SUBSTITUTED 1-PIPERIDIN-3-YL-4-PIPERIDIN-4-YL-PIPERAZINE DERIVATIVES AND THEIR USE AS NEUROKININ ANTAGONISTS

Field of the Invention

This invention concerns substituted 1-piperidin-3-yl-4-piperidin-4-yl-piperazine derivatives having neurokinin antagonistic activity, in particular NK_1 antagonistic activity, a combined NK_1/NK_3 antagonistic activity and a combined $NK_1/NK_2/NK_3$ antagonistic activity, their preparation, compositions comprising them and their use as a medicine, in particular for the treatment of schizophrenia, emesis, anxiety and depression, irritable bowel syndrom (IBS), circadian rhythm disturbances, visceral pain, neurogenic inflammation, asthma, micturition disorders such as urinary incontinence and nociception.

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 (NK_A) and Neurokinin B (NK_B) with preferential affinity for three distinct 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 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 neurotransmission 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.

Irritable bowel syndrome (IBS)

Patients with irritable bowel syndrome (IBS) experience impaired quality of life, and utilise health care resources extensively as they seek better "solutions" (including unnecessary repeated investigations or even surgery). Although these patients suffer from a 'benign' disorder (in other words, they will never die or develop significant complications), they nevertheless cause a significant economic burden by extensive health care resource utilisation, and absence from work.

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.

Background prior art

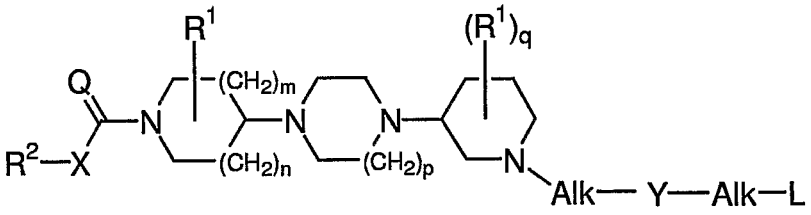
Compounds containing the 1-piperidin-4-yl-piperazinyl moiety were published in WO 97/16440-A1, published May 9, 1997 by Janssen Pharmaceutica N.V. for use as substance P antagonists, in WO 02/32867, published April 25, 2002 by Glaxo Group Ltd. for their special advantages as neurokinin antagonists (more 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 moiety, being a substituted piperidinyl moiety as well as in their improved ability as potent, orally and centrally active neurokinin

antagonists with therapeutic value, especially for the treatment of schizophrenia, emesis, anxiety and depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, visceral pain, neurogenic inflammation, asthma, micturition disorders such as urinary incontinence and nociception.

Description of the Invention

The present invention relates to novel substituted 1-piperidin-3-yl-4-piperidin-4-yl-piperazine 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 :

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 ;
p	is an integer equal to 1 or 2 ;
q	is an integer equal to 0 or 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 ;
each R^1	independently from each other, is selected from the group of Ar^1, Ar^1-alkyl and di(Ar^1)-alkyl ;
R^2	is Ar^2, Ar^2-alkyl, di(Ar^2)alkyl, Het^1 or Het^1-alkyl ;
Y	is a covalent bond or a bivalent radical of formula -C(=O)-,-SO_2-, >C=CH-R or >C=N-R, wherein R is CN or nitro ;
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

phenyl, halo, cyano, hydroxy, formyl and amino radicals ;

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

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, Ar^1carbonyloxycarbonyl, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and cyano ;

Het^1 is a monocyclic heterocyclic radical selected from the the group of pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, 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, benzothienyl and 4a,8a-dihydro-2*H*-chromenyl ; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of halo, oxo and alkyl ;

Het^2 is a monocyclic heterocyclic radical selected from the group of tetrahydrofuranyl, 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, benzothienyl, benzo

[2,1,3]oxadiazolyl, imidazo[2,1-b]thiazolyl , 2,3-dihydrobenzo[1,4]dioxyl and octahydrobenzo[1,4]dioxyl ;
each radical may optionally be substituted with one or more radicals selected from the group of Ar^1, Ar^1alkyl, Ar^1alkyloxyalkyl, halo, hydroxy, alkyl, alkylcarbonyl, alkyloxy, alkyloxyalkyl, alkyloxycarbonyl, piperidinyl, pyridinyl, pyrrolyl, thienyl, oxo and oxazolyl ; 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.

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 :

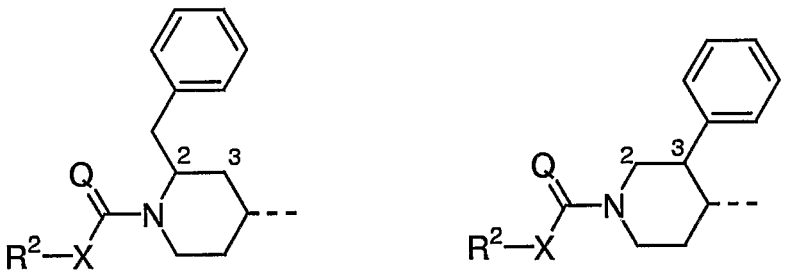
n is 1 ;
m is 1 ;
p is 1 ;
q is 0 ;
Q is O ;
X is a covalent bond ;
each R^1 is Ar^1 or Ar^1-alkyl ;
R^2 is Ar^2 ;
Y is a covalent bond or a bivalent radical of formula -C(=O)-, -SO_2- or >C=CH-R or >C=N-R, wherein R is CN or nitro ;
each Alk represents, independently from each other, a covalent bond ; a bivalent straight or branched, saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; each radical optionally substituted on one or more carbon atoms with one or more hydroxy radicals ;
L is selected from the group of hydrogen, alkyl, alkyloxy, alkylcarbonyloxy, mono- and di(alkyl)amino, mono-and di(Ar^3)amino, Ar^3, Het^2 and Het^2carbonyl ;
Ar^1 is phenyl ;
Ar^2 is phenyl, optionally substituted with 1, 2 or 3 alkyl radicals ;
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, hydroxy, Ar^1carbonyloxycarbonyl and cyano;

Het^2 is a heterocyclic radical selected from the group of tetrahydrofuranyl, pyrrolidinyl, imidazolyl, pyrazolyl, furanyl, thienyl, isoxazolyl, thiazolyl, thiadiazolyl, pyridinyl, pyrazinyl, benzo [2,1,3]oxadiazolyl and imidazo[2,1-b]thiazolyl ; each radical optionally substituted with one or more Ar^1alkyloxyalkyl, halo, alkyl, alkylcarbonyl, pyridinyl or oxazolyl radicals ; and

alkyl is a straight hydrocarbon radical having 1 to 6 carbon atoms, optionally substituted with one or more radicals selected from the group of halo and hydroxy;

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.



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 p is 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 Y is -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 Alk is a covalent bond.

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 Het^2.

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 compound is a compound selected from the group of compounds with compound number 25, 48, 79, 39, 15, 41, 64, 88, 50, 59 and 3, as mentioned in any one of Tables 1-2 further in this application.

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 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 will 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,

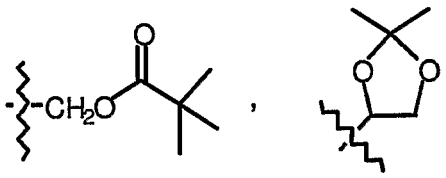
stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds 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, denoted by an asterisk in Tables 1 and 2.

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

Substance P and other neurokinins are involved in a variety of biological actions such as pain transmission (nociception), neurogenic inflammation, smooth muscle contraction, plasma protein extravasation, vasodilation, secretion, mast cell degranulation, and also in activation of the immune system. A number of diseases are deemed to be engendered by activation of neurokinin receptors, in particular the NK_1 receptor, by excessive release of substance P and other neurokinins in particular cells such as cells in the neuronal plexi of the gastrointestinal tract, unmyelinated primary sensory afferent neurons, sympathetic and parasympathetic neurons and nonneuronal cell types (DN&P **8(1)**:5-23 (1995) and Longmore J. *et al.*,"Neurokinin Receptors" *Pharmacological Reviews* **46(4)**:551-599 (1994)).

The compounds of the present invention are potent inhibitors of neurokinin-mediated effects, in particular those mediated via the NK_1, NK_2 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 ^3H-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 neurokinins by blocking the neurokinin receptors, and in particular by blocking the NK_1, NK_2 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.

More in particular, it has been found that some compounds exhibit NK_1 antagonistic activity, a combined NK_1/NK_3 antagonistic activity and a combined $NK_1/NK_2/NK_3$ antagonistic activity as can be seen from the Table 8 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 invention for the manufacture of a medicament for treating, either prophylactic or therapeutic or both, tachykinin mediated conditions.

The compounds according to the invention are useful in the treatment of CNS disorders, in particular schizoaffective disorders, depression, anxiety disorders, stress-related disorders, sleep disorders, cognitive disorders, personality 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 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; 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 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 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 as 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.

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 treating schizophrenia, emesis, anxiety, depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pain, neurogenic inflammation, asthma, micturition disorders such as urinary incontinence and nociception.

The present invention also relates to a method for the treatment and/or prophylaxis of tachykinin-mediated diseases, in particular for the treatment and/or prophylaxis of schizophrenia, emesis, anxiety, depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pain, neurogenic inflammation, asthma, micturition disorders such as urinary incontinence and nociception 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.

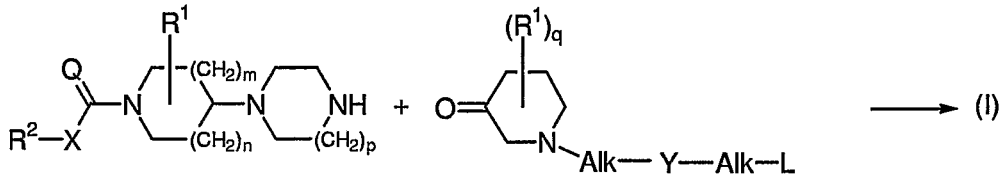
It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity 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, NK_1/NK_3 and $NK_1/NK_2/NK_3$-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 final compounds of Formula (I) are conveniently prepared by reductively *N*-alkylating an intermediate compound of Formula (II) with an intermediate compound of Formula (III) . 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 favour 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.

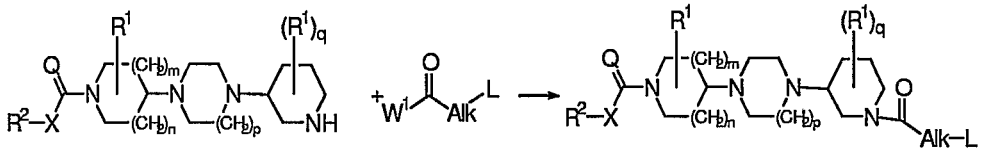


(II) (III)

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 advantageous is the preparation of a final compound according to Formula (I) according to the previously mentioned 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 final compound is pharmacologically active and can be converted into a final 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 final compound according to the invention can then be converted into other compounds according to Formula (I) by art-known transformations, e.g. acylation and alkylation.

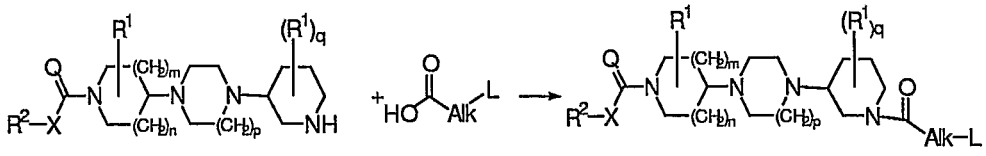
In particular, the final compounds of Formula (I^a) can be prepared by reacting a final compound of Formula (I') with an intermediate compound of Formula (V) wherein W^1 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzene-sulfonyloxy. The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane 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)

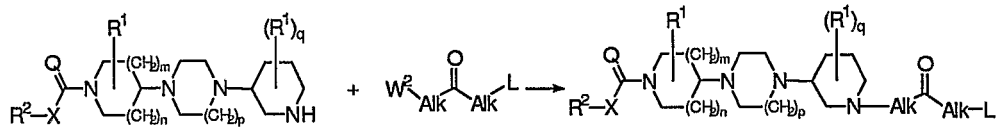
Alternatively, the final compounds of Formula (I^a) can also be prepared by reacting a final compound of Formula (I') with a carboxylic acid of Formula (VI). The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine and in the presence of an activator, such as e.g. DCC (dicyclohexylcarbodiimide), CDI (carbonyldiimidazol) and EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.HCl).

