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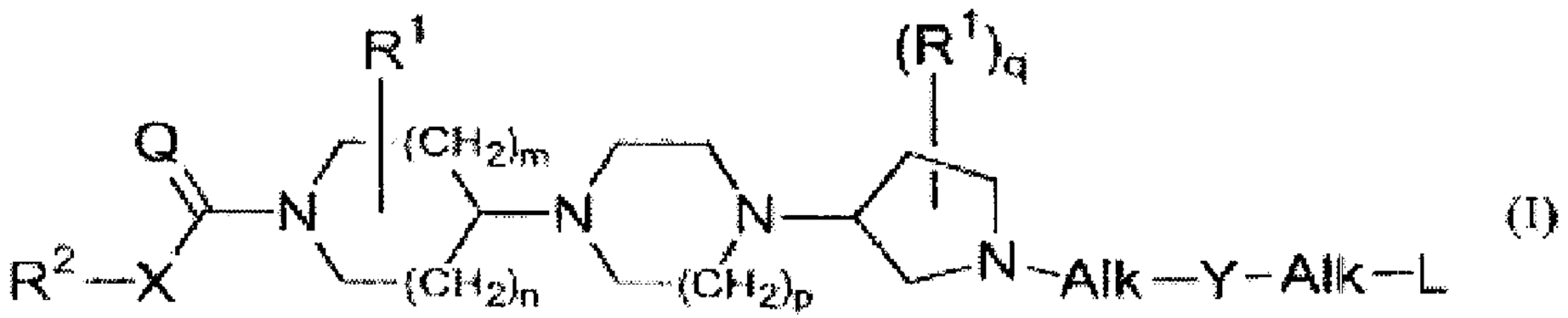
(72) Inventeurs/Inventors:
JANSSENS, FRANS EDUARD, BE;
SOMMEN, FRANCOIS MARIA, BE;
DE BOECK, BENOIT CHRISTIAN ALBERT GHISLAIN, BE;
LEENAERTS, JOSEPH ELISABETH, BE

(73) Propriétaire/Owner:
JANSSEN PHARMACEUTICA N.V., BE

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : DERIVES 1-PIPERIDIN-4-YL-4-PYRROLIDIN-3-YL-PIPERAZINE SUBSTITUEE, UTILISATIONS DE CES DERNIERS EN TANT QU'ANTAGONISTES DE LA NEUROKININE

(54) Title: SUBSTITUTED 1-PIPERIDIN-4-YL-4-PYRROLIDIN-3-YL-PIPERAZINE DERIVATIVES AND THEIR USE AS NEUROKININ ANTAGONISTS



(I)

(57) Abrégé/Abstract:
This invention concerns substituted 1-piperidin-4-yl-4-pyrrolidin-3-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, anxiety, depression, emesis and IBS. The compounds according to the invention can be represented by general Formula (I) and comprises also the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the N-oxide form thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1.

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(71) Applicant *(for all designated States except US)*: **JANSSEN PHARMACEUTICA N.V.** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JANSSENS, Frans, Eduard** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2460 Beerse (BE). **SOMMEN, François, Maria** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **DE BOECK, Benoît, Christian, Albert, Ghislain** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **LEENAERTS, Joseph, Elisabeth** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Common Representative: **JANSSEN PHARMACEUTICA N.V.**; Turnhoutseweg 30, B-2340 Beerse (BE).

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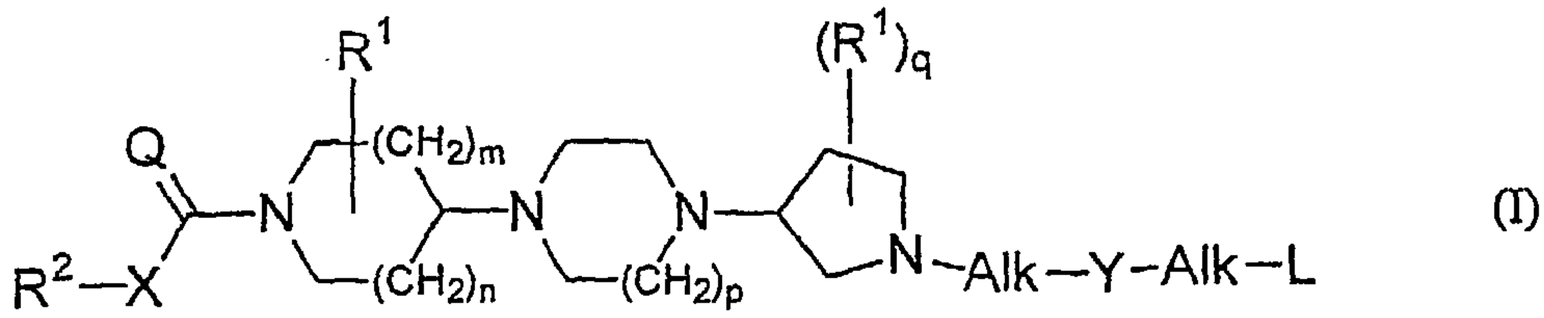
(54) Title: SUBSTITUTED 1-PIPERIDIN-4-YL-4-PYRROLIDIN-3-YL-PIPERAZINE DERIVATIVES AND THEIR USE AS NEUROKININ ANTAGONISTS



(I)

(57) Abstract: This invention concerns substituted 1-piperidin-4-yl-4-pyrrolidin-3-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, anxiety, depression, emesis and IBS. The compounds according to the invention can be represented by general Formula (I) and comprises also the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, wherein all substituents are defined as in Claim 1.

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

Field of the Invention

This invention concerns substituted 1-piperidin-4-yl-4-pyrrolidin-3-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 syndrome (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 (NKA) and Neurokinin B (NKB) with preferential affinity for three distinct neurokinin receptor subtypes, termed NK_1, NK_2, and NK_3, respectively. However, functional studies on cloned receptors suggest strong functional cross-interaction between the 3 tachykinins and their corresponding neurokinin receptors (Maggi and Schwartz, *Trends Pharmacol. Sci.* **18**: 351-355 (1997)).

Species differences in structure of NK_1 receptors are responsible for species-related potency differences of NK_1 antagonists (Maggi, *Gen. Pharmacol.* **26**:911-944 (1995) ; Regoli *et al.*, *Pharmacol. Rev.* **46(4)**:551-599 (1994)). The human NK_1 receptor closely resembles the NK_1 receptor of guinea-pigs and gerbils but differs markedly from the NK_1 receptor of rodents. The development of neurokinin antagonists has led to date to a series of peptide compounds of which might be anticipated that they

are metabolically too labile to be employed as pharmaceutically active substances (Longmore J. *et al.*, *DN&P* **8(1)**:5-23 (1995)).

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

Schizophrenia

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

Anxiety and depression

Depression is one of the most common affective disorders of modern society with a high and still increasing prevalence, particularly in the younger members of the population. The life time prevalence rates of Major depression (MDD, DSM-IV) is currently estimated to be 10-25 % for women and 5-12 % for men, whereby in about 25 % of patients the life time MDD is recurrent, without full inter-episode recovery and superimposed on dysthymic disorder. There is a high co-morbidity of depression with other mental disorders and, particularly in younger population high association with drug and alcohol abuse. In the view of the fact that depression primarily affects the population between 18-44 years of age e.g. the most productive population, it is obvious that it imposes a high burden on individuals, families and the whole society.

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

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

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

The NK_1 receptor is widely distributed throughout the limbic system and fear-processing pathways of the brain, including the amygdala, hippocampus, septum, hypothalamus, and periaqueductal grey. Additionally, substance P is released centrally in response to traumatic or noxious stimuli and substance P-associated 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 $5\text{-}HT_3$ receptor antagonists. Although this discovery led to a successful therapy for the treatment of chemotherapy- and radiation-induced sickness in cancer patients, $5\text{-}HT_3$ 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

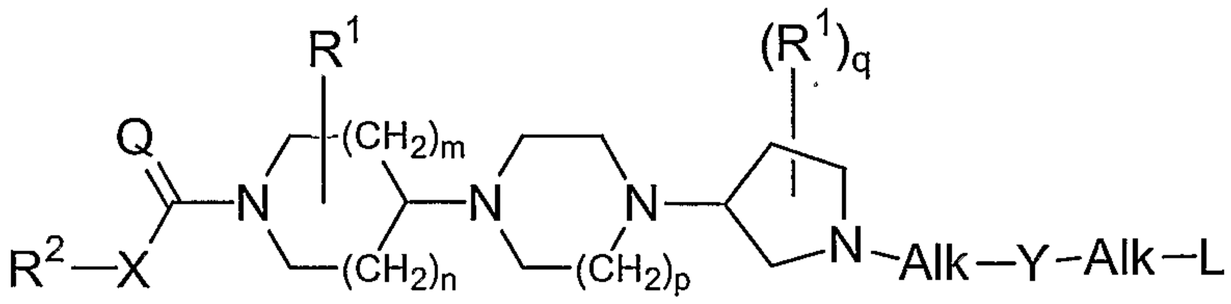
Compounds containing the 1-piperidin-4-yl-piperazinyl moiety were published in WO 97/16440-A1, published May 9, 1997 by Janssen Pharmaceutica N.V. for use as substance P antagonists, in WO 02/32867, published April 25, 2002 by Glaxo Group Ltd. for their special advantages as neurokinin antagonists (more 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 pyrrolidinyl 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-4-yl-4-pyrrolidin-3-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 :

