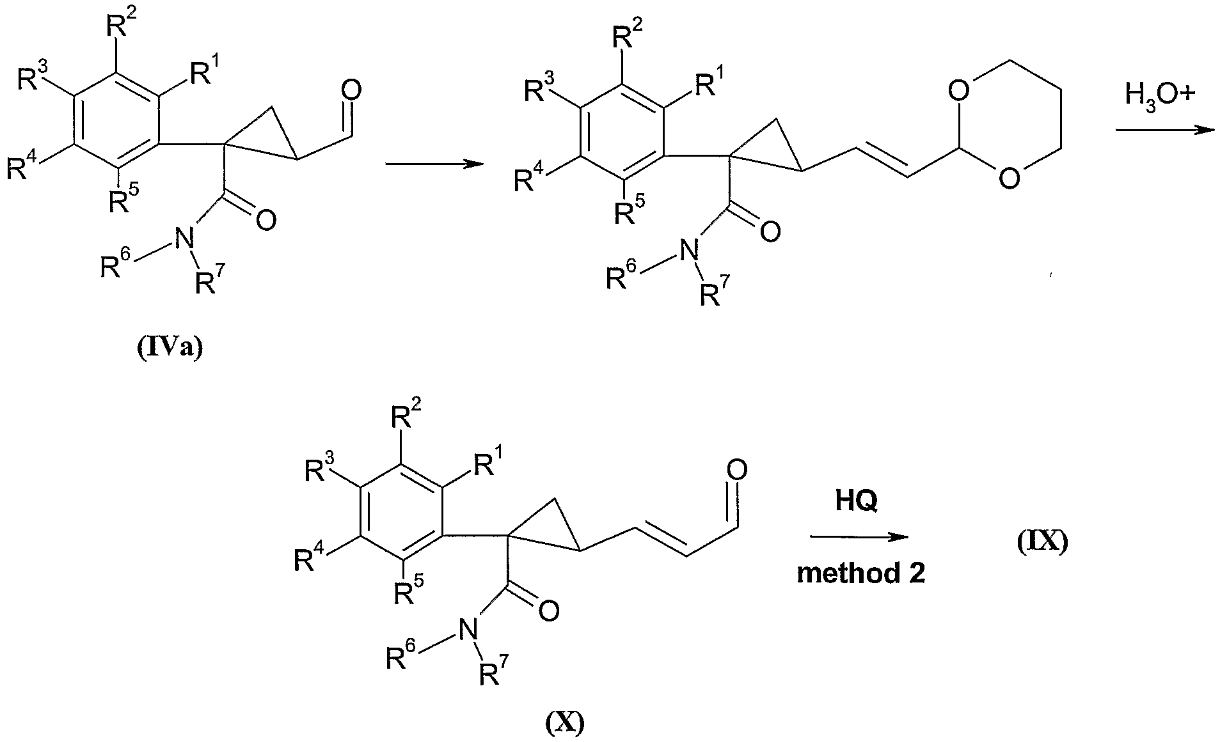
The reductive alkylation according to **method 2** is performed by standard literature methods. Aldehydes or acids of the formula IV can be prepared by methods analogues to those described in e.g. Shuto *et al. J. Org. Chem.* 1996, 61, 915 and Shuto *et al. J. Med. Chem. 1996,38,* 2964 and Shuto *et al. J. Chem. Soc., Perkin Trans. 1*, 2002, 1199 and Bonnaud *et al. J. Med. Chem.* 1987, 30, 318. The reaction can be performed in two steps, e.g. coupling of amines of formula III with reagent of formula IV by standard methods *via* the carboxylic acid chloride, activated esters or by the use of carboxylic acids in combination with a coupling reagents such as e.g. dicyclohexyl carbodiimide, followed by reduction of the resulting amide with lithium aluminium hydride or alane. Alternatively, the reaction can be performed in one step by reductive amination of an aldehyde of formula IV with an amine of formula III according to methods described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions.

The acylation of amine VI in **method 3** with an ester of formula VII can be performed by methods analogues to those described in the literature e.g. Lesimple *et al. Synthesis* 1991, 306. Amines of formula VI are either commercially available or can be prepared by methods known in the literature according to methods described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions and esters of fomula VII can be made by methods analogues to those described in the literature e.g. Shuto *et al. J. Org. Chem.* 1996, 61, 915 and Ronsisvalle *et al. Biorg. Med. Chem.* 2000, 8, 1503 and Bonnaud *et al. J. Med. Chem.* 1987, 30, 318.

The acylation of amine VI in **method 4** with an acid of formula VIII can be performed by standard methods *via* the carboxylic acid chloride, activated esters or by the use of carboxylic acids in combination with a coupling reagent such as e.g. dicyclohexyl carbodiimide, carbonyl diimidazole or benzotriazol-1-loxytris(dimethylamino)phosphonium hexafluorophosphate as described in standard works e.g. Bodanszky "*The practice of peptide synthesis*",1994 Springer verlag Berlin, ISBN 3-540-57505-7 and Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-

Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York. The acid of formula VIII can be prepared by standard basic hydrolysis of the ester described in **method 3** and in the Examples.

The reduction of amine **IX** in **method 5** can be performed by standard methods e.g. hydrogenate using a Parr apparatus (ambient temperature, 3 atm. H_2) and adding a catalyst e.g. Crabtree's catalyst ([(1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate]), palladium or platinum oxide. The amine of formula **IX** can be prepared by the same procedure as described in **method 2**, using an oxo-alkenyl compound of formula **X**, which can be prepared by a wittig reaction between an aldehyde of formula **IVa** and a wittig reagent derived from (1,3-Dioxolan-2-ylmethyl)triphenylphosphonium bromide in the presence of a suitable base.



The invention disclosed herein is further illustrated by the following non-limiting examples.

EXAMPLES

General Methods

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (C18 column 4.6 × 30 mm with a particle size of 3.5 μm) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 4 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times, R_t, are expressed in minutes.

Mass spectra were obtained by an alternating scan method to give molecular weight information. The molecular ion, MH+, was obtained at low orifice voltage (5-20V) and fragmentation at high orifice voltage (100-200V).

Preparative LC-MS-separation was performed on the same instrument. The LC conditions (C18 column 20 × 50 mm with a particle size of 5 μm) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (5:95:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet. NMR signals corresponding to acidic protons are generally omitted. For column chromatography silica gel of type Kieselgel 60, 230-400 mesh ASTM was used. For ion-exchange chromatography (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. No. 220776) was used. Prior use of the SCX-columns was pre-conditioned with 10% solution of acetic acid in methanol (3 mL).

The enantiomeric purity was measured using capillary electrophoresis. Capillary length 48,5 cm x 50μm I.D. at 30°C using a fixed current of 80μA. The buffer used was 25 mM sodium hydrogen phosphate pH 3.0 containing 4% (w/v) sulphated β-cyclodextrin. Detection was done using UV-spectrometer at 192 nm. Sample concentration was 500 μg/ml in methanol and injection was performed by pressure at 50 mbar for 5 seconds.

Alternatively, the enantiomeric purity was measured by chiral HPLC using a Gilson SF3 supercritical fluid chromatography system equipped with chiralcelOD columns (4.6 mm x 25 cm for analytical and 10 mm x 25 cm for preparative runs). The particle size in the columns was 10 μm. The column was eluted with carbondioxide – modifier (75:25). The modifier was 2-propanol with diethylamine (0.5%) and trifluoracetic acid (0.5%). The flow was 18.9 mL/min at 20 Mpa. Fraction collection was triggered by UV-detection (210 nM).

Preparation of intermediates

Example 1 Synthesis of racemic 1-(3,4-Difluorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one

(3,4-Difluorophenyl)acetic acid (52 g; 0.3 mol) was dissolved in *N,N*-dimethylformamid (200 mL). Potassium carbonate (61 g, 0.45 mol) was added and the mixture was stirred at room temperature (rt) for 15 min. Allyl bromide (47 g, 0.39 mol) was added and the suspension was stirred at room temperature for 20 h. The mixture was thrown into water (250 mL) and extracted with diethylether (2X 300 mL). The combined organic phases were washed with water (4 x 100 mL), dried (Magnesium sulphate) and evaporated *in vacuo* to give 64 g (3,4-Difluoro-phenyl)acetic acid allyl ester as a clear oil.

(3,4-Difluoro-phenyl)acetic acid allyl ester (64g) was dissolved in acetonitrile (400 mL) and 4-acetamidobenzenesulfonyl azide (p-ABSA, 87 g, 0.36 mol) was added and the mixture stirred at room temperature for 15 min. The mixture was then cooled to 0°C and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 58.6 mL) was added dropwise at 0°C during 30 min. The mixture was allowed to warm up to rt (room temperature) and stirred at rt for 4-20 h (until TLC showed completion of reaction). Saturated ammonium chloride (500 mL) was added and the organic phase was separated from the water phase. The water phase was extracted with diethylether (3 x 200 mL) and the four combined organic phases were dried (Magnesium sulphate) and evaporated *in vacuo*. The resulting solid was extracted with a

50:50 mixture of diethylether/pentane (3 x 200 mL). The combined ether phases were evaporated *in vacuo* (keep temperature below 40°) and purified by flash column chromatography (silicagel, eluent: 10:90 mixture of diethylether/pentane). The yellow fractions were combined and evaporated *in vacuo* (keep temperature below 40°) to give 70 g diazo-(3,4-Difluoro-phenyl)acetic acid allyl ester.

Diazo-(3,4-Difluoro-phenyl)acetic acid allyl ester (70 g) was dissolved in dichloromethane (1000 mL) and added slowly during 36 h via a syringe pump (alternatively it is added dropwise via an addition funnel; 30 mL pr. hour) to a refluxing solution of rhodium (II) octanoate dimer (1.17 g, 1.5 mmol) in dichloromethane (200 mL). After all diazo compound has been added, the mixture is refluxed for another 30 min, then was evaporated *in vacuo* and crystallised by addition of cyclohexane (200 mL). This gave 30 g crystalline . Further 15 g was isolated from the motherliq. by repeated evaporation and crystallisation giving in total 45 g 1-(3,4-Difluoro-phenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one.