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') (VI) (I^a)

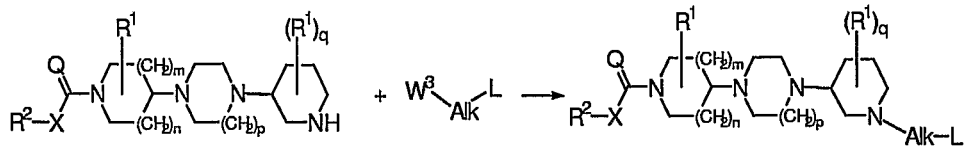
In particular, the final compounds of Formula (I^b) can be prepared by reacting a final compound of Formula (I') with a compound of Formula (VII) wherein W^2 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy 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 out at a temperature ranging between room temperature and reflux temperature.



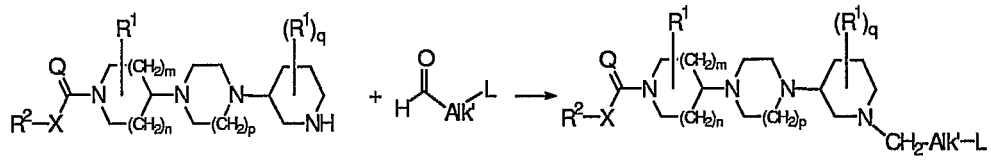
(I') (VII) (I^b)

The final compounds of Formula (I^c) and Formula (I^d) can be prepared either by reductive amination or alkylation of a final compound of Formula (I') with either a compound of Formula (VIII) or (IX) wherein W^3 in Formula (VIII) 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 and wherein $-CH_2-Alk'$ in Formula (I^d) is Alk. 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.



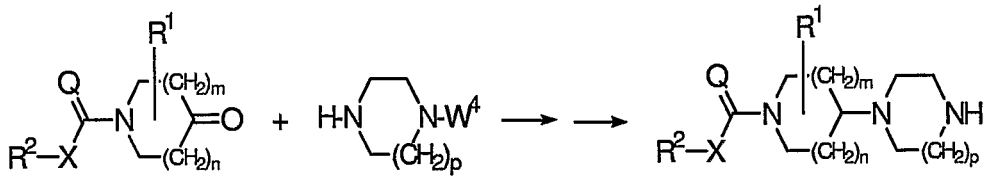
(I') (VIII) (I^c)



(I') (IX) (I^d)

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. For example, intermediate compounds of Formula (II) may be prepared by reductively *N*-alkylating an intermediate compound of Formula (XI) with an intermediate compound of Formula (XII) in which W^4 is a benzyl radical, after which the resulting compound is subsequently reduced to yield an intermediate compound according to Formula (II). Said reductive *N*-alkylation may be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol, 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)iso-propylate 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 favour 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.



(XI) (XII) (II)

The preparation of intermediate compounds (XI) and (XII) and other intermediates is described 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.

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

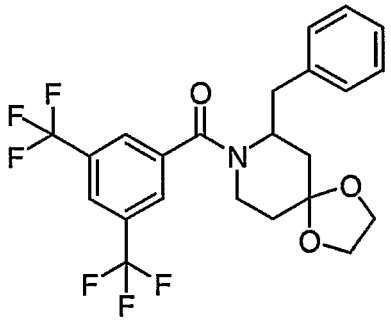
Experimental Part

Hereinafter "RT" means room temperature, "THF" means tetrahydrofuran, "DIPE" means diisopropylether, "DCM" means dichloromethane, "DMF" means *N,N*-dimethylformamide, "MIK" means methyl isobutyl keton, "EDCI" means 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide. and "HOBT" means 1-Hydroxy-1*H*-benzotriazole.

A. Preparation of the intermediate compounds

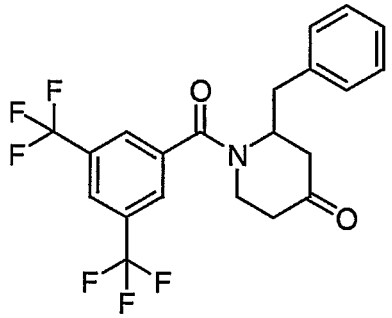
Example A1

a. Preparation of intermediate compound 1



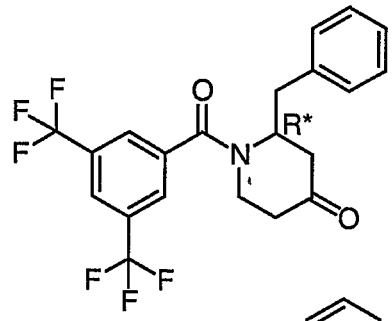
Et_3N (0.55 mol) was added to a stirring mixture of 7-(phenylmethyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.5 mol) in toluene (1500ml). 3,5-Bis(trifluoromethyl)benzoyl chloride (0.5 mol) was added over a 1-hour period (exothermic reaction). The mixture was stirred at room temperature for 2 hours, then allowed to stand for the weekend and washed three times with water (500 ml, 2x250 ml). The organic layer was separated, dried, filtered and the solvent was evaporated. Yield: 245 g (100%). Part of this fraction was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 1.06 g of intermediate compound 1.

b1. Preparation of intermediate compound 2

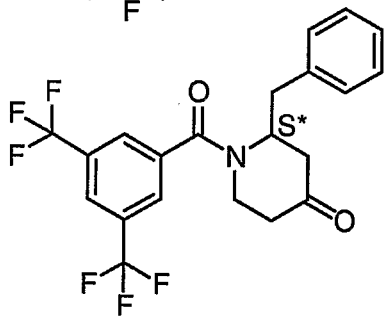


HCl cp (300 ml) was added to a mixture of intermediate compound 1 (0.5 mol) in ethanol (300 ml) and H_2O (300 ml). The reaction mixture was stirred at 60°C for 20 hours. The precipitate was filtered off, ground, stirred in H_2O, filtered off, washed with petroleum ether and dried. Yield: 192 g of intermediate compound 2 ((+-)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinone) (89.4%) (mixture of R and S enantiomers).

b2. Preparation of intermediate compound 9 and intermediate compound 10.



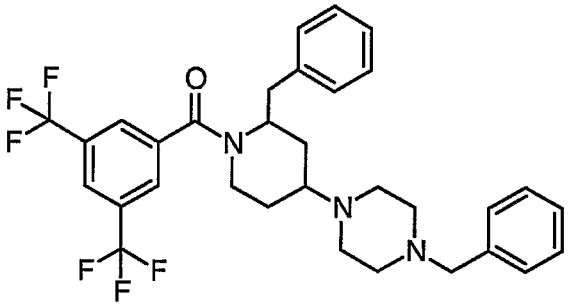
(9)



(10)

Intermediate compound 2 was separated into its optical isomers by chiral column chromatography over Chiralpak (CHIRALPAK AS 1000 Å 20 mm (DAICEL); eluent: hexane/2-propanol 70/30). Two product fractions were collected and each solvent was evaporated. Yield Fraction 1: 32.6 g of intermediate compound 9 (R) and Fraction 2: 30.4 g of intermediate compound 10 (S).

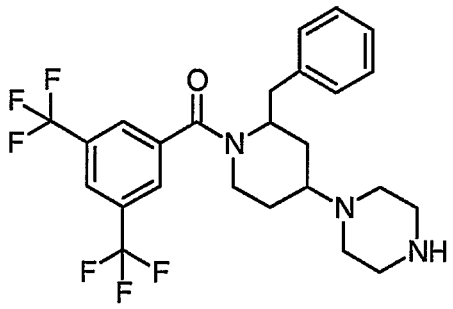
c. Preparation of intermediate compound 3



A mixture of intermediate compound 2 (0.046 mol), 1-(phenylmethyl)piperazine (0.051 mol) and Ti-tetraisopropyloxide (0.056 mol) was stirred for 2 hours at 40°C. The reaction mixture was cooled to room temperature. Ethanol, p.a. (350 ml) was added. $NaBH_4$ (0.138 mol) was added. The resulting reaction mixture was stirred for one hour at room temperature, then for one hour at 50°C. More $NaBH_4$ (5.2 g) was added and the reaction mixture was stirred for 2 hours at 50°C. Again, $NaBH_4$ was added and the reaction mixture was stirred overnight at room temperature, then for 2 hours at 50°C. Water (10 ml) was added. The mixture was stirred for 15 min. CH_2Cl_2 (200 ml) was added and the mixture was stirred for 15 min. The organic phase was separated, dried

($MgSO_4$), dicalite was added, the mixture was filtered over dicalite, and the filtrate was evaporated. This fraction was separated into (CIS) and (TRANS) by column chromatography over silica gel. The desired (TRANS)-fractions were collected and the solvent was evaporated, giving 14.8 g of residue ((I), 1.06% (CIS)) and 4.9 g of residue ((II), 6% (CIS)). Resolution and purification of those (TRANS)-fractions (± 20 g in total) was obtained by chromatography over stationary phase Chiralcel OD (1900Gr) in Prochrom LC110 35 bar (eluent: hexane/ethanol 90/10). The desired fractions were collected and the solvent was evaporated. Yield: 9.5 g of intermediate compound 3 (2R-trans)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-[4-(phenylmethyl)-1-piperazinyl]piperidine.

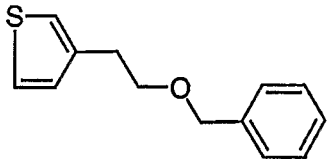
d. Preparation of intermediate compound 4



A solution of intermediate compound 3 (0.288 mol) in methanol (700 ml) was hydrogenated at 40°C with Pd/C, 10% (5 g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. Yielding 141.2 g of intermediate compound 4 (+)-(2R-trans)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-(1-piperazinyl)piperidine.

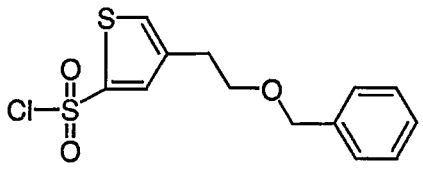
Example A2

a. Preparation of intermediate compound 5



NaH (0.086 mol) was added portionwise to a solution of 3-thiophene ethanol (0.078 mol) in THF at 5 °C under N_2 flow. The mixture was stirred for 1 hour at 5°C. Bu_4NI (0.001 mol) and (bromomethyl)benzene (0.080 mol) were added. The mixture was stirred at room temperature for 3 hours, taken up in H_2O and extracted with AcOEt. The organic layer was separated, dried ($MgSO_4$) and solvent was evaporated. The concentrate 1 (18 g) was purified by column chromatography over silica gel (gradient eluent: Cyclohexane/AcOEt 100/0 to 80/20). The pure fractions were collected and the solvent was evaporated. Yield: 9.9 g intermediate compound 5 (58 %).

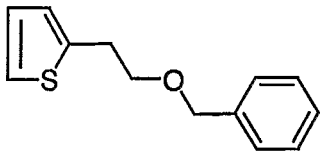
b. Preparation of intermediate compound 6



To a solution of intermediate compound 16 (0.023 mol) in THF (50 ml) at –50 °C, BuLi[1.6M] (0.025 mol) was added portionwise under N_2 flow. The temperature was raised slowly to 0°C. The mixture was stirred at 0 °C for 1 hour and cooled to –40°C. A solution of SO_2Cl_2 (0.046 mol) in pentane (50 ml) was added at –40°C. The mixture was stirred at –40°C for 1 hour. The concentrate was hydrolyzed, extracted with AcOEt, washed with a saturated solution of NaCl, dried over $MgSO_4$ and concentrated, providing 9 g. The concentrate was purified by column chromatography over silica gel (gradient eluent: Cyclohexane/AcOEt 100/0 to 80/20). Yield 1.2 g of intermediate compound 6 (16 %).

