SUBSTITUTED 4-ALKYL- AND 4-ALKANOYL-PIPERIDINE DERIVATIVES AND THEIR USE AS NEUROKININ ANTAGONISTS

Field of the Invention

This invention concerns substituted 4-alkyl- and 4-alkanoyl-piperidine derivatives having neurokinin antagonistic activity, in particular NK_1 antagonistic activity and a combined NK_1/NK_3 antagonistic activity, compositions comprising them and their use as a medicine, in particular for the treatment and/or prophylaxis of schizophrenia, emesis, anxiety and depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pre-eclampsia, nociception, pain, in particular visceral and neuropathic pain, pancreatitis, neurogenic inflammation, asthma, chronic obstructive pulmonary disease (COPD) and micturition disorders such as urinary incontinence.

Background of The Invention

Tachykinins belong to a family of short peptides that are widely distributed in the mammalian central and peripheral nervous system (Bertrand and Geppetti, *Trends Pharmacol. Sci.* **17**:255-259 (1996) ; Lundberg, *Can. J. Physiol. Pharmacol.* **73**:908-914 (1995) ; Maggi, *Gen. Pharmacol.* **26**:911-944 (1995) ; Regoli *et al.*, *Pharmacol. Rev.* **46** (1994)). They share the common C-terminal sequence Phe-Xaa-Gly-Leu-Met-NH_2. Tachykinins released from peripheral sensory nerve endings are believed to be involved in neurogenic inflammation. In the spinal cord/central nervous system, tachykinins may play a role in pain transmission/perception and in some autonomic reflexes and behaviors. The three major tachykinins are Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB) with preferential affinity for three distinct neurokinin receptor subtypes, termed NK_1, NK_2, and NK_3, respectively. However, functional studies on cloned receptors suggest strong functional cross-interaction between the 3 tachykinins and their corresponding neurokinin receptors (Maggi and Schwartz, *Trends Pharmacol. Sci.* **18**: 351-355 (1997)).

Species differences in structure of NK_1 receptors are responsible for species-related potency differences of NK_1 antagonists (Maggi, *Gen. Pharmacol.* **26**:911-944 (1995) ; Regoli *et al.*, *Pharmacol. Rev.* **46(4)**:551-599 (1994)). The human NK_1 receptor closely resembles the NK_1 receptor of guinea-pigs and gerbils but differs

markedly from the NK_1 receptor of rodents. The development of neurokinin antagonists has led to date to a series of peptide compounds of which might be anticipated that they are metabolically too labile to be employed as pharmaceutically active substances (Longmore J. *et al.*, *DN&P* **8(1)**:5-23 (1995)).

The tachykinins are involved in schizophrenia, depression, (stress-related) anxiety states, emesis, inflammatory responses, smooth muscle contraction and pain perception. Neurokinin antagonists are in development for indications such as emesis, anxiety and depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, visceral pain, neurogenic inflammation, asthma, micturition disorders, and nociception. In particular, NK_1 antagonists have a high therapeutic potential in emesis and depression and NK_2 antagonists have a high therapeutic potential in asthma treatments. NK_3 antagonists seem to play a role in the treatment of pain/inflammation (Giardina, G. *et al. Exp. Opin. Ther. Patents,* **10(6)**: 939-960 (2000)) and schizophrenia.

Schizophrenia

The NK_3 antagonist SR142801 (Sanofi) was recently shown to have antipsychotic activity in schizophrenic patients without affecting negative symptoms (Arvantis, L. *ACNP Meeting*, December 2001). Activation of NK_1 receptors causes anxiety, stressfull events evoke elevated substance P (SP) plasma levels and NK_1 antagonists are reported to be anxiolytic in several animal models. The NK_1 antagonist from Merck, MK-869 shows antidepressant effects in major depression, but data were not conclusive due to a high placebo response rate. Moreover, the NK_1 antagonist from Glaxo-Welcome (S)-GR205,171 was shown to enhance dopamine release in the frontal cortex but not in the striatum (Lejeune et al. *Soc. Neurosci.*, November 2001). It is therefore hypothesized that NK_3 antagonism in combination with NK_1 antagonism would be beneficial against both positive and negative symptoms of schizophrenia.

Anxiety and depression

Depression is one of the most common affective disorders of modern society with a high and still increasing prevalence, particularly in the younger members of the population. The life time prevalence rates of Major depression (MDD, DSM-IV) is currently estimated to be 10-25 % for women and 5-12 % for men, whereby in about 25

% of patients the life time MDD is recurrent, without full inter-episode recovery and superimposed on dysthymic disorder. There is a high co-morbidity of depression with other mental disorders and, particularly in younger population high association with drug and alcohol abuse. In the view of the fact that depression primarily affects the population between 18-44 years of age e.g. the most productive population, it is obvious that it imposes a high burden on individuals, families and the whole society.

Among all therapeutic possibilities, the therapy with antidepressants is incontestably the most effective. A large number of antidepressants have been developed and introduced to the market in the course of the last 40 years. Nevertheless, none of the current antidepressants fulfill all criteria of an ideal drug (high therapeutic and prophylactic efficacy, rapid onset of action, completely satisfactory short- and long-term safety, simple and favourable pharmacokinetics) or is without side effects which in one or the other way limits their use in all groups and subgroups of depressed patients.

Since no treatment of the cause of depression exists at present, nor appears imminent, and no antidepressant is effective in more than 60-70 % of patients; the development of a new antidepressant which may circumvent any of the disadvantages of the available drugs is justified.

Several findings indicate involvement of SP in stress-related anxiety states. Central injection of SP induces a cardiovascular response resembling the classical "fight or flight" reaction characterised physiologically by vascular dilatation in skeletal muscles and decrease of mesenteric and renal blood flow. This cardiovascular reaction is accompanied by a behavioural response observed in rodents after noxious stimuli or stress (Culman and Unger, *Can. J. Physiol. Pharmacol.* **73**:885-891 (1995)). In mice, centrally administered NK_1 agonists and antagonists are anxiogenic and anxiolytic, respectively (Teixeira *et al.*, *Eur. J. Pharmacol.* **311**:7-14 (1996)). The ability of NK_1 antagonists to inhibit thumping induced by SP (or by electric shock; Ballard *et al.*, *Trends Pharmacol. Sci.* **17**:255-259 (2001)) might correspond to this antidepressant / anxiolytic activity, since in gerbils thumping plays a role as an alerting or warning signal to conspecifics.

The NK_1 receptor is widely distributed throughout the limbic system and fear-processing pathways of the brain, including the amygdala, hippocampus, septum, hypothalamus, and periaqueductal grey. Additionally, substance P is released centrally

in response to traumatic or noxious stimuli and substance P-associated neuro-transmission may contribute to or be involved in anxiety, fear, and the emotional disturbances that accompany affective disorders such as depression and anxiety. In support of this view, changes in substance P content in discrete brain regions can be observed in response to stressful stimuli (Brodin *et al.*, *Neuropeptides* **26**:253-260 (1994)).

Central injection of substance P mimetics (agonists) induces a range of defensive behavioural and cardiovascular alterations including conditioned place aversion (Elliott, *Exp. Brain. Res.* **73**:354-356 (1988)), potentiated acoustic startle response (Krase *et al.*, *Behav. Brain. Res.* **63**:81-88 (1994)), distress vocalisations, escape behaviour (Kramer *et al.*, *Science* **281**:1640-1645 (1998)) and anxiety on the elevated plus maze (Aguiar and Brandao, *Physiol. Behav.* **60**:1183-1186 (1996)). These compounds did not modify motor performance and co-ordination on the rotarod apparatus or ambulation in an activity cage. Down-regulation of substance P biosynthesis occurs in response to the administration of known anxiolytic and antidepressant drugs (Brodin *et al.*, *Neuropeptides* **26**:253-260 (1994) ; Shirayama *et al.*, *Brain. Res.* **739**:70-78 (1996)). Similarly, a centrally administered NK_1 agonist-induced vocalisation response in guinea-pigs can be antagonised by antidepressants such as imipramine and fluoxetine as well as L-733,060, an NK_1 antagonist. These studies provide evidence suggesting that blockade of central NK_1 receptors may inhibit psychological stress in a manner resembling antidepressants and anxiolytics (Rupniak and Kramer, *Trends Pharmacol. Sci.* **20**:1-12 (1999)), but without the side effects of present medications.

Emesis

Nausea and vomiting are among the most distressing side effects of cancer chemotherapy. These reduce the quality of life and may cause patients to delay or refuse, potentially curative drugs (Kris *et al.*, *J. Clin. Oncol.*, **3**:1379-1384 (1985)). The incidence, intensity and pattern of emesis is determined by different factors, such as the chemotherapeutic agent, dosage and route of administration. Typically, early or acute emesis starts within the first 4 h after chemotherapy administration, reaching a peak between 4 h and 10 h, and decreases by 12 to 24 h. Delayed emesis (developing after 24 h and continuing until 3-5 days post chemotherapy) is observed with most

'high-emetogenic' chemotherapeutic drugs (level 4 and 5 according to Hesketh *et al.*, *J. Clin. Oncol.* **15**:103 (1997)). In humans, these 'high-emetogenic' anti-cancer treatments, including cis-platinum, induce acute emesis in > 98% and delayed emesis in 60-90% of cancer patients.

Animal models of chemotherapy such as cisplatin-induced emesis in ferrets (Rudd and Naylor, *Neuropharmacology* **33**:1607-1608 (1994) ; Naylor and Rudd, *Cancer. Surv.* **21**:117-135 (1996)) have successfully predicted the clinical efficacy of the 5-HT_3 receptor antagonists. Although this discovery led to a successful therapy for the treatment of chemotherapy- and radiation-induced sickness in cancer patients, 5-HT_3 antagonists such as ondansetron and granisetron (either or not associated with dexamethasone) are effective in the control of the acute emetic phase (the first 24 h) but can only reduce the development of delayed emesis (> 24 h) with poor efficacy (De Mulder *et al.*, *Annuals of Internal Medicine* **113**:834-840 (1990) ; Roila, *Oncology* **50**:163-167 (1993)). Despite these currently most effective treatments for the prevention of both acute and delayed emesis, still 50% of patients suffer from delayed vomiting and/or nausea (Antiemetic Subcommittee, *Annals Oncol.* **9**:811-819 (1998)).

In contrast to 5-HT_3 antagonists, NK_1 antagonists such as CP-99,994 (Piedimonte *et al.*, *L. Pharmacol. Exp. Ther.* **266**:270-273 (1993)) and aprepitant (also known as MK-869 or L-754,030 ; Kramer *et al.*, *Science* **281**:1640-1645 (1998) ; Rupniak and Kramer, *Trends Pharmacol. Sci.* **20**:1-12 (1999)) have now been shown to inhibit not only the acute but also the delayed phase of cisplatin-induced emesis in animals (Rudd *et al.*, *Br. J. Pharmacol.* **119**:931-936 (1996) ; Tattersall *et al.*, *Neuropharmacology* **39**:652-663 (2000)). NK_1 antagonists have also been demonstrated to reduce 'delayed' emesis in man in the absence of concomitant therapy (Cocquyt *et al.*, *Eur. J. Cancer* **37**:835-842 (2001) ; Navari *et al.*, *N. Engl. L. Med.* **340**:190-195 (1999)). When administered together with dexamethasone and 5-HT_3 antagonists, moreover, NK_1 antagonists (such as MK-869 and CJ-11,974, also known as Ezlopitant) have been shown to produce additional effects in the prevention of acute emesis (Campos *et al.*, *J. Clin. Oncol.* **19**:1759-1767 (2001) ; Hesketh *et al.*, *Clin. Oncol.* **17**:338-343 (1999)).

Central neurokinin NK_1 receptors play a major role in the regulation of emesis. NK_1 antagonists are active against a wide variety of emetic stimuli (Watson *et al.*, *Br. J. Pharmacol.* **115**:84-94 (1995) ; Tattersall *et al.*, *Neuropharmacol.* **35**:1121-1129

(1996) ; Megens *et al.*, *J. Pharmacol. Exp. Ther.* **302**:696-709 (2002)). The compounds are suggested to act by blocking central NK_1-receptors in the nucleus tractus solitarius. Apart from NK_1 antagonism, CNS penetration is thus a prerequisite for the antiemetic activity of these compounds. Loperamide-induced emesis in ferrets can be used as a fast and reliable screening model for the antiemetic activity of NK_1 antagonists. Further evaluation of their therapeutic value in the treatment of both the acute and the delayed phases of cisplatin-induced emesis has been demonstrated in the established ferret model (Rudd *et al.*, *Br. J. Pharmacol.* **119**:931-936 (1994)). This model studies both 'acute' and 'delayed' emesis after cisplatin and has been validated in terms of its sensitivity to 5-HT_3 receptor antagonists, glucocorticoids (Sam *et al.*, *Eur. J. Pharmacol.* **417**:231-237 (2001)) and other pharmacological challenges. It is unlikely that any future anti-emetic would find clinical acceptance unless successfully treating both the 'acute' and 'delayed' phases of emesis.

Visceral pain and Irritable bowel syndrome (IBS)

Visceral sensation refers to all sensory information that originates in the viscera (heart, lungs, GI tract, hepatobiliary tract and urogenital tract), and is transmitted to the central nervous system resulting in conscious perception. Both the vagal nerve via the nodose ganglion and the primary sympathetic afferent nerves via dorsal root ganglias (DRG) and second order neurons in the dorsal horn serve as the initial pathways along which visceral sensory information is conveyed to the brain stem and to the viscero-somatic cortex. Visceral pain may be caused by neoplastic processes (e.g. pancreas cancer), inflammation (e.g. cholecystitis, peritonitis), ischemia and mechanical obstruction (e.g. urether stone).

The mainstay of medical treatment for visceral pain linked to organic disorders (in casu cancer of the viscera) still focuses on opiates.

Recent evidence suggests that non-organic visceral disorders such as irritable bowel syndrome (IBS), non-cardiac chest pain (NCCP) and chronic pelvic pain may originate from a state of "visceral hyperalgia". The latter is defined as a condition in which physiological, non-painful visceral stimuli (e.g. gut distension) lead to conscious perception of pain due to a decreased threshold for pain. Visceral hyperalgesia may reflect a state of a permanent, post-inflammatory resetting of the threshold for

membrane depolarization at neuronal synapses within visceral sensory pathways. The initial inflammation may occur at the periphery (e.g. infectuous gastroenteritis) or at the site of visceral sensory information integration (neurogenic inflammation in the dorsal horn). Both SP and calcitonin gene-related peptide (CGRP) have been shown to act as pro-inflammatory neuropeptides in neurogenic inflammation.

Visceral hyperalgesia is currently considered as one of the prime targets for drug development aimed at treating functional bowel diseases, which occur in 15 to 25% of the western population. They constitute an enormous socio-economic problem in terms of medical care costs, prescription costs and absenteism. Current treatment options include anti-spasmodics (IBS and NCCP), promotility agents (e.g. tegasorod in constipation-IBS), laxatives (constipation-IBS), and loperamide (diarrhea-IBS), amongst others. None of these approaches has been shown to be very effective, particularly in treating pain. Low dose tricyclic antidepressants and SSRIs are used to treat visceral hyperalgesia in pain-predominant IBS, but both classes of compounds may have considerable effects on colonic transit. Ongoing research in this field has identified a considerable number of molecular targets that could serve for drug development in visceral hyperalgesia. These include NK receptors, the CGRP receptor, 5-HT_3 receptors, glutamate receptors, and the kappa opioid receptor. Ideally, a "visceral analgesic compound" should block heightened sensory transfer from the viscera to the CNS without affecting the normal physiological homeostasis of the GI tract with regards to propulsive motor activity, absorption and secretion, and sensation.

There is compelling evidence linking tachykinin to visceral nociceptive signalling. A number of pre-clinical publications on the role of NK_1, NK_2 and NK_3 receptors in visceral pain and visceral hyperalgesia indicate a discrepancy between the implication of NK_1, NK_2 and NK_3 receptors in the different inflammation hypersensitivity rodent models. Recently, Kamp *et al.*, *J. Pharmacol. Exp.* Ther.**299**:105-113 (2001) suggested that a combined neurokinin receptor antagonist could be more active than a selective neurokinin receptor antagonist. Substance P and NK_1, NK_2 and NK_3 receptors are elevated in clinical pain states, including visceral pain states (Lee *et al.*, *Gastroenterol.* **118**: A846 (2000)). Given the recent failures of NK_1 receptor antagonists as an analgesic in human pain trials (Goldstein *et al.*, *Clin. Pharm. Ther. 67:419-426 (*2000)), combinations of antagonists may be necessary to have a significant clinical effect. NK_3

receptor antagonists are anti-hyperalgesic (Julia *et al.*, *Gastroenterol.* **116**:1124-1131 (1999)) ; *J. Pharmacol. Exp.* Ther.**299**:105-113 (2001)). Recently, the involvement of NK_1 and NK_3 receptors but not NK_2 receptors at spinal level was demonstrated in visceral hypersensitivity mediated by nociceptive and non-nociceptive afferent inputs (Gaudreau & Ploudre, *Neurosci. Lett.* **351**:59-62 (2003). Combining the NK_{1-2-3} antagonistic activity could therefore represent an interesting therapeutic target for the development of novel treatments for visceral hyperalgesia.