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 H , 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, alkyloxyalkyloxy, alkylcarbonyloxy, alkyloxycarbonyl, mono- and di(alkyl)amino, mono- and di(alkyloxycarbonyl)amino, mono- and di(alkylcarbonyl)amino, mono-and di(Ar^3)amino, mono-and di(Ar^3alkyl)amino, mono-and di(Het^2)amino,

mono-and di(Het^2alkyl)amino, alkylsulfanyl, adamantyl, Ar^3, Ar^3-oxy, Ar^3carbonyl, Het^2,Het^2-oxy 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, Ar^1carbonyloxyalkyl, Ar^1alkyloxycarbonyl, Ar^1alkyloxyalkyl, alkyl, halo, hydroxy, pyridinyl, morpholinyl, pyrrolidinyl, imidazo[1,2-*a*]pyridinyl, morpholinylcarbonyl, pyrrolidinylcarbonyl, amino and cyano ;

Het^1 is a monocyclic heterocyclic radical selected from the 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, indanyl and chromenyl; each heterocyclic radical may optionally be substituted on any atom by one or more radicals elected from the group of halo, oxo and alkyl;

Het^2 is a monocyclic heterocyclic radical selected from the group of pyrrolidinyl, dioxolyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 2H-pyrrolyl, pyrrolinyl, imidazolinyl, pyrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, dioxazolyl, oxazolidinyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl ;
or a bicyclic heterocyclic radical selected from the group of 2,3-dihydro-benzo[1,4]dioxine, octahydro-benzo[1,4]dioxine, benzopiperidinyl, quinolinyl, quinoxalinyl, indolyl, isoindolyl, chromanyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl and benzothienyl ;
or the tricyclic heterocyclic radical 8,9-dihydro-4*H*-1-oxa-3,5,7a-triaza-cyclopenta[f]azulenyl ; 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, piperidinyl, pyrrolyl, thienyl, oxo, alkyloxy, alkylcarbonyl, Ar^1carbonyl, mono- and di(alkyl)aminoalkyl, alkyloxyalkyl and alkyloxycarbonyl ; and

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

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

n is an integer, equal to 1;

m is an integer, equal to 1;

p is an integer equal to 1 or 2;

q is an integer equal to 0;

Q is O

X is a covalent bond;

R^1 is Ar^1-alkyl;

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

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 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 phenyl, halo and hydroxy radicals;

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

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

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, alkyl and alkyloxy;

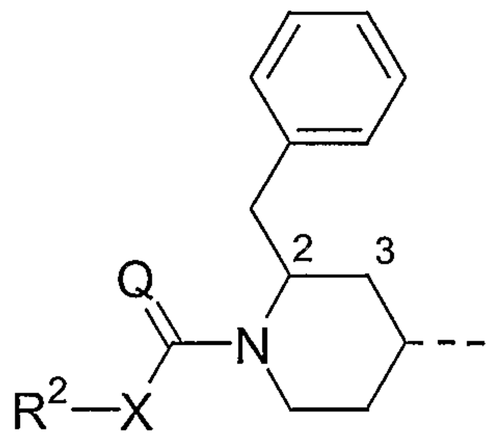
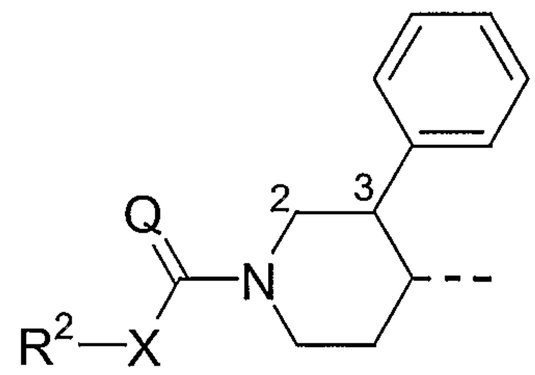
Ar^3 is naphthalenyl or phenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other, selected from the group of alkyloxy, Ar^1alkyloxycarbonyl, Ar^1alkyloxyalkyl, alkyl, halo and cyano;

Het^1 is pyridinyl or a bicyclic heterocyclic radical selected from the group of quinoxalinyl, indolyl, benzothienyl, indanyl and chromenyl; each heterocyclic radical may optionally be substituted on any atom by one or more radicals selected from the group of oxo and alkyl ;

Het^2 is a monocyclic heterocyclic radical selected from the group of pyrrolidinyl, dioxolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuranyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, dioxazolyl, oxazolidinyl, isoxazolyl, thiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocyclic radical selected from the group of 2,3-dihydro-benzo[1,4]dioxine, octahydro-benzo[1,4]dioxine, quinoxalinyl, indolyl, chromanyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, benzisoxazolyl, benzothiazolyl,benzofuranyl and benzothienyl ; or the tricyclic heterocyclic radical 8,9-dihydro-4*H*-1-oxa-3,5,7a-triaza-cyclopenta[f]azulenyl ; each radical may optionally be substituted with one or more radicals selected from the group of Ar^1, Ar^1alkyloxyalkyl, halo, alkyl, oxo, alkyloxy, alkylcarbonyl, Ar^1carbonyl, mono- and di(alkyl)aminoalkyl, alkyloxyalkyl and alkyloxycarbonyl ; and

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms ; optionally substituted on one or more carbon atoms with one or more radicals selected from the group of phenyl, halo 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. Preferably, Ar^1methyl is a benzyl radical.

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

More in particular, the invention relates to a compound according to the general Formula (I), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and a prodrug thereof, wherein 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 with compound number 219, 270, 269,

281, 408, 393, 72, 164, 253, 258, 267, 286, 317, 318, 313, 308, 331, 366, 31, 32, 4, 71, 218, 259, 287, 285, 306 and 321, as mentioned in any one of Tables 1-6 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-L denotes -H.

The pharmaceutically acceptable salts are defined to comprise the therapeutically active non-toxic acid addition salts forms that the compounds according to Formula (I) are able to form. Said salts can be obtained by treating the base form of the compounds according to Formula (I) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid,

succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicylic acid, p-aminosalicylic acid and pamoic acid.

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

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

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

The *N*-oxide forms of the compounds according to Formula (I) are meant to comprise those compounds of Formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more tertiary nitrogens (e.g of the piperazinyl or pyrrolidinyl 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 possibly 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.

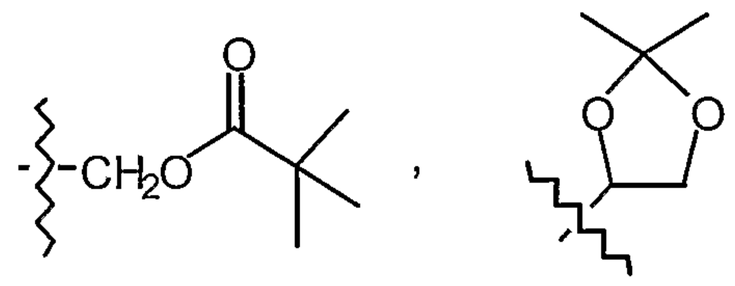
The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms that the compounds of Formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms having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

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

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

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

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



Amidated groups include groups of the formula $-CONR^yR^z$, wherein R^y is H, C_{1-6}alkyl, phenyl or benzyl and R^z is –OH, H, C_{1-6}alkyl, phenyl or benzyl. Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

The compounds of Formula (I) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers that can be separated from one another following art-known resolution procedures. The racemic compounds of Formula (I) may be converted into the corresponding diastereomeric salt forms by

reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of Formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

Pharmacology

Substance P and other tachykinins 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 ^{3}H-substance-P as radioligand. The subject compounds also show substance-P antagonistic activity *in vivo* as may be evidenced by, for instance, the antagonism of substance P-induced plasma extravasation in guinea-pigs, or the antagonism of drug-induced emesis in ferrets (Watson *et al.*, *Br. J. Pharmacol.* **115**:84-94 (1995)).

In view of their capability to antagonize the actions of tachykinins by blocking the neurokinin receptors, and in particular by blocking the NK_1, 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. In particular are compounds according to the invention are useful as orally active, centrally penetrating medicines in the prophylactic and therapeutic treatment of tachykinin-mediated conditions.

More in particular, it has been found that some compounds exhibit a combined NK_1/NK_3 antagonistic activity or a combined $NK_1/NK_2/NK_3$ antagonistic activity as can be seen from the Table 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 any one of claims 1-3 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 ; eye and dental inflammation and pancreatitis, in particular chronic and acute pancreatitis.

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

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

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

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

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, depression, anxiety disorders, emesis and irritable bowel syndrome (IBS) 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

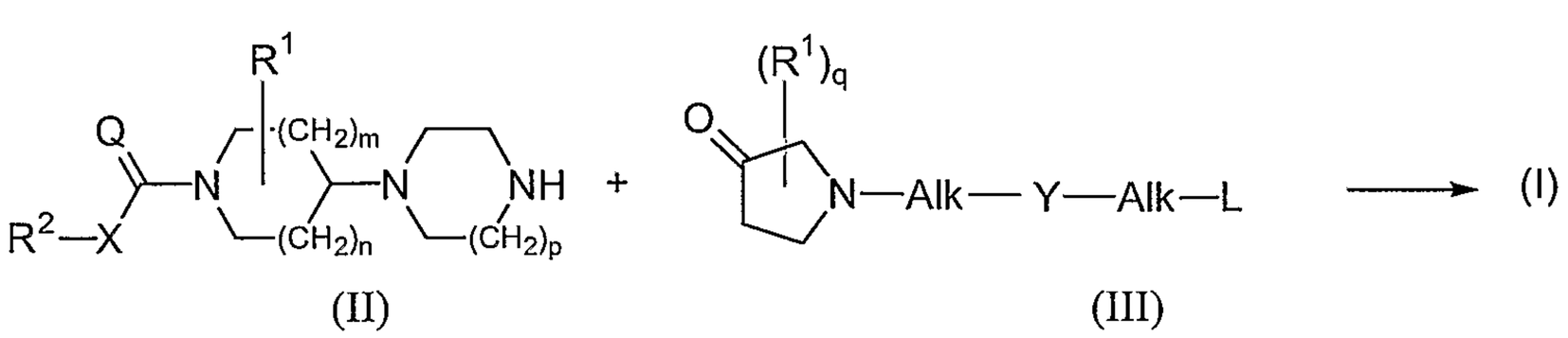
tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Since the compounds according to the invention are potent orally, mainly centrally active 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.