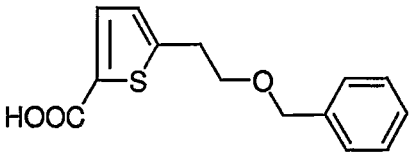
Example A3

a. Preparation of intermediate compound 7



NaH (60 % in oil) (0.086 mol, 3.4 g) was added portionwise to a solution of 2-(2-thienyl)ethanol (0.078 mol, 10 g) in THF (150 ml) under N_2 flow at 5°C. The mixture was stirred at 5°C during 1 hour. Tetrabutylammonium iodide (0.001 mol, 0.3 g) and then (bromomethyl)benzene (0.080 mol, 9.5 ml) were added to the solution. The mixture was stirred at room temperature during 3 hours, poured into water, extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. The crude product (18 g) was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/Cyclohexane 0/100 to 20/80) and the product fractions were concentrated. Yield: 11.4 g of intermediate compound 7 (66 %).

b. Preparation of intermediate compound 8



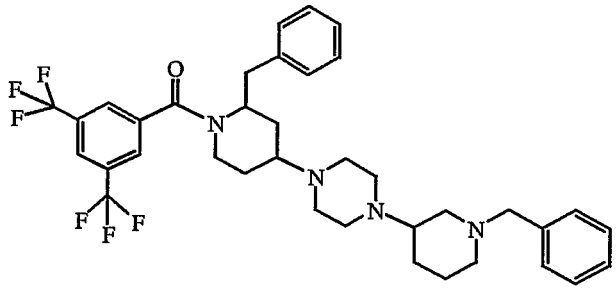
n-BuLi (1.6 M) (0.015 mol, 9.45 ml) was added slowly to a solution of intermediate compound 7 (0.014 mol, 3 g) in THF (30 ml) under N_2 flow at -40°C. The reaction was allowed to warm up slowly to 0°C and cooled to -70°C. Dry ice (~ 2 g) was added. The temperature was slowly allowed to rise to room temperature. NaOH (1 mol per liter, 30

ml) was added, the mixture was washed with diethyl ether. The aqueous layer was acidified with HCl (1N) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. Yield: 2.6 g of intermediate compound 8 (71%).

B. Preparation of the final compounds

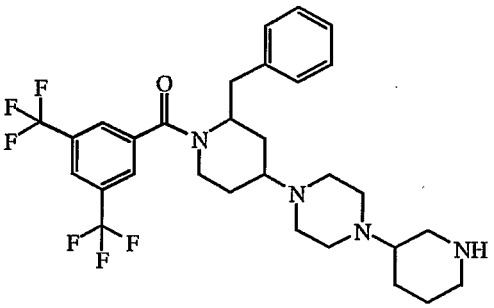
Example B1

a) Preparation of final compound 1



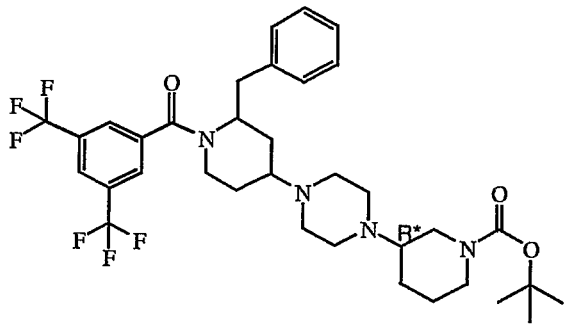
A mixture of intermediate compound 4 (0.005 mol), 1-(phenylmethyl)-3-piperidinone (0.005 mol) and potassium acetate in methanol (150 ml) was hydrogenated at 50°C with Pd/C 10% (1 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H_2 (1 equiv.), the catalyst was filtered off and the filtrate was concentrated. The residue was purified by flash column chromatography over silica gel (eluent : CH_2Cl_2/(MeOH/NH_3) 95/5). The product fractions were collected and the solvent was evaporated. Yield : 2.5 g of final compound 1 (74%).

b) Preparation of final compound 2

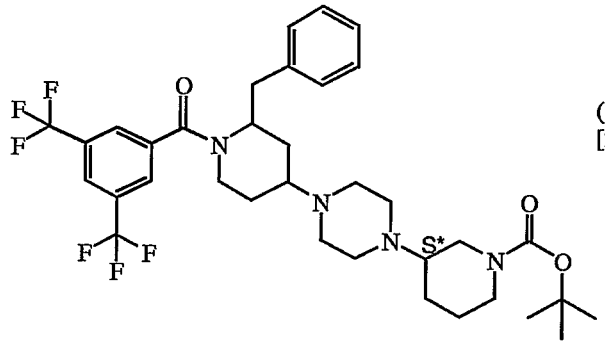


A solution of final compound 1 (prepared according to B1.a) (0.09 mol) in methanol (500 ml) was hydrogenated at 50°C with Pd/C 10% (5 g) as a catalyst. After uptake of H_2 (1 equiv.), the catalyst was filtered off and the filtrate was concentrated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/(MeOH/NH_3) 85/15). The product fractions were collected and the solvent was evaporated. Yield : 41.3 g of final compound 2 (78.7%).

c) Preparation of final compounds 105 and 71



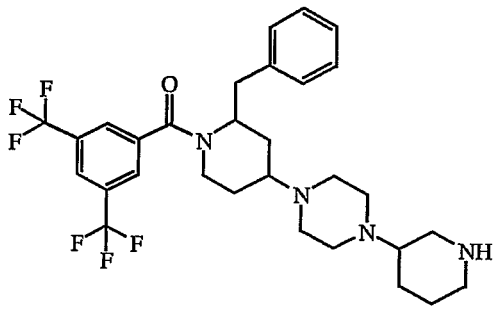
(105)
[2R-[2α,4β(R*)]]



(71)
[2R-[2α,4β(S*)]]

Bis(1,1-dimethylethyl)dicarbonic acid ester (0.008 mol) was added to a solution of final compound 2 (prepared according to B1.b) (0.007 mol) in CH_2Cl_2, p.a. (100 ml) and the reaction mixture was stirred for 6 hours at room temperature. The solvent was evaporated and the dry residue was filtered over silica gel (eluent: CH_2Cl_2/CH_3OH 95/5). The product fractions were collected and the solvent was evaporated. The obtained residue was separated by Chiral separation on AD column (eluent: hexane/EtOH 95/5). Two product fractions were collected and their solvent was evaporated. Each residue was purified on a glass filter (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10), then the desired products were collected and their solvent was evaporated. Yield fraction 1: 1.2 g of final compound 105 ([2R-[2α,4β(R*)]]). Yield fraction 2: 0.75 g of final compound 71 ([2R-[2α,4β(S*)]]).

d) Preparation of final compound 108

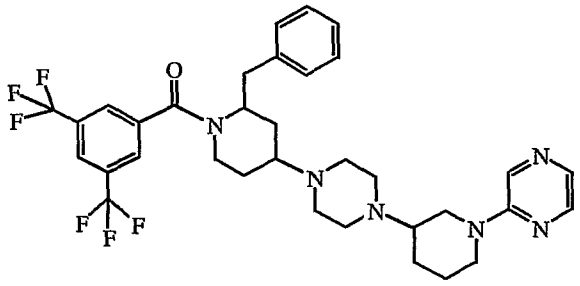


HCl/2-propanol (5 ml) was added to a solution of final compound 105 (prepared according to B1.c) (0.00175 mol) in 2-propanol (50 ml). The reaction mixture was

stirred and refluxed for 90 minutes. The solvent was evaporated and the residue was suspended in DIPE. The resulting precipitate was filtered off and taken up in H_2O. The mixture was alkalised with a NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), filtered off and the solvent was evaporated. Finally, the desired product was dried. Yield: 0.550 g of final compound 108 (54 %) (2R-[2α,4β(R*)]).

Example B2

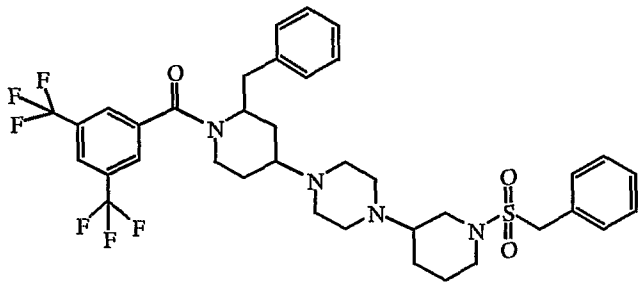
Preparation of final compound 26



Final compound 2 (prepared according to B1b) (0.007 mol) was dissolved in MIK (50 ml). Chloropyrazine (0.11 g) and Na_2CO_3 (0.5 g) were added. The mixture was stirred and refluxed for 44 hours, then washed with water, dried and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 90/10). The product fractions were collected and the solvent was evaporated. Yield: 54 mg of final compound 26.

Example B3

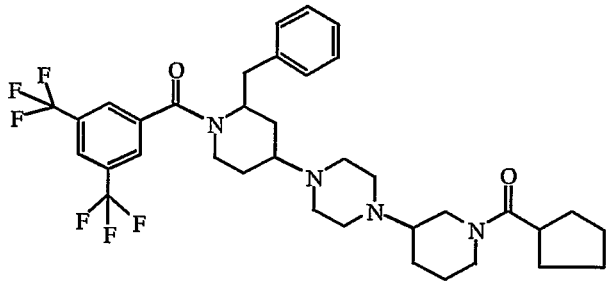
Preparation of final compound 49



Final compound 2 (prepared according to B1b) (0.0007 mol) was dissolved in CH_2Cl_2 (20 ml). Benzenemethanesulfonyl chloride (0.0008 mol) was added. The reaction mixture was stirred. Then Na_2CO_3 (0.5 g) was added and the mixture was stirred for 3 hours. The reaction mixture was purified by column chromatography over silicagel (eluent CH_2Cl_2/MeOH 95/5). The desired fractions were collected and the solvent evaporated. The residue was dried. Yield: 0.237 g of final compound 49.

Example B4

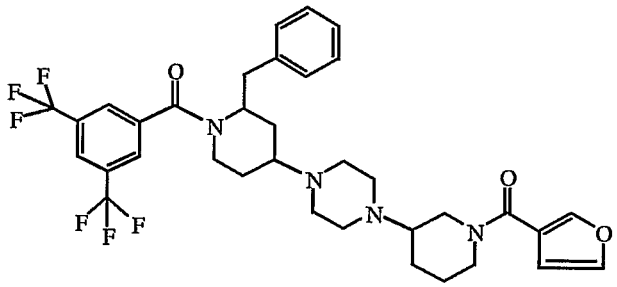
Preparation of final compound 41



Cyclopentanecarbonyl chloride (0.0008 mol) was added to a solution of final compound 2 (prepared according to B1.b) (0.0007 mol) in CH_2Cl_2 (20 ml) and the mixture was stirred, then Na_2CO_3 (0.005 mol) was added and the reaction mixture was stirred overnight at room temperature. The mixture was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10). The product fractions were collected, the solvent was evaporated and the residue was dried. Yield: 0.296 g of final compound 41.