A reasonable number of pre-clinical publications over the role of NK_1 receptors in visceral pain has been published. Using NK_1 receptor knockout mice and NK_1 antagonists in animal models, different groups have demonstrated the important role played by the NK_1 receptor in hyperalgesia and visceral pain. The distribution of NK_1 receptors and substance P favours a major role in visceral rather than in somatic pain. Indeed more than 80% of visceral primary afferent contain substance P compared with only 25% skin afferents. NK_1 receptors are also involved in gastrointestinal motility (Tonini *et al.*, *Gastroenterol.* **120**:938-945 (2001) ; Okano *et al.*, *J. Pharmacol. Exp. Ther.* **298**:559-564 (2001)). Because of this dual role in both gastrointestinal motility and in nociception, NK_1 antagonists are considered to have potential to ameliorate symptoms in IBS patients.

Urinary incontinence

Urge urinary incontinence is caused by urinary bladder or detrusor hyperreflexia ("irritable bladder"). This hyperreflexia relates to hyperexcitability of bladder sensory afferent C-fibers projecting to the spinal cord. The origin of C-fiber hyperexcitability is multifactorial but occurs for example after bladder infection and chronic distention of the bladder wall (eg. benign prostate hypertrophy, BPH). Hence, treatment should be aimed at decreasing neuronal hyperexcitability. Intravesical instillation of vanilloids (eg. capsaicin) results in a long-term beneficial effect on detrusor hyperreflexia refractory to conventional treatment with anticholinergic drugs. Analogous to animal studies, the effect of vanilloids is mediated through a neurotoxic effect on sensory nerve terminals. In human bladder, subendothelial sensory nerves contain tachykinins, which drive detrusor hyperexcitability. The NK receptors involved in this effect are peripheral NK_2 receptors and to a lesser extent, also NK_1 receptors. The latter are claimed to play a role

in bladder hyperreflexia at the level of the spinal cord. As a consequence, a centrally acting NK_1/peripherally acting NK_2 antagonist is preferred for the treatment of detrusor hyperexcitability. Interestingly, activation of NK_2 receptors increases aromatase activity in Sertoli cells. NK_2 receptor antagonists reduce serum testosterone levels in mice, and this may be of therapeutic importance in BPH.

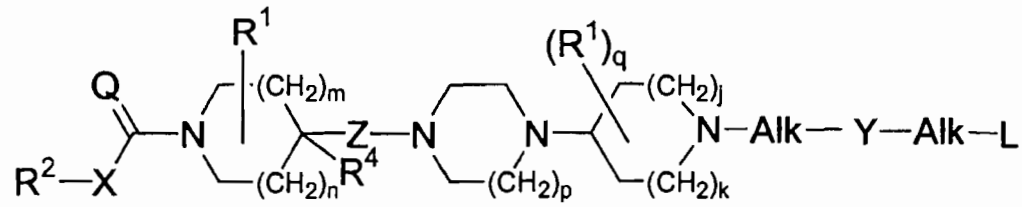
Background prior art

Compounds containing a 1-piperidin-4-yl-piperazinyl moiety were published in WO 97/16440-A1, published May 9, 1997 by Janssen Pharmaceutica N.V. for use as substance P antagonists, in WO 02/32867, published April 25, 2002 by Glaxo Group Ltd. for their special advantages as neurokinin antagonists (more specifically were disclosed 4-piperazin-1-yl-piperidine-1-carboxylic acid amide derivatives), in WO 01/30348-A1, published May 03, 2001 by Janssen Pharmaceutica N.V., for use as substance P antagonists for influencing the circadian timing system, and in WO 02/062784-A1, published August 15, 2002 by Hoffmann-La Roche AG for use as neurokinin 1 antagonists.

The compounds of the present invention differ from the compounds of the prior art in the substitution of the piperazinyl/imidazolidinyl moiety, as well as in their improved ability as potent, orally and centrally active neurokinin antagonists with therapeutic value, especially for the treatment and/or prophylaxis of schizophrenia, emesis, anxiety and depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pre-eclampsia, nociception, pain, in particular visceral and neuropathic pain, pancreatitis, neurogenic inflammation, asthma, chronic obstructive pulmonary disease (COPD) and micturition disorders such as urinary incontinence.

Description of the Invention

The present invention relates to novel 4-alkyl- and 4-alkanoyl-piperidine derivatives according to the general Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, wherein :

n is an integer, equal to 0, 1 or 2 ;

m is an integer, equal to 1 or 2, provided that if m is 2, then n is 1 ;

each R^1 independently from each other, is selected from the group of Ar^1, Ar^1-alkyl and di(Ar^1)-alkyl ;

R^4 is selected from the group of hydrogen, hydroxy and alkyloxy ;

Z is a bivalent radical $-(CH_2)_r-$, wherein r is an integer equal to 1, 2, 3, 4 or 5 and wherein one radical $-CH_2-$ is optionally replaced by a >C=O radical ; or

R^4 and Z are taken together to form a trivalent radical $=CH-(CH_2)_{r-1}-$, wherein r is an integer equal to 2, 3, 4 or 5 and wherein one radical $-CH_2-$ is optionally replaced by a >C=O radical ;

p is an integer equal to 1 or 2 ;

Q is O or NR^3 ;

X is a covalent bond or a bivalent radical of formula -O-, -S- or $-NR^3-$;

each R^3 independently from each other, is hydrogen or alkyl ;

R^2 is alkyl, Ar^2, Ar^2-alkyl, Het^1 or Het^1-alkyl ;

q is an integer, equal to 0 or 1 ;

j is an integer, equal to 0, 1 or 2 ;

k is an integer, equal to 0, 1 or 2 ;

Y is a covalent bond or a bivalent radical of formula >C(=O) or $-SO_2-$;

each Alk represents, independently from each other, a covalent bond ; a bivalent straight or branched, saturated or unsaturated hydrocarbon radical having from 1 to 6 carbon atoms ; or a cyclic saturated or unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; each radical optionally substituted on one or more carbon atoms with one or more alkyl, phenyl, halo, cyano, hydroxy, formyl and amino radicals ;

L is selected from the group of hydrogen, alkyl, alkyloxy, Ar^3-oxy, alkyloxycarbonyl, mono- and di(alkyl)amino, mono- and di(Ar^3)amino, mono- and di(alkyloxycarbonyl)amino, Ar^3, Ar^3-carbonyl, Het^2 and Het^2-carbonyl ;

Ar^1 is phenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, alkyl, cyano, aminocarbonyl and alkyloxy ;

Ar^2 is naphthalenyl or phenyl, each optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, nitro, amino, mono- and di(alkyl)amino, cyano, alkyl, hydroxy, alkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl and mono- and di(alkyl)aminocarbonyl ;

Ar^3 is naphthalenyl or phenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of alkyloxy, alkyl, halo, hydroxy, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and cyano ;

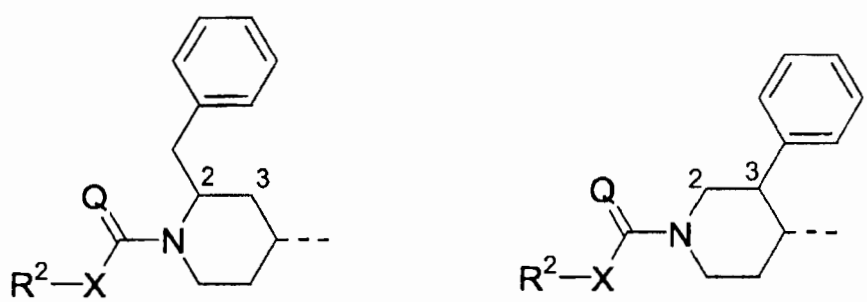
Het^1 is a monocyclic heterocyclic radical selected from the group of pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl ; or a bicyclic heterocyclic radical selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of halo and alkyl ;

Het^2 is a monocyclic heterocyclic radical selected from the group of pyrrolidinyl, dioxolyl, imidazolidinyl, pyrrazolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 2H-pyrrolyl, pyrrolinyl, imidazolinyl, pyrrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl ; or a bicyclic heterocyclic radical selected from the group of benzopiperidinyl, quinolinyl,

quinoxalinyl, indolyl, isoindolyl, chromenyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of Ar^1, Ar^1alkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo, alkyloxy, alkyloxyalkyl and alkyloxycarbonyl ; and

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms ; optionally substituted on one or more carbon atoms with one or more radicals selected from the group of phenyl, halo, cyano, oxo, hydroxy, formyl and amino radicals.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein R^1 is Ar^1methyl and attached to the 2-position or R^1 is Ar^1 and attached to the 3-position, as exemplified in either of the following formulas for compounds according to Formula (I) wherein m and n are equal to 1 and Ar is an unsubstituted phenyl. Preferably, Ar^1 is an unsubstituted phenyl radical and Ar^1methyl is an unsubstituted benzyl radical.



More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein the R^2-X-C(=Q)- moiety is 3,5-di-(trifluoromethyl) phenylcarbonyl.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the

stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein m and n are both equal to 1.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein Z is selected from the group of $-CH_2-$, $>C=O$, $-CH_2CH_2-$ and $-CH_2C(=O)-$ or wherein Z and R^4 are taken together to form the trivalent radical $=CH-C(=O)-$.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein R^4 is selected from the group of hydrogen, hydroxy and methoxy.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein p is equal to 1.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein j is equal to 1 and k is equal to 0 or 1.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein Alk is a covalent bond, $-CH_2-$, $CH(CH_3)-$, -CH(phenyl)-, $-CH_2CH$(phenyl)- or $-CH_2CH=CH-$.

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein L is selected from the group of hydrogen, alkyl, alkyloxy, Ar^3-oxy, mono- and di(Ar^3)amino, Ar^3, Het^2 and Het^2carbonyl and Ar^3 and Het^2 are defined as in Formula(I).

More in particular, the invention relates to a compound according to the general

Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein :

	n	is an integer, equal to 1 ;
	m	is an integer, equal to 1 ;
	R^1	is Ar^1-alkyl ;
	R^4	is selected from the group of hydrogen, hydroxy or alkyloxy ;
	Z	is a bivalent radical $-(CH_2)_r-$, wherein r is 1 or 2 and wherein one radical $-CH_2-$ is optionally replaced by a >C=O radical ; or
	R^4 and Z	are taken together to form a trivalent radical $=CH-(CH_2)_{r-1}$, wherein r is 2 and wherein one radical $-CH_2-$ is replaced by a >C=O radical ;
	p	is an integer, equal to 1 ;
	Q	is O ;
	X	is a covalent bond ;
	R^2	is Ar^2 ;
	q	is an integer, equal to 0 ;
	j	is an integer, equal to 1 ;
	k	is an integer, equal to 0 or 1 ;
	Y	is a covalent bond or a bivalent radical of formula >C(=O) or $-SO_2-$;
	each Alk	represents, independently from each other, a covalent bond ; a bivalent straight or branched, saturated or unsaturated hydrocarbon radical having from 1 to 6 carbon atoms ; each radical optionally substituted on one or more carbon atoms with a phenyl radical ;
	L	is selected from the group of hydrogen, alkyl, alkyloxy, Ar^3-oxy, mono- and di(Ar^3)amino, Ar^3 and Het^2 ;
	Ar^1	is phenyl ;
	Ar^2	is phenyl, optionally substituted with 2 alkyl substituents ;
	Ar^3	is phenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other selected from the group of alkyloxy, alkyl, halo and hydroxy ;
	Het^2	is a monocyclic heterocyclic radical selected from the group of tetrahydrofuranyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, isoxazolyl,

thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl ; or a bicyclic heterocyclic radical selected from the group of quinolinyl, indolyl, chromenyl and benzimidazolyl ; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of Ar^1, halo, alkyl and oxo ; and

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms.

In the framework of this application, alkyl is defined as a monovalent straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms, for example methyl, ethyl, propyl, butyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl ; alkyl further defines a monovalent cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, for example cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The definition of alkyl also comprises an alkyl radical that is optionally substituted on one or more carbon atoms with one or more phenyl, halo, cyano, oxo, hydroxy, formyl and amino radicals, for example hydroxyalkyl, in particular hydroxymethyl and hydroxyethyl and polyhaloalkyl, in particular difluoromethyl and trifluoromethyl.

In the framework of this application, halo is generic to fluoro, chloro, bromo and iodo.

In the framework of this application, with "compounds according to the invention" is meant a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof.

In the framework of this application, especially in the moiety Alk^a-Y-Alk^b in Formula (I), when two or more consecutive elements of said moiety denote a covalent bond, then a single covalent bond is denoted. For example, when Alk^a and Y denote both a covalent bond and Alk^b is -CH_2-, then the moiety Alk^a-Y-Alk^b denotes -CH_2-. Similary, if Alk^a, Y and Alk^b each denote a covalent bond and L denotes H, then the moiety Alk^a-Y-Alk^b-L denotes -H.

The pharmaceutically acceptable salts are defined to comprise the therapeutically active non-toxic acid addition salts forms that the compounds according to Formula (I)

are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

The compounds according to Formula (I) containing acidic protons may also be converted into their therapeutically active non-toxic metal or amine addition salts forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said salts forms can be converted into the free forms by treatment with an appropriate base or acid.

The term addition salt as used in the framework of this application also comprises the solvates that the compounds according to Formula (I) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

The *N*-oxide forms of the compounds according to Formula (I) are meant to comprise those compounds of Formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more tertiary nitrogens (e.g of the piperazinyl or piperidinyl radical) are *N*-oxidized. Such *N*-oxides can easily be obtained by a skilled person without any inventive skills and they are obvious alternatives for the compounds according to Formula (I) since these compounds are metabolites, which are formed by oxidation in the human body upon uptake . As is generally known, oxidation is normally the first step involved in drug metabolism (Textbook of Organic Medicinal and Pharmaceutical Chemistry, 1977, pages 70- 75). As is also generally known, the metabolite form of a compound can also be administered to a human instead of the compound per se, with much the same effects.

The compounds according to the invention possess at least 2 oxydizable nitrogens (tertiary amines moieties). It is therefore highly likely that *N*-oxides are to form in the human metabolism.

The compounds of Formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of Formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of Formula (I) are obviously intended to be embraced within the scope of this invention.

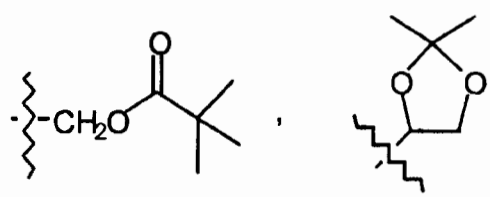
Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. R* and S* each indicate optically pure stereogenic centers with undetermined absolute configuration. If "α" and "β" are used : the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "α" position of the mean plane

determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system (hydrogen atom in compounds according to Formula (I)) relative to the position of the highest priority substituent on the reference atom is denominated "α", if it is on the same side of the mean plane determined by the ring system, or "β", if it is on the other side of the mean plane determined by the ring system.

Compounds according to Formula (I) and some of the intermediate compounds have at least two stereogenic centers in their structure.

The invention also comprises derivative compounds (usually called "pro-drugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

Pro-drugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof and the *N*-oxide form thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the formula $-COOR^x$, where R^x is a C_{1-6}alkyl, phenyl, benzyl or one of the following groups :



Amidated groups include groups of the formula $-CONR^yR^z$, wherein R^y is H, C_{1-6}alkyl, phenyl or benzyl and R^z is –OH, H, C_{1-6}alkyl, phenyl or benzyl. Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde

such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

The compounds of Formula (I) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers that can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

Pharmacology

The compounds of the present invention are potent inhibitors of neurokinin-mediated effects, in particular those mediated via the NK_1 and NK_3 receptor, and may therefore be described as neurokinin antagonists, especially as substance P antagonists, as may be indicated *in vitro* by the antagonism of substance P-induced relaxation of pig coronary arteries. The binding affinity of the present compounds for the human, guinea-pig and gerbil neurokinin receptors may also be determined *in vitro* in a receptor binding test using ^{3}H-substance-P as radioligand. The subject compounds also show substance-P antagonistic activity *in vivo* as may be evidenced by, for instance, the antagonism of substance P-induced plasma extravasation in guinea-pigs, or the antagonism of drug-induced emesis in ferrets (Watson *et al.*, *Br. J. Pharmacol.* **115**:84-94 (1995)).