The following compounds were prepared in a similar way:
1-(3,4-dichlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one
1-(4-chlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one
1-(4-fluorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one
1-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one

Example 2 Synthesis of (1S,5R)-1-(3,4-Dichlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one

A solution of 3,4-dichlorophenylacetonitrile (62 g, 332 mmol) in benzene (250 mL) was added slowly to a suspension of sodium amide (28.1 g, 720 mmol) in benzene (250 mL) at 0 °C under argon, and the mixture was stirred at room temperature for 3 h. To the resulting mixture, a solution of (R)-epichlorohydrin (30.1 g, 288 mmol] in benzene (250 mL) was added at 0 °C during 45 minutes, and the whole was stirred at room temperature for 16 h. After the solvent was evaporated, EtOH (1250 mL) and 2 N NaOH (500 mL) were added to the residue, and the mixture was heated under reflux for 15 h and then acidified with 12 N HCl at 0°C (pH of the mixture was about 1). The resulting mixture was evaporated, and AcOEt (900 mL) was added to the residue. Insoluble salts were filtered off, and the filtrate was washed with brine, dried (Na2SO4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/heptane, 20:80) to give the product as orange crystals (31.2 g, 39%). mp °C. $[\alpha]_{20\,D}$ = -69.5 *(c* 1.0, MeOH). 1 H-NMR (500 MHz, DMSO-d_6) 1.38 (1 H, dd), 1.75 (1 H, dd,), 2.85 (1 H, ddd), 4.25 (1 H, d), 4.46 (1 H, dd), 7.45 (1 H, d), 7.65 (1 H, d), 7.75 (1 H, s),

The following compounds were prepared in a similar way:
(1S,5R)-1-(4-chlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one
(28 g, 41%). mp °C. $[\alpha]_{20\,D}$ = -66.1 *(c* 1.0, MeOH). 1 H-NMR (500 MHz, $CDCl_3$) 1.35 (1 H, dd), 1.60 (1 H, dd,), 2.55 (1 H, ddd), 4.25 (1 H, d), 4.40 (1 H, dd), 7.30-7.44 (5 H, m)
(1S,5R)-1-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one
(36 g, 41%). mp 56-57 °C. $[\alpha]_{20\,D}$ = -77.3 *(c* 1.0, MeOH). 1 H-NMR (500 MHz, $CDCl_3$) 1.45 (1 H, dd), 1.65 (1 H, dd,), 2.55 (1 H, ddd), 4.30 (1 H, d), 4.45 (1 H, dd), 7.30-7.44 (5 H, m)
(1S,5R)-1-(4-fluorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one
$[\alpha]_{20\,D}$ = -63.9 - *(c* 1.0, MeOH).
(1S,5R)-1-(3,4-difluorophenyl-3-oxa-bicyclo[3.1.0]hexan-2-one
$[\alpha]_{20\,D}$ –55.7 *(c* 1.0, MeOH).
(1S,5R)-1-(4-methylphenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one
(1S,5R)-1-(4-methoxyphenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one
(1S,5R)-1-(3-fluorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one
(1S,5R)-1-(3-chlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one

Example 3 (1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide

To a solution of *(1S,5R)*-1-phenyl-3-oxa-bicyclo[3.1.0]hexan-2-one (10.5 g, 60.0 mmol) in CH_2Cl_2 (200 mL) was added AlC13 (16.0 g, 120 mmol) and then the mixture was cooled to 0° C, and then benzyl methyl amine (240 mmol, as a 2.0M solution of benzyl methyl amine in THF) was added slowly. The mixture was stirred at room temperature for 24 h, and then the reaction was quenched with saturated aqueous NH4Cl. After addition of CH_2Cl_2 and H2O, the resulting mixture was partitioned. The organic layer was washed with 1N HCl and brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane, 1:4) to give (1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide.

The following compounds were prepared in a similar way:

(1S,2R)-1-(4-Chlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid benzyl methyl amide;

(1S,2R)-1-(4-Fluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid benzyl methyl amide;

(1S,2R)-1-(3,4-Difluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid benzyl methyl amide;

(1S,2R)-1-(3,4-Dichlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid benzyl methyl amide;

(1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid methyl (1-phenylethyl) amide;

(1S,2R)-1-(4-Chlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid methyl (1-phenylethyl) amide;

(1S,2R)-1-(4-Fluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid methyl (1-phenylethyl) amide;

(1S,2R)-1-(3,4-Difluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid methyl (1-phenylethyl) amide;

(1S,2R)-1-(3,4-Dichlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid methyl (1-phenylethyl) amide;

(1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

(1S,2R)-1-(4-Chlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

(1S,2R)-1-(4-Fluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

(1S,2R)-1-(3,4-Difluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

(1S,2R)-1-(3,4-Dichlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluorobenzyl) methyl amide;

(1S,2R)-2-Hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide;

(1S,2R)-1-(4-Chlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide;

(1S,2R)-1-(4-Fluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide;

(1S,2R)-1-(3,4-Difluorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide;

(1S,2R)-1-(3,4-Dichlorophenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (2-chlorobenzyl) methyl amide.

Example 4 Esters of the formula VII

(1S,5R)-1-(3,4-Dichlorophenyl)-3-oxa-bicyclo[3.1.0]hexan-2-one (22.6 g) was dissolved in 33% HBr/glacial acetic acid and heated to 80°C for 5h, cooled to rt and thrown into 1300 ml ice-water and stirred at rt for 16 h. The precipitated acid was isolated by filtration, redissolved in toluene (1000 ml), dried over anhydrous magnesium sulphate and evaporated *in vacuo* to give 30 g of the intermediate (1S,2R)-2-(bromomethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid. The (1S,2R)-2-(bromomethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid (30 g) was dissolved in anhydrous toluene (200 ml) and thionylchloride (18 ml) was added dropwise during 15 min. afterwhich the mixture was refluxed for 60 min. The reaction mixture was cooled to 5°C and methanol (200 ml) was added and the mixture was allowed to warm to rt and stirred at rt for 2 h. The mixture was evaporated *in vacuo*, redissolved in diethylether, washed with saturated aqueous sodium hydrogen carbonate 25 ml), brine (25 ml), dried over anhydrous magnesium sulphate and evaporated *in vacuo*. To give the intermediate (1S,2R)-2-(bromomethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid methyl ester (27 g). The (1S,2R)-2-(bromomethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid methyl ester (15 mmol) was dissolved in acetonitrile (50 ml) and added to a mixture an amine of formula III (15 mmol) in a mixture of acetonitrile (50 ml) and ethyl diisopropylamine (30 mmol). The mixture was stirred at room temperature for 16 h, evaporated *in vacuo*, taken up in ethyl acetate (200 ml) and washed successively with saturated sodium hydrogen carbonate (50 ml) and brine (50 ml, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to give the crude product ester of formula VII. Esters of formula VII were generally purified by precipitation of the oxalate salt from acetone.

Other esters of formula VII could be prepared by this method by using the appropriately substituted (1S,5R)-1-aryl-3-oxa-bicyclo[3.1.0]hexan-2-one and amine of formula III.

Example 5 Acids of the formula VIII

The oxalate salt of (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid methyl ester (10 mmol) was dissolved in methanol (80 mL) and water (20 ml). Lithium hydroxide (50 mmol) was added and the mixture was heated to reflux for 2 h. The mixture was cooled to rt and acidified to pH 3 with concentrated hydrochloric acid and the precipitated product (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)cyclopropanecarboxylic acid hydrochloride was isolated by filtration and dried *in vacuo.*

Other acids of formula VIII could be prepared by this method by using the appropriately substituted esters of formula VII.

Example 6 Piperidines of the formula III

The spiropiperidine-derivatives HQ of formula (vii), wherein X is oxygen, Z is $CR^{27}R^{28}$, Y is a bond, i.e. spiro[isobenzofuran-1(*3*H),4'-piperidines] are prepared according to the methods described by Marxer et al. *J. Org. Chem.* 1975, *40*, 1427, by Parham et al. *J. Org. Chem.* 1976, *41*, 2628 and by Bauer et al. *J. Med. Chem.* 1976, *19*, 1315.

The following compounds were prepared in a similar way:

6-Fluorospiro[isobenzofuran-1(*3*H),4'-piperidine],
6-trifluoromethylspiro[isobenzofuran-1(*3*H),4'-piperidine],
6-fluoro-3-methylspiro[isobenzofuran-1(*3*H),4'-piperidine],
6-trifluoromethyl-3-methylspiro[isobenzofuran-1(*3*H),4'-piperidine],
5-methylspiro[isobenzofuran-1(*3*H),4'-piperidine],
6-fluoro-3-isobutylspiro[isobenzofuran-1(*3*H),4'-piperidine],
6-fluoro-3-cyclohexylspiro[isobenzofuran-1(*3*H),4'-piperidine] and
6-fluoro-3-(4-fluorophenyl)spiro[isobenzofuran-1(*3*H),4'-piperidine]

The spiropiperidine-derivatives HQ of formula (vii), wherein X is $CR^{27}R^{28}$, Z is NR^{26}, Y is a bond are prepared according to the methods described by Maligres et al. *Tetrahedron* 1997, 53, 10983, and by Cheng et al. *Tet. Lett.* 1997, 38, 1497.

The following compounds were prepared in a similar way:

1-Acetyl-5-fluoro-spiro[2,3-dihydro-*1*H-indol-3,4'-piperidine];

1-Acetyl-spiro[2,3-dihydro-*1*H-indol-3,4'-piperidine];
1-Methanesulphonyl-spiro[2,3-dihydro-*1*H-indol-3,4'-piperidine].

The spiropiperidine-derivatives HQ of formula (vii), wherein the X is $CR^{27}R^{28}$, Z is oxygen, Y is a bond, i.e. 2,3-dihydro-spiro(benzofuran-3,4'-piperidines), are prepared according to the methods described by Chen, Meng-Hsin; Abraham, John A. *Tetrahedron Lett.* 1996, *37*, 5233-5234 and Slade, P.D. et al. *J. Med. Chem.* 1998, *41*, 1218-1235.

The following compounds were prepared in a similar way:
2,3-Dihydro-5-fluorospiro[benzofuran-3,4'-piperidine] and
2,3-dihydro-5,6-difluorospiro[benzofuran-3,4'-piperidine]

The substituents R^{33}–R^{36} are introduced by applying suitably substituted starting compounds to methods analogous to the above mentioned.

Example 7 1-(*tert*-butoxycarbonyl)-4-isocyanato-4-phenyl-piperidine

Triethylamine (5.02mL, 36.1mmol) and diphenylhosphoryl azide (4.24mL, 19.7mmol) are added to a solution of 1-(tert-butoxycarbonyl)-4-phenyl-4-piperidinecarboxylic acid (5.0g, 16.4mmol) in dry DMF (50mL) under nitrogen at ambient temperature. The mixture is stirred at ambient temperature for 2h, and then heated to 60°C for 3h. The mixture is slightly cooled and concentrated *in vacuo*. Water (75mL) is added to the remanence followed by extraction with ethyl acetate (2x75mL). Combined organic fractions are washed with brine (3x50mL), dried ($MgSO_4$) and evaporated to dryness. The crude mixture is purified by silica gel chromatography eluting with ethyl acetate-heptane (1:4). This furnishes 4.8g (98%) of the wanted 1-(tert-butoxycarbonyl)-4-isocyanato-4-phenyl-piperidine as a clear oil. LC/MS (*m/z*) 203.2 (M-boc+H^+); t_R = 3.64 min. ^1H NMR ($CDCl_3$) 1.49 (s, 9H); 1.92 (bd, 2H); 2.02 (dt, 2H); 3.15 (bt, 2H); 4.17 (bs, 2H); 7.26 (dd, 1H); 7.39 (dt, 2H); 7.44 (dd, 2H).