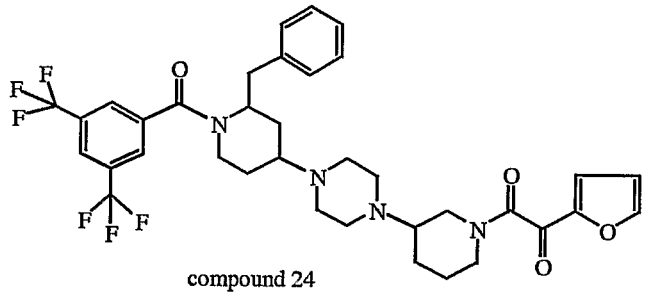
Example B5

Preparation of final compound 17

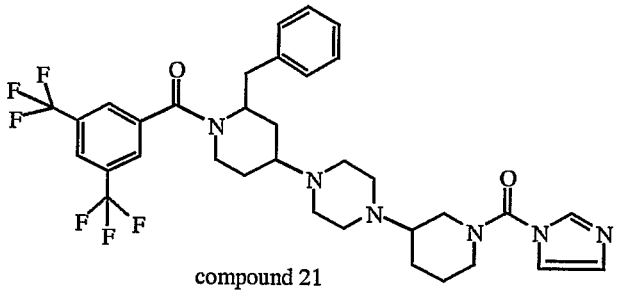


1,1'-Carbonylbis-1*H*-imidazole (0.0025 mol) was added to a solution of 3-furancarboxylic acid (0.0025 mol) in CH_2Cl_2 (50 ml) and the mixture was stirred for 2 hours at room temperature. Final compound 2 (prepared according to B1.b) (0.002 mol) was added and the reaction mixture was stirred for 18 hours at room temperature. The mixture was washed with a diluted NaOH solution and with water, dried and the solvent was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 98/2 - 90/10). The product fractions were collected, the solvent was evaporated and the residue was dried. Yield: 0.915 g of final compound 17.

Example B6
Preparation of final compound 24 and 21



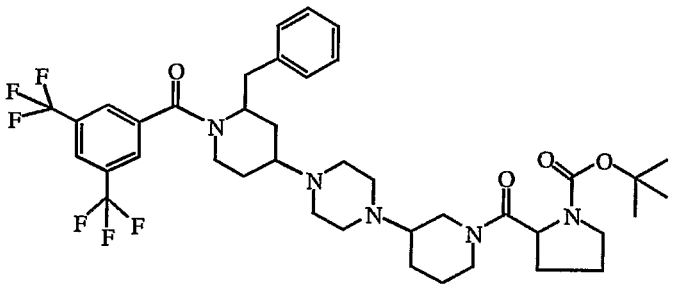
compound 24



compound 21

A mixture of α-oxo-2-furanacetic acid (0.001 mol) and 1,1'-carbonylbis-1*H*-imidazole (0.0011 mol) in CH_2Cl_2 (50 ml) was stirred for 4 hours at room temperature, then final compound 2 (prepared according to B1.b) (0.001 mol) was added and the reaction mixture was stirred overnight. The mixture was washed for 30 min. with a diluted NaOH solution and with water, dried and the solvent was evaporated. The residue was purified by column chromatography (gradient eluent: CH_2Cl_2/CH_3OH 98/2 - 90/10). Two product fractions were collected, their solvent was evaporated and each residue was dried. Yield fraction 1: 0.120 g of compound 24 and yield fraction 2: 0.147 g of compound 21.

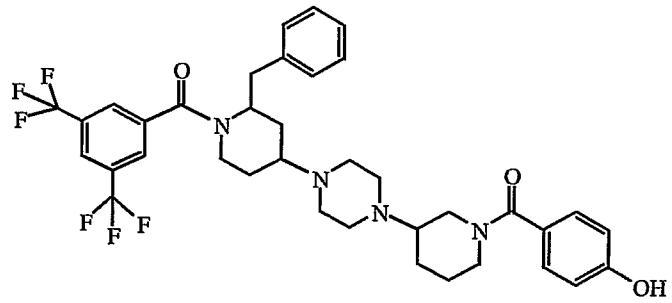
Example B7
Preparation of final compound 54



Et_3N (0.0051 mol) was added to a mixture of (2S)-1-(1,1-dimethylethyl)-1,2-pyrrolidinedicarboxylic acid ester (0.0028 mol), *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine (0.0038 mol) and final compound 2 (prepared according to B1.b) (0.0025 mol) in CH_2Cl_2, p.a. (50 ml). The reaction mixture was stirred at

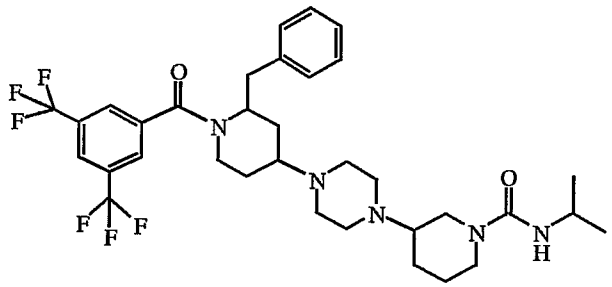
room temperature for 1.5 hours and was left to stand overnight. The solution was washed with NaOH (0.3N); the organic layer was separated, dried (MgSO4), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH from 100/0 to 90/10). The product fractions were collected, the solvent was evaporated and the residue was dried (vacuum) at 50°C for 2 days. Yield: 1.01 g of final compound 54 (52 %).

Example B8
Preparation of final compound 67



EDCI (0.001 mol) was added portionwise to a solution of final compound 2 (prepared according to B1.b) (0.001 mol), 4-hydroxybenzoic acid (0.001 mol), HOBT (0.001 mol) and Et_3N (0.001 mol) in CH_2Cl_2 (5ml). The mixture was stirred at room temperature for 8 hours then washed with H_2O. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (0.5g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 96/4/0.1). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.14 g of final compound 67 (23%).

Example B9
Preparation of final compound 66

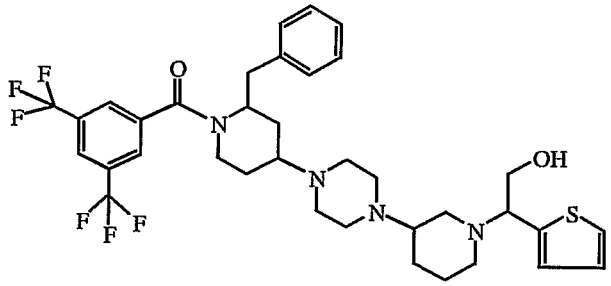


2-Isocyanatopropane (0.0007 mol) was added at room temperature to a mixture of final compound 2 (prepared according to B1.b) (0.0006 mol) in THF (5 ml). The mixture was stirred at room temperature for 2 hours. H_2O was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent

was evaporated. The residue (0.4 g) was purified by column chromatography over kromasil (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 95/5/0.1). The pure fractions were collected and the solvent was evaporated. Yield: 0.2 g of compound 66 (43%).

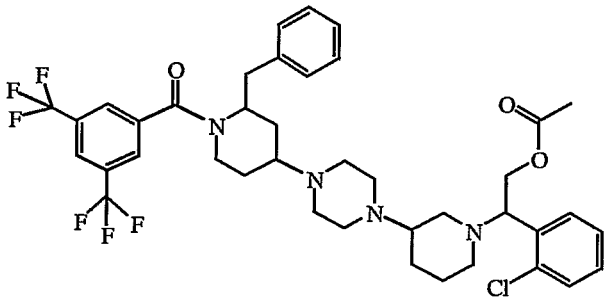
Example B10

a. Preparation of final compound 77



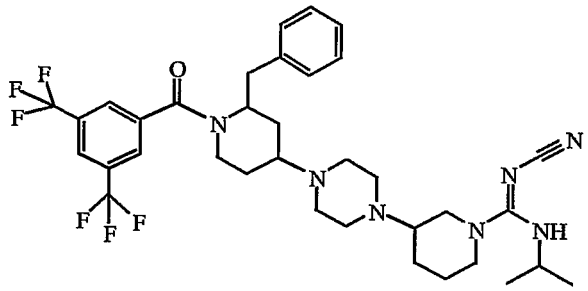
A mixture of final compound 2 (prepared according to B1.b) (0.001 mol), 2-thienylboronic acid (0.001 mol) and 1,4-dioxane-2,5-diol (0.001 mol) in ethanol (5 ml) was stirred at room temperature for 18 hours. The solvent was evaporated till dryness. The residue was dissolved in CH_2Cl_2. The organic layer was washed with K_2CO_3 10%, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.6 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.5). The pure fractions were collected and the solvent was evaporated. Yield: 0.13 g of final compound 77 (21%).

b. Preparation of final compound 124



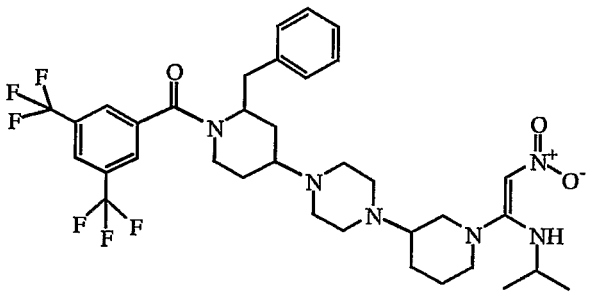
Acetic anhydride (0.003 ml , 0.301 mmol) was added to a mixture of final compound 89 (prepared according to B10.a) (0.185 g, 0.251 mmol) and dimethylaminopyridine (0.05 g , 0.376 mmol) in CH_2Cl_2 (2 ml) at room temperature. The mixture was stirred at room temperature for 1 hour, poured in K_2CO_3 10%, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/MeOH/NH_4OH$ 97/3/0.3). The pure fractions were collected and the solvent evaporated. Yield: 0.147 g of final compound 124 (75%).

Example B11
Preparation of final compound 91



A mixture of dimethyl-N-cyanodithioiminocarbonate (1 g; 6.8 mmol) and isopropylamine (0.6 ml; 6.8 mmol) in 10 ml of acetonitrile was heated under reflux for 5 hours. After cooling the solution to -10°C, final compound 2 (prepared according to B1.b) (3.87 g; 6.8mmol) and a 3N NaOH solution (2.3 ml; 6.8 mmol) were consecutively added. The mixture was stirred for 5 minutes and silver nitrate (1.16 g; 6.8 mmol) in acetonitrile (5 ml) was added dropwise. The reaction mixture was stirred at 0°C for 2 hours then at room temperature for 2 hours. The reaction mixture was filtered and the residue washed with acetonitrile. The solvent was evaporated and the residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 95/5/0.5). The pure fractions were collected and the solvent evaporated. Yield: 0.96 g of final compound 91 (21%).

Example B12
Preparation of final compound 103

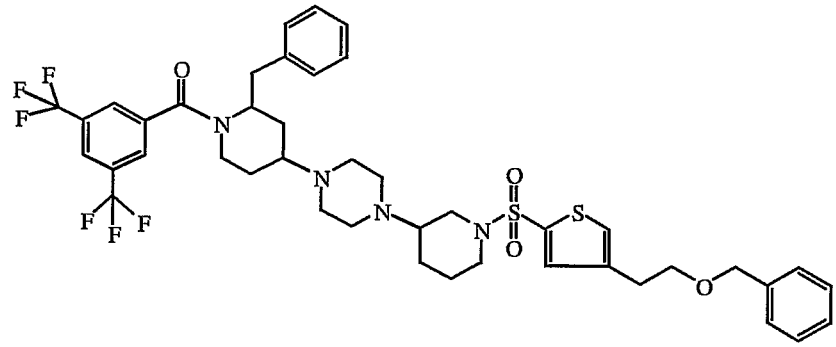


A mixture of 1,1-bis(methylthio)-2-nitroethylene (0.30 g; 1.8 mmol) and isopropylamine (0.16 ml; 1.8 mmol) in acetonitrile (5 ml) was heated under reflux overnight. After cooling the solution to -10°C, final compound 2 (prepared according to B1.b) (0.529 g; 0.9 mmol) and a 3N sodium hydroxide solution (0.9 ml; 0.9 mmol) were consecutively added. The mixture was stirred for 5 minutes and a solution of silver nitrate (0.16 g; 0.9 mmol) in acetonitrile (5 ml) was added dropwise.
The reaction mixture was stirred at 0°C for 2 hours then at room temperature overnight. The solution was filtered and the residue washed with acetonitrile. The solvent was evaporated and the residue was purified by column chromatography over silica gel

(Kromasil 10 µm, eluent: CH_2Cl_2/MeOH/NH_4OH 96/4/0.1). The pure fractions were collected and evaporated. Yield: 0.217 g of final compound 103 (34%).