In view of their capability to antagonize the actions of tachykinins by blocking the neurokinin receptors, and in particular by blocking the NK_1 and NK_3 receptor, the compounds according to the invention are useful as a medicine, in particular in the prophylactic and therapeutic treatment of tachykinin-mediated conditions. In particular

are compounds according to the invention are useful as orally active, centrally penetrating medicines in the prophylactic and therapeutic treatment of tachykinin-mediated conditions.

More in particular, it has been found that some compounds exhibit a combined NK_1/NK_3 antagonistic activity as can be seen from the Tables in the experimental section.

The invention therefore relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, for use as a medicine.

The invention also relates to the use of a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof for the manufacture of a medicament for treating, either prophylactic or therapeutic or both, neurokinin mediated conditions.

The compounds according to the invention are useful in the treatment of CNS disorders, in particular depression, anxiety disorders, stress-related disorders, sleep disorders, cognitive disorders, personality disorders, schizoaffective disorders, eating disorders, neurodegenerative diseases, addiction disorders, mood disorders, sexual dysfunction, pain and other CNS-related conditions ; inflammation ; allergic disorders ; emesis ; gastrointestinal disorders, in particular irritable bowel syndrome (IBS); skin disorders ; vasospastic diseases ; fibrosing and collagen diseases ; disorders related to immune enhancement or suppression and rheumatic diseases and body weight control.

In particular, the compounds according to the invention are useful in the treatment or prevention of depression including but not limited to major depressive disorders including bipolar depression ; unipolar depression ; single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, and, in the case of recurrent episodes, with or without seasonal pattern. Other mood disorders encompassed within the term "major depressive disorder" include dysthymic disorder with early or late onset and with or without atypical features, bipolar I disorder, bipolar II disorder, cyclothymic disorder, recurrent brief depressive disorder, mixed affective disorder, neurotic

depression, post traumatic stress disorder and social phobia ; dementia of the Alzheimer's type with early or late onset, with depressed mood ; vascular dementia with depressed mood ; substance-induced mood disorders such as mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances ; schizoaffective disorder of the depressed type ; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

In particular, the compounds according to the invention are useful in the treatment or prevention of anxiety disorders, including but not limited to panic attack ; agoraphobia ; panic disorder without agoraphobia ; agoraphobia without history of panic disorder ; specific phobia ; social phobia ; obsessive-compulsive disorder ; post-traumatic stress disorder ; acute stress disorder ; generalized anxiety disorder ; anxiety disorder due to a general medical condition ; substance-induced anxiety disorder ; and anxiety disorder not otherwise specified.

In particular, the compounds according to the invention are useful in the treatment or prevention of stress-related disorders associated with depression and/or anxiety, including but not limited to acute stress reaction ; adjustment disorders, such as brief depressive reaction, prolonged depressive reaction, mixed anxiety and depressive reaction, adjustment disorder with predominant disturbance of other emotions, adjustment disorder with predominant disturbance of conduct, adjustment disorder with mixed disturbance of emotions and conduct and adjustment disorders with other specified predominant symptoms ; and other reactions to severe stress.

In particular, the compounds according to the invention are useful in the treatment or prevention of sleep disorders, including but not limited to dysomnia and/or parasomnias as primary sleep disorders ; insomnia ; sleep apnea ; narcolepsy ; circadian rhythms disorders ; sleep disorders related to another mental disorder ; sleep disorder due to a general medical condition ; and substance-induced sleep disorder.

In particular, the compounds according to the invention are useful in the treatment or prevention of cognitive disorders, including but not limited to dementia ; amnesic disorders and cognitive disorders not otherwise specified, especially dementia caused by degenerative disorders, lesions, trauma, infections, vascular disorders, toxins, anoxia,

vitamin deficiency or endocrinic disorders ; dementia of the Alzheimer's type, with early or late onset, with depressed mood ; AIDS-associated dementia or amnesic disorders caused by alcohol or other causes of thiamin deficiency, bilateral temporal lobe damage due to Herpes simplex encephalitis and other limbic encephalitis, neuronal loss secondary to anoxia / hypoglycemia / severe convulsions and surgery, degenerative disorders, vascular disorders or pathology around ventricle III. Furthermore, the compounds according to the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

In particular, the compounds according to the invention are useful in the treatment or prevention of personality disorders, including but not limited to paranoid personality disorder ; schizoid personality disorder ; schizotypical personality disorder ; antisocial personality disorder ; borderline personality disorder ; histrionic personality disorder ; narcissistic personality disorder ; avoidant personality disorder ; dependent personality disorder ; obsessive-compulsive personality disorder and personality disorder not otherwise specified.

In particular, the compounds according to the invention are useful in the treatment or prevention of schizoaffective disorders resulting from various causes, including schizoaffective disorders of the manic type, of the depressive type, of mixed type ; paranoid, disorganized, catatonic, undifferentiated and residual schizophrenia ; schizophreniform disorder ; schizoaffective disorder ; delusional disorder ; brief psychotic disorder ; shared psychotic disorder ; substance-induced psychotic disorder ; and psychotic disorder not otherwise specified.

In particular, the compounds according to the invention are also useful in the treatment or prevention of eating disorders, including anorexia nervosa ; atypical anorexia nervosa ; bulimia nervosa ; atypical bulimia nervosa ; overeating associated with other psychological disturbances ; vomiting associated with other psychological disturbances ; and non-specified eating disorders.

In particular, the compounds according to the invention are also useful in the treatment or prevention of neurodegenerative diseases, including but not limited to Alzheimer's disease ; Huntington's chorea ; Creutzfeld-Jacob disease ; Pick's disease ; demyelinating disorders, such as multiple sclerosis and ALS ; other neuropathies and neuralgia ; multiple sclerosis ; amyotropical lateral sclerosis ; stroke and head trauma.

In particular, the compounds according to the invention are also useful in the treatment or prevention of addiction disorders, including but not limited to substance dependence or abuse with or without physiological dependence, particularly where the substance is alcohol, amphetamines, amphetamine-like substances, caffeine, cocaine, hallucinogens, inhalants, nicotine, opioids (such as cannabis, heroin and morphine), phencyclidine, phencyclidine-like compounds, sedative-hypnotics, benzodiazepines and/or other substances, particularly useful for treating withdrawal from the above substances and alcohol withdrawal delirium.

In particular, the compounds according to the invention are also useful in the treatment or prevention of mood disorders induced particularly by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances.

In particular, the compounds according to the invention are also useful in the treatment or prevention of sexual dysfunction, including but not limited to sexual desire disorders ; sexual arousal disorders ; orgasmic disorders ; sexual pain disorders ; sexual dysfunction due to a general medical condition ; substance-induced sexual dysfunction and sexual dysfunction not otherwise specified.

In particular, the compounds according to the invention are also useful in the treatment or prevention of pain, including but not limited to traumatic pain such as postoperative pain ; traumatic avulsion pain such as brachial plexus ; chronic pain such pancreatitis induced chronic pain or arthritic pain such as occurring in osteo- rheumatoid or psoriatic arthritis ; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy and phantom limb pain ; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain and cluster headache ; odontalgia ; cancer pain ; visceral pain ; gastrointestinal pain ; nerve entrapment pain ; sport's injury pain ; dysmennorrhoea ; menstrual pain ; meningitis ; arachnoiditis ; musculoskeletal pain ; low back pain such as spinal stenosis, prolapsed disc, sciatica, angina, ankylosing spondyolitis ; gout ; burns ; scar pain ; itch ; and thalamic pain such as post stroke thalamic pain.

In particular, the compounds according to the invention are also useful in the treatment or prevention of the following other CNS-related conditions : akinesia, akinetic-rigid syndromes, dyskinesia and medication-induced parkinsonism, Gilles de la Tourette syndrome and its symptoms, tremor, chorea, myoclonus, tics and dystonia, attention-deficit / hyperactivity disorder (ADHD), Parkinson's disease, drug-induced Parkinsonism, post-encephalitic Parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification, behavioral disturbances and conduct disorders in dementia and the mentally retarded, including restlessness and agitation, extra-pyramidal movement disorders , Down's syndrome and Akathisia.

In particular, the compounds according to the invention are also useful in the treatment or prevention of inflammation, including but not limited to inflammatory conditions in asthma, influenza, chronic bronchitis and rheumatoid arthritis ; inflammatory conditions in the gastrointestinal tract such as, but not limited to Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage ; inflammatory conditions of the skin such as herpes and eczema ; inflammatory conditions of the bladder such as cystitis and urge incontinence ; and eye and dental inflammation and pancreatitis, in particular chronic and acute pancreatitis.

In particular, the compounds according to the invention are also useful in the treatment or prevention of allergic disorders, including but not limited to allergic disorders of the skin such as but not limited to urticaria ; and allergic disorders of the airways such as but not limited to rhinitis.

In particular, the compounds according to the invention are also useful in the treatment or prevention of emesis, i.e. nausea, retching and vomiting, including but not limited to acute emesis, delayed emesis and anticipatory emesis ; emesis induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, for example cyclophosphamide, carmustine, lomustine and chlorambucil ; cytotoxic antibiotics, for example dactinomycin, doxorubicin, mitomycin-C and bleomycin ; anti-metabolites, for example cytarabine, methotrexate and 5-fluorouracil ; vinca alkaloids, for example etoposide, vinblastine and vincristine ; and other drugs such as cisplatin, dacarbazine, procarbazine and hydroxyurea ; and combinations thereof ; radiation sickness ; radiation

therapy, such as in the treatment of cancer ; poisons ; toxins such as toxins caused by metabolic disorders or by infection, such as gastritis, or released during bacterial or viral gastrointestinal infection ; pregnancy ; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease ; post-operative sickness ; gastrointestinal obstruction ; reduced gastrointestinal motility ; visceral pain, such as myocardial infarction or peritonitis ; migraine ; increased intracranial pressure ; decreased intracranial pressure (such as altitude sickness) ; opioid analgesics, such as morphine ; gastro-oesophageal reflux disease ; acid indigestion ; over-indulgence of food or drink ; acid stomach ; sour stomach ; waterbrash/regurgitation ; heartburn, such as episodic heartburn, nocturnal heartburn and meal induced heartburn ; and dyspepsia.

In particular, the compounds according to the invention are also useful in the treatment or prevention of gastrointestinal disorders, including but not limited to irritable bowel syndrome (IBS), skin disorders such as psoriasis, pruritis and sunburn ; vasospastic diseases such as angina, vascular headache and Reynaud's disease, cerebral ischaemia such as cerebral vasospasm following subarachnoid haemorrhage ; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis ; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis ; cough ; and body weight control, including obesity.

Most in particular, the compounds according to the invention are useful for the manufacture of a medicament for the treatment and/or prophylaxis of schizophrenia, emesis, anxiety and depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pre-eclampsia, nociception, pain, in particular visceral and neuropathic pain, pancreatitis, neurogenic inflammation, asthma, chronic obstructive pulmonary disease (COPD) and micturition disorders such as urinary incontinence.

The present invention also relates to a method for the treatment and/or prophylaxis of neurokinin-mediated diseases, in particular for the treatment and/or prophylaxis of schizophrenia, emesis, anxiety and depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pre-eclampsia, nociception, pain, in particular visceral and neuropathic pain, pancreatitis, neurogenic inflammation, asthma, chronic obstructive pulmonary disease (COPD) and micturition disorders such as urinary incontinence, comprising administering to a human in need of such administration an

effective amount of a compound according to the invention, in particular according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof, as well as the pro-drugs thereof.

The invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention, in particular a compound according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof

The compounds according to the invention, in particular the compounds according to Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and the prodrugs thereof, or any subgroup or combination thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally, rectally, percutaneously, by parenteral injection or by inhalation. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture

of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

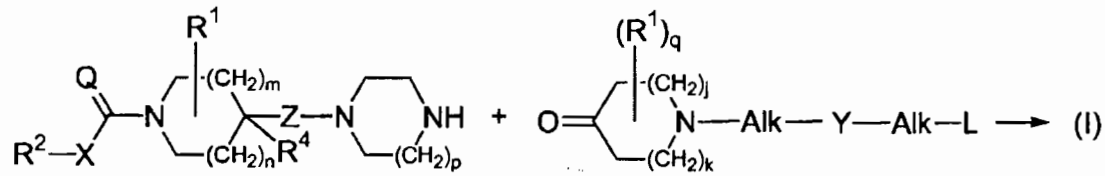
Since the compounds according to the invention are potent orally administrable NK_1 and NK_1/NK_3 antagonists, pharmaceutical compositions comprising said compounds for administration orally are especially advantageous.

Synthesis

The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person.

The compounds of Formula (I) are conveniently prepared by reductively *N*-alkylating an intermediate of Formula (II) wherein R^1, R^2, R^4, X, Q, m, n, p and Z are defined as in Formula (I), with a *N*-substituted piperidinon of Formula (III) wherein R^1, Alk, Y, L, j, k and q are defined as in Formula (I). Said reductive *N*-alkylation may be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol or toluene or a mixture thereof, and in the presence of an appropriate reducing agent such as, for example, a borohydride, e.g. sodium borohydride, sodium cyanoborohydride or

triacetoxy borohydride. In case a borohydride is used as a reducing agent, it may be convenient to use a complex-forming agent such as, for example, titanium(IV)-isopropylate as described in J. Org. Chem, 1990, *55*, 2552-2554. Using said complex-forming agent may also result in an improved *cis/trans* ratio in favor of the *trans* isomer. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. In case hydrogen is used as reducing agent, it may be advantageous to add a dehydrating agent to the reaction mixture such as, for example, aluminium *tert*-butoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene or quinoline-sulphur. Stirring and optionally elevated temperatures and/or pressure may enhance the rate of the reaction.

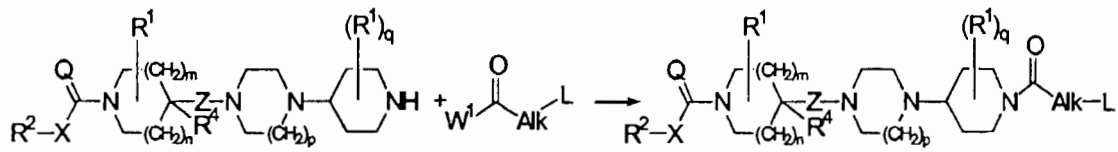


(II) (III)

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

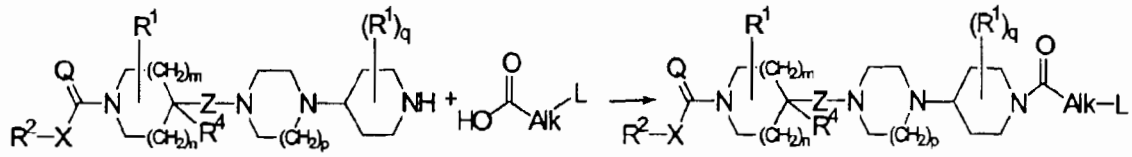
Especially advantage is the preparation of a compound according to the invention according to the previous reaction scheme in which the Alk-Y-Alk-L-moiety is benzyl, thus giving rise to a compound according to Formula (I) in which the Alk-Y-Alk-L-moiety is benzyl. Said compound is pharmacological active and can be converted into a compound according to the invention in which the Alk-Y-Alk-L-moiety is hydrogen by reductive hydrogenation using e.g. hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. The resulting compound according to the invention can then be converted into other compounds according to the invention by art-known transformations, e.g. acylation and alkylation.

In particular, the compounds of Formula (I^a) can be prepared by reacting a final compound of Formula (I') wherein R^1, R^2, R^4, X, Q, Z, m, n, p and q are defined as in Formula (I), with an acyl compound of Formula (V) wherein Alk and L are defined as in Formula (I) and W^1 is an appropriate leaving group such as, for example, a halo, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzenesulfonyloxy. The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature.