Example 8 Piperidines of formula III where Q is (iii), and R^{12} is phenyl and R^{13} is a group $-NHCONR^{20}R^{21}$

1-(tert-butoxycarbonyl)-4-isocyanato-4-phenyl-piperidine (1 mmol) was dissolved in anhydrous THF and an amine $HNR^{20}R^{21}$ (1 mmol) was added, the mixture was stirred at rt for 16 h, evaporated *in vacuo* and redissolved in a 50:50 mixture of dichloromethane and trifluoroacetic acid (10 ml) and stirred at rt for 60 min. The mixture was evaporated *in vacuo* to give the product piperidine as the trifluoroacetic acid salt.

Example 9 Piperidines of formula III where Q is (iii), and R^{12} is phenyl and R^{13} is H

N-(4-Fluoro-2-piperidin-4-yl-phenyl)-acetamide hydrochloride

2-Bromo-4-fluoro-acetanilide (3.00 g, 12.9 mmol) and pyridine-4-boronic acid (1.60 g, 12.9 mmol) are dissolved in 1,2-dimethoxyethane (70 ml). Tetrakis(triphenylphosphine)palladium(0) (0.89 g, 0.77mmol) is added followed by sodium carbonate (4.10 g, 38.7 mmol) dissolved in water (25 ml). The mixture is heated at reflux for 3 hours, then stirred at ambient temperature overnight. Solvents are evaporated *in vacuo*, then ethyl acetate (50ml) and aqueous ammonia (dil.) are added to the remanence. The phases are separated and the aqueous layer is extracted with ethyl acetate (2 x 50 ml). The combined organic fractions are washed with brine (sat.), dried ($MgSO_4$), filtered and concentrated by means of evaporation. The product is purified by silica gel chromatography eluting with ethyl acetate:heptane:triethylamine (70:30:4) followed by ethyl acetate:ethanol:triethylamine (90:10:4) to furnish 2.37 g (80%) of the title compound as an oil. LC/MS (*m/z*) 231.0 ($M+H^+$). ^1H NMR ($CDCl_3$): 2.03 (t, 3H); 6.99 (dd, 1H); 7.11 (dt, 1H); 7.28 (dd, 2H); 7.65 (b, 1H, NH); 7.87 (dd, 1H); 8.62 (dd, 2H).

N-(4-Fluoro-2-pyridin-4-yl-phenyl)-acetamide (2.37 g, 10.3 mmol) is dissolved in methanol (40 ml), then platinum oxide (0.2 g, 0.88 mmol) and glacial acetic acid (10 ml) are added. The mixture is hydrogenated at a Parr apparatus (ambient temperature, 3 atm. H_2) for 24 hours. The catalyst is removed by filtering through celite and the mixture is concentrated *in vacuo*. The remanence is redissolved in ethyl acetate (40 ml) and a small amount of water (10 ml) is added. The aqueous phase is made basic by addition of 2M NaOH and the layers are separated. The aqueous phase is extracted again with ethyl acetate (2 x 30 ml), then the combined organic fractions are washed with brine (sat.), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The hydrochloride salt is prepared by addition of ethereal HCl to a solution of the crude product in acetone. Precipitated material is filtered off and dried *in vacuo* to furnish 1.20 g (49%) of the title compound as a white crystalline material. LC/MS (*m/z*) 237.0 ($M+H^+$). ^1H NMR (DMSO-d_6): 1.82 (m, 4H); 2.07 (s, 3H); 2.95 (m, 2H); 3.03 (m, 1H); 3.36 (m, 2H); 7.00 (dd, 1H); 7.05 (dd, 1H); 7.28 (dd, 1H); 8.75-8.91 (bd, 1H, NH, HCl); 9.48 (s, 1H, NH).

Example 10 (4-Phenyl-piperidine-4-yl)-piperidin-1-yl-methanone

Under a stream of nitrogen N,N′-carbonyldiimidazole (3.62g, 22.3mmol) followed by piperidine (3.74g, 43.9mmol) is added to a solution of 1-(tert-butoxycarbonyl)-4-phenyl-4-piperidinecarboxylic acid (3.40g, 11.1mmol) in dry THF (50mL). The mixture is heated to reflux 18h, then cooled to ambient temperature and concentrated by means of evaporation. The remanence is redissolved in ethyl acetate (150mL) and successively washed with $NaHCO_3$ (50mL, aq, sat.), dilute HCl (50mL) at pH 3, brine (50mL), then dried ($MgSO_4$) and evaporated to dryness. This intermediate is purified by silica gel chromatography eluting with ethyl acetate-heptane-triethylamine (40:50:10) to furnish 1.01g (24%) of 4-phenyl-4-(piperidine-1-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester as a white crystalline solid. This is dissolved in a mixture of MeOH (10mL) and THF (10mL), then 2M HCl in MeOH (5mL) is added and the mixture is stirred at ambient temperature for 2h. Water (20mL) is added and pH is adjusted to pH 12 by addition of 2M NaOH. The organic phase is separated and the aqueous phase is extracted with ethyl acetate (30mL). Combined organic fractions are dried ($MgSO_4$) and concentrated *in vacuo* to furnish 0.47g (63%) of (4-Phenyl-piperidine-4-yl)-piperidin-1-yl-methanone. LC/MS (m/z) 273.1 ($M+H^+$); $t_R = 1.65$ min.

Example 11 Piperidines of formula III where Q is (iii), and R^{12} is phenyl and R^{13} is a group $-CONR^{25}R^{26}$

These piperidines were prepared by the method used in Example 9 using the appropriate amine $HNR^{25}R^{26}$.

Example 12 Piperidines of formula III where Q is (iii), and R^{12} is phenyl and R^{13} is a group $-NR^{14}COR^{15}$

1-Benzyl-4-phenyl-piperidin-4-ylamine (*Bioorg.Med.Chem.Lett.* 1996; 2307; *Collect.Czech.Chem.Commun.* 1987; 52, 2095; *Synthesis* 2000, 1709) (1 mmol) was dissolved in a mixture of anhydrous acetonitrile and ethyl diispropylamine (1 mmol). An acid chloride $ClCOR^{15}$ (1 mmol) was added at 0°C and the mixture was stirred at 0° for 60 min. The mixture was evaporated *in vacuo*, taken up in ethyl acetate (50 ml), washed with saturated aqueous sodium hydrogen carbonate 25 ml), brine (25 ml), dried over anhydrous magnesium sulphate and evaporated *in vacuo*. The crude product was taken up in ethanol

(50 ml), 5% palladium on charcoal (50 mg) was added and the mixture was hydrogenated for 24 h at 3 bar in a Parr hydrogenation apparatus. The mixture was filtrated and evaporated *in vacuo* to give the final piperidines.

Example 13 Piperidines of formula III where Q is (iii), and R^{12} is phenyl and R^{13} is a group -$NR^{16}CONR^{17}R^{18}$

1-Benzyl-4-phenyl-piperidin-4-ylamine (*Bioorg.Med.Chem.Lett.* 1996; 2307; *Collect.Czech.Chem.Commun.* 1987; 52, 2095; *Synthesis* 2000, 1709) (1 mmol) was dissolved in a mixture of anhydrous acetonitrile and ethyl diispropylamine (1 mmol). An acid chloride $ClCOCONR^{17}R^{18}$ (1 mmol) was added at 0°C and the mixture was stirred at 0° for 60 min. The mixture was evaporated *in vacuo*, taken up in ethyl acetate (50 ml), washed with saturated aqueous sodium hydrogen carbonate 25 ml), brine (25 ml), dried over anhydrous magnesium sulphate and evaporated *in vacuo*. The crude product was taken up in ethanol (50 ml), 5% palladium on charcoal (50 mg) was added and the mixture was hydrogenated for 24 h at 3 bar in a Parr hydrogenation apparatus. The mixture was filtrated and evaporated *in vacuo* to give the final piperidines.

Example 14 Piperidines of formula III where Q is (iii), and R^{12} is phenyl and R^{13} is a group -$NR^{22}SO_2R^{23}$

1-Benzyl-4-phenyl-piperidin-4-ylamine (*Bioorg.Med.Chem.Lett.* 1996; 2307; *Collect.Czech.Chem.Commun.* 1987; 52, 2095; *Synthesis* 2000, 1709) (1 mmol) was dissolved in a mixture of anhydrous acetonitrile and ethyl diispropylamine (1 mmol). A sulphonyl chloride $ClSO_2R^{23}$ (1 mmol) was added at 0°C and the mixture was stirred at 0° for 60 min. The mixture was evaporated *in vacuo*, taken up in ethyl acetate (50 ml), washed with saturated aqueous sodium hydrogen carbonate 25 ml), brine (25 ml), dried over anhydrous magnesium sulphate and evaporated *in vacuo*. The crude product was taken up in ethanol (50 ml), 5% palladium on charcoal (50 mg) was added and the mixture was hydrogenated for 24 h at 3 bar in a Parr hydrogenation apparatus. The mixture was filtrated and evaporated *in vacuo* to give the final piperidines.

Example 15 Aldehyde reagent of formula IV:

For n=0: (1S,2R)-1-(3,4-Dichloro-phenyl)-2-formyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide

(1S,2R)-1-(3,4-Dichloro-phenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide (4.60 g, 12.0 mmol) is dissolved in acetone (240 ml) and IBX (10.1 g, 36.1 mmol) is added (IBX concentration 0.15M). The mixture is heated to reflux for 2 hours, then cooled to ambient temperature. The solids are filtered off and the filtrate concentrated *in vacuo*. The crude product is eluted through a short silica gel column with ethyl acetate:heptane (50:50). 3.57 g (78%) of the product is obtained as a highly viscous light yellow oil. LC/MS (*m/z*) 380.0 ($M+H^+$).

For n=2: (1S,2S)-1-(3,4-Dichloro-phenyl)-2-((E)-3-oxo-propenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide

The isomer mixture (1S,2S)-1-(3,4-dichloro-phenyl)-2-((Z/E)-2-[1,3]dioxolan-2-yl-vinyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide (845 mg, 1.88 mmol) is dissolved in acetone (20 ml), p'-toluenesulphonic acid (162 mg, 0.94 mmol) is added and the mixture is stirred at ambient temperature for 1.5 hours. The solvent is removed by means of evaporation and the crude mixture is purified by silica gel chromatography eluting with ethyl acetate:heptane (40:60) to obtain the wanted product as an oil. Yield 480 mg, 63%). LC/MS (*m/z*) 406.0 ($M+H^+$).