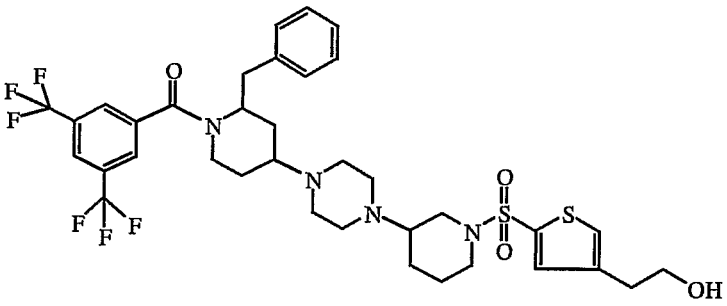
Example B13

a. Preparation of final compound 83



Intermediate compound 6 (prepared according to A2.b) (0.002 mol, 0.55 g) was added portionwise to a solution of final compound 2 (prepared according to B1.b) (0.002 mol, 1.0 g) in dichloromethane at room temperature. The mixture was stirred at room temperature during 18 hours, washed with K_2CO_3 10%, dried over $MgSO_4$ and concentrated. The crude product (1.6 g) was purified by column chromatography over silica gel (Kromasil 10 µm, eluent: CH_2Cl_2/MeOH/NH_4OH 99/1/0.2). The pure fractions were collected and evaporated. Yield: 1.19 g of final compound 83 (77%).

b. Preparation of final compound 96

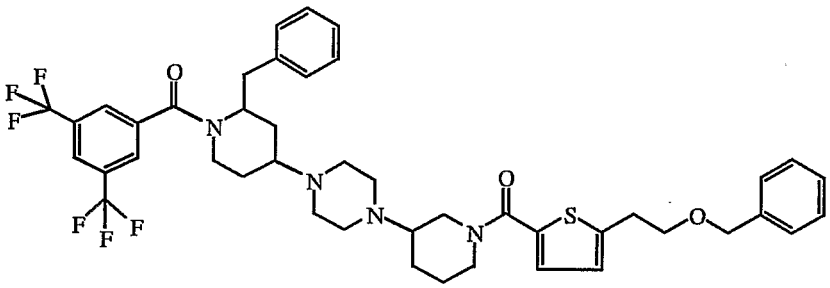


Boron tribromide (1M in CH_2Cl_2) (0.009 mol, 5.2 ml) was slowly added to a solution of final compound 83 (prepared according to B13.a) (0.001 mol, 0.9 g) in dichloromethane (10 ml) at -70°C under N_2 flow. The temperature of the reaction was allowed to rise slowly to -50°C and the mixture was stirred at -50°C for 1 hour. The mixture was hydrolyzed with K_2CO_3 10%, extracted with dichloromethane , dried over $MgSO_4$ and concentrated. The crude product (0.65 g) was purified by column chromatography over silica gel (Kromasil 10 µm, gradient eluent:

CH_2Cl_2/MeOH/NH_4OH 96/4/0.1 to 92/8/0.5). The pure fractions were collected and evaporated. Yield: 0.11 g of final compound 96 (14%).

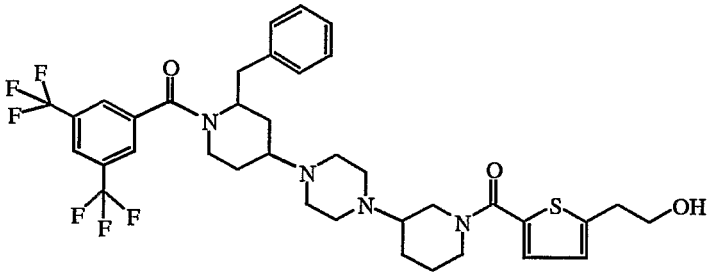
Example B14

a. Preparation of final compound 93



1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.002 mol, 0.32 g) was added portionwise to a solution of final compound 2 (prepared according to B1.b) (0.002 mol, 1 g), intermediate compound 8 (prepared according to A3.b) (0.002 mol, 0.54 g) , 1-hydroxybenzotriazole (0.002 mol, 0.28 g) and triethylamine (0.003 mol, 0.36 ml) in dichloromethane (10 ml) at room temperature. The mixture was stirred at room temperature during 18 hours, then washed with K_2CO_3 10%, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography over silica gel (Kromasil 10 µm, eluent: CH_2Cl_2/MeOH/NH_4OH 97/3/0.1). The pure fractions were collected and evaporated. Yield: 1.07 g of final compound 93 (65%).

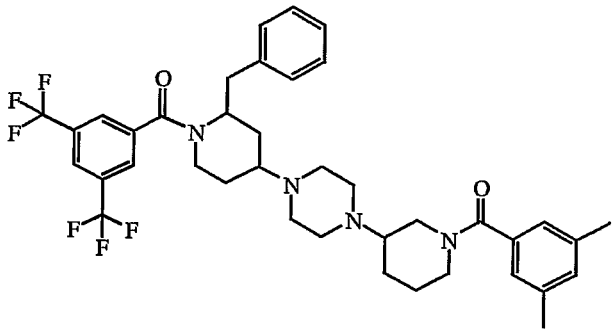
b. Preparation of final compound 98



The same procedure as described in Example B13.b but instead of the use of final compound 83 (prepared according to B13.a), final compound 93 (prepared according to B14.a) was used.

Example B15

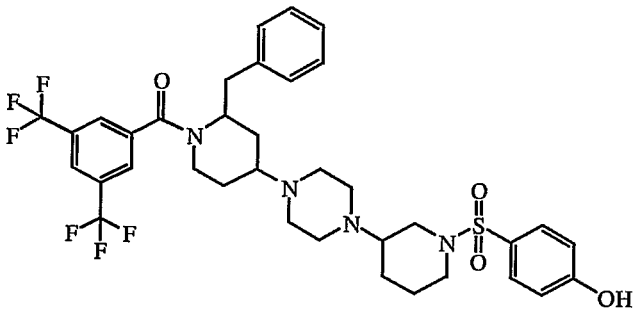
Preparation of final compound 3



3,5-Dimethylbenzoylchloride (0.00309 mol) was added to a solution of final compound 2 (prepared according to B1.b) (0.00257 mol), Et_3N p.a. (0.0035 mol) and *N,N*-dimethyl-4-pyridinamine (0.01 g) in CH_2Cl_2 p.a. (10 ml) at room temperature and the mixture was stirred overnight. The reaction mixture was partitioned between H_2O and CH_2Cl_2. The separated organic layer was washed with H_2O, dried and was concentrated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 95/5). The product fractions were collected and the solvent was evaporated. This fraction (pale yellow oil) was purified again by column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 98/2). The product fractions were collected and the solvent was evaporated. Yield : 1.75 g. This fraction was washed with a NaOH-solution and H_2O, then dried and the solvent was evaporated. Yield: 1.3 g of final compound 3.

Example B16

Preparation of final compound 78

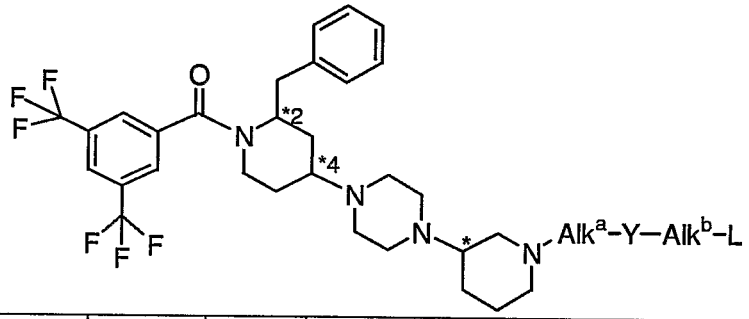


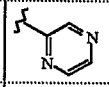
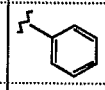
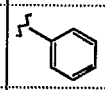
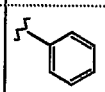
BBr_3 (0.005 mol) was added slowly at –70°C to a solution of final compound 72 (prepared according to B3) (0.001 mol) in CH_2Cl_2 (10 ml). The mixture was cooled slowly to room temperature then stirred for 18 hours. H_2O was added. The mixture was basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (0.8 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH

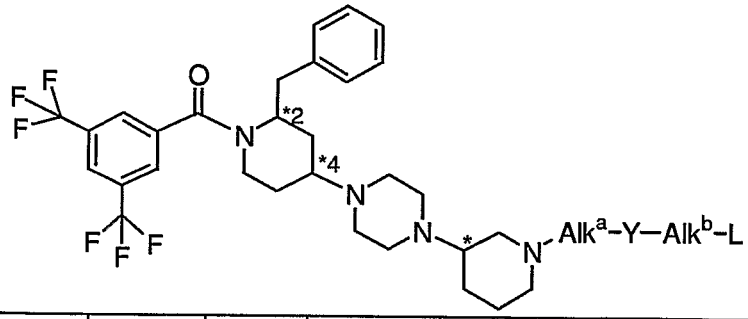
97/3/0.1). The pure fractions were collected and the solvent was evaporated. Yield: 0.497 g of final compound 78 (63%).

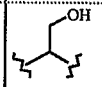
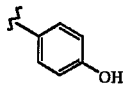
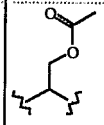
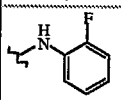
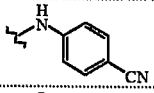
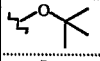
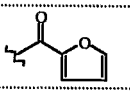
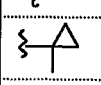
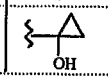
The compounds exemplified in the following Tables 1 and 2 were prepared in a manner analogous to one of the foregoing examples.