(I') (V) (I^a)

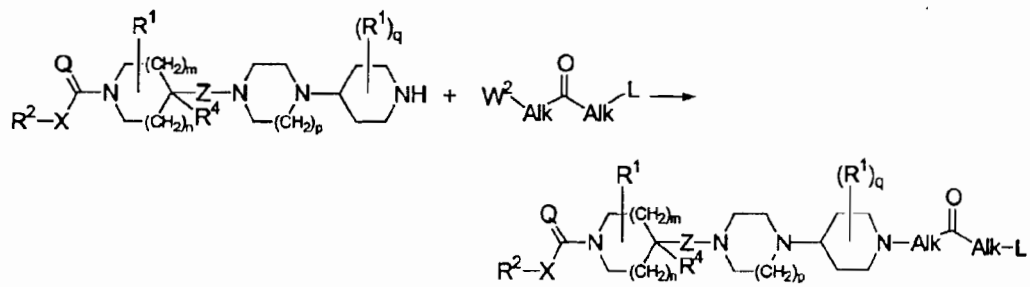
Alternatively, the compounds of Formula (I^a) can also be prepared by reacting a final compound of Formula (I') wherein R^1, R^2, R^4, X, Q, Z, m, n, p and q are defined as in Formula (I) with a carboxylic acid of Formula (VI) wherein Alk and L are defined as in Formula (I)(base-catalyzed nucleophilic addition reaction). The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried at a temperature ranging between room temperature and reflux temperature.



(I') (VI) (I[a])

The above reaction may also be carried out under equivalent conditions with the carboxylic ester of the carboxylic acid of Formula (VI).

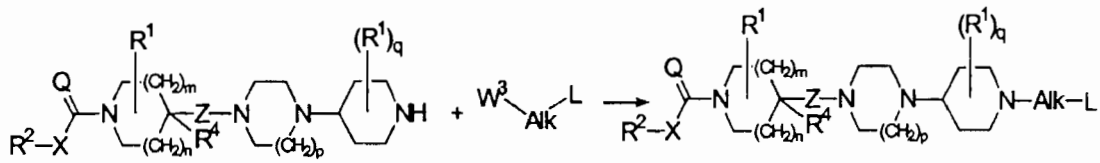
In particular, the compounds of Formula (I[b]) can be prepared by reacting a final compound of Formula (I') wherein R^1, R^2, R^4, X, Q, Z, m, n, p and q are defined as in Formula (I) with a keto-compound of Formula (VII) wherein Alk and L are defined as in Formula (I) and wherein W^2 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzenesulfonyloxy. The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried at a temperature ranging between room temperature and reflux temperature.



(I') (VII) (I[b])

The compounds of Formula (I[c]) can be prepared by reductive amination/ alkylation of a final compound of Formula (I') wherein R^1, R^2, R^4, X, Q, Z, m, n, p and q are defined as in Formula (I) with a compound of Formula (VIII) wherein Alk and L are defined as in Formula (I) and W^3 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy

or benzenesulfonyloxy. The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, an alcohol, e.g. ethanol, or a ketone, e.g. methyl isobutylketone, and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried at a temperature ranging between room temperature and reflux temperature.



(I') (VIII) (I^c)

The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art. The preparation of intermediates is i.a. described in the experimental section, in WO 97/16440-A1, published May 9, 1997 by Janssen Pharmaceutica N.V, which is disclosed herein by reference as well as in other publications mentioned in WO 97/16440-A1, such as , e.g. EP-0,532,456-A.

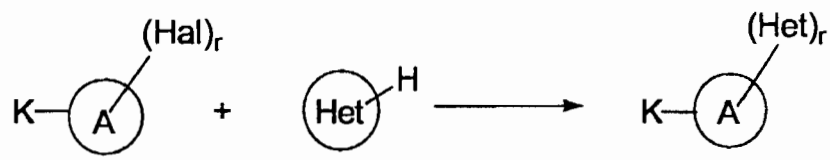
Compounds according to the invention may be converted into each other following art-known transformation reactions, such as illustrated further.

More specifically, compounds of Formula (XIII), wherein A is an aryl or heteroaryl, K may be any moiety, preferably a moiety K^1 as defined below, Het is an unsaturated heteroaryl and r is an integer ranging from 1 to a number equal to the number of available carbon atoms in the aryl or heteroaryl-moiety A, e.g. 5 in phenyl and 4 in pyrrolyl, may be obtained by a novel type of Heck-reaction wherein a compound of Formula (XI), wherein K, A and r are as defined in Formula (XIII) and Hal is a halogen, thus comprising an active or non-active halo-substituted aryl or halo-substituted heteroaryl, more preferably a mono or polysubstituted bromo- and/or iodoaryl or -heteroaryl moiety is reacted with an unsaturated heteroaryl according to Formula (XII) in the presence of catalytic amounts of $Pd(OAc)_2$ and 1,3-bis diphenyl-phosphinopropane, in the presence of a suitable base, preferably Cs_2CO_3 or K(AcO), in a reaction-inert polar solvent such as, preferably NMP, DMA, DMF or the like and at an

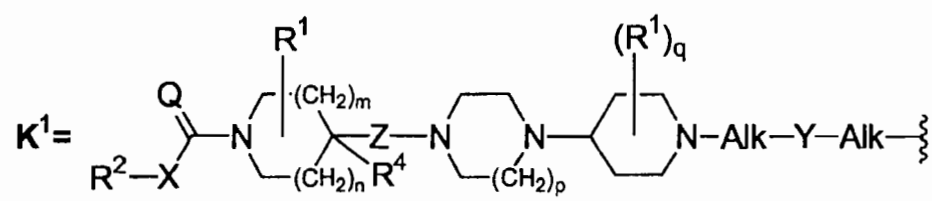
elevated reaction temperature, preferably at 140-150 °C for a certain period of time, preferably about 6-20 hours, more preferably 12-18 hours.

Preferably, r is 1. Het may be a unsaturated monocyclic or bicyclic heteroaryl moiety, such as for instance imidazo[1,2-*a*]pyridinyl, pyrrolyl, thienyl, thiazolyl, imidazolyl, oxazolyl, furanyl, thienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzofuranyl, benzothienyl or indolyl or such as any of the unsaturated radicals in the groups Het^1 and Het^2 as defined in Formula (I), optionally substituted with one or more radicals selected from the group of Ar^1, Ar^1alkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo, alkyloxy, alkyloxyalkyl and alkyloxycarbonyl. Preferably, A is phenyl or pyridinyl.

Said reaction has an improved yield over the process according to the prior art (Yutaka Aoyagi et al., *Heterocycles*, 1992, 33, 257 and Sommai Pivsa-Art, *Bull.Chem.Soc. Jpn.*, 1998, 71, 467).



(XI) (XII) (XIII)



Also, compounds according to the invention may be converted into an acid addition salt by treatment with an acid, or into a base addition salt by treatment with a base, or conversely, the acid addition salt form may be converted into the free base by treatment with alkali, or the base addition salt may be converted into the free acid by treatment with an acid.

The following examples are intended to illustrate and not to limit the scope of the present invention.

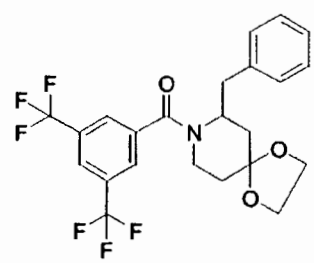
Experimental Part

Hereinafter "RT" means room temperature, "CDI" means 1,1'-carbonyldiimidazole, "DIPE" means diisopropylether, "MIK" means methyl isobutyl keton, "BINAP" means [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine], "NMP" means 1-methyl-2-pyrrolidinone, "$Pd_2(dba)_3$" means tris(dibenzylideneacetone)dipalladium, "DMF" means *N,N*-dimethylformamid, "DMAP" means *N,N*-dimethyl-4-pyridinamine, "EDCI" means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide .HCl and "HOBT" means hydroxybenzotriazole.

Preparation of the intermediate compounds

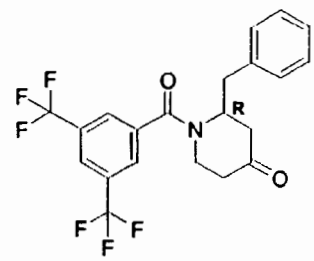
Example A1

a. Preparation of intermediate compound 1

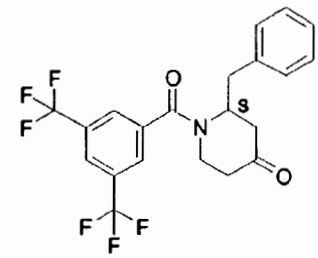


Et_3N (0.55 mol) was added to a stirring mixture of 7-(phenylmethyl)-1,4-dioxa-8-azaspiro[4.5]decane (prepared according to teachings in WO97/24350 of which the content is herein included by reference) (0.5 mol) in toluene (1500 ml). 3,5-Bis(trifluoromethyl)benzoyl chloride (0.5 mol) was added over a 1-hour period (exothermic reaction). The mixture was stirred at room temperature for 2 hours, then allowed to stand for the weekend and washed three times with water (500 ml, 2 x 250 ml). The organic layer was separated, dried, filtered and the solvent was evaporated, yielding 245 g of fraction 1 (100 %). Part of this fraction was crystallized from petroleum ether. The precipitate was filtered off and dried, yielding 1.06 g of intermediate compound 1.

b. Preparation of intermediate compound 2 and 3



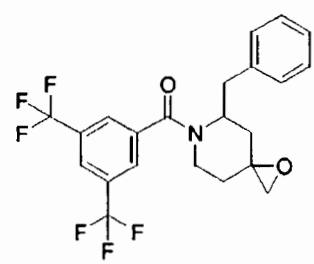
Intermediate compound 2



Intermediate compound 3

HCl cp (300 ml) was added to a mixture of intermediate compound 1 (prepared according to A1.a) (0.5 mol) in ethanol (300 ml) and H_2O (300 ml). The reaction mixture was stirred at 60 °C for 20 hours. The precipitate was filtered off, ground, stirred in H_2O, filtered off, washed with petroleum ether and dried, yielding 192 g of fraction 1 (89.4 %). Part (75 g) of this fraction was separated into its optical isomers by chiral column chromatography over Chiralcel AS (20 µm, 100 Å; eluent: hexane/2-propanol 70/30). Two fraction groups were collected and their solvent was evaporated. Yield: 36.9 g of intermediate compound 2 and 37.5 g of intermediate compound 3.

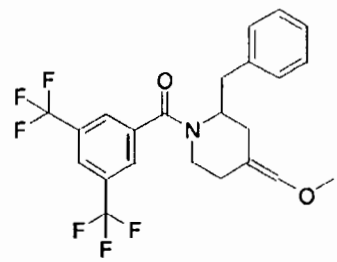
c. Preparation of intermediate compound 4



NaH, 60 % (0.04 mol) was washed 3 times with hexane, then DMSO (30 ml) was added and the mixture was stirred for 1 hour under N_2 and at 60 °C. The mixture was cooled to room temperature and THF (40 ml) was added. The resulting mixture was cooled to 0 °C and a solution of trimethylsulfoxonium iodide (0.032 mol) in DMSO (40 ml) was added dropwise. After stirring for 30 min. at 0°C, a solution of intermediate compound 2 (prepared according to A1.b) (0.02 mol) in DMSO (20 ml) was added dropwise and the reaction mixture was stirred for 3 hours at room temperature. The mixture was poured out into ice, washed with a NH_4Cl soln. and the layers were separated. The organic layer was dried ($MgSO_4$), filtered off and the solvent was evaporated. Yield: 7.3 g of intermediate compound 4 (83 %).

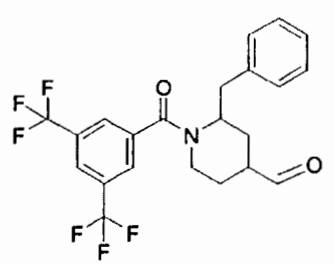
Example A2

a. Preparation of intermediate compound 5



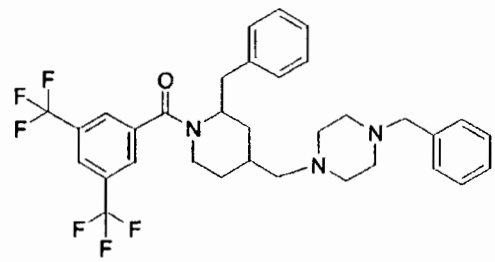
Reaction under N_2 atmosphere. A mixture of (methoxymethyl)triphenylphosphonium chloride (0.0055 mol) and *N*-(1-methylethyl)-2-propanamine (0.0083 mol) in THF, p.a., dry (20 ml) was stirred at -70 °C. 2.3 M BuLi/hexane (0.0055 mol) was added dropwise. More 2.3 M BuLi/hexane (2.2 ml) was added. The mixture was allowed to warm to room temperature. The reaction mixture was stirred for 30 min at 20 °C. The mixture was re-cooled to -25 °C. A solution of 1-[3.5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinone (prepared according to teachings in WO97/24350 of which the content is herein included by reference) (0.005 mol) in some THF, p.a.,dry was added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred overnight at room temperature, then decomposed with water. The organic solvent was evaporated and the aqueous concentrate was extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. Yield: 1.30 g of intermediate compound 5 (57 %).

b. Preparation of intermediate compound 6



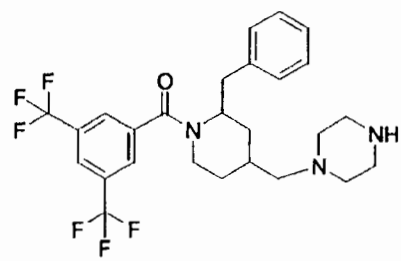
A mixture of intermediate compound 5 (prepared according to A2.a) (0.0028 mol) in 1.6 N HCl (6 ml) and THF (6 ml) was stirred for one hour at 40 °C. The THF was evaporated and the aqueous concentrate was extracted with CH_2Cl_2. The separated organic layer was washed with an aqueous Na_2CO_3 solution, dried, filtered and the solvent evaporated. Yield: 1.24 g of intermediate compound 6 (100 %).

c. Preparation of intermediate compound 7



A mixture of intermediate compound 6 (prepared according to A2.b) (0.0028 mol) and 1-(phenylmethyl)piperazine (0.0028 mol) in THF (5 ml) and methanol (100 ml) was hydrogenated with Pd/C, 10 % (0.5 g) as a catalyst in the presence of thiophene solution (0.5 ml). After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was treated with (E)-2-butenedioic acid in methanol. The salt was filtered off and re-converted into the free base with 50 % NaOH, then extracted with CH_2Cl_2. The separated organic layer was dried, filtered and the solvent evaporated. The residue solidified spontaneously and was dried. Yield: 0.56 g of intermediate compound 7 (33 %).

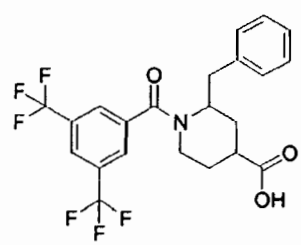
d. Preparation of intermediate compound 8



A mixture of intermediate compound 7 (prepared according to A2.c) (0.133 mol) in methanol (500 ml) was hydrogenated over the weekend with Pd/C, 10 % (5 g) as a catalyst. After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. Yield: 67.5 g of intermediate compound 8.

Example A3

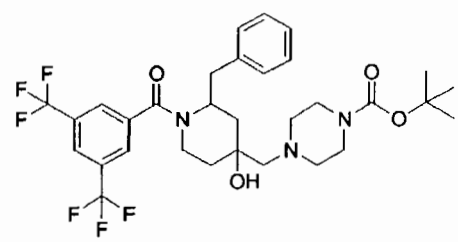
Preparation of intermediate compound 9



A mixture of intermediate compound 6 (prepared according to A2.b) (0.0081 mol) in CH_3CN (p.a) (20 ml) was stirred on an ice bath, giving mixture (I). A mixture of $NaOCl_2$ (0.00975 mol) dissolved in H_2O (20 ml) was added dropwise at <10 °C to mixture (I). The reaction mixture was stirred for 2 hours at <10 °C and was stirred overnight at room temperature. NaOH (25 ml, 10 %) was added dropwise to the mixture at room temperature and the reaction mixture was washed with DIPE (2 times). The aqueous layer was acidified with HCl (10 %) at <10 °C, then extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and filtered off. The solvent was evaporated and the residue was crystallised from DIPE. Yield: 3.0 g of intermediate compound 9 (80 %).