Example 16 Alkylating reagents of formula II

__For n=0:__ A suitable substituted (1S,2R)-2-hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid amide (with R^1-R^{36} and n as defined herein prepared as described in example 3) (1 mmol) was dissolved in dichloromethane (20 ml) and phosphorus tribromide (3 mmol) was added and the mixture stirred at rt for 3 h. Water (10 ml) was added and after stirring for 10 minutes the dichloromethane phase was isolated, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to a clear oil which was used immediately without further purification

__For n=1:__ (1S,2S)-2-(2-Chloro-ethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide

(1S,2R)-1-(3,4-Dichloro-phenyl)-2-hydroxymethyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide (4.60 g, 12.0 mmol) is dissolved in acetone (240 ml) and IBX (10.1 g, 36.1 mmol) is added (IBX concentration 0.15M). The mixture is heated to reflux for 2 hours, then cooled to ambient temperature. The solids are filtered off and the filtrate concentrated *in vacuo*. The crude product is eluted through a short silica gel column with ethyl acetate:heptane (50:50). 3.57 g (78%) of the product is obtained as a highly viscous light yellow oil. LC/MS (*m/z*) 380.0 ($M+H^+$).

Cloromethyltriphenylphosphonium chloride (2.74 g, 7.89 mmol) is suspended in dry THF (30 ml) under Argon and KHMDS (1.57 g, 7.89 mmol) is added portionwise at 0°C. The mixture is stirred at 0°C for 30 minutes, then allowed to warm to ambient temperature. (1S,2R)-1-(3,4-Dichloro-phenyl)-2-formyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide (1.0 g, 2.63 mmol) dissolved in dry THF (10 ml) is added dropwise and the mixture is stirred at ambient temperature for 2.5 hours. The reaction mixture is then poured onto ice cold water (30 ml) and the layers are separated. The aqueous phase is extracted with ethyl acetate (2 x 30 ml) and the combined organic fractions are washed with brine (sat.), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product is purified by silica gel chromatography, eluting with a gradient of ethyl acetate:heptane (0:100) – (50:50). The product is isolated as a Z/E isomer mixture. Yield 630 mg (57%). LC/MS (*m/z*) 412.1 ($M+H^+$).

The isomer mixture (1S,2S)-2-((Z/E)-2-chloro-vinyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide (170 mg, 0.41 mmol) is dissolved in dichloromethane (10 ml). N_2 is bubbled through the solution for 15 minutes before adding Crabtree's catalyst (66.4 mg, 0.082 mmol, [(1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate]). The reaction mixture is hydrogenated at a Parr apparatus (ambient temperature, 3 atm. H_2) for 4 hours. The solvent is removed by evaporation and the residue is subjected to silica gel chromatography eluting with ethyl acetate:heptane (20:80). 91 mg (53%) of the title compound is isolated as an oil. LC/MS (*m/z*) 415.9 ($M+H^+$).

Example 17 (1S,2S)-1-(3,4-Dichloro-phenyl)-2-((Z/E)-2-[1,3]dioxolan-2-yl-vinyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide

(1,3-Dioxolan-2-ylmethyl)triphenylphosphonium bromide (3.39 g, 7.89 mmol) is suspended in dry THF (50 ml) under Argon and KHMDS (1.57 g, 7.89 mmol) is added portionwise at 0°C. The mixture is stirred at 0°C for 30 minutes, then allowed to warm to ambient temperature. (1S,2R)-1-(3,4-Dichloro-phenyl)-2-formyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide (1.0 g, 2.63 mmol) dissolved in dry THF (10 ml) is added dropwise and the mixture is stirred at ambient temperature for 2 hours. The reaction mixture is then poured onto ice cold water (30 ml) and the layers are separated. The aqueous phase is extracted with ethyl acetate (3 x 30 ml) and the combined organic fractions are washed with brine (sat.), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product is purified by silica gel chromatography, eluting with a gradient of ethyl acetate:heptane (20:80) – (50:50). The product is isolated as a Z/E isomer mixture. Yield 1.07 g (91%). LC/MS (*m/z*) 450.1 ($M+H^+$).

Example 18 (1S,2S)-2-[(E)-3-(4-Acetylamino-4-phenyl-piperidin-1-yl)-propenyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide

N-(4-Phenyl-piperidin-4-yl)-acetamide (140 mg, 0.64 mmol) dissolved in ethanol (3 ml) is added to (1S,2S)-1-(3,4-Dichloro-phenyl)-2-((E)-3-oxo-propenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide dissolved in ethanol (5 ml) followed by dropwise addition of sodium cyanoborohydride (1.0M in THF, 1.97 ml, 1.97 mmol) at 0°C. After complete addition the mixture is kept at ambient temperature for 2 hours. The reaction is quenched by addition of sodium bicarbonate (3ml, sat.) and the ethanol is removed by means of evaporation. Ethyl acetate (30 ml) is added to the remanence. The organic fraction is washed successively with sodium bicarbonate (10ml, sat.) and brine (10 ml, sat.), dried ($MgSO_4$) and concentrated *in vacuo*. The residue is purified by silica gel chromatography eluting with ethyl acetate:ethanol:triethylamine (95:0:5) – (90:5:5) to furnish the title compound as an oil. Yield 81 mg (27%). LC/MS (*m/z*) 610.3 ($M+H^+$).

Example 19 Preparation of the compounds of the invention

The compounds of the present invention were prepared by one of two general methods:

Method A: Alkylating a piperidine of formula III with an alkylating derivative of formula II:

For n= 0: A suitable substituted (1S,2R)-2-hydroxymethyl-1-phenyl-cyclopropanecarboxylic acid amide (1 mmol) was dissolved in dichloromethane (20 ml) and phosphorus tribromide (3 mmol) was added and the mixture stirred at rt for 3 h. Water (10 ml) was added and after stirring for 10 minutes the dichloromethane phase was isolated, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to a clear oil which was used immediately without further purification by dissolving in anhydrous acetonitile (10 ml) and added to a mixture of a piperidine of formula III (1 mmol), and ethyl diisopropyl amine (1.3 mmol) in acetonitrile (10 mL) and the mixture was heated to 85 °C for 3 h. The mixture was cooled to room temperature and evaporated *in vacuo*. The product was purified by chromatography either on silicagel using as eluent ethylacetate/triethylamine (99:1) or by purified by HPLC.

Fractions containing the product were pooled and evaporated *in vacuo* and characterised by HPLC-UV-ELSD-MS. The measured HPLC-retention time, the measured molecular mass and UV- and ELSD-purities are shown in Table 1.

For n= 1: (1S,2S)-2-[2-(4-Acetylamino-4-phenyl-piperidin-1-yl)-ethyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide:

(1S,2S)-2-(2-Chloro-ethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide (91 mg, 0.22 mmol) is dissolved in acetonitrile (10 ml). Potassium iodide (73 mg, 0.44 mmol), potassium carbonate (91 mg, 0.66 mmol) and N-(4-Phenyl-piperidin-4-yl)-acetamide hydrochloride (67 mg, 0.26 mmol) are added. The reaction mixture is heated to reflux for 72 hours, then cooled to ambient temperature and concentrated *in vacuo*. The remanence is redissolved in ethyl acetate (15 ml), washed with water (10 ml), brine (10 ml), then dried over $MgSO_4$, filtered and concentrated to an oil. The product is filtered through a plug of silica gel eluting with ethyl acetate:heptane:triethylamine (50:50:5) followed by ethyl acetate:ethanol:triethylamine (80:20:5) to furnish 70 mg (54%) of the title compound. LC/MS (*m/z*) 596.3 ($M+H^+$).

Method B: Reacting an amine of formula VI with an acid of formula VIII by the use of an activating reagent or a coupling reagent:

(1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl) cyclopropanecarboxylic acid hydrochloride (0.05 mmol) was dissolved in anhydrous DMF. Ethyl diisopropylamine (0.15 mmol), benzylamine (0.075 mmol), dimethylaminopyridine (0.05 mmol) and BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate 0.1 mmol) were added and the mixture stirred at rt for 2 h. The reaction mixture was evaporated *in vacuo* and the product purified by HPLC. Fractions containing the product were pooled and evaporated *in vacuo* and characterised by HPLC-UV-ELSD-MS. The measured HPLC-retention time, the measured molecular mass and UV- and ELSD-purities are shown in **table 1**.

Method C Reducing an amine of formula IX:

For n= 2: ***(1S,2R)-2-[3-(4-Acetylamino-4-phenyl-piperidin-1-yl)-propyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide:***

(1S,2S)-2-[(E)-3-(4-Acetylamino-4-phenyl-piperidin-1-yl)-propenyl]-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide (65 mg, 0.11 mmol) is dissolved in dichloromethane (10 ml). N_2 is bubbled through the solution for 15 minutes before adding Crabtree's catalyst (17.7 mg, 0.022 mmol, [(1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate]). The reaction mixture is hydrogenated at a Parr apparatus (ambient temperature, 3 atm. H_2) for 3 hours. The solvent is removed by evaporation and the residue is subjected to silica gel chromatography eluting with ethyl acetate:ethanol:triethylamine (95:0:5) – (85:10:5). Evaporation from heptane furnishes the title compound as a white solid. Yield 25 mg (38%). LC/MS (*m/z*) 610.3 ($M+H^+$).

The following compounds were made by the methods indicated in the table. Analytical data are shown in table 1.

compound	$M+H^+$	RT min.	UV-purity (%)	ELSD-purity (%)	Synthesis method
1a	564,2	2,5	98.49	97.90	A
2a	578,5	2,7	41.8	99.2	A
3a	576,3	2,6	82.5	98.3	A
4a	594,3	2,6	98.17	98.59	A

compound	M+H$^+$	RT min.	UV-purity (%)	ELSD-purity (%)	Synthesis method
5a	590,2	2,6	82.6	100	A
6a	608,5	2,8	96.65	99.48	A
7a	550,2	2,5	97.87	99.93	A
8a	544,2	2,4	82.38	99.91	A
9a	481,3	2,3	92.92	100	A
10a	557,1	2,6	75.95	99.33	A
12a	530,2	2,2	95.68	99.83	A
13a	584,3	2,5	97.25	99.47	A
14a	544,1	2,7	93.6	99.8	A
15a	515,2	2,4	72.36	99.83	A
16a	542,3	2,5	88.53	100	A
17a	560,3	2,4	98.21	99.95	A
18a	546,4	2,4	96.39	99.87	A
19a	560,3	2,3	90.62	100	A
20a	576,4	2,4	94.47	100	A
21a	514,2	2,4	99.42	99.84	A
22a	528,4	2,2	96.9	99.8	A
23a	526,4	2,3	75.77	99.95	A
24a	575,1	2,2	97.43	99.74	A
25a	544,3	2,6	90.09	99.48	A
26a	562	2,3	96.58	99.84	A
27a	604,4	2,4	95.66	100	A
28a	533,1	2,5	99.44	100	A
29a	560,1	2,5	98.16	99.81	A
30a	578,2	2,4	97.01	99.87	A
31a	586,2	2,4	97.17	100	A
32a	562,2	2,6	91.69	99.36	A
33a	604,4	2,3	93.68	99.44	A
34a	606,5	2,6	84.9	99.19	A
35a	580,4	2,4	96.74	98.84	A
36a	618,2	2,4	92.3	99.95	A
37a	549,2	2,8	100	99.34	A
38a	558,3	2,6	97.21	99.97	A
39a	578,3	2,4	99.62	98.43	A
40a	632,4	2,5	100	99.77	A
41a	592,2	2,9	99.11	98.91	A