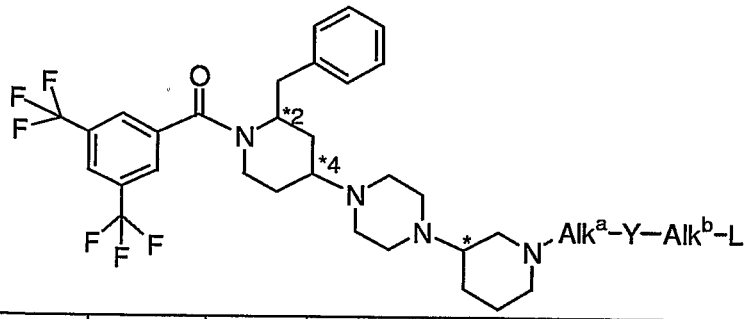
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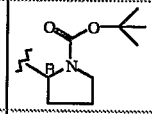
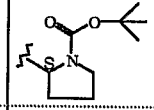
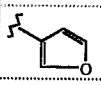
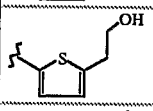
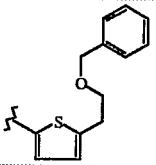
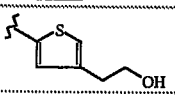


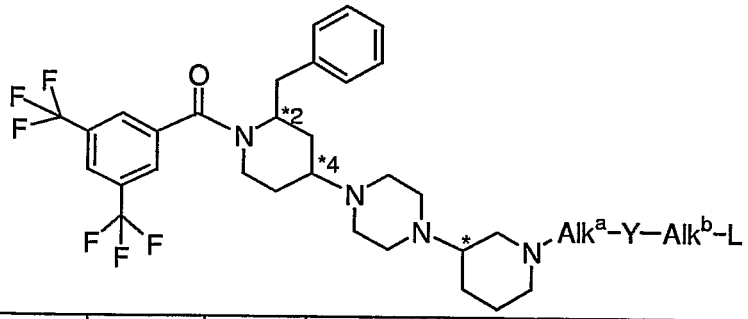
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109	B1.d	cb	cb	cb	H	[2R[2α,4β(S*)]]
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26	B2	cb	cb	cb		2R-trans
1	B1.a	-CH_2-	cb	cb		2R-trans
6	B1.a	-CH_2-	cb	cb		cis
5	B1.a	-CH_2-	cb	cb		cis; (E)-2-butene-dioate(1:2)
77	B10.a		cb	cb		2R-trans
76	B10.a		cb	cb		2R-trans
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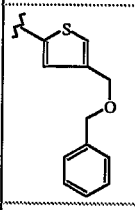
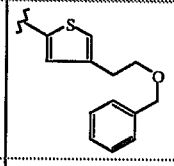
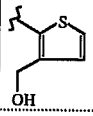
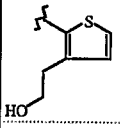
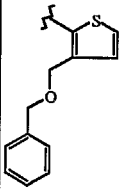
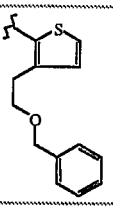
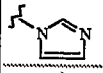
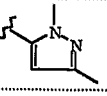


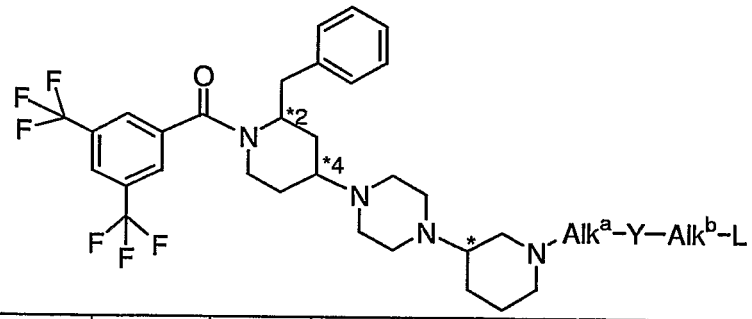
Co. Nr.	Exp. Nr.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
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106	B10.a		cb	cb		2R-trans
124	B10.b		cb	cb		2R-trans
66	B11	cb	C=O	cb		2R-trans
65	B11	cb	C=O	cb		2R-trans
74	B11	cb	C=O	cb		2R-trans
105	B1.c	cb	C=O	cb		[2R-[2α,4β(R*)]]
71	B1.c	cb	C=O	cb		[2R-[2α,4β(S*)]]
24	B6	cb	C=O	cb		2R-trans
51	B4	cb	C=O	cb		[2R-[2α,4β(R*)]]
52	B4	cb	C=O	cb		[2R-[2α,4β(S*)]]
15	B4	cb	C=O	cb		2R-trans
14	B5	cb	C=O	cb		2R-trans
61	B8	cb	C=O	cb		2R-trans

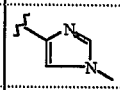
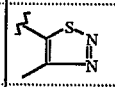
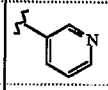
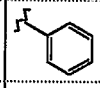
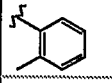
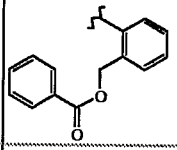
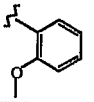
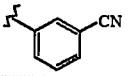
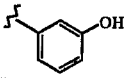
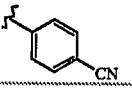


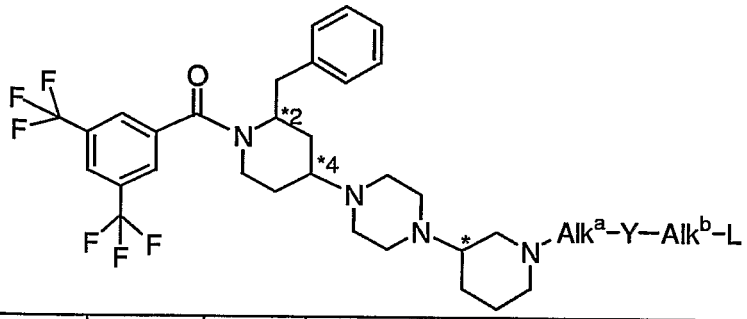
Co. Nr.	Exp. Nr.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
41	B4	cb	C=O	cb		2R-trans
60	B7	cb	C=O	cb		2R-trans
53	B7	cb	C=O	cb		2R-trans
54	B7	cb	C=O	cb		2R-trans
16	B5	cb	C=O	cb		2R-trans
17	B5	cb	C=O	cb		2R-trans
18	B4	cb	C=O	cb		2R-trans
19	B5	cb	C=O	cb		2R-trans
20	B4	cb	C=O	cb		2R-trans
98	B14.b	cb	C=O	cb		2R-trans
93	B14.a	cb	C=O	cb		2R-trans
100	B14.b	cb	C=O	cb		2R-trans

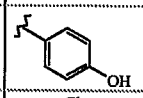
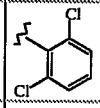
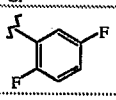
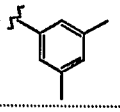
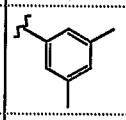
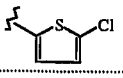


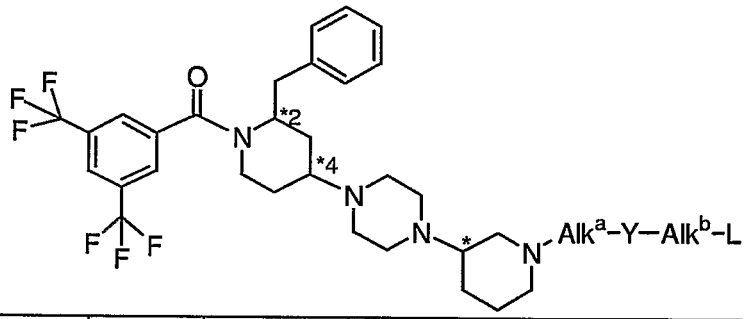
Co. Nr.	Exp. Nr.	Alk^a	Y	Alk^b	L	Stereo descriptors
85	B14.a	cb	C=O	cb		2R-trans
99	B14.a	cb	C=O	cb		2R-trans
97	B14.b	cb	C=O	cb		2R-trans
101	B14.b	cb	C=O	cb		2R-trans
88	B14.a	cb	C=O	cb		2R-trans
102	B14.a	cb	C=O	cb		2R-trans
21	B6	cb	C=O	cb		2R-trans
42	B4	cb	C=O	cb		2R-trans

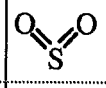
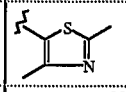
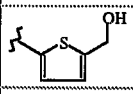
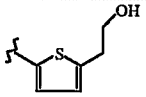
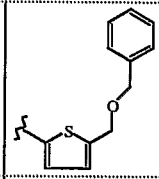
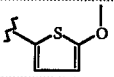
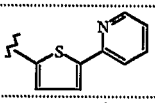
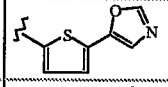
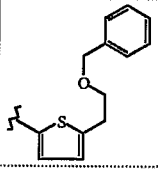
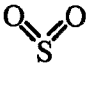
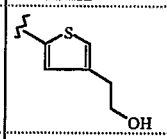
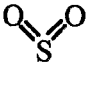
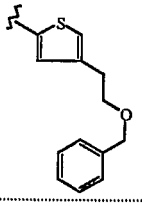


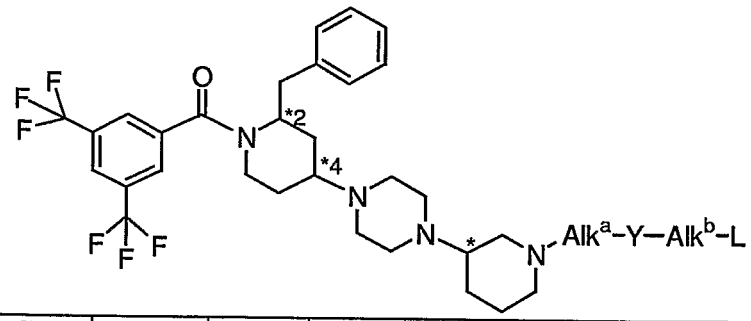
Co. Nr.	Exp. Nr.	Alk^a	Y	Alk^b	L	Stereo descriptors
63	B8	cb	C=O	cb		2R-trans
22	B4	cb	C=O	cb		2R-trans
23	B4	cb	C=O	cb		2R-trans
8	B4	cb	C=O	cb		2R-trans
11	B4	cb	C=O	cb		2R-trans
82	B8	cb	C=O	cb		2R-trans
75	B8	cb	C=O	cb		2R-trans
9	B4	cb	C=O	cb		2R-trans
10	B4	cb	C=O	cb		2R-trans
47	B4	cb	C=O	cb		2R-trans
57	B5	cb	C=O	cb		2R-trans
70	B8	cb	C=O	cb		2R-trans
62	B5	cb	C=O	cb		2R-trans

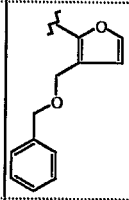
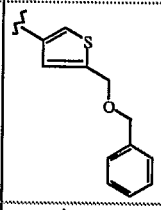
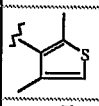
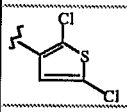
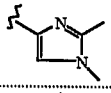
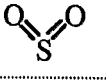
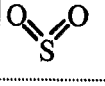
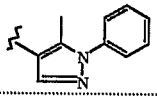
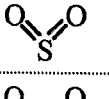
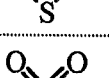


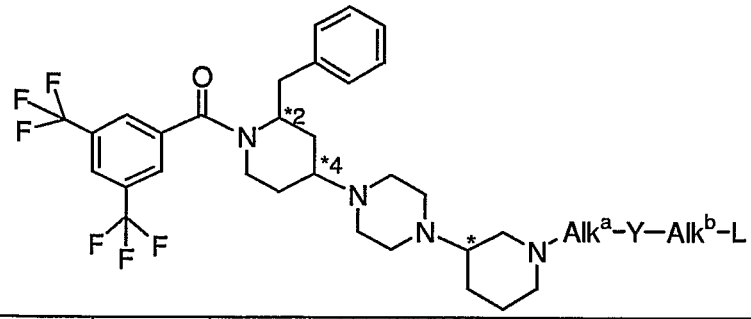
Co. Nr.	Exp. Nr.	Alk^a	Y	Alk^b	L	Stereo descriptors
67	B8	cb	C=O	cb		2R-trans
64	B4	cb	C=O	cb		2R-trans
12	B4	cb	C=O	cb		2R-trans
3	B4	cb	C=O	cb		2R-trans
13	B15	cb	C=O	cb		2R-cis; (E)-2-butene-dioate(1:2)
43	B4	cb	C=O			2R-trans
48	B4	cb	C=O			2R-trans
56	B8	cb	C=O			2R-trans
35	B3	cb		cb		2R-trans
25	B3	cb		cb		2R-trans
55	B3	cb		cb		[2R-[2α,4β(R*)]]
59	B3	cb		cb		[2R-[2α,4β(S*)]]
36	B3	cb		cb		2R-trans

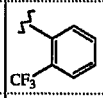
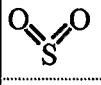
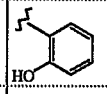
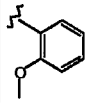
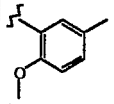
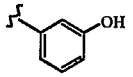
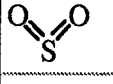
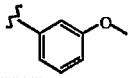
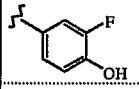
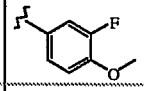
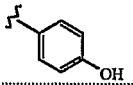
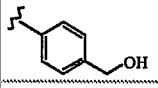
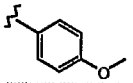
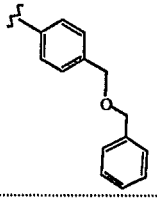