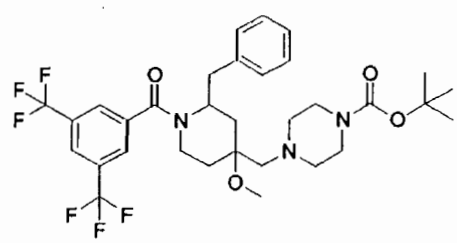
Example A4

a. Preparation of intermediate compound 10



A mixture of intermediate compound 4 (prepared according to A1.c) (0.0165 mol) and 1,1-dimethylethyl-1-piperazinecarboxylic acid ester (0.0165 mol) in ethanol p.a. (100 ml) was stirred and refluxed for 14 hours. The solvent was evaporated and the residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 97.5/2.5). The product fractions were collected and the solvent was evaporated. Yield: 8.3 g of intermediate compound 10 (80 %).

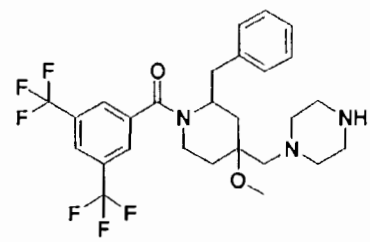
b. Preparation of intermediate compound 11



A mixture of intermediate compound 10 (prepared according to A4.a) (8.3 g; 0.0132 mol) in DMF p.a. (250 ml) was stirred at room temperature under N_2. NaH 60 % (0.64 g; 0.016 mol) was added and the reaction mixture was stirred for 1 hour at room

temperature. A mixture of CH_3I (2.25 g; 0.0158 mol) dissolved in DMF was added dropwise. The reaction mixture was stirred for 18 hours at room temperature. Extra NaH 60 % (0.64 g) was added and the mixture was stirred for 1 hour at room temperature. Extra CH_3I (2.25 g) was added and the mixture was stirred for 18 hours at room temperature. Then the mixture was poured into H_2O and extracted with DIPE. The organic layer was dried with $MgSO_4$, filtered and evaporated. Yield: 6.4 g of intermediate compound 11 (75 %).

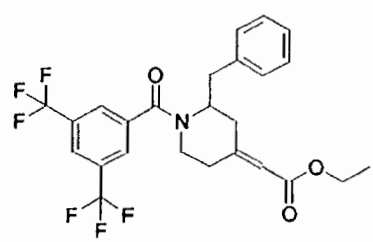
c. Preparation of intermediate compound 12



A mixture of intermediate compound 11 (prepared according to A4.b) (6.0 g; 0.0093 mol), HCl/iPrOH (25 ml) and methanol (100 ml) was stirred at 50 °C for 1 hour. The solvent was evaporated and the residue was poured out into H_2O. K_2CO_3 10 % (3 g) was added. The filtrate was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered, and the solvent was evaporated. Yield: 5.1 g of intermediate compound 12 (100 %).

Example A5

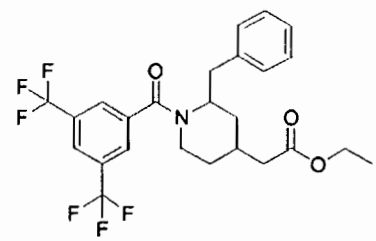
a) Preparation of intermediate compound 13



A mixture of NaH, 60 % (0.036 mol) in THF, p.a., dried on molecular sieves (200 ml) was stirred at room temperature and a solution of (diethoxyphosphinyl)acetic acid ethyl ester (0.036 mol) in THF, p.a., dried on molecular sieves (q.s.) was added dropwise, then the mixture was stirred for 30 min. at room temperature and a solution of intermediate compound 2 (prepared according to A1.b) (0.03 mol) in THF, p.a., dried on molecular sieves (q.s.) was added dropwise. The reaction mixture was stirred for 90 min. at room temperature. NH_4Cl (15 g) and H_2O (200 ml) were added. The organic

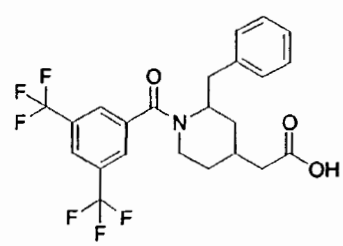
solvent was evaporated and the aqueous concentrate was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent gradient: CH_2Cl_2/CH_3OH from 100/0 to 98/2). The product fractions were collected and the solvent was evaporated. Yield: 14.3 g of intermediate compound 13 (95 %).

b) Preparation of intermediate compound 14



A mixture of intermediate compound 13 (prepared according to A5.a) (0.0126 mol) in ethanol (100 ml) was hydrogenated at 20 °C for 18 hours with Pd/C 10 % (1 g) as a catalyst. After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. Yield: 7.1 g of intermediate compound 14 (100 %).

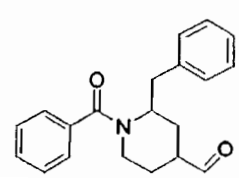
c) Preparation of intermediate compound 15

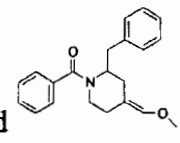


A mixture of intermediate compound 14 (prepared according to A5.b) (0.014 mol) in NaOH (1N) (75 ml), methanol (70 ml) and H_2O (70 ml) was stirred at room temperature for 24 hours. The organic solvent was evaporated, HCl (100 ml, 1N) was added and the reaction mixture was extracted (2 times) with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. Yield: 5.5 g of intermediate compound 15 (83 %).

Example A6

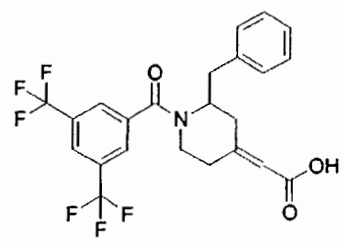
Preparation of intermediate compound 16



A mixture of intermediate compound  (2R) (prepared according to A2.a) (0.0133 mol) in 37 % HCl (10 ml), H_2O (30 ml) and THF (40 ml) was stirred for 2 hours at 50 °C, then the organic solvent was evaporated and the aqueous concentrate was extracted with CH_2Cl_2. The organic layer was washed with a $NaHCO_3$ soln. and with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent gradient: CH_2Cl_2/CH_3OH from 100/0 to 98/2). The product fractions were collected and the solvent was evaporated. Yield: 2.7 g of intermediate compound 16 (66 %).

Example A7

Preparation of intermediate compound 17

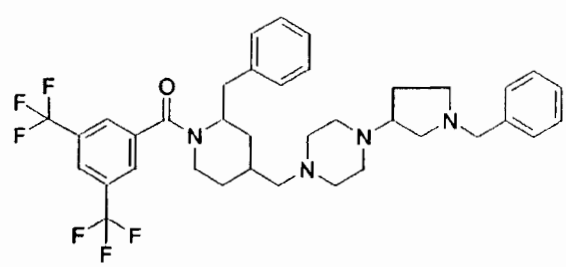


A mixture of intermediate compound 13 (prepared according to A5.a) (0.0143 mol) in NaOH (1N) (75 ml), methanol (170 ml) and H_2O (100 ml) was stirred at room temperature for 48 hours. The solvent was evaporated until water and the residue was washed with DIPE. HCl (100 ml, 1N) was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent gradient: CH_2Cl_2/CH_3OH from 100/0 to 90/10). The product fractions were collected and the solvent was evaporated. Yield: 5.9 g of intermediate compound 17 (88 %).

Preparation of the final compounds

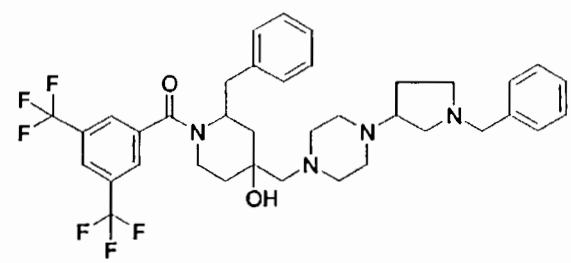
Example B1

a) Preparation of final compound 1



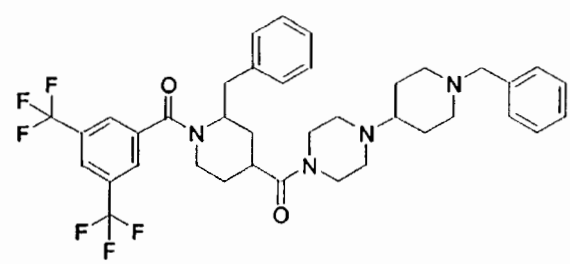
A mixture of intermediate compound 8 (prepared according to A2.d) (0.04 mol) and 1-(phenylmethyl)-3-pyrrolidinone (0.04 mol) in methanol (250 ml) was hydrogenated at 50 °C for 18 hours with Pd/C 10 % (3 g) as a catalyst in the presence of thiophene solution (2 ml). After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in H_2O/CH_2Cl_2 and K_2CO_3 (5 g). The layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the organic layer was dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent gradient: CH_2Cl_2/CH_3OH from 95/5 to 90/10). The product fractions were collected and the solvent was evaporated. Yield: 22.0 g of final compound 1 (82 %).

b) Preparation of final compound 2



A mixture of intermediate compound 4 (prepared according to A1.c) (0.0165 mol) and 1-[1-(phenylmethyl)-3-pyrrolidinyl]piperazine (prepared according to teachings in WO96/20173, of which the content is herein included by reference) (0.0165 mol) in ethanol p.a. (100 ml) was stirred and refluxed overnight. The solvent was evaporated and the residue was purified over silica gel on a glass filter (eluent gradient: CH_2Cl_2/CH_3OH from 95/5 to 90/10). The product fractions were collected and the solvent was evaporated. Yield: 7.6 g of final compound 2 (67 %).

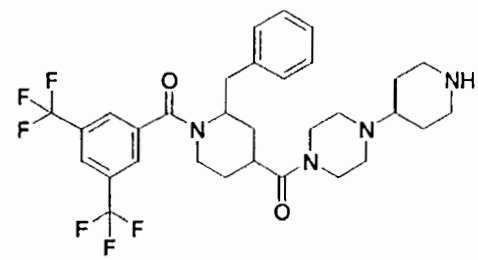
c) Preparation of final compound 3



A mixture of intermediate compound 9 (prepared according to A3) (0.02 mol), *N,N*-dimethyl-4-pyridinamine (0.028 mol) and Et_3N (0.028 mol) in CH_2Cl_2, p.a. (300 ml) was stirred at room temperature, then EDCI (0.028 mol) was added portionwise and the

reaction mixture was stirred for 5 hours at room temperature. A solution of 1-[1-(phenylmethyl)-4-piperidin-yl]piperazine (prepared according to teachings in WO96/20173, of which the content is herein included by reference) (0.02 mol) in CH_2Cl_2 was added dropwise and the mixture was stirred over the weekend at room temperature. NaOH (150 ml, 1 N) was added and the reaction mixture was stirred for 15 min. at room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. Yield: 3.2 g of final compound 3 (23 %).

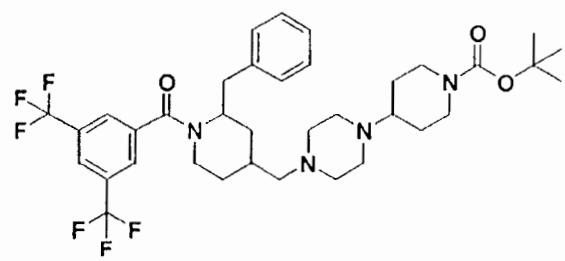
d) Preparation of final compound 4

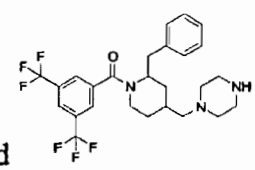


A mixture of final compound 3 (0.0041 mol) in H_2 (50 ml) was hydrogenated at room temperature for 72 hours with Pd/C 10 % (0.5 g) as a catalyst. After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. Yield: 2.4 g of final compound 4 (96 %).

Example B2

a) Preparation of final compound 5

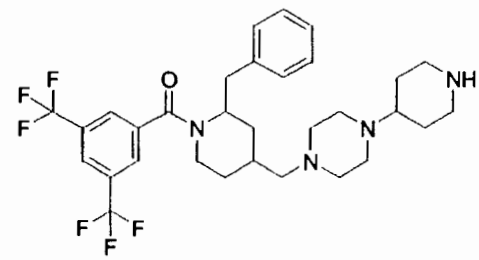




A mixture of intermediate compound (trans) (prepared according to A2.d) (0.02 mol) and 1,1-dimethylethyl 4-oxo-1-piperidine-carboxylic acid ester (0.02 mol) in methanol (250 ml) was hydrogenated at 50°C with Pd/C 10 % (2 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H_2 (1 eq.), the catalyst was filtered off and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent gradient : CH_2Cl_2/MeOH from 97/3 to 94/6). The

desired fractions were collected and the solvent was evaporated. Yield : 10.4 g of final compound 5 (75 %).

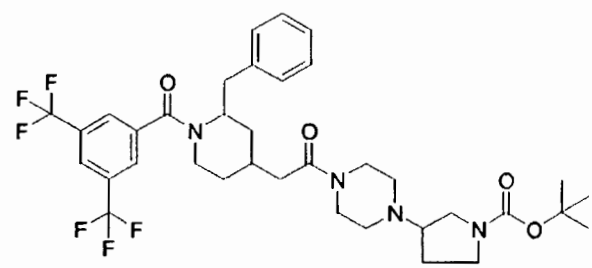
b) Preparation of final compound 6



Final compound 5 (prepared according to B2.a) (0.0139 mol) in HCl/2-propanol (15 ml) and 2-propanol (60 ml) was stirred at 50 °C for 3 hours. The solvent was evaporated. Yield : 9.3 g of final compound 6 (95 %).

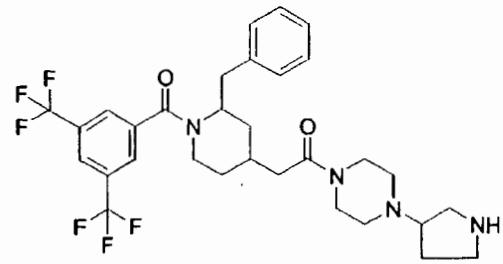
Example B3

a) Preparation of final compound 7



A mixture of intermediate compound 15 (prepared according to A5.c) (0.006 mol), DMAP (0.0077 mol) and Et_3N (0.0077 mol) in CH_2Cl_2 (100 ml) was stirred at room temperature. EDCI (0.0077 mol) was added and the mixture was stirred for 2 hours at room temperature, giving mixture (I). A mixture of 1,1-dimethylethyl 3-(1-piperazinyl)-1-pyrrolidinecarboxylic acid ester ((prepared according to the teachings in WO2004/056799 of which the content is included herein) (0.006 mol) dissolved in CH_2Cl_2 was added dropwise to mixture (I) and the reaction mixture was stirred overnight at room temperature. H_2O (100 ml) and NaOH (50 ml, 1 N) were added and the mixture was stirred for 5 min. at room temperature. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent gradient: CH_2Cl_2/CH_3OH from 100/0 to 90/10). The product fractions were collected and the solvent was evaporated. Yield: 2.1 g of final compound 7 (50 %).

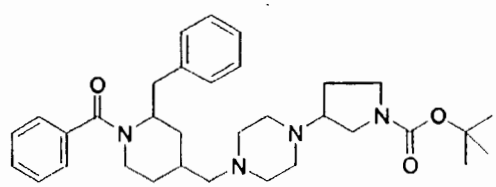
b) Preparation of final compound 8



A mixture of final compound 7 (0.00295 mol) in CF_3COOH (20 ml) was stirred at room temperature for 1 hour. The reaction mixture was poured out into ice/H_2O/K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 and the organic layer was dried ($MgSO_4$), filtered off and the solvent was evaporated. Yield: 1.7 g of final compound 8 (94 %).

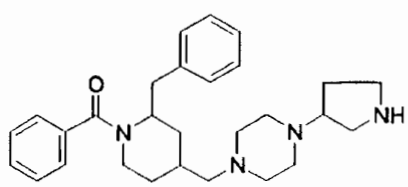
Example B4

a) Preparation of final compound 9



A mixture of intermediate compound 16 (prepared according to A6) (0.0088 mol) and 1,1-dimethylethyl 3-(1-piperazinyl)-1-pyrrolidinecarboxylic acid ester ((prepared according to the teachings in WO2004/056799 of which the content is included herein by reference) (0.01 mol) in methanol (150 ml) was hydrogenated at 50 °C for 48 hours with Pd/C 10 % (1 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent gradient: CH_2Cl_2/CH_3OH from 100/0 to 95/5). The product fractions were collected and the solvent was evaporated. Yield: 3.6 g of final compound 9 (75 %).

b) Preparation of final compound 10

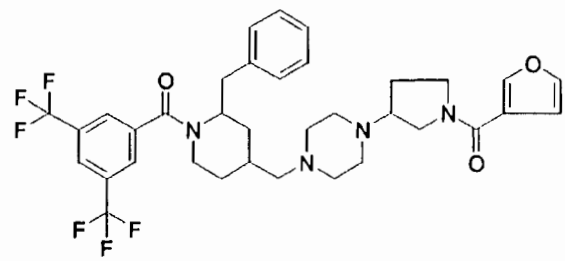


A mixture of final compound 9 (prepared according to B4.a) (0.0066 mol) in HCl/2-propanol (10 ml) and methanol (40 ml) was stirred and refluxed for 1 hour. The solvent was evaporated and the residue was taken up in H_2O. The mixture was alkalised

with NaOH and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. Yield: 2.6 g of final compound 10 (88 %).