compound	$M+H^+$	RT min.	UV-purity (%)	ELSD-purity (%)	Synthesis method
42a	568,5	2,5	99.3	99.97	A
43a	602,3	2,5	87	99.68	A
44a	548,3	2,7	94.96	99.24	A
45a	564,1	2,5	96.864	98.061	A
46a	618,2	2,4	97.35	99.74	A
47a	580,4	2,8	93.59	98.34	A
48a	594,3	2,5	93.88	98.39	A
49a	562,2	2,5	98.65	99.69	A
50a	580,5	2,4	94.44	99.91	A
51a	598	2,4	92.14	99.97	A
52a	654,3	2,5	96.76	99.82	A
53a	614,1	2,8	92.98	98.17	A
54a	610,3	2,6	100	100	A
55a		2,6	99.79	99.89	B
56a		2,7	95.24	99.87	B
57a	614,1	2,79	100	99.96	A
58a	610,3	2,45	58.47	99.76	A
59a		2,51			A
60a		2,31			A
61a		2,31			A
62 a	579,7	2,5	58,47	99,76	A
63 a	593,1	2,8	43,8	99,7	A
64 a	591,6	2,6	93,8	99,6	A
65 a	609,5	2,6	96,3	99,7	A
66 a	496,4	2,1	97,5	100	A
67 a	632,6	2,9	98,56	99,24	A
68 a	608,4	2,6	99,22	99,37	A
69 a	568,3	2,5	79,36	99,97	A
70 a	499,3	2,4	96,75	99,88	A
71 a	580,1	2,4	72,93	99,12	A
72 a	546,4	2,3	72,08	99,94	A
73 a	517,2	2,4	99,56	99,88	A
74 a	544,2	2,3	95,31	99,94	A
75 a	535,2	2,4	87,78	98,21	A
76 a	561,9	2,3	85,12	99,62	A
77 a	582,5	2,6	98,18	99,36	A
78 a	549,3	2,6	95,56	99,92	A
79 a	576,3	2,4	99,76	99,77	A
80 a	548,3	2,3	97,01	99,9	A
81 a	602,3	2,6	91,01	98,89	A
82 a	566,3	2,3	96,79	99,89	A
83 a	620,3	2,7	96,06	98,97	A

compound	$M+H^+$	RT min.	UV-purity (%)	ELSD-purity (%)	Synthesis method
84 a	578,3	2,4	99,48	99,97	A
85 a	596,2	2,4	98,72	99,64	A
86 a	563	2,8	75,93	99,76	B
87 a	553,3	2,4	100	99,92	B
88 a	536,1	1,9	97,04	97,15	B
89 a	578,2	2,1	98,94	98,53	B
90 a	508,1	0,3	100	97,06	A
91 a	506,2	2,2	100	96,9	A
92 a	560,3	2,8	100	95,22	A
93 a	488,4	0,2	100	94,2	A
94 a	454,3	2,0	100	93,98	A
95 a	542,3	2,8	100	90,31	A
96 a	526,4	2,67	99,68	94,67	A
97 a	550,2	2,4	75,05	100	B
98 a	598,2	2,5	94,43	100	B
99 a	608,5	2,6	72	99,96	B
100 a	586,3	2,4	85,68	100	B
101 a	620,2	2,6	76,84	100	B
102 a	550,2	2,4	81,65	96,17	B
103 a		2,3	79,033	95,204	A
104 a		2,5	96,808	99,264	A
105 a		2,4	89,646	99,617	A
106 a		2,4	100	97,591	A
107 a		2,3	91,596	99,140	A
108 a		2,3	89,427	99,205	A
109 a		2,4	90,019	99,287	A
110 a		2,2	83,676	99,134	A
111 a	515,3	2,2	100,0	96,5	A
112 a	565,1	2,5	88,545	92,457	A
113 a	529,3	2,2	93,664	99,867	A
114 a	581,2	2,5	96,751	99,232	B
115 a	543,3	2,3	95,946	98,700	B
116 a	593,1	2,6	95,664	99,544	A
117 a	550,2	2,4	80,435	98,991	A
118 a	602,2	2,6	85,679	99,662	A
119 a	530	2,5	86,245	98,629	A
120 a	580,4	2,6	79,450	99,148	A
121 a	593,2	2,6	78,272	98,414	A
122 a	543,3	2,4	98,860	98,734	A
123 a	596.3	2,4	77,0	99,2	A
124 a	610.3	2,5	82,4	98,8	C
125 a	600,2	2,5	73,000	98,462	B
126 a	542,4	2,5	90,187	98,575	A
127 a	582,3	2,5	100	96,845	A
128 a	519,9	2,3	84,144	95,282	A

compound	M+H$^+$	RT min.	UV-purity (%)	ELSD-purity (%)	Synthesis method
129 a	532,3	2,3	80,554	99,653	A
130 a	557,2	2,4	100	97,176	B
131 a	644,3	2,3	84,144	95,282	B
132 a	614,3	2,3	80,554	99,653	B

Example 20 Receptor binding assay (Ki)

The binding assay is based on previously described methods (Chung FZ et al: Mol Pharmacol. 1995 48 p711-6 and Sarau HM et al: J Pharmacol Exp Ther. 1997 281 p1303-11).

Membrane preparation:

Membranes were isolated from baby hamster kidney (BHK) cells stably expressing the human NK1 or NK3 receptors or from Chinese hamster ovary (CHO) cells stably expressing the human NK2 receptor. 24 hours before harvesting, the BHK cells were treated with trichostatin A (TSA) to increase expression. The cells were washed twice with icecold phosphate-buffered saline without Mg^{2+}, Ca^{2+} and Sodium bicarbonate (PBS). The cells were scraped of in 10 ml PBS and centrifuged for 3 min at 4°C and 1500 g. The supernatant was discarded and the pellet was resuspended in 10 ml of 15 mM Tris-HCl pH 7,5 buffer containing 2 mM $MgCl_2$, 0,3 mM EDTA, 1 mM EGTA (buffer A) and subsequently Dounce homogenised. (For the NK1 receptor containing membranes an extra step with 5 min centrifugation at 4°C and 1500 g followed by resuspension of the pellet in 10 ml buffer A was included to enrich the membrane preparation). The suspension was centrifuged for 25 min at 4°C and 40000 g. The supernatant was discarded, the pellet was washed with 10 ml buffer A and the suspension was centrifuged for 25 min at 4°C and 40000 g. The supernatant was discarded and the pellet was resuspended in 7,5 mM Tris-HCl pH 7,5 containing 12,5 mM $MgCl_2$, 0,3 mM EDTA, 1 mM EGTA and 250 nM sucrose, frozen in liquid nitrogen and stored at -80 °C.

Competition binding assay:

For the NK3 binding assay, membranes were incubated with 0,1 nM ^{125}I-eledoisin in 50 mM Tris pH 7.4 buffer containing 3 mM $MnCl_2$, 40μg/ml bacitracin, 2μg/ml chymostatin,

2μM phosphoramidon, 4μg/ml leupeptin, 0,02% bovine serum albumin (BSA) and selected concentrations of compounds for 60 min at 25 °C.
For the NK1 and NK2 binding assay, the membranes were incubated with 0,1 nM ^{125}I-substance P or 0,1 nM ^{125}I-NKA, respectively in 50 mM Tris pH 7.4 buffer containing 3 mM $MnCl_2$ and 0,02% BSA and selected concentrations of compounds for 60 min at 25 °C. The assay was terminated by rapid filtration through GF/C UniFilters presoaked with 1% BSA (NK3 binding assay) or 0,1% polyethyleneimine (NK1 and NK2 binding assays) using a Tomtec harvester. The filters were washed 3 times with ice-cold 50 mM Tris pH 7,4, dried and added scintillant before counting in a Wallac scintillation counter.
For each compound, the IC_{50} value (the concentration required to obtain 50% inhibition of the radioligand) was determined from concentration-response curves and used to calculate the apparent affinity K_i from the equation $K_i = IC_{50}/(1+L/K_d)$, where L is the concentration of radioligand. K_d is the dissociation constant of the radioligand and was determined from saturation binding experiments.

When tested as described above the compounds 1a-56a all had an apparent NK3 affinity (Ki) of less than 50 nM, the compounds 57a-64a all had an apparent NK3 affinity (Ki) of less than 1000 nM, the compounds 65a-85a all had an apparent NK3 affinity (Ki) of less than 200 nM and the compounds 86a-132a all had an apparent NK3 affinity (Ki) of less than 1000 nM.

Example 21 The Fluorometric Imaging Plate Reader (FLIPR) assay: The compounds were analysed for efficacy profile in FLIPR assays similar to assays described in Jerman, JC et al: Eur J Pharmacol. 2001, 414, p23-30. BHK cells (cf. Example 20) stably expressing the human NK3 receptor were seeded in 100 μl media in black walled clear-base 96-wells plates (Costar) aiming at a confluency of 95-100% at the day of assay. The assay was performed according to the calcium assay kit (Molecular Devices). Briefly, the calcium assay reagent was dissolved in Hanks BSS (HBSS) buffer, pH 7,4 containing 20 mM Hepes and 2,5 mM probinicid. An equal volume (100 μl) of the calcium assay reagent solution was added to the wells and the plates were incubated for 60 min at 37°C. The plates were subsequently placed in the FLIPR for examination of fluorescence.

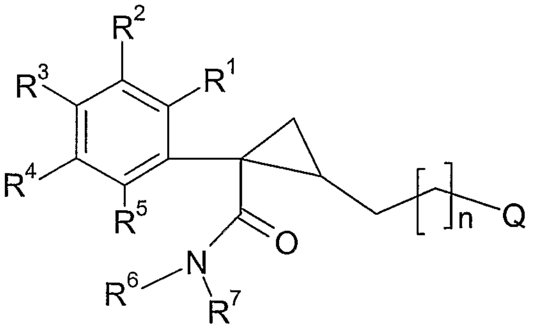
Compounds were diluted in HBSS buffer containing 20 mM Hepes prior to test. For test of agonist activity 50 μl of compound was added to the wells and the plates were analysed for

3 minutes in the FLIPR. For test of antagonist activity, 25 µl of compound was added to the wells and the plate was analysed for a 5 minute period. Subsequently, the wells were added 25 µl of an EC_{85} (final concentration) of NKB (app. 1 nM) previously determined from a dose-response curve with NKB. The plates were subsequently read for 3 minutes before termination. As controls, selected wells on all plates were added only 100 nM of the NK3 receptor agonist NKB or 2 µM of the calcium ionophor ionomycin. The maximal increase in fluorescence over background following each ligand addition was determined and analysed.