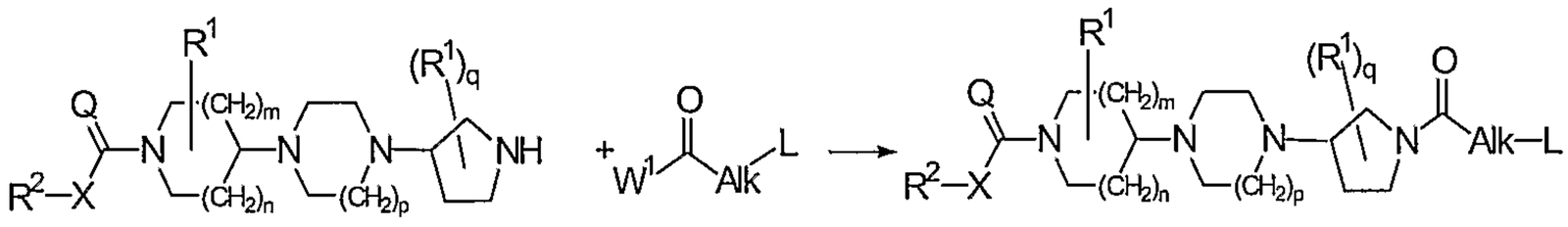
The final compounds of Formula (I) are conveniently prepared by reductively *N*-alkylating an intermediate compound of Formula (II) with an intermediate compound of Formula (III) . Said reductive *N*-alkylation may be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol 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.



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.

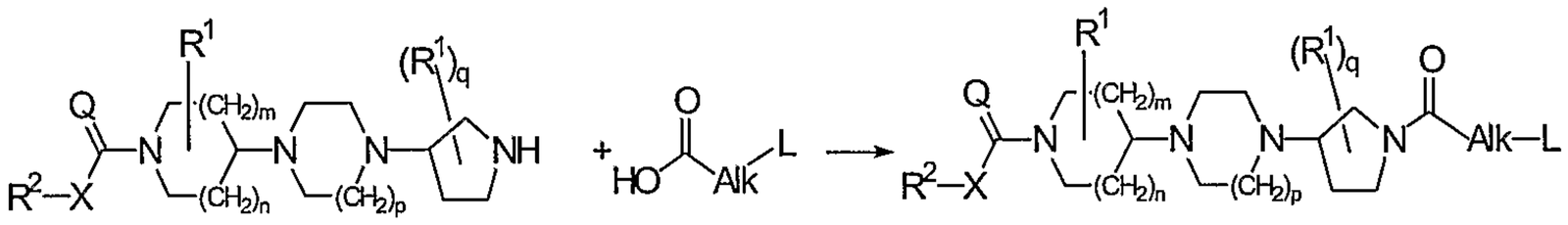
In particular, the final compounds of Formula (I^a) can be prepared by reacting a final compound of Formula (I') with an intermediate compound of Formula (V) wherein W^1 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy or benzenesulfonyloxy. 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)

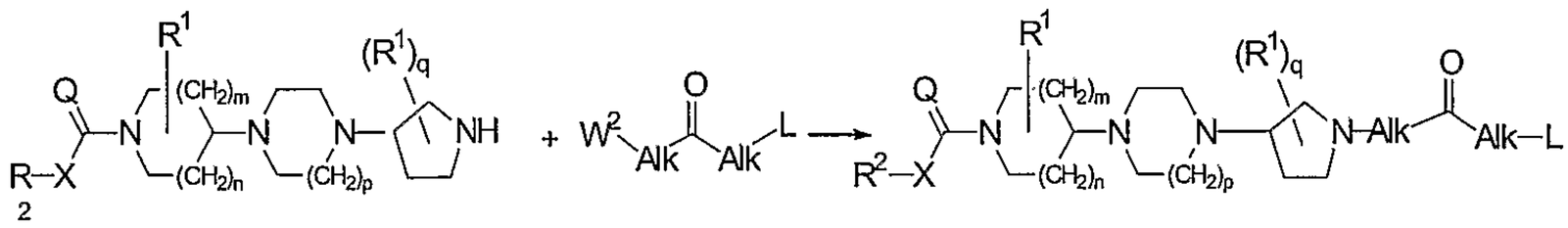
Alternatively, the final compounds of Formula (I^a) can also be prepared by reacting a final compound of Formula (I') with a carboxylic acid of Formula (VI). The reaction can be performed in a reaction-inert solvent such as, for example, a chlorinated hydrocarbon, e.g. dichloromethane, in the presence 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 (carbonyldiimidazole) 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])

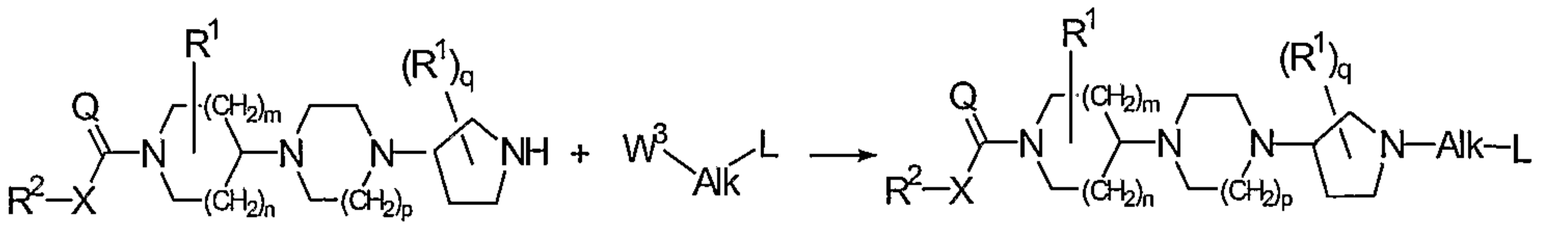
In particular, the final compounds of Formula (I[b]) can be prepared by reacting a final compound of Formula (I') with a compound of Formula (VII) wherein W^2 is an appropriate leaving group such as, for example, a halogen, e.g. chloro or bromo, or a sulfonyloxy leaving group, e.g. methanesulfonyloxy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



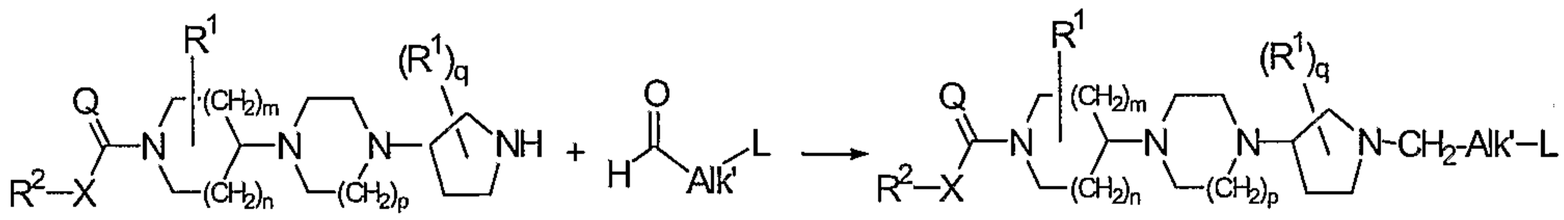
(I') (VII) (I[b])

The final compounds of Formula (I[c]) and Formula (I[d]) can be prepared either by alkylation or reductive amination 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 Alk in Formula (I[d]) is defined as $-CH_2-Alk'$. 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.



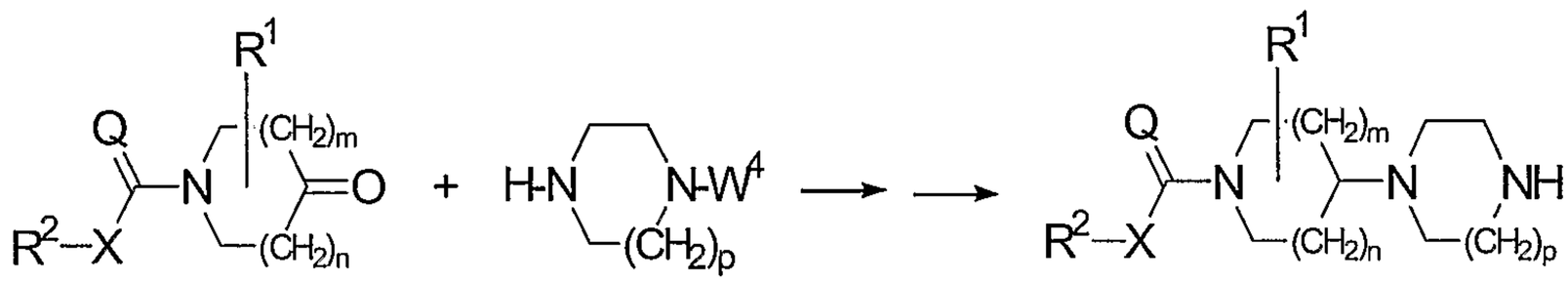
(I') (VIII) (I^c)



(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.