Example B5

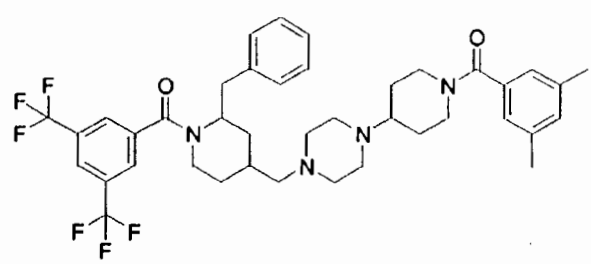
Preparation of final compound 11



A mixture of 3-furancarboxylic acid (0.0027 mol), DMAP (0.0027 mol) and Et_3N (0.0027 mol) in CH_2Cl_2, p.a. (100 ml) was stirred at room temperature. Then, EDCI (0.0027 mol) was added and the reaction mixture was stirred at room temperature for 1 hour, giving mixture (I). A mixture of final compound 60 (prepared according to B1.d) (0.002 mol) dissolved in CH_2Cl_2 was added dropwise to mixture (I) and the reaction mixture was stirred overnight at room temperature. The mixture was poured out into NaOH (1 N) and stirred for 15 min. at room temperature. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the organic layer was dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent gradient: CH_2Cl_2/CH_3OH from 100/0 to 90/10). The product fractions were collected and the solvent was evaporated. Yield: 0.914 g of final compound 11 (67 %)

Example B6

Preparation of final compound 12

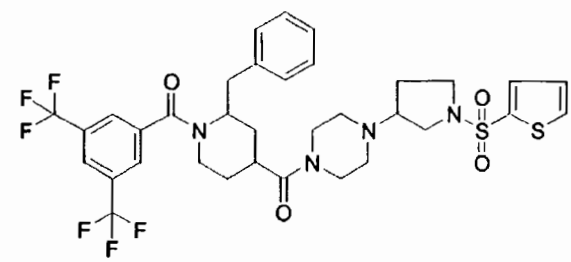


A mixture of final compound 6 (prepared according to B1.d) (0.0021 mol) and Et_3N (0.01 mol) in CH_2Cl_2, p.a. (50 ml) was stirred on an ice-bath. 3.5-dimethylbenzoyl chloride (0.0025 mol) was dissolved in CH_2Cl_2 and added dropwise to the reaction

mixture which was stirred for 1 hour at room temperature. K_2CO_3 (2 g) was added and H_2O and the mixture was extracted. The separated aqueous layer was extracted with CH_2Cl_2 and the separated combined organic layers were dried ($MgSO_4$), filtered and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent gradient : CH_2Cl_2/MeOH from 100/0 to 90/10). The product fractions were collected and the solvent was evaporated. Yield : 1.38 g of final compound 12 (90 %).

Example B7

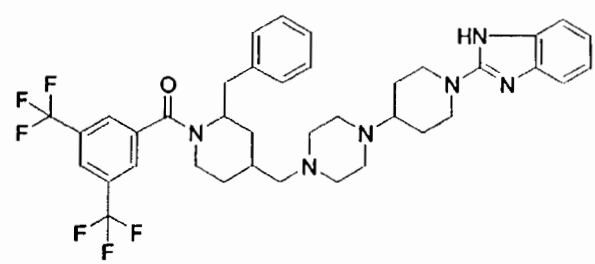
Preparation of final compound 13



A mixture of final compound 66 (prepared according to B1.d) (0.00134 mol) and Et_3N (0.01 mol) in CH_2Cl_2, p.a. (40 ml) was stirred at room temperature, then a solution of 2-thiophenesulfonyl chloride (0.0016 mol) in CH_2Cl_2, p.a. (q.s.) was added dropwise and the reaction mixture was stirred overnight at room temperature. NaOH (1 N, 20 ml) was added dropwise, the resulting mixture was stirred for 10 min. at room temperature and then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 ; the organic layer was washed with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent gradient: CH_2Cl_2/CH_3OH from 100/0 to 90/10). The product fractions were collected and the solvent was evaporated. Yield: 0.791 g of final compound 13 (80 %).

Example B8

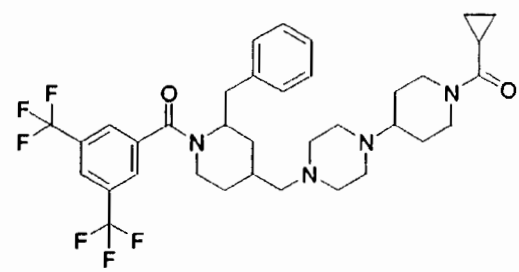
Preparation of final compound 14



Final compound 6 (prepared according to B2.b) (0.000168 mol) was converted into the free base. A mixture of the free base of final compound 6 (0.000168 mol), 2-chloro-1*H*-benzimidazole (0.000182 mol) and CuO (0.010 g) in *N,N*-dimethylacetamide (3 ml) was stirred for 3 hours at 150 °C and then the solvent was evaporated. The obtained residue was taken up in CH_2Cl_2 (5 ml) and H_2O/NH_3 was added. The mixture was stirred for 2 hours and was filtered through Extrelut, then the filter residue was washed with CH_2Cl_2 (2 x 2 ml) and purified by high-performance liquid chromatography (eluent: CH_2Cl_2/CH_3OH 90/10). The product fractions were collected and the solvent was evaporated. Yield: 0.011 g of final compound 14.

Example B9

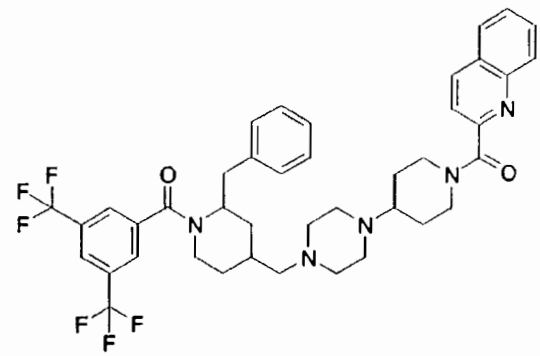
Preparation of final compound 15



Final compound 6 (prepared according to B2.b) (0.000168 mol) was converted into the free base. A mixture of the free base of final compound 6 (0.000168 mol), cyclopropanecarbonyl chloride (0.001182 mol) and Et_3N (0.0005 mol) in CH_2Cl_2 (4 ml) was stirred over the weekend at room temperature and then H_2O (2 ml) was added. The mixture was stirred for 30 min. and was filtered through Extrelut, then the filter residue was washed with CH_2Cl_2 (2 x 2 ml) and purified by high-performance liquid chromatography (eluent: CH_2Cl_2/CH_3OH 90/10). The product fractions were collected and the solvent was evaporated. Yield: 0.109 g of final compound 15.

Example B10

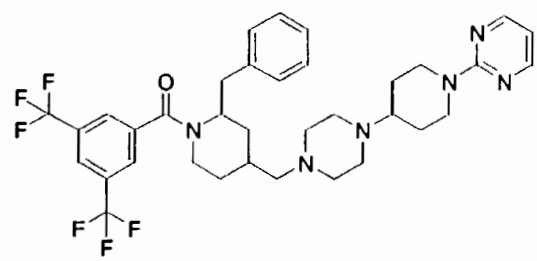
Preparation of final compound 16



Final compound 6 (prepared according to B2.b) (0.000168 mol) was converted into the free base. A mixture of 2-quinolinecarboxylic acid (0.000182 mol), Et_3N (0.0005 mol) and PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) (0.0002 mol) in CH_2Cl_2 (4 ml) was stirred for 3 hours, then the free base of final compound 6 (0.000168 mol) was added and the reaction mixture was stirred over the weekend at room temperature. The solvent was evaporated and the residue was purified by reversed-phase high-performance liquid chromatography. The product fractions were collected and the solvent was evaporated. Yield: 0.083 g of final compound 16.

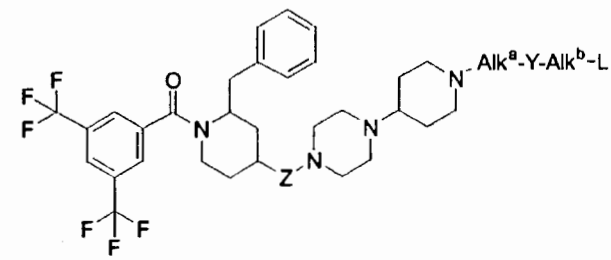
Example B11

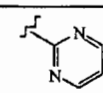
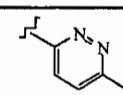
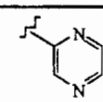
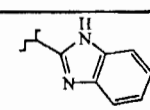
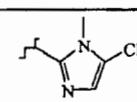
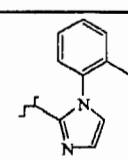
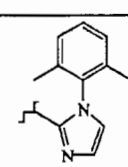
Preparation of final compound 17

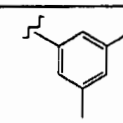
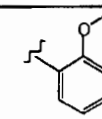
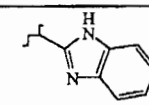
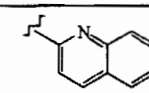
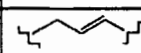
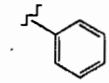
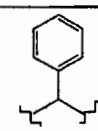
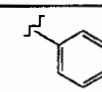
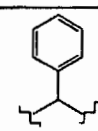
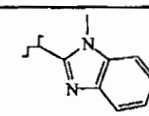
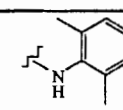
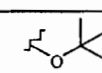
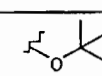
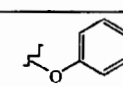
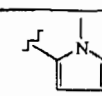
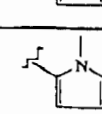


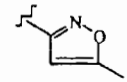
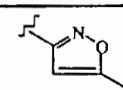
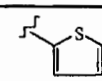
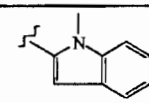
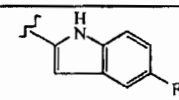
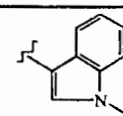
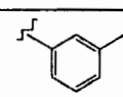
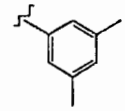
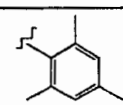
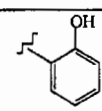
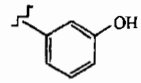
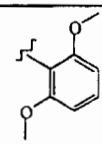
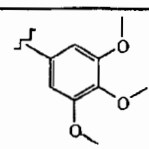
Final compound 6 (prepared according to B2.b) (0.000168 mol) was converted into the free base. A mixture of the free base of final compound 6 (0.000168 mol), 2-chloropyrimidine (0.000182 mol) and Na_2CO_3 (0.0005 mol) in *N,N*-dimethylacetamide (4 ml) was stirred over the weekend at 60 °C and then the solvent was evaporated. The obtained residue was taken up in CH_2Cl_2 (5 ml) and H_2O (2 ml) was added. The mixture was stirred for 30 min. and was filtered through Extrelut, then the filter residue was washed with CH_2Cl_2 (2 x 2 ml) and purified by high-performance liquid chromatography (gradient 90/10). The product fractions were collected and the solvent was evaporated. Yield: 0.059 g of final compound 17.

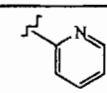
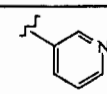
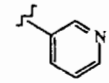
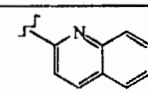
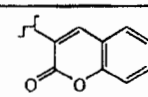
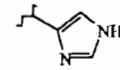
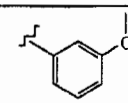
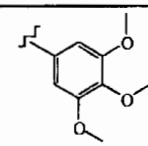
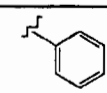
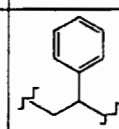
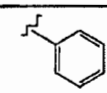
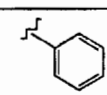
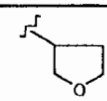
Table 1

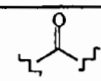
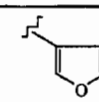
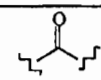
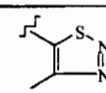
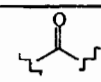


Comp. No.	Exp. No.	Z	Alk[a]	Y	Alk[b]	L	Sterco descriptors
6	B2.b	$-CH_2-$	cb	cb	cb	H	trans; .HCl(1:3) .H_2O(1:2)
100	B2.b	$-CH_2-$	cb	cb	cb	H	2S-trans
17	B11	$-CH_2-$	cb	cb	cb		trans
18	B8	$-CH_2-$	cb	cb	cb		trans
19	B8	$-CH_2-$	cb	cb	cb		trans
14	B8	$-CH_2-$	cb	cb	cb		trans
20	B11	$-CH_2-$	$-CH_2-$	cb	cb		trans
21	B11	$-CH_2-$	$-CH_2-$	cb	cb		trans
22	B11	$-CH_2-$	$-CH_2-$	cb	cb		trans

Comp. No.	Exp. No.	Z	Alk[a]	Y	Alk[b]	L	Stereo descriptors
23	B11	$-CH_2-$	$-CH_2-$	cb	cb		trans
24	B11	$-CH_2-$	$-CH_2-$	cb	cb		trans
25	B11	$-CH_2-$	$-CH_2-$	cb	cb		trans
26	B11	$-CH_2-$	$-CH_2-$	cb	cb		trans
27	B11	$-CH_2-$		cb	cb		trans
28	B11	$-CH_2-$		cb	cb		trans
29	B11	$-CH_2-$		cb	cb		trans
30	B11	$-CH_2-$	$-CH_2-$	C=O	cb		trans
5	B2.a	$-CH_2-$	cb	C=O	cb		trans
99	B2.a	$-CH_2-$	cb	C=O	cb		2S-trans
31	B9	$-CH_2-$	cb	C=O	cb		trans
32	B6	$-CH_2-$	cb	C=O	cb		2S-trans
15	B9	$-CH_2-$	cb	C=O	cb		trans
33	B10	$-CH_2-$	cb	C=O	cb		trans
34	B6	$-CH_2-$	cb	C=O	cb		2S-trans

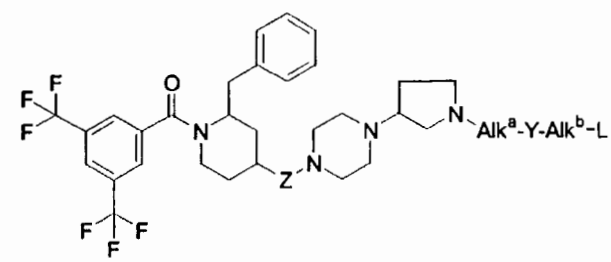
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36	B6	$-CH_2-$	cb	C=O	cb		2S-trans
37	B9	$-CH_2-$	cb	C=O	cb		trans
38	B10	$-CH_2-$	cb	C=O	cb		trans
39	B10	$-CH_2-$	cb	C=O	cb		trans
40	B10	$-CH_2-$	cb	C=O	cb		trans
41	B6	$-CH_2-$	cb	C=O	cb		2S-trans
12	B6	$-CH_2-$	cb	C=O	cb		trans
42	B9	$-CH_2-$	cb	C=O	cb		trans
43	B10	$-CH_2-$	cb	C=O	cb		trans
44	B10	$-CH_2-$	cb	C=O	cb		trans
45	B9	$-CH_2-$	cb	C=O	cb		trans
46	B9	$-CH_2-$	cb	C=O	cb		trans