Compounds 1a–7a, 11a–21a, 23a, 25a, 27a–30a, 32a, 33a, 35a–39a, 42a, 44a, 45a, 51a–53a, 62a, 63a were tested in the FLIPR assay described above and inhibited the NKB-mediated activation of the NK3 receptor expressed in the BHK cells. The results showed that the compounds are NK3 receptor antagonists.

CLAIMS

1. A compound of formula I



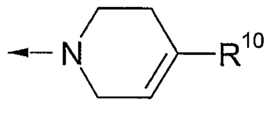
(I)

or a salt thereof, such as a pharmaceutically acceptable salt;

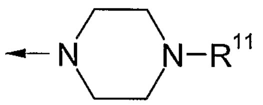
wherein

- R^1-R^5 are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, amino, C_{1-6}-alk(en/yn)ylamino, di-(C_{1-6}-alk(en/yn)yl)amino, C_{1-6}-alk(en/yn)ylcarbonyl, aminocarbonyl, C_{1-6}-alk(en/yn)ylaminocarbonyl, di-(C_{1-6}-alk(en)yl)aminocarbonyl, hydroxy, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylthio, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)ylsulfonyl, halo-C_{1-6}-alk(en/yn)ylsulfanyl, and C_{1-6}-alk(en/yn)ylsulfonyl;
- R^6 is selected from hydrogen, halo-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl ;
- R^7 is an aryl or a heteroaryl; or R^7 is a group aryl-CR^8R^9-, wherein R^8 and R^9 are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl;
- n is 0, 1, or 2;

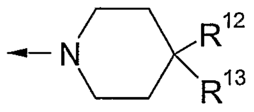
Q is selected from (i)-(vii), the arrow indicating the attachment point:



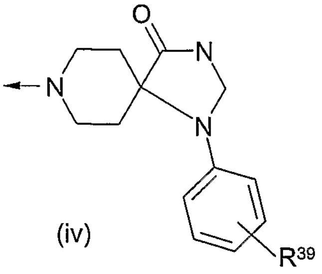
(i) ;



(ii) ;

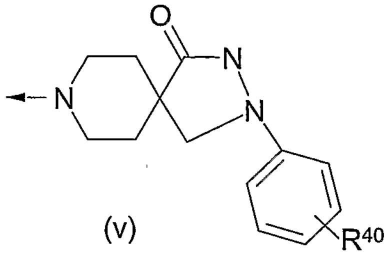


(iii)



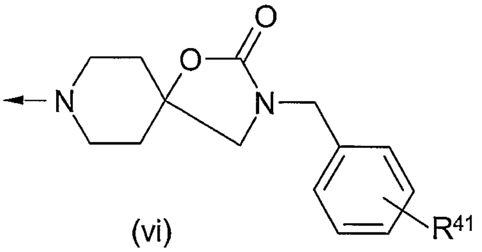
(iv)

;



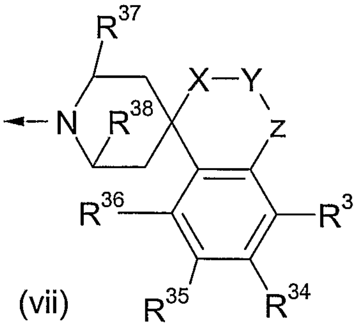
(v)

;



(vi)

;



(vii)

;

wherein R^{10} is an aryl;

wherein R^{11} is selected from an aryl or benzyl, halo-C_{1-6}-alk(en/yn)ylsulfonyl, C_{1-6}-alk(en/yn)ylsulfonyl, arylsulphonyl, arylacyl, C_{1-6}-alk(en/yn)ylcarbonyl, aminocarbonyl, C_{1-6}-alk(en/yn)ylaminocarbonyl, and di-(C_{1-6}-alk(en)yl)aminocarbonyl;

wherein R^{12} is an aryl;

wherein R^{13} is hydrogen, hydroxy, cyano, or amino, or one of the following groups:

-NHC_{1-6}-alk(en/yn)yl;

-N(C_{1-6}-alk(en/yn)yl)$_2$;

-$NR^{14}COR^{15}$, wherein R^{14} is hydrogen or C_{1-6}-alk(en/yn)yl and R^{15} is C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl;

-$NR^{16}COCONR^{17}R^{18}$, wherein R^{16} is hydrogen or C_{1-6}-alk(en/yn)yl and R^{17} and R^{18} are selected independently from hydrogen, C_{1-6}-alk(en/yn)yl and C_{3-8}-cycloalkyl; or R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl are optionally substituted with a C_{1-6}-alk(en/yn)yl;

-$NR^{19}CONR^{20}R^{21}$, wherein R^{19} is hydrogen or C_{1-6}-alk(en/yn)yl and R^{20} and R^{21} are selected independently from hydrogen and C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalkyl; or R^{20} and R^{21} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a C_{1-6}-alk(en/yn)yl;

-$NR^{22}SO_2R^{23}$, wherein R^{22} is hydrogen, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalkyl and R^{23} are amino, C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalkyl;

-COR^{24}, wherein R^{24} is C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalkyl;

-$CONR^{25}R^{26}$, wherein R^{25} and R^{26} independently are selected from hydrogen, C_{1-6}-alk(en/yn)yl and C_{3-8}-cycloalkyl; or R^{25} and R^{26} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl is optionally substituted with a C_{1-6}-alkyl;

-$NHCOOR^{42}$, wherein R^{42} is C_{1-6}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl;

wherein X, Y, and Z are selected independently from a bond; O; NR^{27}; $CR^{28}R^{29}$ and $S(O)_m$, wherein m is 0, 1 or 2;

wherein R^{27} is selected from hydrogen, C_{1-6}-alk(en/yn)yl , C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, trifluoromethyl, acyl, thioacyl and trifluoromethylsulfonyl; or

R^{27} is a group $R^{30}SO_2$-, $R^{30}OCO$- or $R^{30}SCO$-, wherein R^{30} is C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalkyl, or C_{3-8}-cycloalkyl-C_{1-6}-alkyl; or

R^{27} is a group $R^{31}R^{32}NCO$- or $R^{31}R^{32}NCS$-, wherein R^{31} and R^{32} are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl and aryl; or wherein R^{31} and R^{32} together with the N-atom to which they are linked, form a pyrrolidinyl, piperidinyl or perhydroazepinyl group;

wherein R^{28} and R^{29} are independently selected from hydrogen, fluoro, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalkyl, and C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

wherein R^{33}-R^{36} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl;

wherein R^{37}-R^{38} are either both hydrogen or are fused together in an ethylene chain CH^2-CH^2- forming an aza-bicyclo[3.2.1]octane-yl;

wherein R^{39}-R^{41} are independently selected from the group consisting of hydrogen and halogen;

provided that no more than one of X, Y and Z may be a bond, and provided that two adjacent groups X, Y or Z may not at the same time be selected from O and S.

2. The compound or salt of claim 1, wherein R^1-R^5 are independently selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylthio, and halo-C_{1-6}-alkyl, .e.g trifluoromethyl.

3. The compound or salt of claim 1, wherein R^1-R^5 is hydrogen.

4. The compound or salt of claim 1, wherein R^1-R^5 are independently selected from hydrogen and halogen.

5. The compound or salt of claim 1, wherein R^1-R^5 are independently selected from hydrogen and chloro.

6. The compound or salt of claim 1, wherein R^1-R^5 are independently selected from hydrogen and fluoro.

7. The compound or salt of claim 5, wherein R^2 is chloro and R^3 is hydrogen.

8. The compound or salt of claim 5, wherein R^2 and R^3 are chloro.

9. The compound or salt of claim 6, wherein R^2 is fluoro and R^3 is hydrogen.

10. The compound or salt of claim 6, wherein R^2 and R^3 are fluoro.

11. The compound or salt of any of claims 7-10, wherein R^1, R^4 and R^5 are hydrogen.

12. The compound or salt of any of claims 1-11, wherein R^6 is selected from hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl, and C_{3-8}-cycloalkyl-C_{1-6}-alkyl.

13 The compound or salt of any of claims 1-11, wherein R^6 is selected from hydrogen and C_{1-6}-alk(en/yn)yl.

14. The compound or salt of any of claims 1-11, wherein R^6 is hydrogen.

15. The compound or salt of of any of claims 1-11, wherein R^6 is a C_{1-6}-alkyl.

16. The compound or salt of claim 15, wherein R^6 is methyl.

17. The compound or salt of any of claims 1-16, wherein R^7 is the group [aryl-CR^8R^9-].

18. The compound or salt of claim 17, wherein R^8 and R^9 are independently selected from hydrogen, C_{1-6}-alkyl, C_{3-8}-cycloalkyl and C_{3-8}-cycloalkyl-C_{1-6}-alkyl.

19. The compound or salt of claim 17, wherein R^8 and R^9 are independently selected from hydrogen and C_{1-6}-alkyl.

20. The compound or salt of claim 17, wherein R^8 and R^9 are independently selected from hydrogen and methyl.

21. The compound or salt of claim 17, wherein R^8 and R^9 are hydrogen.

22. The compound or salt of claim 17, wherein R^8 is hydrogen and R^9 is methyl.

23. The compound of any of claims 1-16, wherein R^7 is an aryl or a heteroaryl.

24. The compound or salt of any of claims 17-23, wherein said aryl or heteroaryl is monocyclic or bicyclic.

25. The compound or salt of any of claims 17-24, wherein said aryl or heteroaryl is unsubstituted.

26. The compound or salt of any of claims 17-24, wherein said aryl or heteroaryl is substituted with one or more substituents.

27. The compound or salt of claim 26, wherein said aryl or heteroaryl is substituted with one or more substituents selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl,

C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylcarbonyl C_{1-6}-alkylamino, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl , difluoromethyl, fluoromethyl and trifluoromethylsulfonyl.

28. The compound or salt of any of claims 24-27, wherein R^7 is the group aryl-CR^8R^9- as defined in any of claims 17-22, and the aryl of said group aryl-CR^8R^9- is as defined in any of claims 24-27.

29. The compound or salt of claim 28, wherein said aryl is an optionally substituted phenyl.

30. The compound or salt of claim 28 or 29, wherein said aryl is mono- or poly-substituted, e.g. di-substituted, with a halogen, e.g. fluoro or chloro.

31. The compound of claim 17, wherein R^7 is the group aryl-CR^8R^9- and R^7 is selected from benzyl, or halogen substitued benzyl, e.g. 4-halo benzyl, such as 4-fluorobenzyl, or 2-halo-benzyl, such as 2-chloro-benzyl.