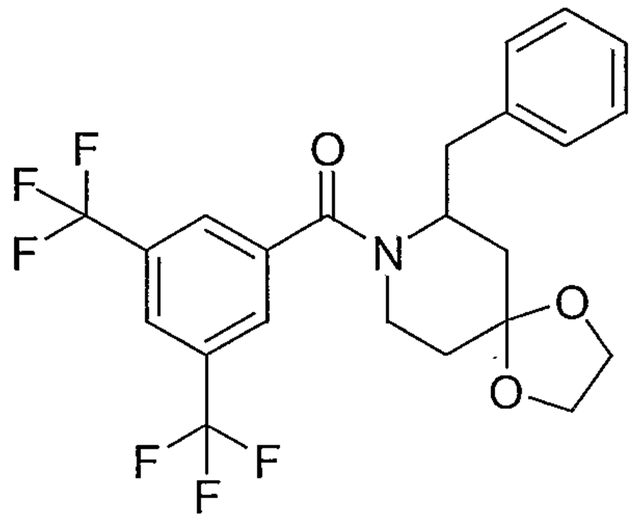
Experimental Part

Hereinafter "RT" means room temperature, "THF" means tetrahydrofuran, "DIPE" means diisopropylether and "DMF" means *N*,*N*-dimethylformamide.

A. Preparation of the intermediate compounds

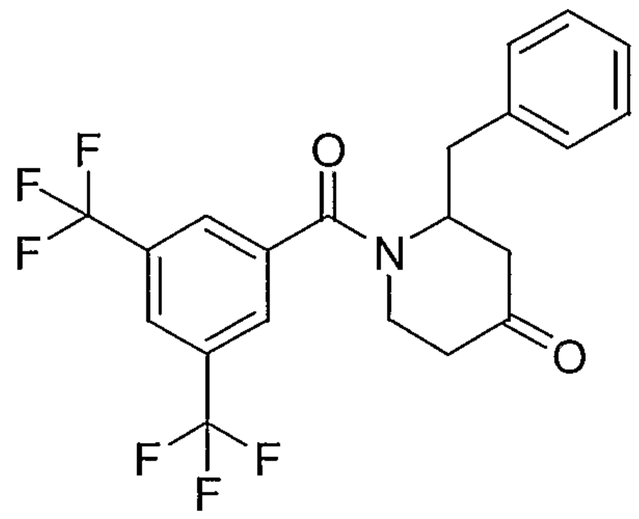
Example A1

a. Preparation of intermediate compound 1



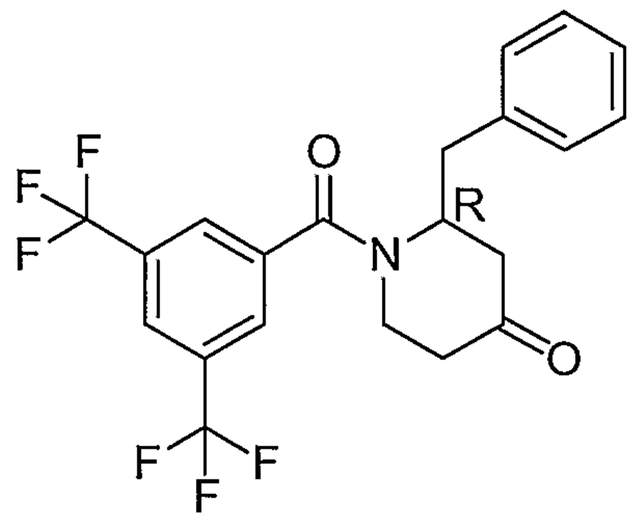
Et_3N (0.55 mol) was added to a stirring mixture of 7-(phenylmethyl)-1,4-dioxa-8-azaspiro[4.5]decane (0.5 mol) in toluene (1500 ml). 3,5-Bis(trifluoromethyl)benzoyl chloride (0.5 mol) was added over a 1-hour period (exothermic reaction). The mixture was stirred at room temperature for 2 hours, allowed 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

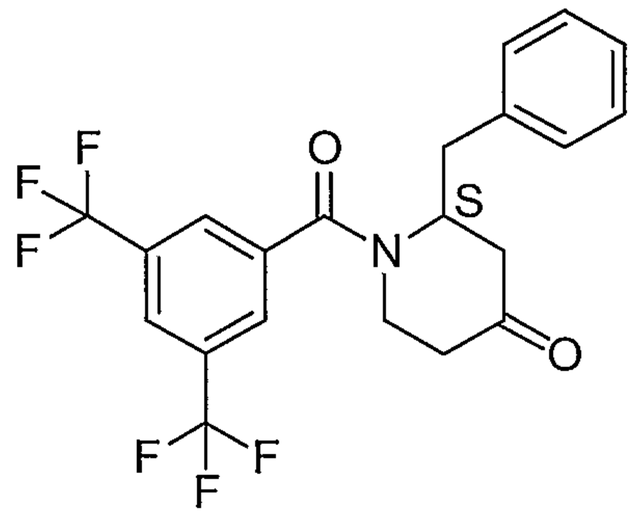


HCl cp (300 ml) was added to a mixture of intermediate compound 1 (0.5 mol) in ethanol (300 ml) and H_2O (300 ml). The reaction mixture was stirred at 60 °C for 20 hours. The precipitate was filtered off, ground, stirred in H_2O, filtered off, washed with petroleum ether and dried. Yield: 192 g of intermediate 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 10 and intermediate compound 11.



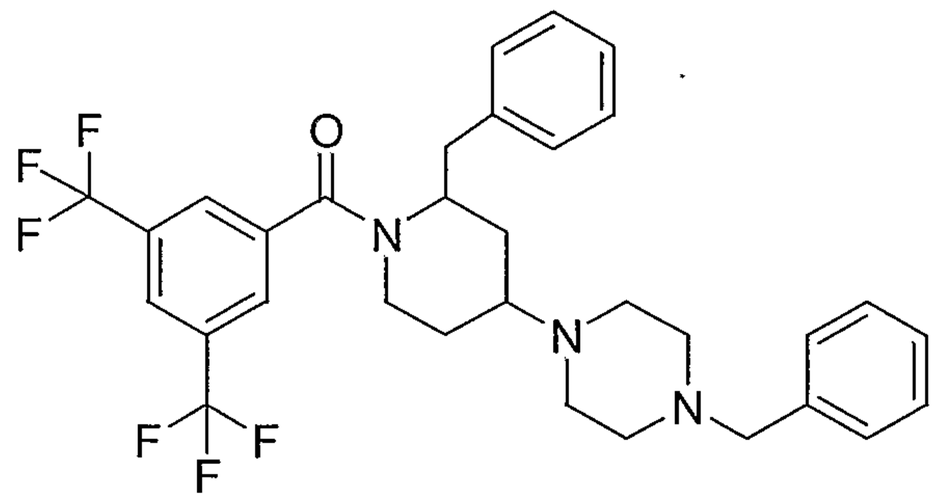
(10)



(11)

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 10 (R), and Fraction 2: 30.4 g of intermediate compound 11 (S).

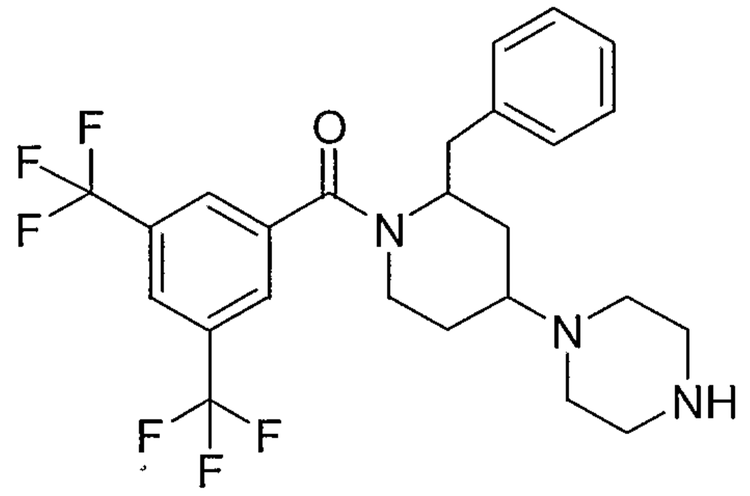
c. Preparation of intermediate compound 3



A mixture of intermediate compound 10 (0.046 mol), 1-(phenylmethyl)piperazine (0.051 mol) and Ti-isopropoxide (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 and 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 and 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. It is without saying that the same reaction can be carried out on compound 11 for obtaining the S-isomer, as well as on any mixture of them. It is also without saying that also the cis-isomer can be used in all reactions in this application exemplified for the trans-isomer or for a mixture of cis and trans-isomers.

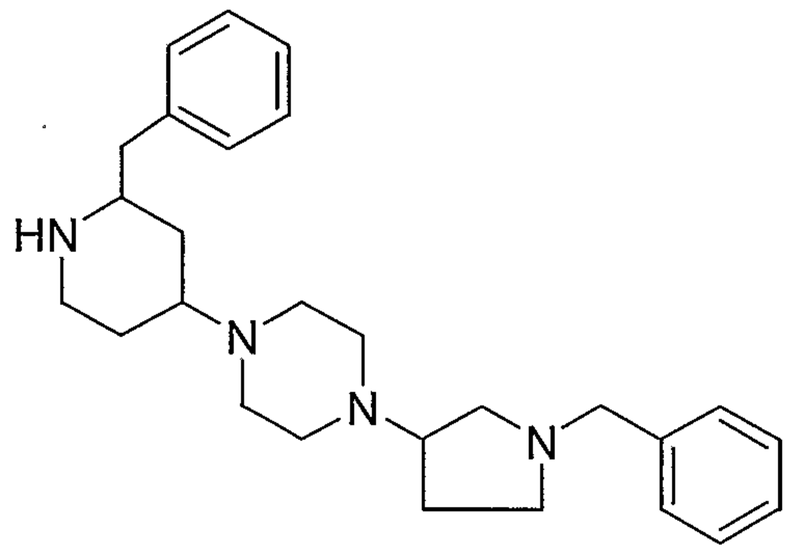
d. Preparation of intermediate compound 4



A mixture 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 eq.), the catalyst was filtered off and the filtrate was evaporated. Yield: 141.2 g of intermediate compound 4 (+)-(2R-trans)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-(1-piperazinyl)piperidine.