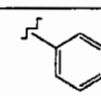
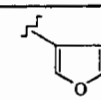
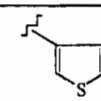
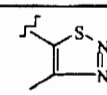
Comp. No.	Exp. No.	Z	Alk[a]	Y	Alk[b]	L	Stereo descriptors
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48	B6	$-CH_2-$	cb	C=O	cb		2S-trans
49	B9	$-CH_2-$	cb	C=O	cb		trans
16	B10	$-CH_2-$	cb	C=O	cb		trans
50	B10	$-CH_2-$	cb	C=O	cb		trans
51	B10	$-CH_2-$	cb	C=O	$-CH_2-$		trans
52	B9	$-CH_2-$	cb	C=O	$-CH_2-$		trans
53	B10	$-CH_2-$	cb	C=O	$-CH_2-$		trans
54	B9	$-CH_2-$	cb	C=O			trans
55	B10	$-CH_2-$	cb	C=O			trans
4	B1.d		cb	cb	cb	H	2S-trans
3	B1.c		$-CH_2-$	cb	cb		2S-trans
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92	B5		cb	C=O	cb		2S-trans

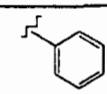
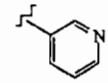
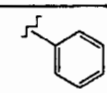
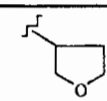
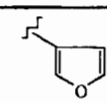
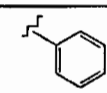
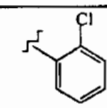
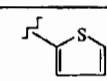
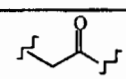
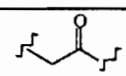
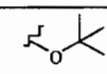
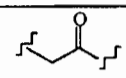
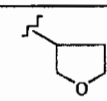
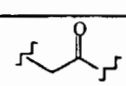
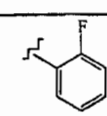
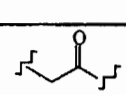
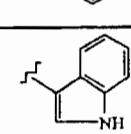
Comp. No.	Exp. No.	Z	Alk[a]	Y	Alk[b]	L	Stereo descriptors
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58	B6		cb	C=O	cb		2S-trans
59	B6		cb	C=O	cb		2S-trans

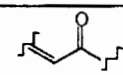
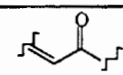
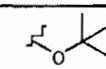
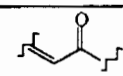
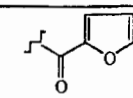
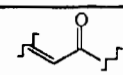
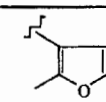
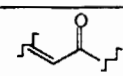
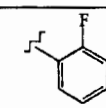
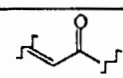
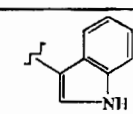
cb = covalent bond

Table 2



Comp. No.	Exp. No.	Z	Alk[a]	Y	Alk[b]	L	Stereo descriptors
60	B1.d	$-CH_2-$	cb	cb	cb	H	trans
1	B1.a	$-CH_2-$	cb	cb	cb		2S-trans
61	B6	$-CH_2-$	cb	C=O	cb		2S-trans
11	B5	$-CH_2-$	cb	C=O	cb		2S-trans
62	B5	$-CH_2-$	cb	C=O	cb		2S-trans
63	B6	$-CH_2-$	cb	C=O	cb		2S-trans

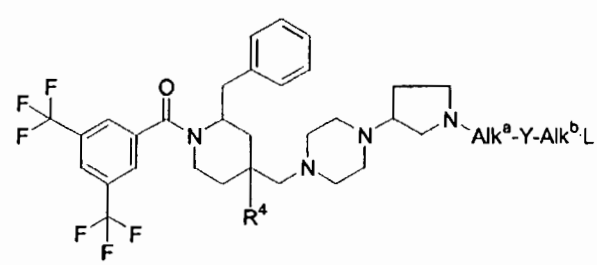
Comp. No.	Exp. No.	Z	Alk[a]	Y	Alk[b]	L	Stereo descriptors
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66	B1.d		cb	cb	cb	H	2S-trans
67	B1.a		$-CH_2-$	cb	cb		2S-trans
68	B6		cb	C=O	cb		2S-trans
69	B5		cb	C=O	cb		2S-trans
70	B5		cb	C=O	cb		2S-trans
71	B6		cb	C=O	cb		2S-trans
72	B6		cb	C=O	cb		2S-trans
13	B7		cb		cb		2S-trans
8	B3.b		cb	cb	cb	H	2R cis/trans
7	B3.a		cb	C=O	cb		2R cis/trans
73	B5		cb	C=O	cb		2R cis/trans
74	B6		cb	C=O	cb		2R cis/trans
75	B5		cb	C=O	cb		2R cis/trans

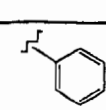
Comp. No.	Exp. No.	Z	Alk[a]	Y	Alk[b]	L	Stereo descriptors
94	B3.b		cb	cb	cb	H	2R E/Z
83	B3.a		cb	C=O	cb		2R E/Z
98	B5		cb	C=O	cb		2R E/Z
95	B5		cb	C=O	cb		2R E/Z
96	B5		cb	C=O	cb		2R E/Z
97	B5		cb	C=O	cb		2R E/Z

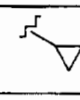
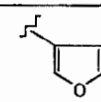
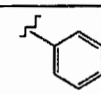
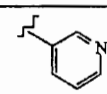
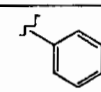
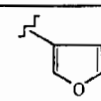
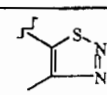
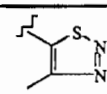
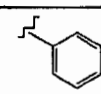
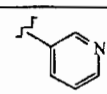
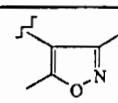
cb = covalent bond

Some of the experimental numbers refer to analogs; however the compounds according to this Table 2 were prepared in an analogous way with intermediate compounds as described above.

Table 3

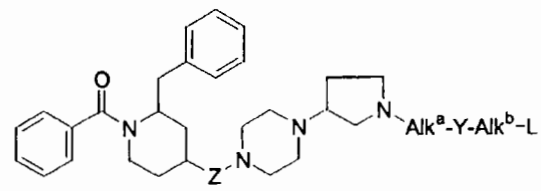


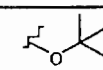
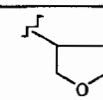
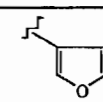
Comp. No.	Exp. No.	R[4]	Alk[a]	Y	Alk[b]	L	Stereo descriptors
76	B1.d	-OH	cb	cb	cb	H	2R-cis
2	B1.b	-OH	$-CH_2-$	cb	cb		2R-cis

Comp. No.	Exp. No.	R^4	Alk[a]	Y	Alk[b]	L	Stereo descriptors
77	B6	-OH	cb	C=O	cb		2R-cis
78	B5	-OH	cb	C=O	cb		2R-cis
79	B6	-OH	cb	C=O	cb		2R-cis
80	B6	-OH	cb	C=O	cb		2R-cis
81	B1.d	$-OCH_3$	cb	cb	cb	H	2R-cis
82	B1.a	$-OCH_3$	$-CH_2-$	cb	cb		2R-cis
84	B6	$-OCH_3$	cb	C=O	cb		2R-cis
85	B5	$-OCH_3$	cb	C=O	cb		2R-cis
86	B6	$-OCH_3$	cb	C=O	cb		2R-cis
93	B6	-OH	cb	C=O	cb		2R-cis
87	B6	$-OCH_3$	cb	C=O	cb		2R-cis
88	B6	$-OCH_3$	cb	C=O	cb		2R-cis
89	B7	$-OCH_3$	cb		cb		2R-cis

cb = covalent bond

Table 4



Comp. No.	Exp. No.	Z	Alk[a]	Y	Alk[b]	L	Stereo descriptors
10	B4.b	$-CH_2-$	cb	cb	cb	H	2S-trans
9	B4.a	$-CH_2-$	cb	C=O	cb		2S-trans
90	B5	$-CH_2-$	cb	C=O	cb		2S-trans
91	B5	$-CH_2-$	cb	C=O	cb		2S-trans

cb = covalent bond

C. Analytical data

For a number of compounds, either melting points or LCMS data were recorded.

1. LCMS conditions

The HPLC gradient was supplied by a Waters Alliance HT 2790 system with a columnheater set at 40°C. Flow from the column was split to a Waters 996 photodiode array (PDA) detector and a Waters-Micromass ZQ mass spectrometer with an electrospray ionization source operated in positive and negative ionization mode. Reversed phase HPLC was carried out on a Xterra MS C18 column (3.5 µm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. Three mobile phases (mobile phase A 95% 25mM ammoniumacetate + 5% acetonitrile; mobile phase B: acetonitrile; mobile phase C: methanol) were employed to run a condition from 100 % A to 50 % B and 50 % C in

6.5 min., to 100 % B in 1 min, 100% B for 1 min. and reequilibrate with 100 % A for 1.5 min. An injection volume of 10 µL was used.

Mass spectra were acquired by scanning from 100 to 1000 in 1 s using a dwell time of 0.1 s. The capillary needle voltage was 3 kV and the source temperature was maintained at 140 °C . Nitrogen was used a the nebulizer gas. Cone voltage was 10 V for positive ionzation mode and 20 V for negative ionization mode. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

Table 5 : LCMS parent peak and retention time for selected compounds.

Comp. no.	Retention time (minutes)	LCMS (MH+)
1	8.1	673
2	8.42	689
3	6.6	701
4	5.13	611
5	8.21	697
6	6.55	597
7	7.88	711
8	6.3	611
9	6.6	547
11	7.3	677
12	8.1	729
13	5.8	743
14	7.33	713
15	7.3	665
16	7.66	752
18	7.31	689
19	7.71	675
21	7.96	767
22	8.46	781
23	8.71	715
25	7.54	727

Comp. no.	Retention time (minutes)	LCMS (MH+)
26	8.04	738
27	8.19	713
28	8.11	763
29	8.81	817
30	7.84	758
31	8.21	717
32	7.46	665
33	7.56	704
34	7.8	704
35	7.36	706
36	7.53	706
37	7.54	707
38	8.14	754
39	8.07	758
40	8.01	754
41	7.86	715
42	8.23	743
43	7.56	717
44	7.2	717
45	7.51	761
46	7.46	789
47	7.26	702
48	7.01	702
49	7	702
50	7.54	769
51	6.89	705
52	7.78	745
53	7.54	805
54	8.14	729
55	8.46	805
56	5.8	679
57	5.77	705
58	5.79	737

Comp. no.	Retention time (minutes)	LCMS (MH+)
59	5.99	715
61	7.36	651
62	7.61	693
63	7.36	709
64	7.55	687
65	7.19	688
66	5.2	597
67	6.38	687
68	5.58	665
69	5.42	695
70	5.72	691
71	6.14	701
72	6.24	735
73	6.79	709
74	7.33	733
75	6.13	755
76	6.58	599
77	7.36	667
78	7.29	693
79	7.52	703
80	6.88	704
81	6.78	613
82	8.34	703
84	7.74	683
85	7.64	707
86	7.59	739
87	7.79	717
88	7.25	718
89	7.99	772
90	4.73	545
91	5.07	541
92	5.61	709
93	7.33	725

D. Pharmacological example

Example D.1 : Binding experiment for h-NK_1, h-NK_2 and h-NK_3 receptors

The compounds according to the invention were investigated for interaction with various neurotransmitter receptors, ion channels and transporter binding sites using the radioligand binding technique. Membranes from tissue homogenates or from cells, expressing the receptor or transporter of interests, were incubated with a radioactively labelled substance ([^{3}H]- or [^{125}I] ligand) to label a particular receptor. Specific receptor binding of the radioligand was distinguished from the non-specific membrane labelling by selectively inhibiting the receptor labelling with an unlabelled drug (the blank), known to compete with the radioligand for binding to the receptor sites. Following incubation, labelled membranes were harvested and rinsed with excessive cold buffer to remove non-bound radioactivity by rapid filtration under suction. Membrane bound radioactivity was counted in a scintillation counter and results were expressed in counts per minute (cpm).

The compounds were dissolved in DMSO and tested at 10 concentrations ranging from 10^{-10} to 10^{-5} M.

The ability of the compounds according to the invention to displace [^{3}H]-Substance P from cloned human h-NK_1 receptors expressed in CHO cells, to displace [^{3}H]-SR-48968 from cloned human h-NK_2 receptors expressed in Sf9 cells, and to displace [^{3}H]-SR-142801 from cloned human h-NK_3 receptors expressed in CHO cells was evaluated.

The receptor binding values (pIC_{50}) for the h-NK_1 ranges for all compounds according to the invention between 10 and 6.

Example D.2 : Signal transduction (ST)

This test evaluates in vitro functional NK_1 antagonistic activity. For the measurements of intracellular Ca^{++} concentrations the cells were grown on 96-well (black wall/transparent bottom) plates from Costar for 2 days until they reached confluence. The cells were loaded with 2 µM Fluo3 in DMEM containing 0.1% BSA and 2.5 mM probenecid for 1 h at 37°C. They were washed 3x with a Krebs buffer (140 mM NaCl, 1 mM $MgCl_2x6H_2O$, 5 mM KCl, 10 mM glucose, 5 mM HEPES; 1.25 mM $CaCl_2$; pH

7.4) containing 2.5 mM probenecid and 0.1 % BSA (Ca^{++}-buffer). The cells were preincubated with a concentration range of antagonists for 20 min at RT and Ca^{++}-signals after addition of the agonists were measured in a Fluorescence Image Plate Reader (FLIPR from Molecular Devices, Crawley, England). The peak of the Ca^{++}-transient was considered as the relevant signal and the mean values of corresponding wells were analysed as described below.

The sigmoidal dose response curves were analysed by computerised curve-fitting, using the GraphPad Program. The EC_{50}-value of a compound is the effective dose showing 50 % of maximal effect. For mean curves the response to the agonist with the highest potency was normalised to 100 %. For antagonist responses the IC_{50}-value was calculated using non-linear regression.

The pIC_{50} data for the signal transduction testing for a representative selection of compounds are presented in Table 6. The last colums indicates - without being limited thereto - for which use the compounds might be most suitable. Ofcourse, since for some neurokinin receptors no data was determined, it is obvious that these compounds might be attributed to another suitable use.

Table 6 : Pharmacological data for the signal transduction for selected compounds. (n.d.= not determined)

Comp. No.	NK_1 pIC_{50}	NK_2 pIC_{50}	NK_3 pIC_{50}	Suitable for
40	6.46	n.d.	n.d.	NK1
3	6.46	n.d.	<5	NK1
12	6.50	n.d.	n.d.	NK1
52	6.50	5.63	~5.01	NK1
8	6.52	n.d.	<5	NK1
19	6.54	<5	5.1	NK1
37	6.56	5.05	5.15	NK1
4	6.60	n.d.	<5	NK1
18	6.64	<5	<5	NK1

Comp. No.	NK_1 pIC_{50}	NK_2 pIC_{50}	NK_3 pIC_{50}	Suitable for
46	6.64	n.d.	n.d.	NK1
33	6.65	n.d.	n.d.	NK1
66	6.67	n.d.	5.17	NK1
34	6.68	n.d.	n.d.	NK1
5	6.68	n.d.	<5	NK1
47	6.69	n.d.	n.d.	NK1
81	6.70	n.d.	<5	NK1
15	6.72	~5.5	~5.11	NK1
60	6.74	<5	<5	NK1
7	6.76	n.d.	<5	NK1
41	6.78	n.d.	n.d.	NK1
76	6.83	<5	<5	NK1
16	6.86	n.d.	n.d.	NK1
43	6.91	n.d.	n.d.	NK1
51	6.92	n.d.	n.d.	NK1
64	6.93	<5	<5	NK1
87	6.94	n.d.	<5	NK1
65	6.98	<5	<5	NK1
62	7.00	5.14	<5	NK1
20	7.03	<5	<5	NK1
32	7.04	n.d.	5.41	NK1
50	7.04	n.d.	n.d.	NK1
44	7.06	n.d.	n.d.	NK1
84	7.06	n.d.	<5	NK1
17	7.07	5.14	5.28	NK1
53	7.07	n.d.	n.d.	NK1
67	7.12	n.d.	<5	NK1
61	7.13	<5	<5	NK1
63	7.15	<5	<5	NK1
86	7.17	n.d.	4.99	NK1

Comp. No.	NK_1 pIC_{50}	NK_2 pIC_{50}	NK_3 pIC_{50}	Suitable for
85	7.19	n.d.	<5	NK1
88	7.21	n.d.	<5	NK1
89	7.22	n.d.	5.45	NK1
74	7.25	n.d.	~5.45	NK1
11	7.3	5.13	~5.1	NK1
36	7.33	n.d.	n.d.	NK1
77	7.37	5.1	5.54	NK1
73	7.38	n.d.	<5	NK1
93	7.4	5.11	5.37	NK1
69	7.4	n.d.	5.22	NK1
78	7.44	5.05	5.6	NK1
79	7.5	5.04	5.14	NK1
72	7.5	n.d.	<5	NK1
80	7.52	5.09	<5	NK1
48	7.59	<5	n.d.	NK1
70	7.59	n.d.	<5	NK1
57	7.64	n.d.	5.61	NK1
75	7.8	n.d.	5.22	NK1
68	7.88	n.d.	5.18	NK1
13	7.88	n.d.	5.60	NK1
59	7.97	n.d.	5.02	NK1
58	8.06	n.d.	<5	NK1
92	7.62	5.17	6.06	NK1/NK3
56	7.91	5.33	6.16	NK1/NK3

E. Composition examples

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof.