32. The compound or salt of any of claims 1-31, wherein Q is (i).

33. The compound or salt of claim 32, wherein R^{10} is an aryl as defined in any of claims 24-30.

34. The compound or salt of any of claims 1-31, wherein Q is (ii).

35. The compound or salt of claim 34, wherein R^{11} is selected from an optionally substituted aryl or optionally substituted benzyl, trifluoromethylsulfonyl, C_{1-6}-alkylsulfonyl, arylsulphonyl, arylacyl, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl and di-(C_{1-6}-alkyl)aminocarbonyl).

36. The compound or salt of claim 34 or 35, wherein R^{11} is an aryl as defined in any of claims 24-30.

37. The compound or salt of claim 34, wherein R^{11} is an arylsulphonyl or an arylcarbonyl, wherein the aryl part of said arylsulphonyl or arylacyl is as defined in any of claims 24-30.

38 The compound or salt of any of claims 1-31, wherein Q is selected from (iii-vii).

39. The compound or salt of claim 38, wherein Q is (iii).

40. The compound or salt of claim 39, wherein R^{12} is an aryl as defined in any of claims 24-30.

41. The compound or salt of claim 39, wherein R^{12} is a phenyl.

42. The compound or salt of claim 39, wherein R^{12} is a phenyl substituted with one or more substituents.

43. The compound or salt of claim 40 or 42, wherein said aryl in R^{12} is substituted with one or more substituents selected from a halogen and trifluoromehtyl.

44. The compound or salt of claim 39, wherein R^{12} is 4-chloro-3-triflurometlyl-phenyl.

45. The compound or salt of any of claims 39-44, wherein R^{13} is selected from hydroxy, $-NR^{14}COR^{15}$, $-NR^{16}COCONR^{17}R^{18}$, $-NR^{19}CONR^{20}R^{21}$, $-NR^{22}SO_2R^{23}$, $-COR^{24}$, and - $CONR^{25}R^{26}$.

46. The compound or salt of any of claims 39-44, wherein R^{13} is hydroxy.

47. The compound or salt of claim 46, wherein R^{12} is as defined in claim 44.

48. The compound or salt of any of claims 39-44, wherein R^{13} is $-NR^{14}COR^{15}$.

49. The compound or salt of claim 48, wherein R^{14} is hydrogen or C_{1-6}-alkyl and R^{15} is C_{1-6}-alkyl or C_{3-8}-cycloalkyl.

50. The compound or salt of claim 48 or 49, wherein R^{14} is hydrogen or methyl.

51. The compound or salt of any of claims 48-50, wherein R^{15} is methyl.

52. The compound or salt of claim 48, wherein R^{14} is hydrogen and R^{15} is methyl; or R^{14} and R^{15} is methyl.

53. The compound or salt of any of claims 39-44, wherein R^{13} is $-NR^{16}COCONR^{17}R^{18}$.

54. The compound or salt of claim 53, wherein R^{16} is hydrogen or C_{1-6}-alkyl and wherein R^{17} and R^{18} are selected independently from hydrogen, C_{1-6}-alkyl and C_{3-8}-cycloalkyl.

55. The compound or salt of claim 53, wherein R^{16} is hydrogen or C_{1-6}-alkyl and wherein R^{17} and R^{18} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl are optionally substituted with a C_{1-6}-alkyl.

56. The compound or salt of claim 53, wherein said R^{16}, R^{17} and R^{18} are hydrogen; R^{16} is C_{1-6}-alkyl, and R^{17} and R^{18} are hydrogen; R^{16} and R^{17} are hydrogen and R^{18} is C_{1-6}-alkyl; R^{16} and R_{17} are C_{1-6}-alkyl and R_{18} is hydrogen; R^{16} is hydrogen and R^{17} and R^{18} are C_{1-6}-alkyl; or R^{16}, R^{17} and R^{18} are C_{1-6}-alkyl.

57. The compound or salt of any of claims 39-44, wherein R^{13} is $-NR^{19}CONR^{20}R^{21}$.

58. The compound or salt of claim 57, wherein R^{19}, R^{20} and R^{21} are independently selected from hydrogen, C_{1-6}-alkyl and C_{3-8}-cycloalkyl.

59. The compound or salt of claim 57, wherein R^{19}, R^{20} and R^{21} are independently selected from hydrogen and C_{1-6}-alkyl.

60. The compound or salt of claim 57, wherein R^{19} is a C_{1-6}-alkyl and R^{20} and R^{21} are hydrogen; R^{19} and R^{20} are hydrogen and R^{21} is a C_{1-6}-alkyl; R^{19} and R^{20} are independently selected from a C_{1-6}-alkyl and R^{21} is H; R^{19} is H, and R^{20} and R^{21} are independently selected from a C_{1-6}-alkyl; or R^{19}, R^{20} and R^{21} are independently selected from a C_{1-6}-alkyl.

61. The compound or salt of claim 59, wherein R^{19}, R^{20} and R^{21} are hydrogen.

62. The compound or salt of any of claims 57-60, wherein R^{19} is H.

63. The compound or salt of any of claims 57-60, wherein R^{20} and R^{21} are independently selected from the group consisting of hydrogen, Me, Et, Bu, and i-Pr.

64. The compound or salt of claim 63, wherein R^{19} is H.

65. The compound or salt of any of claims 39-44, wherein R^{13} is $-NR^{22}SO_2R^{23}$.

66. The compound or salt of claim 65, wherein R^{22} is hydrogen, a C_{1-6}-alkyl or C_{3-8}-cycloalkyl and R^{23} is amino, C_{1-6}-alkyl or C_{3-8}-cycloalkyl.

67. The compound or salt of claim 65 or 66, wherein R^{22} is hydrogen and R^{23} is a C_{1-6}-alkyl or R^{22} and R^{23} are independently selected from a C_{1-6}-alkyl.

68. The compound or salt of any of claims 65-66, wherein R^{22} is hydrogen.

69. The compound or salt of any of claims 65-68, wherein R^{23} is methyl.

70. The compound or salt of any of claims 65-67, wherein R^{22} and R^{23} are methyl.

71. The compound or salt of any of claims 65-67, wherein R^{22} is hydrogen and R^{23} is methyl.

72. The compound or salt of any of claims 39-44, wherein R^{13} is $-COR^{24}$.

73. The compound or salt of claim 73, wherein R^{24} is a C_{1-6}-alkyl.

74. The compound or salt of claim 72, wherein R^{24} is methyl.

75. The compound or salt of any of claims 39-44, wherein R^{13} is $-CONR^{25}R^{26}$.

76 The compound or salt of claim 75, wherein R^{25} and R^{26} are independently selected from hydrogen, C_{1-6}-alkyl and C_{3-8}-cycloalkyl.

77. The compound or salt of claim 75, wherein R^{25} and R^{26} are independently selected from hydrogen and methyl.

78. The compound or salt of claim 75, wherein R^{25} and R^{26} together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or morpholinyl, wherein said piperidinyl, piperazinyl and morpholinyl are optionally substituted with a C_{1-6}-alkyl.

79. The compound or salt of claim 75, wherein R^{25} and R^{26} together with the nitrogen to which they are attached form a piperidinyl, wherein said piperidinyl is optionally substituted with a C_{1-6}-alkyl.

80. The compound or salt of any of claims 1-31, wherein Q is (vii).

81. The compound or salt of claim 80, wherein Y is a bond and X and Z are selected independently from O; NR^{27}; and $CR^{28}R^{29}$ and $S(O)_m$, provided that X and Z may not at the same time be selected from O and S.

82. The compound or salt of claim 80, wherein Y is a bond and said X and Z are selected independently from $CR^{28}R^{29}$ and NR^{27}.

83. The compound or salt of claim 80, wherein X is $CR^{28}R^{29}$, Y is a bond and Z is NR^{27}.

84. The compound or salt of claim 83, wherein R^{28} and R^{29} are hydrogen.

85. The compound or salt of claim 81, wherein X is $CR^{28}R^{29}$ and said R^{28} and R^{29} are hydrogen.

86. The compound or salt of any of claims 80, wherein X is $CR^{28}R^{29}$, Y is a bond and Z is O.

87. The compound or salt of claim 86, wherein R^{28} and R^{29} are hydrogen.

88. The compound or salt of claim 80, wherein X is O, Y is a bond and Z is $CR^{28}R^{29}$.

89. The compound or salt of claim 88, wherein R^{28} and R^{29} are hydrogen.

90. The compound or salt of any of claims 80-89, wherein said R^{27} is an acyl.

91. The compound or salt of claim 90, wherein said R^{27} is a C_{1-6}-alkylcarbonyl.

92. The compound or salt of claim 83, wherein Z is NR^{27} and said R^{27} is a C_{1-6}-alkylcarbonyl.

93. The compound or salt of claim 92, wherein said R^{27} is $-COCH_3$.

94. The compound or salt of any of claims 83, wherein X is $CR^{28}R^{29}$, said R^{28} and R^{29} are hydrogen; Y is a bond; and Z is $-NR^{27}$, said R^{27} is $-COCH_3$.

95. The compound or salt of any of claims 80-89, wherein said R^{27} is selected from the group $R^{30}SO_2$-, $R^{30}OCO$- and $R^{30}SCO$-.

96. The compound or salt of any of claims 80-89, wherein R^{27} is $R^{30}SO_2$.

97. The compound or salt of claim 96, wherein R^{30} is C_{1-6}-alkyl.

98. The compound or salt of claim 96, wherein R^{30} is methyl.

99. The compound or salt of any of claims 96-98, wherein X is $CR^{28}R^{29}$, Y is a bond and Z is NR^{27}.

100. The compound or salt of claim 99, wherein R^{28} and R^{29} are hydrogen.

101. The compound or salt of any of claims 80-89, wherein R^{27} is the group $R^{31}R^{32}NCO$- or $R^{30}R^{31}NCS$-.

102. The compound or salt of any of claims 80-102, wherein at Y is a bond.

103. The compound or salt of any of claims 80-102, wherein R^{33}-R^{36} are independently selected from hydrogen and halogen.

103a. The compound or salt of any of claims 80-103, wherein R^{37}-R^{38} are both hydrogen.

104. The compound or salt of of claim 1, wherein R^{1-5} is as defined in any of claims 3-11, and R^6 is as defined in claim 13.

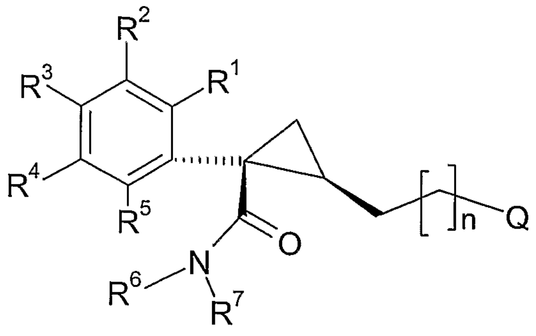
105. The compound or salt of of claim 1, wherein R^{1-5} is as defined in any of claims 3-11, and R^6 is as defined in claim 15, e.g. R^6 is methyl.

106. The compound or salt of claim 1, wherein R^6 is as defined in claim 14 or 15, e.g. R^6 is methyl and R^7 is as defined in claim 31.