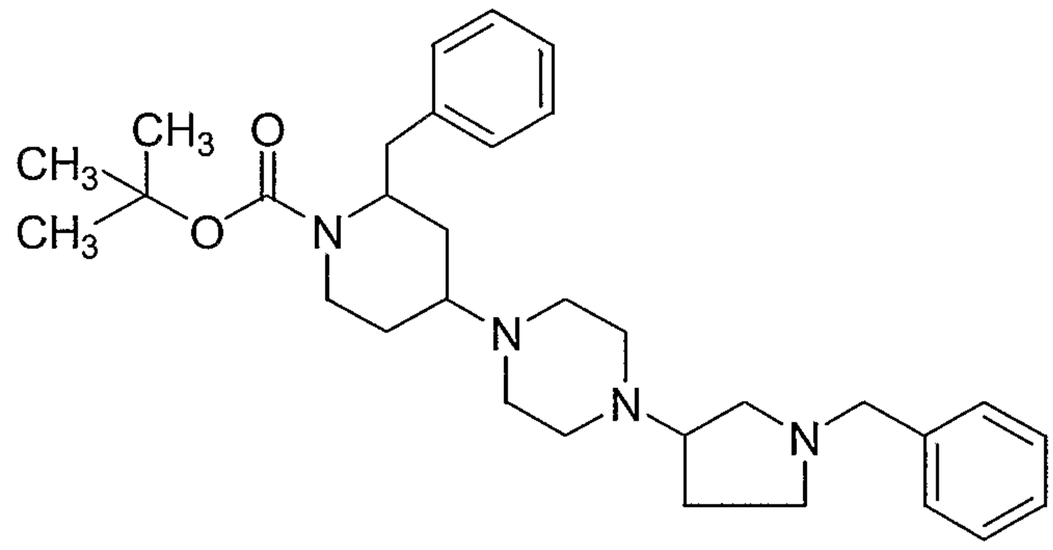
Example A2

a. Preparation of intermediate compound 5



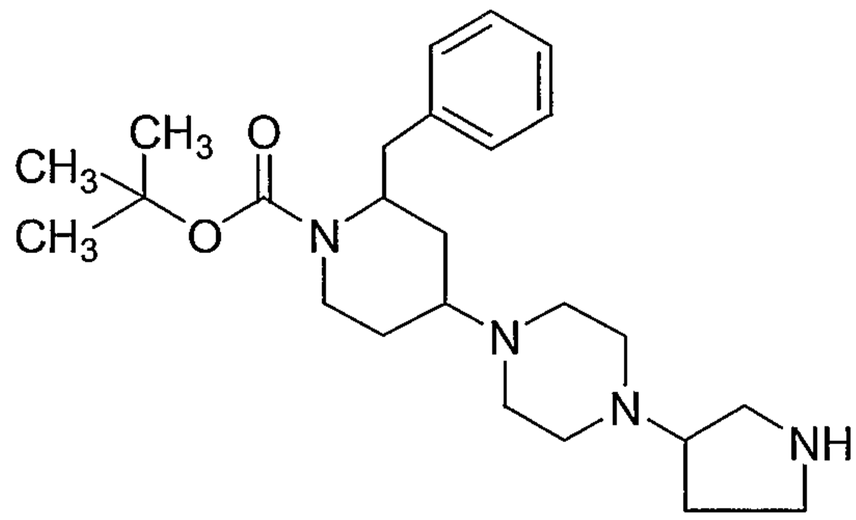
A mixture of final compound 1 (prepared according to B1a) (0.03 mol) in *i*PrOH (150 ml) and KOH (0.3 mol) was stirred and refluxed for 18 hours. The solvent was evaporated and the residue was taken up in CH_2Cl_2/H_2O. The layers were separated. The organic layer was dried and filtered. The solvent was evaporated and the residue purified by column chromatography over silica gel (gradient eluent: $CH_2Cl_2/(MeOH/NH_3)$ 95/5 to 90/10). The product fractions were collected and the solvent evaporated. Yield: 12 g of intermediate compound 5.

b. Preparation of intermediate compound 6



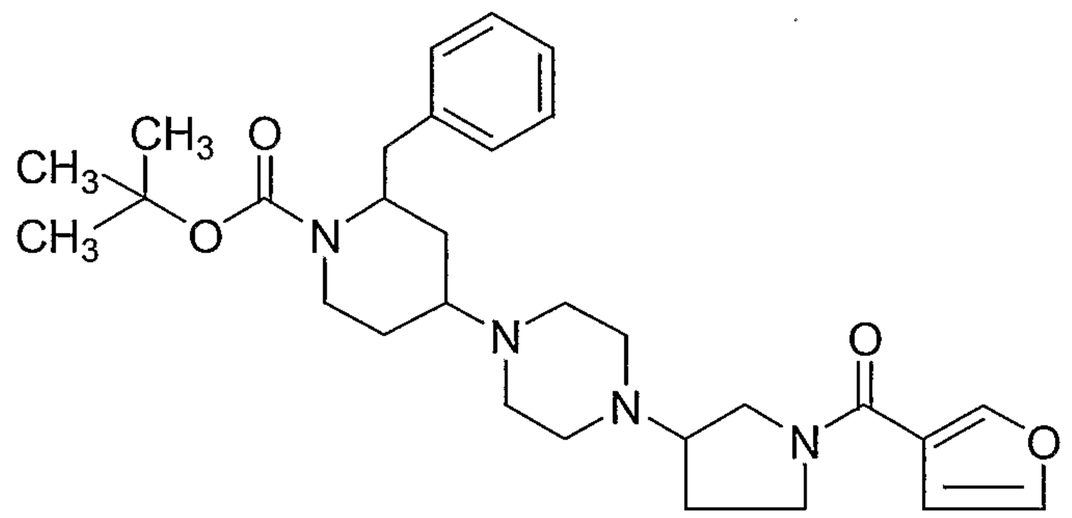
A mixture of intermediate compound 5 (0.029 mol) in bis(1,1-dimethylethyl)-dicarbonic acid ester (0.035 mol) was stirred 18 hours at room temperature. The solvent was evaporated for 30 minutes at 50-60 °C. The residue was taken up in CH_2Cl_2/H_2O and NaOH. The organic layer was separated, washed with water, dried and the solvent evaporated. The residue was suspended in toluene and the solvent was evaporated. Yield : 15.5 g of intermediate compound 6.

c. Preparation of intermediate compound 7



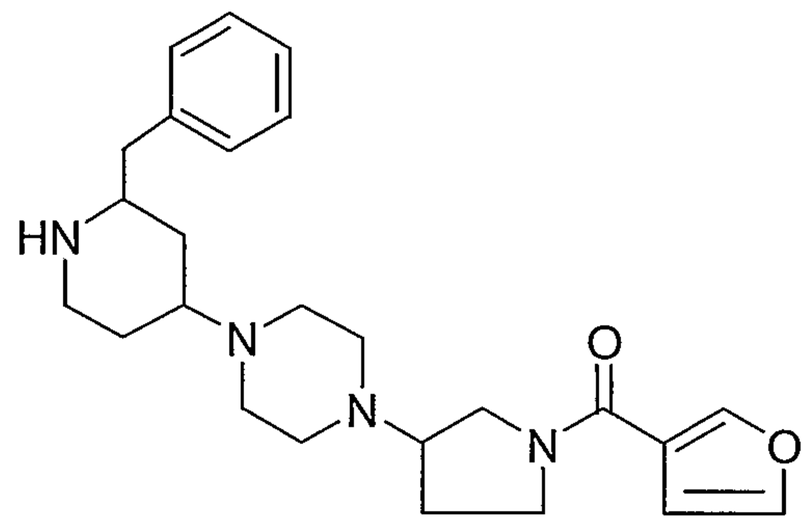
A mixture of intermediate compound 6 (0.03 mol), Pd/C, 10% (2 g), H_2 (1 eq) in methanol (250 ml) was stirred. After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/(MeOH/NH_3) 90/10 to 85/15). The product fractions were collected and suspended in petroleum ether, filtered and dried Yield: 11.6 g of intermediate compound 7.

d. Preparation of intermediate compound 8



A mixture of 3-furancarboxylic acid (0.033 mol) in CH_2Cl_2 (100 ml) and 1,1'-carbonylbis-1*H*-imidazole (0.033 mol) was stirred for 3 hours at room temperature. Intermediate compound 7 (0.027 mol) in CH_2Cl_2 (100 ml) was added and stirred overnight at room temperature. The reaction mixture was washed with aqueous NaOH, with H_2O, dried and the solvent was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/MeOH) 98/2 to 90/10). The product fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The solid was dried. Yield : 7.83 g of intermediate compound 8

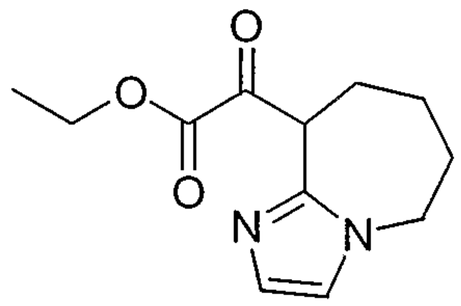
e. Preparation of intermediate compound 9



*i*PrOH.HCl (3 ml) was added to a mixture of intermediate compound 8 (1 g) in *i*PrOH (30 ml). The mixture was stirred at 65 °C for 90 minutes. The solvent was evaporated. The residue was suspended in DIPE. The precipitate was filtered and washed with DIPE. Yield : 0.93 g of intermediate compound 9 (.HCl).