Example E.1 : ORAL DROPS

500 Grams of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 grams of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I. The resulting solution was filled into suitable containers.

Example E.2 : ORAL SOLUTION

9 Grams of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 grams of 2,3-dihydroxybutanedioic acid and thereafter 20 grams of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 Grams of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example E.3 : FILM-COATED TABLETS

Preparation of tablet core

A mixture of 100 grams of the A.I., 570 grams lactose and 200 grams starch was mixed well and thereafter humidified with a solution of 5 grams sodium dodecyl sulfate and 10 grams polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 grams microcrystalline cellulose and 15 grams hydrogenated vegetable oil. The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

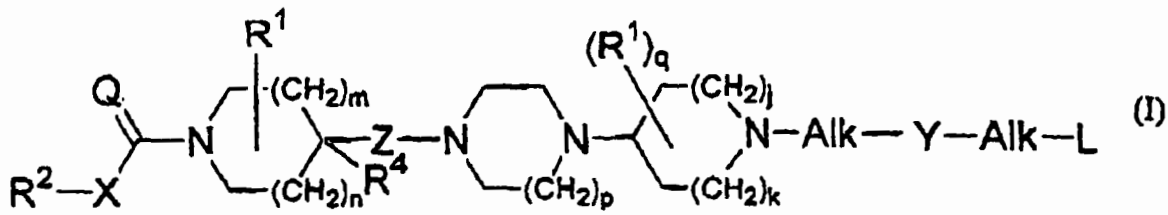
To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 grams of magnesium octadecanoate, 5 grams of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example E.4 : INJECTABLE SOLUTION

1.8 Grams methyl 4-hydroxybenzoate and 0.2 grams propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 grams lactic acid, 0.05 grams propylene glycol and 4 grams of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l, giving a solution comprising 4 mg/ml of A.I.. The solution was sterilized by filtration and filled in sterile containers.

Claims

1. A compound according to the general Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, and the *N*-oxide form thereof wherein :

n is an integer, equal to 1 ;
m is an integer, equal to 1;
each R^1 independently from each other, is selected from the group of Ar^1, Ar^1-alkyl and di(Ar^1)-alkyl ;
R^4 is selected from the group of hydrogen, hydroxy and alkyloxy ;
Z is a bivalent radical $-(CH_2)_r-$, wherein r is an integer equal to 1, 2, 3, 4 or 5 and wherein one radical $-CH_2-$ is optionally replaced by a >C=O radical ; or
R^4 and Z are taken together to form a trivalent radical $=CH-(CH_2)_{r-1}-$, wherein r is an integer equal to 2, 3, 4 or 5 and wherein one radical $-CH_2-$ is optionally replaced by a >C=O radical ;
p is an integer, equal to 1 ;
Q is O Or NR^3 ;
X is a covalent bond or a bivalent radical of formula -O-, -S- or $-NR^3-$;
each R^3 independently from each other, is hydrogen or alkyl ;
R^2 is alkyl, Ar^2, Ar^2-alkyl, Het^1 or Het^1-alkyl ;
q is an integer equal to 0 or 1 ;
j is an integer, equal to 1 ;
k is an integer, equal to 0 or 1 ;
Y is a covalent bond or a bivalent radical of formula >C(=O) or $-SO_2-$;
each Alk represents, independently from each other, a covalent bond ; a bivalent straight or branched, saturated or unsaturated hydrocarbon radical having from 1 to 6 carbon atoms ; or a cyclic saturated or unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; each radical optionally substituted on one or more carbon atoms with one or more alkyl, phenyl, halo, cyano, hydroxy, formyl and amino radicals ;
L is selected from the group of hydrogen, alkyl, alkyloxy, Ar^3-oxy, alkyloxycarbonyl, mono- and di(alkyl)amino, mono- and di(Ar^3)amino, mono- and di(alkyloxycarbonyl)amino, Ar^3, Ar^3-carbonyl, Het^2 and Het^2-carbonyl ;
Ar^1 is phenyl, optionally substituted with 1, 2 or 3 substituents each independently from each other selected from the group of halo, alkyl, cyano, aminocarbonyl and alkyloxy ;
Ar^2 is naphthalenyl or phenyl, each optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of halo, nitro, amino, mono- and di(alkyl)amino, cyano, alkyl, hydroxy, alkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl and mono- and di(alkyl)aminocarbonyl ;
Ar^3 is naphthalenyl or phenyl, optionally substituted with 1, 2 or 3 substituents each independently from each other selected from the group of alkyloxy, alkyl, halo, hydroxy, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*] pyridinyl, morpholinylcarbonyl, pyrrolidinylearbonyl, amino and cyano;
Het^1 is a monocyclic heterocyclic radical selected from the group of pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl ; or a bicyclic heterocyclic radical selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of halo and alkyl ;
Het^2 is a monocyclic heterocyclic radical selected from the group of pyrrolidinyl, dioxolyl, imidazolidinyl, pyrrazolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 2H-

pyrrolyl, pyrrolinyl, imidazolinyl, pyrrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl ; or a bicyclic heterocyclic radical selected from the group of benzopiperidinyl, quinolinyl, quinoxalinyl, indolyl, isoindolyl, chromenyl, benzimidazolyl, imidazo[1,2-a]pyridinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of Ar^1, Ar^1alkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo, alkyloxy, alkyloxyalkyl and alkyloxycarbonyl ; and
alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms ; optionally substituted on one or more carbon atoms with one or more radicals selected from the group of phenyl, halo, cyano, oxo, hydroxy, formyl and amino radicals.

2. A compound according to claim 1, **characterized in that** R^1 is Ar^1 methyl and attached to the 2-position or R^1 is Ar^1 and attached to the 3-position.

3. A compound according to any one of claims 1 to 2, **characterized in that** the R^2-X-C(=Q)- moiety is 3,5-di-(trifluoromethyl) phenylcarbonyl.

4. A compound according to any one of claims I to 3, **characterized in that** Z is selected from the group of $-CH_2-$, $>C=O$, $-CH_2CH_2-$ and $-CH_2C(=O)-$ or **characterized in that** Z and R^4 are taken together to form the trivalent radical $=CH-C(=O)-$.

5. A compound according to any one of claims 1 to 4, **characterized in that** R^4 is selected from the group of hydrogen, hydroxy and methoxy.

6. A compound according to any one of claims 1 to 5, **characterized in that** Alk is a covalent bond, $-CH_2-$, $CH(CH_3)-$, -CH(phenyl)-, $-CH_2CH$(phenyl)- or $-CH_2CH=H-$.

7. A compound according to any one of claims 1 to 6, **characterized in that** L is selected from the group of hydrogen, alkyl, alkyloxy, Ar^3-oxy, mono- and di(Ar^3)amino, Ar^3, Het^2 and Het^2carbonyl and Ar^3 and Het^2 are defined as in Formula(I).

8. A compound according to any one of claims 1 to 7, **characterized in that**

n is an integer, equal to 1 ;
m is an integer, equal to 1 ;
R^1 is Ar^1-alkyl ;
R^4 is selected from the group of hydrogen, hydroxy or alkyloxy ;
Z is a bivalent radical $-(CH_2)_r-$, wherein r is 1 or 2 and wherein one radical $-CH_2-$ is optionally replaced by a $>C=O$ radical ; or
R^4 and Z are taken together to form a trivalent radical $=CH-(CH_2)_{r-1}$, wherein r is 2 and wherein one radical $-CH_2-$ is replaced by a $>C=O$ radical ;
p is an integer, equal to 1 ;
Q is O;
X is a covalent bond;
R^2 is Ar^2 ;
q is an integer, equal to 0 ;
j is an integer, equal to 1 ;
k is an integer, equal to 0 or 1 ;
Y is a covalent bond or a bivalent radical of formula $>C(=O)$ or $-SO_2-$
each Alk represents, independently from each other, a covalent bond ; a bivalent straight or branched, saturated or unsaturated hydrocarbon radical having from I to 6 carbon atoms ; each radical optionally substituted on one or more carbon atoms with a phenyl radical ;
L is selected from the group of hydrogen, alkyl, alkyloxy, Ar^3-oxy, mono- and di(Ar^3)amino, Ar^3, Het^2 and Het^2carbonyl;
Ar^1 is phenyl ;
Ar^2 is phenyl, optionally substituted with 2 alkyl substituents ;
Ar^3 is phenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other selected from the group of alkyloxy, alkyl, halo and hydroxy ;

Het^2 is a monocyclic heterocyclic radical selected from the group of tetrahydrofuranyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, isoxazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl ; or a bicyclic heterocyclic radical selected from the group of quinolinyl, indolyl, chromenyl and benzimidazolyl ; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of Ar^1, halo, alkyl and oxo ; and
alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms.

9. A compound according to any one of claims 1 to 8 for use as a medicine.

10. The use of a compound according to any one of claims 1 to 8 for the manufacture of a medicament for treating neurokinin mediated conditions.

11. The use of a compound according to claim 10 for the manufacture of a medicament for the treatment and/or prophylaxis of schizophrenia, emesis, anxiety and depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pre-eclampsia, nociception, pain, in particular visceral and neuropathic pain, pancreatitis, neurogenic inflammation, asthma, chronic obstructive pulmonary disease (COPD) and micturition disorders such as urinary incontinence.

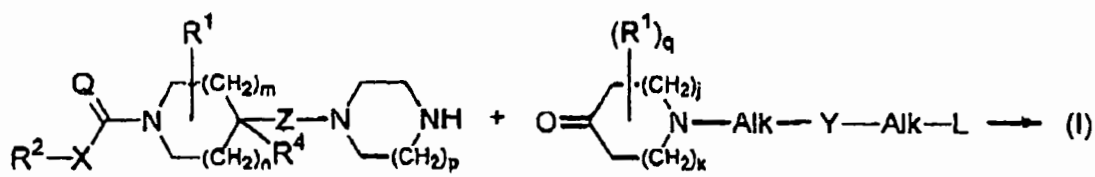
12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to any one of claims 1 to 8.

13. A pharmaceutical composition according to claim 12, **characterized in that** it is in a form suitable to be orally administered.

14. A process for the preparation of a pharmaceutical composition according to any one of claims 12 to 13, **characterized in that** a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8.

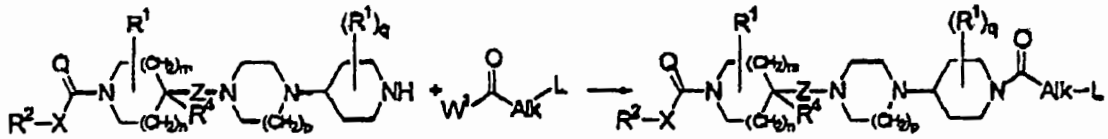
15. A process for the preparation of a compound according to Formula (I), more specifically according to Formula (I^a), Formula (I^b) or Formula (I^c), **characterized in that**

a) a final compound according to Formula (I) is obtained by reductive *N*-alkylation of an intermediate according to Formula (II) wherein wherein R^1, R^2, R^4, X, Q, m, n, p and Z are defined as in Formula (I), with a *N*-substituted piperidinon of Formula (III) wherein R^1, Alk, Y, L, J, k and q are defined as in Formula (I), in a reaction-inert solvent and in the presence of a reducing agent ; or



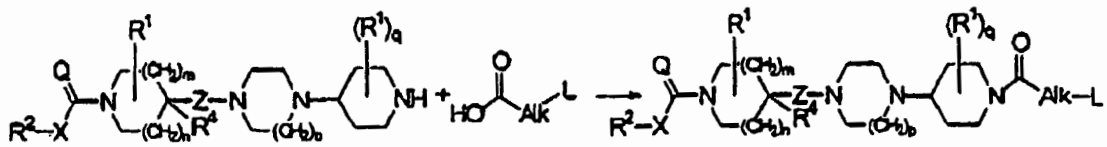
(II) (III)

b) a final compound according to Formula (I^a) is obtained by reacting of a final compound of Formula (I') wherein R^1, R^2, R^4, X, Q, Z, m, n, p and q are defined as in Formula (I), with an acyl compound of Formula (V) wherein Alk and L are defined as in Formula (I) and W^1 is a leaving group, in a reaction-inert solvent and in the presence of a base ; or



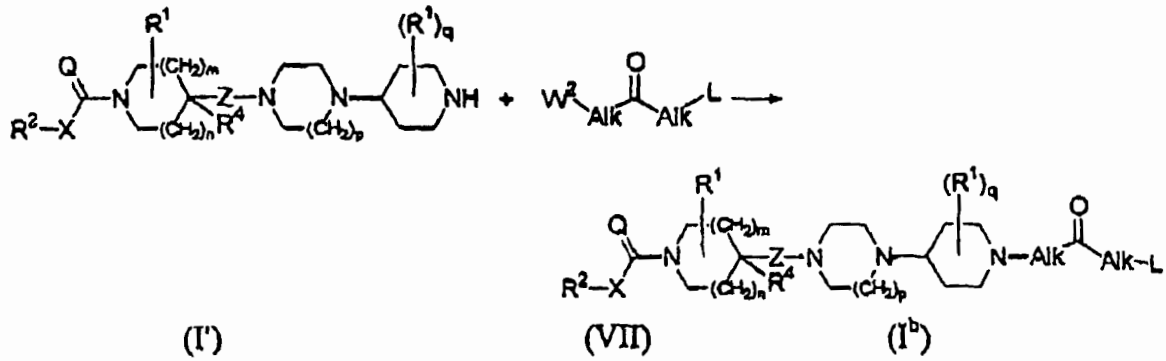
(I') (V) (I[a])

c) a final compound according to Formula (I[a]) is obtained by a base-catalyzed nucleophilic addition reaction of a final compound of Formula (I') wherein R^1, R^2, R^4, X, Q, Z, m, n, p and q are defined as in Formula (I), with a carboxylic acid of Formula (VI) wherein Alk and L are defined as in Formula (I), in a reaction-inert solvent and in the presence of a base; or



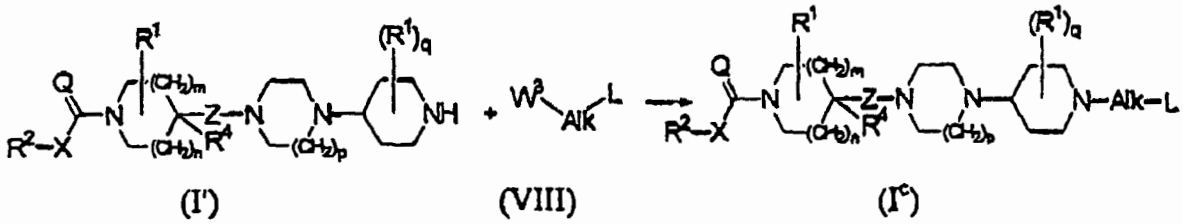
(I') (VI) (I[a])

d) a final compound according to Formula (I[b]) is obtained by a base-catalyzed nucleophilic addition reaction of a final compound of Formula (I') wherein R^1, R^2, R^4, X, Q, Z, m, n, p and q are defined as in Formula (I), with a keto-compound of Formula (VII) wherein Alk and L are defined as in Formula (I) and W^2 is a leaving group, in a reaction-inert solvent and in the presence of a base ; or



(I') (VII) (I[b])

e) a final compound according to Formula (1˚) is obtained by reductive amination/alkylation of a final compound of Formula (I') wherein R^1, R^2, X, Q, m, n, p and q are defined as in Formula (I) with a compound of Formula (VIII) wherein Alk and L are defined as in Formula (I) and W^3 is a leaving group, in a reaction-inert solvent and in the presence of a base ; or



(I') (VIII) (I^c)

f) a final compound according to Formula (I) is obtained by converting compounds according to Formula (I) into each other following art-known transformation reactions ; and further, optionally converting compounds according to Formula (I) into an acid addition salt by treatment with an acid, or into a base addition salt by treatment with a base, or conversely, the acid addition salt form may be converted into the free base by treatment with alkali, or the base addition salt may be converted into the free acid by treatment with an acid ; and by preparing the *N*-oxide and/or stereochemically isomeric forms thereof.