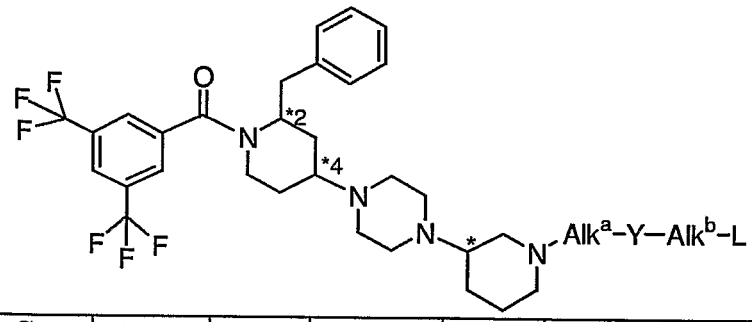
Co. Nr.	Exp. Nr.	Alk^a	Y	Alk^b	L	Stereo descriptors
38	B3	cb		cb		2R-trans
92	B13.b	cb		cb		2R-trans
86	B13.b	cb		cb		2R-trans
87	B13.a	cb		cb		2R-trans
95	B13.a	cb		cb		2R-trans
34	B3	cb		cb		2R-trans
37	B3	cb		cb		2R-trans
84	B13.a	cb		cb		2R-trans
96	B13.b	cb		cb		2R-trans
83	B13.a	cb		cb		2R-trans

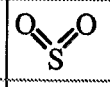
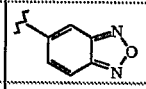
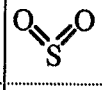
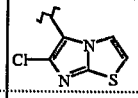
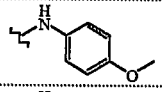
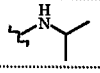


Co. Nr.	Exp. Nr.	Alk^a	Y	Alk^b	L	Stereo descriptors
90	B13.a	cb		cb		2R-trans
29	B3	cb		cb		2R-trans
104	B13.a	cb		cb		2R-trans
33	B3	cb		cb		2R-trans
40	B3	cb		cb		2R-trans
32	B3	cb		cb		2R-trans
39	B3	cb		cb		2R-trans
44	B3	cb		cb		2R-trans
28	B3	cb		cb		2R-trans
30	B3	cb		cb		2R-trans
27	B3	cb		cb		2R-trans



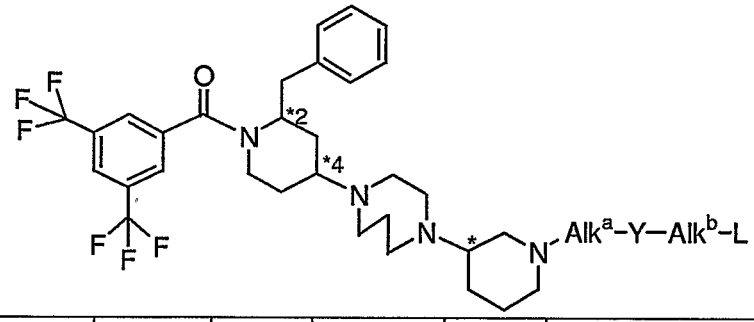
Co. Nr.	Exp. Nr.	Alk^a	Y	Alk^b	L	Stereo descriptors
50	B3	cb		cb		2R-trans
81	B16	cb		cb		2R-trans
68	B3	cb		cb		2R-trans
31	B3	cb		cb		2R-trans
80	B16	cb		cb		2R-trans
69	B3	cb		cb		2R-trans
107	B16	cb		cb		2R-trans
7	B3	cb		cb		2R-trans
78	B16	cb		cb		2R-trans
73	B13.b	cb		cb		2R-trans
72	B3	cb		cb		2R-trans
58	B13.a	cb		cb		2R-trans

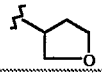
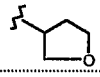
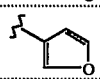
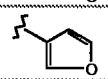
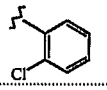
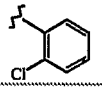


Co. Nr.	Exp. Nr.	Alk^a	Y	Alk^b	L	Stereo descriptors
45	B3	cb		cb		2R-trans
46	B3	cb		cb		2R-trans
49	B3	cb				2R-trans
91	B11	cb	C=N-CN	cb		2R-trans
94	B11	cb	C=N-CN	cb		2R-trans
103	B12	cb	C=CH-NO_2	cb		2R-trans

cb : covalent bond

Table 2:



Co. Nr.	Exp. Nr.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
113	B2	cb	cb	cb	H	2R-cis
117	B2	cb	cb	cb	H	2R-trans
123	B2	cb	cb	cb	H	2R-trans+2R-cis
110	B1	$-CH_2-$	cb	cb		2R-cis
111	B1	$-CH_2-$	cb	cb		2R-trans
114	B4	cb	C=O	cb		2R-cis
121	B5	cb	C=O	cb		2R-cis
115	B5	cb	C=O	cb		2R-trans
112	B5	cb	C=O	cb		2R-cis
116	B5	cb	C=O	cb		2R-trans
119	B4	cb	C=O	cb		2R-cis
118	B4	cb	C=O	cb		2R-trans
120	B3	cb		cb		2R-cis
122	B3	cb		cb		2R-trans

cb = covalent bond

C. Analytical data

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

1. Melting points

If possible, melting points (or ranges) were obtained with a Leica VMHB Koffler bank. The melting points are uncorrected.

Table 3 : Melting points for selected compounds.

Compound no.	Result (°C)
56	83°C
61	104°C
62	114°C
63	110°C
65	94°C
66	97°C
67	150°C

2. LCMS conditions

Method A

The HPLC gradient was supplied by a Waters Alliance HT 2790 system (Waters, Milford, MA) 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 mm, 4.6 x 100 mm) with a flow rate of 1.6 ml/min. Three mobile phases (mobile phase A : 95% 25 mM ammonium acetate + 5% acetonitrile; mobile phase B : acetonitrile ; mobile phase C : methanol) were employed to run a gradient 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 re-equilibrate 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 as the nebulizer gas. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

Table 4 : LCMS parent peak and retention time for selected compounds.

Compound no.	LCMS MS(MH+) Meth. A	Retention time
1	673	6.36
2	583	5.09
3	715	6.34
4	583	5.24
6	673	6.55
8	687	6.02
9	705	6.01
10	721	6.12
11	701	6.14
12	723	6.05
13	715	6.5
14	665	5.93
15	651	5.84
16	681	5.67
17	677	5.82
18	677	5.86
19	691	5.96
20	693	5.99
21	677	5.6
22	709	5.86
23	688	5.61
24	705	5.78
25	729	6.49
26	651	6.01
27	757	6.26
28	723	6.14
29	729	6.44
30	737	6.08
31	767	6.18
32	741	5.63
33	757	6.38
34	806	6.69
35	689	5.94
36	763	6.68
37	796	6.48
38	758	6.51
39	742	6.5
40	761	6.43
41	679	6.58
42	705	6.2

Compound no.	LCMS MS(MH+) Meth. A	Retention time
43	707	6.39
44	803	6.57
45	765	6.51
46	803	6.52
47	717	6.36
48	715	6.61
49	737	6.49
50	791	6.66
51	651	6.20
52	651	6.22
53	780	6.11
54	780	6.10
55	729	5.82
57	712	6.23
58	843	6.50
59	729	5.83
60	722	5.55
64	755	6.26
72	753	6.16
73	753	5.78
74	727	5.90
76	709	6.06
77	709	5.93
78	739	5.84
79	693	5.78
80	739	5.91
82	821	6.39
83	773	5.87
84	863	6.53
85	813	6.37
86	863	6.53
87	849	6.48
88	813	6.39
89	737	6.27
90	819	6.30
91	692	5.79
92	759	5.82
93	827	6.49
94	756	5.86
95	759	6.18
96	773	5.87
97	723	5.75
98	737	5.72

Compound no.	LCMS MS(MH+) Meth. A	Retention time
99	827	6.46
100	737	5.74
101	737	5.80
102	827	6.47
103	711	5.61
104	849	6.45
108	583	5.10
109	583	5.13

Method B

The HPLC gradient was supplied by a Waters Alliance HT 2790 system (Waters, Milford, MA) 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 (5 mm, 3.9 x 150 mm) with a flow rate of 1 ml/min. Two mobile phases (mobile phase A: 85% 6.5mM ammonium acetate + 15% acetonitrile ; mobile phase B : 20% 6.5 mM ammonium acetate + 80% acetonitrile) were employed to run a gradient condition from 100 % A for 3 min to 100% B in 5 min., 100% B for 6 min to 100 % A in 3 min, and re-equilibrate with 100 % A for 3 min). Mass spectra were acquired as in Method A.

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

Compound no.	LCMS MS(MH+) Meth. B	Retention time
68	752	5.10
69	752	5.30
70	703	4.40
75	702	4.50
81	738	4.90
110	687	3.57
111	687	3.43
112	691	4.70
114	665	4.77
115	695	4.30
116	691	4.64
118	735	5.14
119	735	4.30

Method C

The HPLC gradient was supplied by a Waters Alliance HT 2790 system (Waters, Milford, MA) 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 Kromasil C18 column (5 mm, 4.6 x 150 mm) with a flow rate of 1 ml/min. Two mobile phases (mobile phase A: 30% 6.5mM ammonium acetate + 40% acetonitrile + 30% formic acid (2ml/l); mobile phase B: 100% acetonitrile) were employed to run a gradient condition from 100 % A for 1 min to 100% B in 4 min., 100% B for 5 min to 100 % A in 3 min, and re-equilibrate with 100 % A for 2 min). Mass spectra were acquired as in Method A.

Table 6 : LCMS parent peak and retention time for selected compounds.

Compound no.	LCMS MS(MH+) Meth. B	Retention time
120	743	10.2
121	695	8.90
122	743	9.90

Optical rotations

Optical rotations were recorded on a polarimeter (Perkin Elmer) at 20°C in methanol, using a cell pathlength = 1 dm, a volume = 5 ml at a concentration = 0.5 mg/ml.

Table 7 : Optical rotation data for selected compounds.

Compound No.	[α]	Wavelength (nm)
52	+29.84	589 nm
57	-27.07	589 nm

D. Pharmacological example

Example C.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 C.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 8. The last colums indicates - without being limited thereto - for which action the compounds might be most suitable. Of course, since for some neurokinin receptors no data was determined, it is obvious that these compounds might be attributed to another suitable use.

Table 8 : Pharmacological data for the signal transduction for selected compounds (n.d. = not determined).