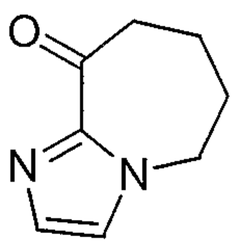
Example A3

a. Preparation of intermediate compound 12



A mixture of 6,7,8,9-tetrahydro-5*H*-imidazo[1,2-a]azepine (0.02 mol) and Et_3N (0.035 mol) in CH_3CN (50 ml) was stirred at room temperature and under N_2 flow. Chloro-oxo acetic acid ethyl ester (0.03 mol) was added dropwise at <10 °C. Stirring was continued overnight. Water was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was separated , dried ($MgSO_4$) , filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 2 g of intermediate compound 12 (42%).

b. Preparation of intermediate compound 13



A mixture of intermediate compound 12 (0.0084 mol) in 2-propanone (30 ml) was stirred, while cooling on an ice-bath. Excess Jones'reagent (prepared according to the method below) was added dropwise at room temperature. The reaction mixture was stirred for a while. Water (50 ml) was added and this mixture was alkalized with K_2CO_3. This mixture was evaporated. The residue was stirred in CH_3OH. The salts were removed by filtration over dicalite. The filtrate was evaporated. The residue was stirred

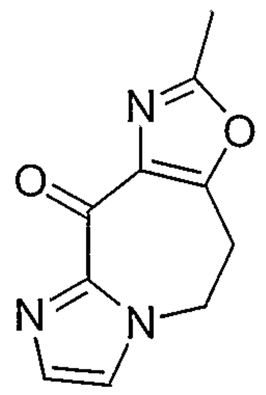
in CH_2Cl_2. The organic layer was decanted, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue (0.56 g) was stirred in DIPE , filtered off and dried. Yield: 0.32 g of intermediate compound 13 (25%).

Preparation of Jones' reagent: CrO_3 (26.72 g) was dissolved in H_2O (50 ml). H_2SO_4 (98%;23 ml) was added dropwise, while cooling. Water was added until a total volume of 100 ml was obtained.

c. Preparation of intermediate compound 14

A mixture of intermediate compound 13 (0.0176 mol) in H_2O (10 ml) and HOAc (3 ml) was stirred at 50 °C. $NaNO_2$ (1.35 g) was added portionwise over a 5 min. period and the mixture was stirred at 50 °C for 1 h. The mixture was cooled on an ice bath and filtered off. The precipitate was washed with icewater and dried in an desiccator. Yield : 1.25 g of intermediate compound 14 (35.8 %).

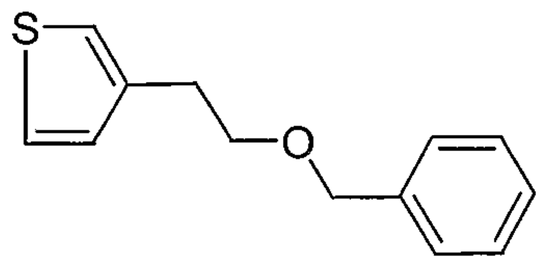
d. Preparation of intermediate compound 15



A mixture of intermediate compound 14 (0.045 mol) in HOAc (90 ml) and acetic acid anhydride (9 ml) was stirred on an oil bath at 85 °C. Acetylchloride (13.7 ml) was added dropwise over a 30 min. period and the mixture was stirred at 85 °C for 1 hour. The mixture was cooled, poured into ice/K_2CO_3 and extracted with $CHCl_3$. The organic layer was dried and evaporated. The residue was boiled up in CH_3CN and cooled. The precipitate was filtered off and dried. Yield : 14.32 g of intermediate compound 15 (47.3 %).

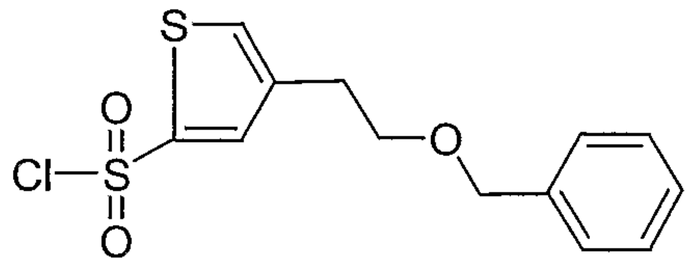
Example A4

a. Preparation of intermediate compound 16



NaH (0.086 mol) was added portionwise to a solution of 3-thiophene ethanol (0.078 mol) in THF at 5 °C. 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 16 (58 %).

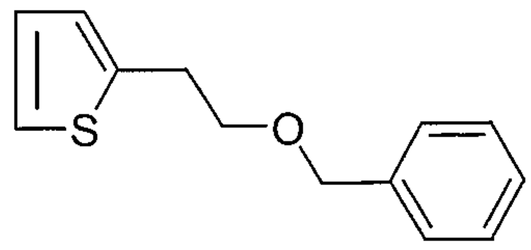
b. Preparation of intermediate compound 17



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. 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 17 (16 %).

Example A5

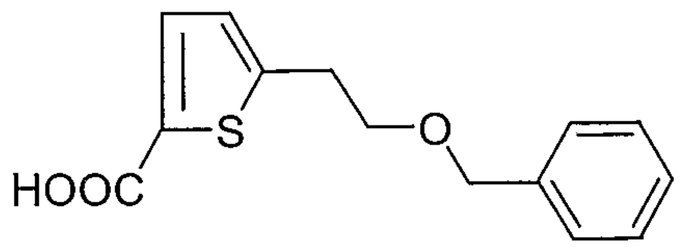
a. Preparation of intermediate compound 18



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 (bromomethyl)benzene (0.080 mol, 9.5 ml) were added consecutively 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 (66 %) of intermediate compound 18.

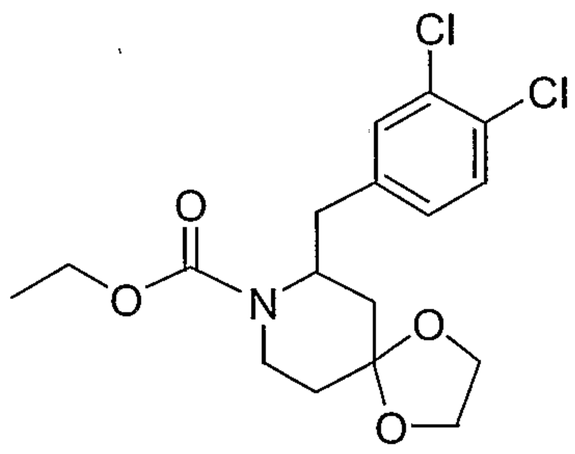
b. Preparation of intermediate compound 19



n-BuLi (1.6 M) (0.015 mol, 9.45 ml) was added slowly to a solution of intermediate compound 18 (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 to yield 2.6 g (71%) of intermediate compound 19.

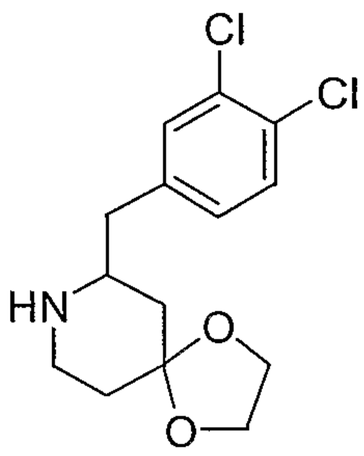
Example A6

a. Preparation of intermediate compound 20



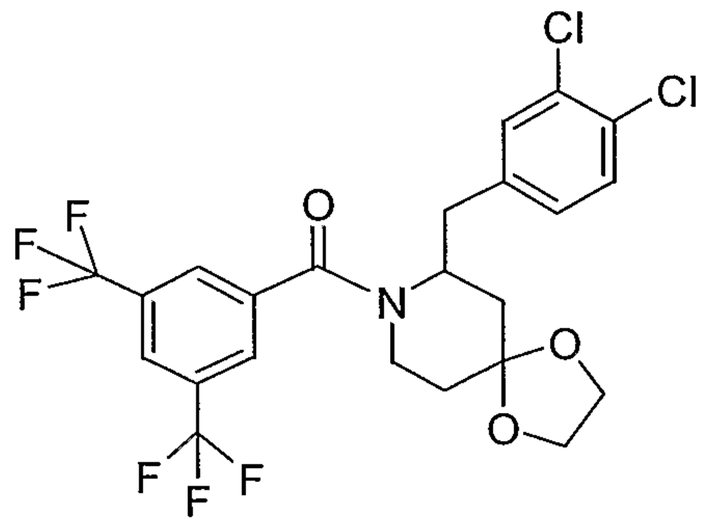
A mixture of 2-[(3,4-dichlorophenyl)methyl]-4-oxo-1-piperidinecarboxylic acid ethyl ester (0.3 mol), 1,2-ethanediol (1.5 mol) and 4-methylbenzenesulfonic acid (2 g) in toluene (750 ml) was stirred and refluxed for 68 hours using a water separator. The solvent was evaporated. The residue was partitioned between water and toluene. The organic layer was separated, washed with water, dried, filtered and the solvent evaporated. Yield: 113.5 g of intermediate compound 20.

b. Preparation of intermediate compound 21



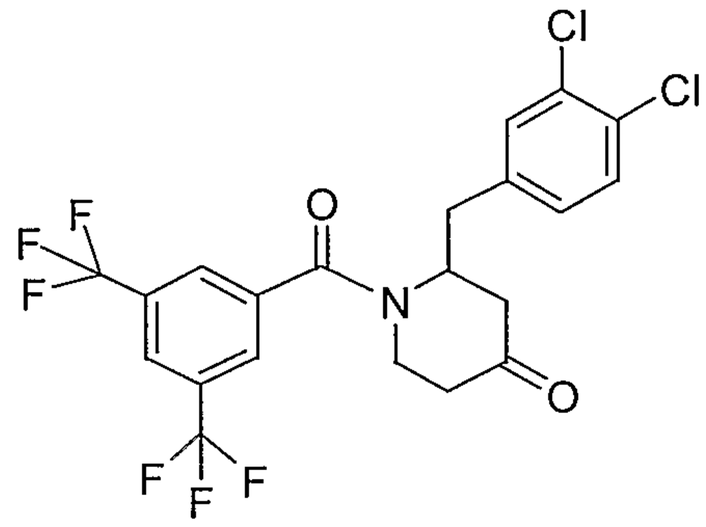
A mixture of intermediate compound 20 (0.1 mol) and KOH (0.9 mol) in 2-propanol (500 ml) was stirred and refluxed overnight. The solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with a small amount of H_2O. The organic layer was dried, filtered and the solvent was evaporated. Yield: 33 g of intermediate compound 21.