107. The compound or salt of any of claims 102-106, wherein Q is (iii) and said R^{12} is as defined in claim 41.

108. The compound or salt of any of claims 1-107, wherein n=0.

109. The compound of or salt of any of the preceding claims, wherein the compound of formula I is the (1S,2R)-isomer, i.e. said compound with absolute configuration as shown in formula IA.



(IA)

110. The compound or salt of any of claims 1-108, wherein the compound of formula I is a racemic mixture comprising the (1S,2R)-isomer as defined in claim 109.

111. The compound or salt of any of claims 1-108, wherein the compound of formula I is a mixure of stereoisomeres of said compound, which mixture comprises the (1S,2R)-isomer as defined in claim 109.

112. The compound or salt of claim 1 selected from:

1a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

2a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

3a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

4a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

5a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

6a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

7a. (1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

8a. (1S,2R)-2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

9a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

10a. (1S,2R)-2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

11a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

12a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

13a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

14a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

15a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

16a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

17a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

18a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

19a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

20a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

21a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

22a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

23a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

24a. (1S,2R)-2-[4-(4-Chloro-3-trifluoromethyl-phenyl)-4-hydroxy-piperidin-1-ylmethyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

25a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

26a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

27a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

28a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

29a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

30a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

31a. (1S,2R)-1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

32a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

33a. (1S,2R)-1-(3,4-Difluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid -methyl-amide;

34a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3,3'-(8'-aza-bicyclo[3.2.1]octane-8'-yl)]-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

35a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

36a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

37a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

38a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

39a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-(1-phenyl-ethyl)-amide;

40a. (1S,2R)- 1-(3,4-Dichloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

41a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

42a. (1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

43a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

44a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

45a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

46a. (1S,2R)-1-(4-Chloro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

47a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-chloro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

48a. (1S,2R)-2-[1-acetyl-5-fluorospiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;

49a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

50a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-difluoro-phenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

51a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

52a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

53a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

54a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl)-methyl-amide;

55a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

56a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide.

57a. (1S,2R)- 2-(4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-ethyl-amide

58a. (1S,2R)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide'-([R]-1-phenyl-ethyl) amide

59a. (1R,2S)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

60a. (1R,2R)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide; and

61a. (1S,2S)- 2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

62a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]1-phenyl-ethyl)-amide;

63a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl)-amide;

64a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl) amide;

65a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([R]-1-phenyl-ethyl) amide;

66a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

67a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl)-amide;

68a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-([S]-1-phenyl-ethyl) amide;

69a. (1S,2R)-1-Phenyl-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

70a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

71a. (1S,2R)-2-[1-methanesulphonyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-fluophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

72a. (1S,2R)-2-[4-(Acetyl-methyl-amino)-4-phenyl-piperidin-1-ylmethyl]-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

73a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

74a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-flurophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

75a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

76a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

77a. (1S,2R)-1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid methyl-([S]1-phenyl-ethyl)-amide;

78a. (1S,2R)-2-(4-Acetyl-4-phenyl-piperidin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

79a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

80a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-fluorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

81a. (1S,2R)-1-(4-Fluoro-phenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

82a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-difluorophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

83a. (1S,2R)-1-(3,4-Difluorophenyl)-2-[4-phenyl-4-(piperidine-1-carbonyl)-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

84a. (1S,2R)-2-[1-acetyl-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

85a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-diflurophenyl)-cyclopropanecarboxylic acid (2-chloro-benzyl)-methyl-amide;

86a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid 3,4-dichloro-benzylamide;

87a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid 3,4-dimethoxy-benzylamide;

88a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid phenylamide;

89a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (1-methyl-1-phenyl-ethyl)-amide;

90a. (1S,2R)-1-Phenyl-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

91a. (1S,2R)-2-(4-Benzyl-piperazin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

92a. (1S,2R)-1-(4-chlorophenyl)-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid 4-fluorobenzyl-methyl-amide;

93a. (1S,2R)-2-(4-Benzyl-piperazin-1-ylmethyl)-1-(4-chlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

94a. (1S,2R)-2-(4-Benzyl-piperazin-1-ylmethyl)-1-phenyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

95a. (1S,2R)-1-(4-chlorophenyl)-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

96a. (1S,2R)-1-phenyl-2-[4-(3-trifluoromethylphenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid 4-fluorobenzyl-methyl-amide;

97a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid benzyl amide;

98a. (1S,2R)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-1-(3,4-difluropheny1)-cyclopropanecarboxylic acid (2-fluoro-benzyl)-amide;

99a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid methyl-[1-(4-methoxyphenyl)-ethyl]-amide;

100a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (2-chlorobenzyl) amide;

101a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid (3,4-dichlorobenzyl) amide;

102a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichloro-phenyl)-cyclopropanecarboxylic acid methyl-phenyl-amide;

103a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

104a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-p-tolyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

105a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-m-tolyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

106a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-m-tolyl-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

107a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-methoxy-phenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

108a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(4-methoxy-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

109a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-p-tolyl-cyclopropanecarboxylic acid benzyl-methyl-amide;

110a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-methoxy-phenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

111a. (1S,2R)-1-Phenyl-2-(4-phenyl-4-ureido-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

112a. (1S,2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-4-ureido-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid -benzyl-methyl-amide;

113a. (1S,2R)-1-Phenyl-2-[4-(3-methyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluorobenzyl)-methyl-amide;

114a. (1S,2R)-2-[4-(3-Methyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid benzyl-methyl-amide;

115a. (1S,2R)-N-(1-{2-[(4-Fluoro-benzyl)-methyl-carbamoyl]-2-phenyl-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-oxalamide;

116a. (1S,2R)-N-(1-{2-[benzyl-methyl-carbamoyl]-2-(3,4-dichlorophenyl)-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-oxalamide;

117a. (1S,2R)-1-Phenyl-2-(4-methanesulfonylamino-4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid -(4-fluorobenzyl)-methyl-amide;

118a. (1S,2R)-2-(4-Methanesulfonylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid -benzyl-methyl-amide;

119a. (1S,2R)-{1-[2-((4-fluoro-benzyl)-methyl-carbamoyl)-2-phenyl-cyclopropylmethyl]-4-phenyl-piperidin-4-yl}-carbamic acid methyl ester

120a. (1S,2R)-(1-{2-benzyl-methyl-carbamoyl]-2-(3,4-dichlorophenyl)-cyclopropylmethyl}-4-phenyl-piperidin-4-yl)-carbamic acid methyl ester

121a. (1S,2R)-1-(3,4-Dichloro-phenyl)-2-[4-(3,3-dimethyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid benzyl-methyl-amide;

122a. (1S,2R)-1-phenyl-2-[4-(3,3-dimethyl-ureido)-4-phenyl-piperidin-1-ylmethyl]-cyclopropanecarboxylic acid (4-fluorobenzyl)-methyl-amide;

123a. (1S,2R)-2-[2-(4-Acetylamino-4-phenyl-piperidin-1-yl)-ethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

124a. (1S,2R)-2-[3-(4-Acetylamino-4-phenyl-piperidin-1-yl)-propyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

125a. (1S,2R)-2-[4-(2-Acetylamino-5-fluorophenyl)-piperidin-1-ylmethyl]-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

126a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dimethylphenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

127a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3,4-dichlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

128a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-chlorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

129a. (1S,2R)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-1-(3-fluorophenyl)-cyclopropanecarboxylic acid (4-fluoro-benzyl)-methyl-amide;

130a. (1S, 2R)-1-(3,4-Dichlorophenyl)-2-(4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;

131a. (1S, 2R)-1-(3,4-Dichlorophenyl)-2-[1-acetyl-5-fluoro-spiro[2,3-dihydro-1H-indol-3-yl-3,4'-piperidine-1'-yl-methyl]-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;

132a. (1S, 2R)-1-(3,4-Dichlorophenyl)-2-(4-Acetylamino-4-phenyl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl-naphthalen-1-ylmethyl-amide;

or a salt thereof.

113. A pharmaceutical composition comprising a compound as defined in any of claims 1-112.

114. Use of a compound as defined in any of claims 1-112 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of diseases selected from the group consisting of: psychotic disorders, schizophrenia, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension, imbalances in water and electrolyte homeostasis, ischemia, oedema, plasma extravasation and obesity.

115. Use of a compound as defined in any of claims 1-112 or a salt thereof for the preparation of a medicament for treatment of schizophrenia.

116. Use according to claim 115 for treatment of the positive symptoms of schizophrenia.

117. Use of a compound as defined in any of claims 1-112 or a salt thereof for the manufacture of a pharmaceutical preparation for treatment of a disorder in the central nervous system.

118. A method for the treatment of diseases selected from the group consisting of: psychotic disorders , schizophrenia, depression, anxiety, Parkinson's disease, pain, convulsions, cough, asthma, airway hyperresponsiveness, microvascular hypersensitivity, bronchoconstriction, gut inflammation, inflammatory bowel disease, hypertension,

imbalances in water and electrolyte homeostasis, ischemia, oedema, plasma extravasation and obesity, comprising administering a therapeutically effective amount of a compound as defined in any of claims 1-112 or a pharmaceutically acceptable salt thereof.

119. The method of the preceding claim, wherein the disease is schizophrenia.

120. A method for treatment of a disorder in the central nervous system comprising administering a therapeutically effective amount of a compound as defined in any of claims 1-112 or a salt thereof.

INTERNATIONAL SEARCH REPORT

Int[illegible]tional Application No
PCT/DK2004/000538

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 C07D471/10 C07D211/64 C07D211/32 C07D211/52
C07D471/20 C07D211/14 A61K31/435 A61K31/495 A61P25/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

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

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97/10211 A (BROECK DIDIER VAN ; PROIETTO VINCENZO (FR); BICHON DANIEL (FR); SANOFI) 20 March 1997 (1997-03-20) cited in the application claim 1 abstract -----	1-120
Y	EP 0 673 928 A (SANOFI SA) 27 September 1995 (1995-09-27) cited in the application claim 1 -----	1-120
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search 25 October 2004	Date of mailing of the international search report 04/11/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Fitz, W

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000538

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 068 999 A (FABRE SA PIERRE) 5 January 1983 (1983-01-05) cited in the application claim 1 page 2, line 14 - line 21 -----	1-120
Y	BONNAUD, BERNARD ET AL: "1-Aryl-2-(aminomethyl)cyclopropanecarboxylic acid derivatives. A new series of potential antidepressants" JOURNAL OF MEDICINAL CHEMISTRY, CODEN: JMCMAR; ISSN: 0022-2623, vol. 30, no. 2, 1987, pages 318-325, XP002282456 page 321; table 2; compound 42 -----	1-120
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INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 118-120 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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Inte[illegible]tional Application No
PCT/DK2004/000538

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Form PCT/ISA/210 (patent family annex) (January 2004)

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International Application No
PCT/DK2004/000538

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