Co. No.	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
5	6.1	n.d.	n.d.	NK_1
13	6.3	n.d.	5.0	NK_1
124	6.4	5.3	5.6	NK_1
87	6.5	6.1	5.1	NK_1
58	6.6	5.7	5.0	NK_1
111	6.6	n.d.	5.1	NK_1
99	6.7	5.2	5.5	NK_1
110	6.7	n.d.	5.0	NK_1
120	6.7	n.d.	5.1	NK_1
90	6.8	5.7	5.0	NK_1
112	6.8	n.d.	5.0	NK_1
93	6.9	5.0	5.3	NK_1
114	6.9	n.d.	5.1	NK_1
119	6.9	n.d.	5.0	NK_1
121	6.9	n.d.	5.1	NK_1
50	7.0	5.2	5.1	NK_1
122	7.0	n.d.	5.0	NK_1
3	7.1	n.d.	5.7	NK_1
85	7.1	5.4	5.3	NK_1
108	7.1	5.0	5.0	NK_1
44	7.2	n.d.	5.3	NK_1

Co. No.	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
82	7.2	5.5	5.1	NK_1
89	7.2	5.3	5.1	NK_1
118	7.2	n.d.	5.6	NK_1
1	7.3	n.d.	n.d.	NK_1
34	7.3	n.d.	5.7	NK_1
109	7.3	5.0	5.0	NK_1
116	7.3	n.d.	5.4	NK_1
115	7.4	n.d.	5.2	NK_1
17	7.5	n.d.	5.6	NK_1
12	7.6	n.d.	5.5	NK_1
19	7.6	n.d.	5.7	NK_1
24	7.6	n.d.	5.4	NK_1
31	7.6	n.d.	5.5	NK_1
2	7.7	n.d.	n.d.	NK_1
18	7.7	n.d.	5.6	NK_1
21	7.7	n.d.	5.9	NK_1
23	7.7	5.4	5.7	NK_1
75	7.7	5.6	5.5	NK_1
81	7.7	5.6	5.8	NK_1
59	7.8	5.5	5.7	NK_1
14	7.9	n.d.	5.7	NK_1
77	7.9	5.7	5.5	NK_1
98	7.9	5.3	5.7	NK_1
35	8.0	n.d.	5.7	NK_1
62	8.0	5.4	5.5	NK_1
65	8.0	5.8	5.2	NK_1
74	8.0	5.4	5.5	NK_1
91	8.0	6.0	5.4	NK_1
97	8.0	5.4	5.6	NK_1
103	8.0	5.2	5.0	NK_1
42	8.1	n.d.	5.6	NK_1
56	8.1	6.0	5.7	NK_1
61	8.1	5.5	5.2	NK_1
67	8.2	5.3	5.8	NK_1
60	8.3	n.d.	5.2	NK_1
63	8.3	5.5	5.2	NK_1
66	8.3	5.5	5.5	NK_1
84	6.6	6.3	5.9	$NK_1/NK_2/NK_3$
83	6.8	6.1	6.4	$NK_1/NK_2/NK_3$
104	6.9	5.9	6.5	$NK_1/NK_2/NK_3$
48	7.5	6.0	6.2	$NK_1/NK_2/NK_3$
45	7.7	5.8	6.4	$NK_1/NK_2/NK_3$
25	7.8	6.4	7.1	$NK_1/NK_2/NK_3$
30	7.8	6.2	6.2	$NK_1/NK_2/NK_3$
46	7.8	6.3	6.1	$NK_1/NK_2/NK_3$

Co. No.	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
49	7.8	6.2	6.5	$NK_1/NK_2/NK_3$
96	7.8	6.4	7.0	$NK_1/NK_2/NK_3$
79	7.9	5.8	6.0	$NK_1/NK_2/NK_3$
92	7.9	6.3	6.8	$NK_1/NK_2/NK_3$
55	8.0	6.1	7.0	$NK_1/NK_2/NK_3$
80	8.0	6.1	6.3	$NK_1/NK_2/NK_3$
68	8.0	5.8	5.8	$NK_1/NK_2/NK_3$
73	8.1	6.1	6.6	$NK_1/NK_2/NK_3$
29	8.2	5.9	6.5	$NK_1/NK_2/NK_3$
38	8.2	6.7	6.6	$NK_1/NK_2/NK_3$
39	8.2	6.2	6.3	$NK_1/NK_2/NK_3$
86	8.2	6.4	6.3	$NK_1/NK_2/NK_3$
32	8.3	6.2	7.0	$NK_1/NK_2/NK_3$
78	8.4	6.1	6.5	$NK_1/NK_2/NK_3$
7	7.3	n.d.	6.0	NK_1/NK_3
33	7.4	n.d.	6.0	NK_1/NK_3
88	7.4	5.6	6.2	NK_1/NK_3
20	7.5	5.7	6.6	NK_1/NK_3
36	7.5	5.3	6.2	NK_1/NK_3
95	7.5	5.5	5.9	NK_1/NK_3
10	7.6	5.4	6.3	NK_1/NK_3
40	7.6	5.1	6.6	NK_1/NK_3
8	7.7	5.0	6.6	NK_1/NK_3
11	7.7	5.5	6.0	NK_1/NK_3
27	7.7	n.d.	5.9	NK_1/NK_3
72	7.7	5.7	5.9	NK_1/NK_3
76	7.7	5.7	5.8	NK_1/NK_3
94	7.7	5.4	6.0	NK_1/NK_3
9	7.8	5.6	6.1	NK_1/NK_3
47	7.8	5.3	6.3	NK_1/NK_3
69	7.8	5.6	6.2	NK_1/NK_3
107	7.8	n.d.	5.9	NK_1/NK_3
15	7.9	5.2	6.8	NK_1/NK_3
16	7.9	5.0	6.0	NK_1/NK_3
37	7.9	5.7	6.2	NK_1/NK_3
57	7.9	5.5	6.1	NK_1/NK_3
64	7.9	5.2	6.1	NK_1/NK_3
22	8.0	5.6	6.3	NK_1/NK_3
28	8.0	5.7	6.8	NK_1/NK_3
43	8.0	5.7	6.3	NK_1/NK_3
26	8.1	5.1	6.1	NK_1/NK_3
41	8.1	5.5	7.0	NK_1/NK_3
70	8.1	5.4	5.9	NK_1/NK_3
53	8.3	5.7	7.3	NK_1/NK_3
54	8.3	5.7	6.6	NK_1/NK_3

Co. No.	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
52	8.4	5.5	6.3	NK_1/NK_3
51	8.5	5.0	6.1	NK_1/NK_3

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

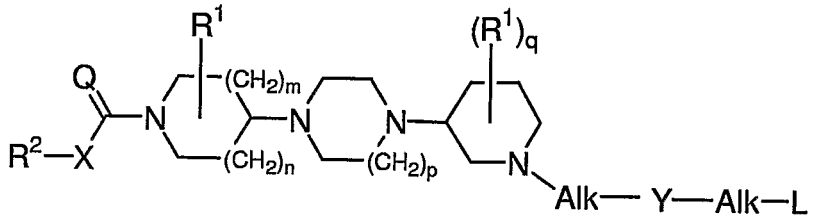
To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 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, 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 ;
p	is an integer equal to 1 or 2 ;
q	is an integer equal to 0 or 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 ;
each R^1	independently from each other, is selected from the group of Ar^1, Ar^1-alkyl and di(Ar^1)-alkyl ;
R^2	is Ar^2, Ar^2-alkyl, di(Ar^2)alkyl, Het^1 or Het^1-alkyl ;
Y	is a covalent bond or a bivalent radical of formula -C(=O)-,-SO_2-, >C=CH-R or >C=N-R, wherein R is CN or nitro ;
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 phenyl, halo, cyano, hydroxy, formyl and amino radicals ;
L	is selected from the group of hydrogen, alkyl, alkyloxy, Ar^3-oxy, alkyloxycarbonyl, alkylcarbonyloxy, mono- and di(alkyl)amino, mono-and di(Ar^3)amino, Ar^3, Ar^3carbonyl, Het^2 and Het^2carbonyl ;
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, Ar^1carbonyloxycarbonyl, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and cyano ;

Het^1 is a monocyclic heterocyclic radical selected from the the group of pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, 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, benzothienyl and 4a,8a-dihydro-2*H*-chromenyl ; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of halo, oxo and alkyl ;

Het^2 is a monocyclic heterocyclic radical selected from the group of tetrahydrofuranyl, 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, benzothienyl, benzo [2,1,3]oxadiazolyl, imidazo[2,1-b]thiazolyl , 2,3-dihydrobenzo[1,4]dioxyl and octahydrobenzo[1,4]dioxyl ;
each radical may optionally be substituted with one or more radicals selected from the group of Ar^1, Ar^1alkyl, Ar^1alkyloxyalkyl, halo, hydroxy, alkyl, alkylcarbonyl, alkyloxy, alkyloxyalkyl, alkyloxycarbonyl, piperidinyl, pyridinyl, pyrrolyl, thienyl, oxo and oxazolyl ; 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.

2. A compound according to claim 1, characterized in that

n is 1 ;

m is 1 ;

p is 1 ;

q is 0 ;

Q is O ;

X is a covalent bond ;

each R^1 is Ar^1 or Ar^1-alkyl ;

R^2 is Ar^2 ;

Y is a covalent bond or a bivalent radical of formula -C(=O)-, $-SO_2-$ or >C=CH-R or >C=N-R, wherein R is CN or nitro ;

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

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

Ar^1 is phenyl ;

Ar^2 is phenyl, optionally substituted with 1, 2 or 3 alkyl radicals ;

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, hydroxy, Ar^1carbonyloxycarbonyl and cyano;

Het^2 is a heterocyclic radical selected from the group of tetrahydrofuranyl, pyrrolidinyl, imidazolyl, pyrazolyl, furanyl, thienyl, isoxazolyl, thiazolyl, thiadiazolyl, pyridinyl, pyrazinyl, benzo [2,1,3]oxadiazolyl and imidazo[2,1-b]thiazolyl ; each radical optionally substituted with one or more Ar^1alkyloxyalkyl, halo, alkyl, alkylcarbonyl, pyridinyl or oxazolyl radicals ; and

alkyl is a straight hydrocarbon radical having 1 to 6 carbon atoms, optionally substituted with one or more radicals selected from the group of halo and hydroxy;

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

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

5. A compound according to any of claims 1-4, characterized in that p is 1.

6. A compound according to any of claims 1-5, characterized in that Y is -C(=O)-.

7. A compound according to any of claims 1-6, characterized in that Alk is a covalent bond.

8. A compound according to any of claims 1-3, characterized in that L is Het^2.

9. A compound selected from the group of compounds with compound number 25, 48, 79, 39, 15, 41, 64, 88, 50, 59 and 3, as mentioned in any one of Tables 1-2.

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

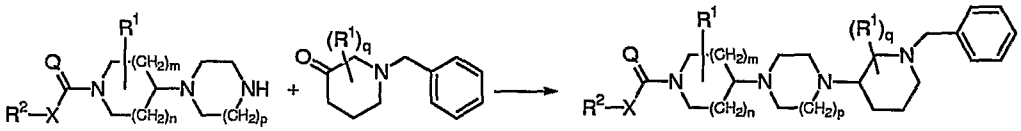
11. The use of a compound according to any one of claims 1-10 for the manufacture of a medicament for treating tachykinin mediated conditions.

12. The use of a compound according to claim 11 for the manufacture of a medicament for treating schizophrenia, emesis, anxiety, depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pain, neurogenic inflammation, asthma, micturition disorders such as urinary incontinence and nociception.

13. 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- 9.

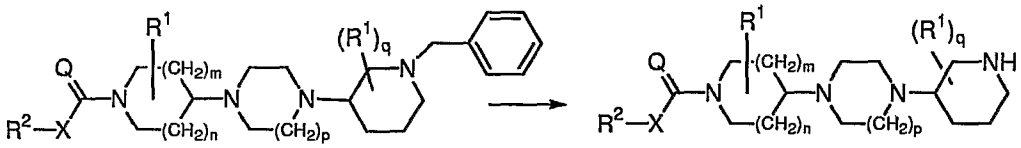
14. A process for preparing a pharmaceutical composition as claimed in claim 13, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in any one of claims 1-9.

15. A process for the preparation of a compound of Formula (I") in which an intermediate compound of Formula (II) is reacted with an intermediate compound of Formula (III), wherein the radicals R^2, X, Q, R^1, m, n, p and q are as defined in claim 1.



(II) (III) (I")

16. A process for the preparation of a compound of Formula (I') in which a final compound of Formula (I") is reductively hydrogenated, wherein the radicals R^2, X, Q, R^1, m, n, p and q are as defined in claim 1.



(I") (I')

17. A process for the preparation of a compound according to Formula (I') comprising the consecutive steps of
1) obtaining a compound of Formula (I") according to claim 15 ;
2) obtaining a compound of Formula (I') according to claim 16.