c. Preparation of intermediate compound 22



Intermediate compound 21 (0.139 mol) was dissolved in CH_2Cl_2 (420 ml) . 3,5-bis(trifluoromethyl)benzoylchloride (0.15 mol) was added dropwise (exothermic). Et_3N (30 ml) was added. The reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was washed with a basic NaOH solution, dried, filtered and the solvent evaporated. The residue was purified over silica gel on a glass filter (gradient eluent: CH_2Cl_2/CH_3OH from 100/0 to 95/5). The product fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE, filtered off and dried. Yield: 56.3 g of fraction 1 . The filtrate was evaporated. The residue was suspended in petroleum ether, filtered off and dried. Yield: 9 g of fraction 2. The total yield (65.3 g) of these fractions was separated and purified by chiral column chromatography (AD-packing, eluent: heptane/ethanol 95/5). Two product fraction groups were collected and their solvent was evaporated. Each residue was crystallized from DIPE, filtered off and dried. Yield: 23.9 g of intermediate compound 22 (optically pure).

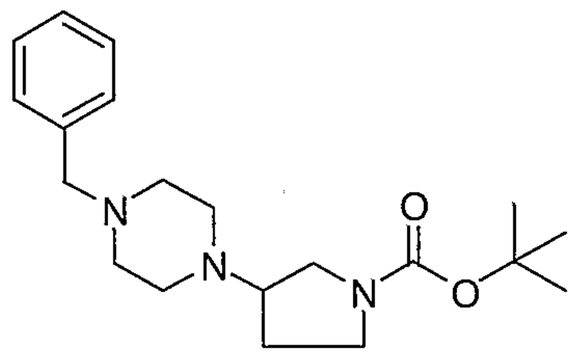
d. Preparation of intermediate compound 23



A mixture of intermediate compound 22 (0.0424 mol) in HCl (6N) (230 ml) was stirred and refluxed for 4 hours. The reaction mixture was stirred overnight and extracted with CH_2Cl_2. The organic layer was separated, washed with water, dried and the solvent was evaporated. Yield: 20 g of intermediate compound 23 (S-isomer).

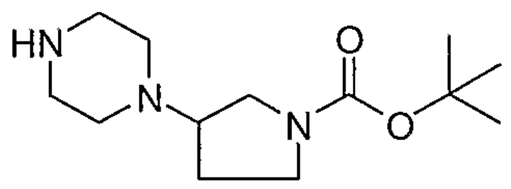
Example A7

a. Preparation of intermediate compound 24, 25 and 26



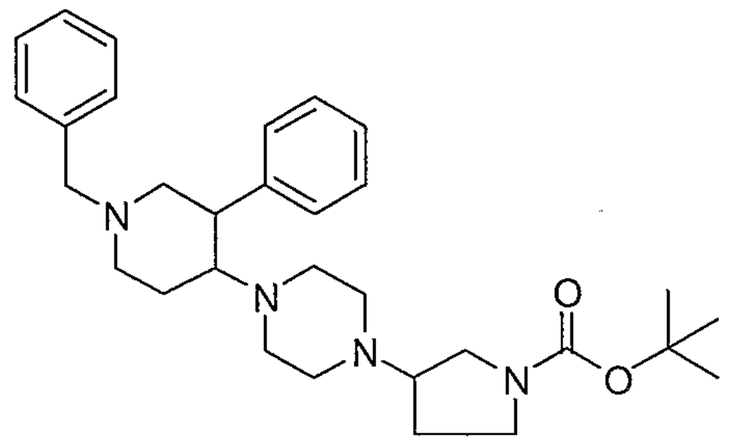
A mixture of 1,1-dimethylethyl-1-pyrrolidinecarboxylic acid ester (0.2 mol) and 1-(phenylmethyl)piperazine (0.2 mol) in methanol (250 ml) was stirred and hydrogenated at 50°C with Pd/C, 10% (3 g) as a catalyst in the presence of thiophene solution (3 ml). After uptake of H_2 (1 eq), the catalyst was filtered off and the filtrate was evaporated. Yield: intermediate compound 24 (racemic mixture). This fraction was separated and purified by column chromatography (DAICEL;AD-packing, 2000 g, 750 ml/min; eluent: heptane/ethanol/methanol 90/5/5). Two product fraction groups were collected and their solvent was evaporated. Yield: 30 g of intermediate compound 25 (S-isomer) (ee: > 99%), and 26 g of intermediate compound 26 (R-isomer) (ee: > 99%).

b. Preparation of intermediate compound 27



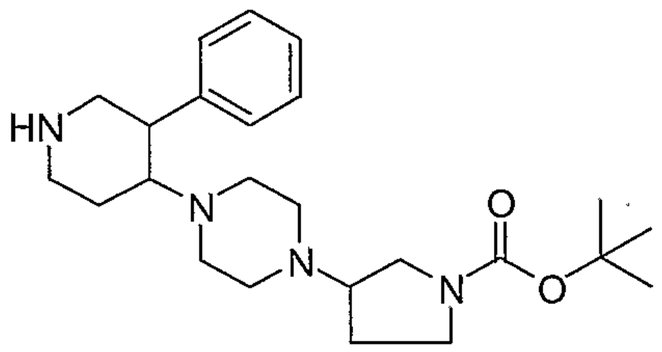
A mixture of intermediate compound 26 (0.078 mol) in methanol (250 ml) was hydrogenated at room temperature with Pd/C 10% (2 g) as a catalyst. After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in CH_2Cl_2 and washed with H_2O. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. Yield: 16.3 g of intermediate compound 27 (82 %) (R-isomer).

c. Preparation of intermediate compound 28



A solution of intermediate compound 27 (0.02 mol) in a small amount of CH_2Cl_2 was added to 3-phenyl-1-(phenylmethyl)-4-piperidinone (0.02 mol) and the mixture was stirred, toluene was added and the reaction mixture was evaporated. Titanium, tetrakis(2-propanolato) (0.025 mol) was added to the residual oil and the mixture was stirred for 3 hours at 50°C, EtOH, p.a. (30 ml) was added and the resulting mixture was stirred for 15 min. at room temperature. Finally $NaBH_3CN$ (0.04 mol) was added and the reaction mixture was stirred for 20 hours at room temperature. The mixture was washed with a basic NaOH solution and CH_2Cl_2 was added. The resulting mixture was stirred for 15 min. and after addition of dicalite the mixture was filtered over dicalite. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified over silica gel on a glass filter (gradient eluent: CH_2Cl_2/CH_3OH 100/0 -> 90/10). The product fractions were collected and the solvent was evaporated. Yield: 6.4 g of intermediate 28.

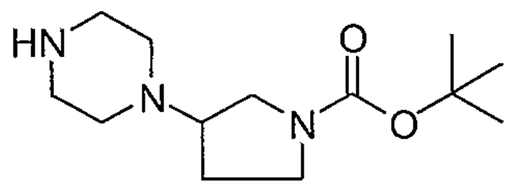
d. Preparation of intermediate compound 29



A mixture of intermediate compound 28 (0.013 mol) in CH_3OH (150 ml) was hydrogenated at 50°C with Pd/C 10% (2 g) as a catalyst. After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 100/0 -> 80/20). The product fractions were collected and the solvent was evaporated. Yield: 2 g of intermediate compound 29.

Example A8

Preparation of intermediate compound 30



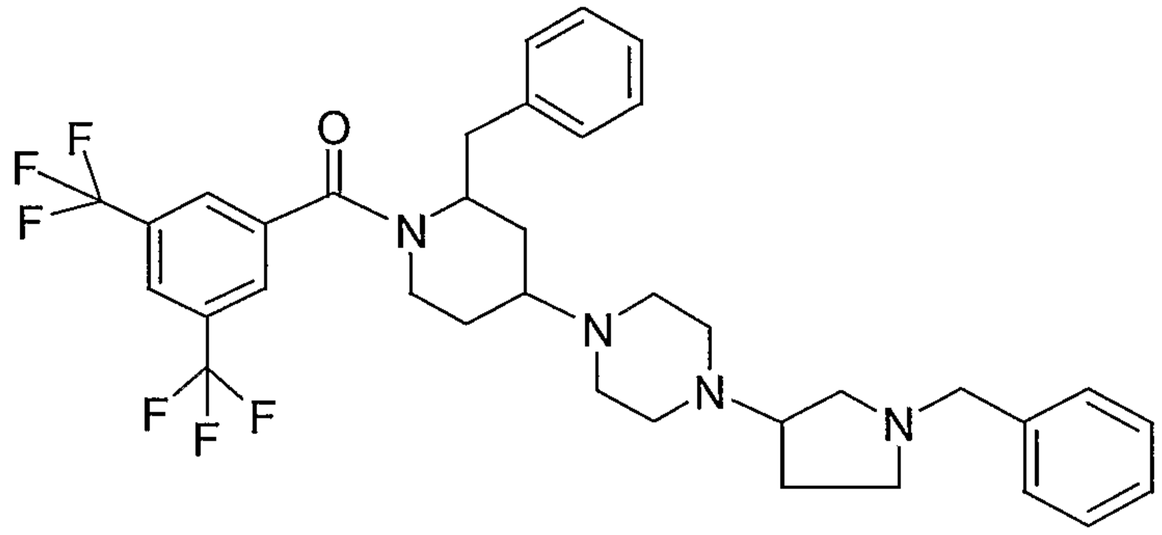
S-isomer

The intermediate compound 30 was obtained by the same method as described in A7.b, but instead of intermediate compound 26 intermediate compound 25 was used.

B. Preparation of the final compounds

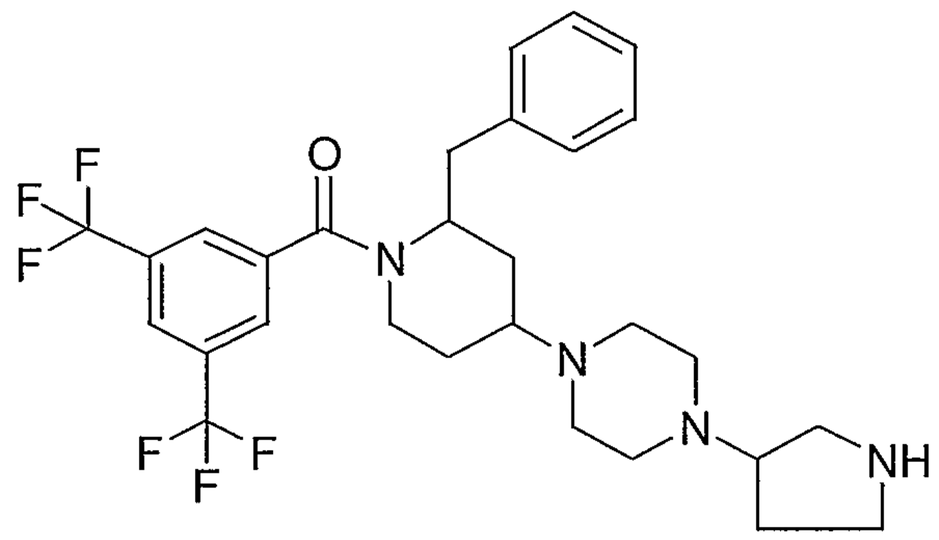
Example B1

a) Preparation of final compound 1



A mixture of (2R-trans) 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-(1-piperazinyl)piperidine [intermediate compound 3] (0.05 mol) and 1-(phenylmethyl)-3-pyrrolidinone (0.05 mol) in methanol (250ml) was hydrogenated at 50 °C with Pd/C 10% (3 g) as a catalyst in the presence of a thiophene solution (2 ml). After uptake of H_2 (1 eq.), the catalyst was filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent : CH_2Cl_2/MeOH 100/0;99/1;98/2;96/4). The desired fractions were collected and the solvent was evaporated. This fraction was recrystallized from DIPE. The precipitate was filtered off, washed with DIPE and dried (vacuum ; 50 °C). Yield : 16.8 g (49 %) of final compound 1.

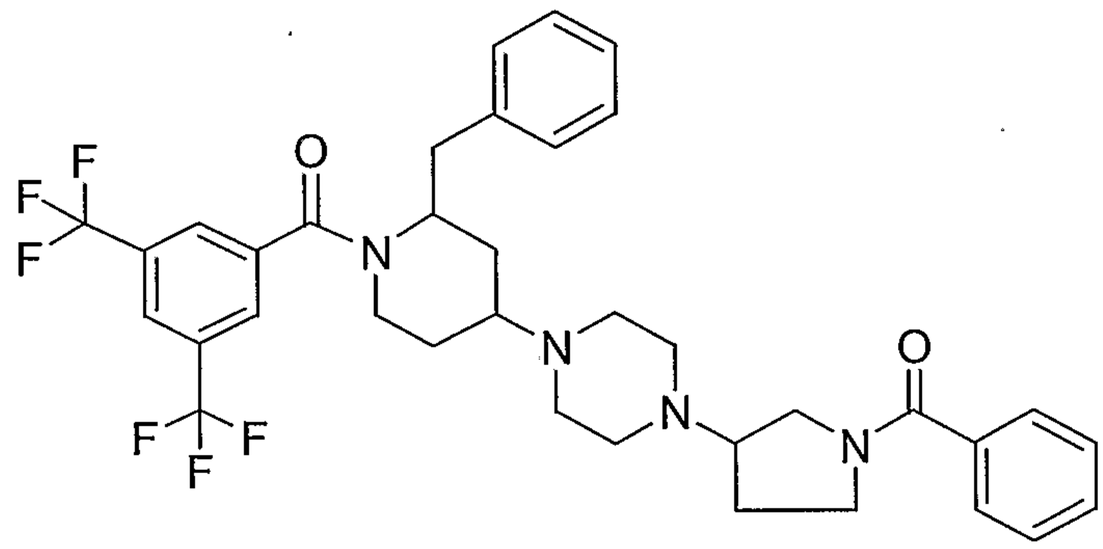
b) Preparation of final compound 2



Final compound 1 (0.022 mol) in methanol (250ml) was hydrogenated with Pd/C 10 % (2 g) as a catalyst. After uptake of H_2 (1 eq.), the catalyst was filtered off and the solvent was evaporated. This fraction was triturated under DIPE. The precipitate was filtered off, washed with DIPE and dried (vacuum ; 50 °C; 3 days). Yield : 11.58 g (92 %) of final compound 2.

Example B2

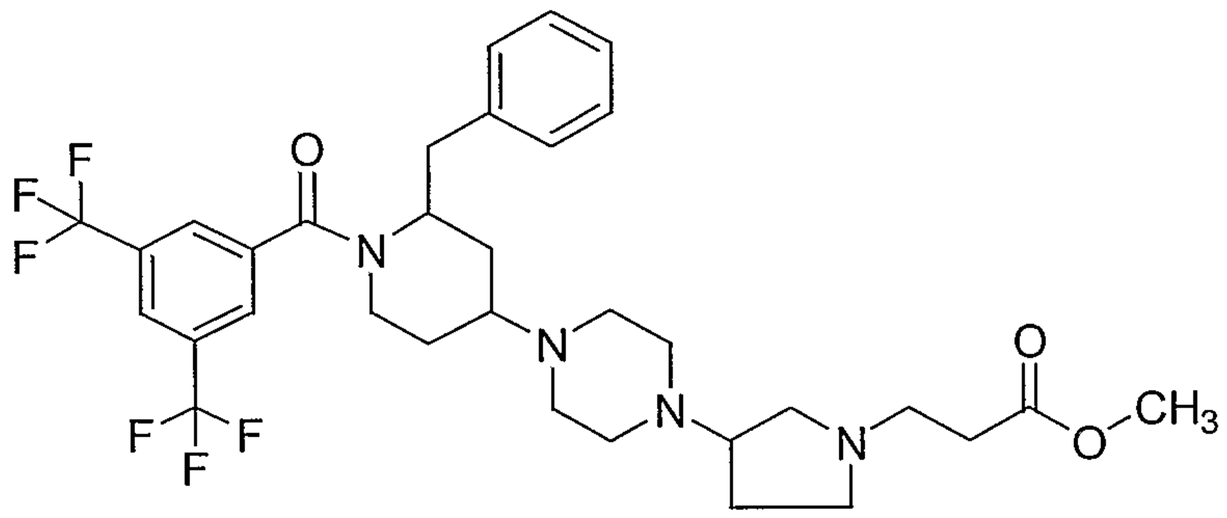
Preparation of final compound 3



A mixture of final compound 2 (0.0016 mol), benzoylchloride (0.0018 mol) and Et_3N (0.0018 mol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 3 hours. The reaction mixture was washed with aq. diluted NaOH solution. The separated organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. This fraction was purified by column chromatography over silica gel (gradient eluent : CH_2Cl_2/MeOH 100/0 to 90/10). The desired fractions were collected and the solvent was evaporated. The residue was dried (vacuum ; 50 °C). Yield : 0.410 g of final compound 3.

Example B3

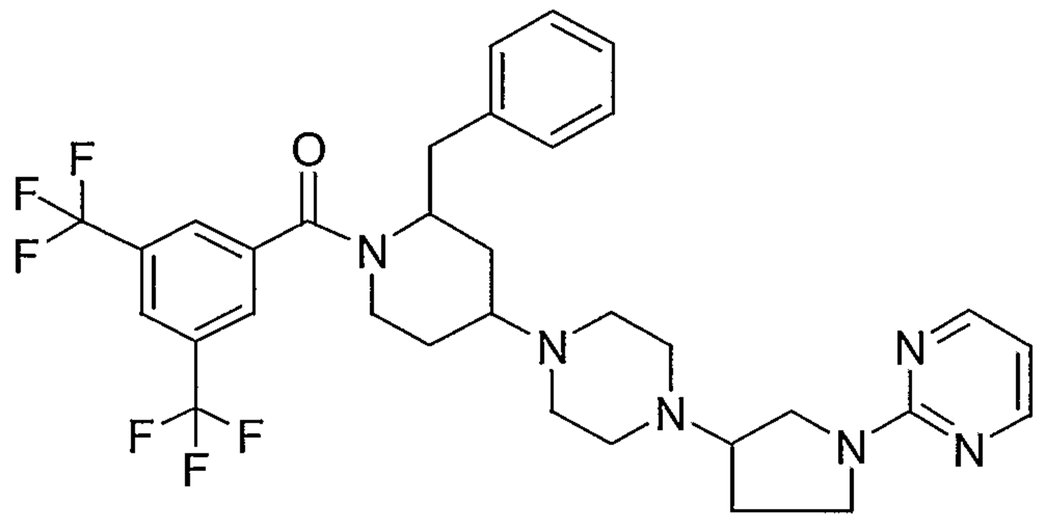
Preparation of final compound 80



A mixture of final compound 2 (0.0017 mol), methyl acrylate (0.0019 mol) in methanol (50 ml) was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by column chromatography over silica gel (gradient eluent : CH_2Cl_2/MeOH 100/0 to 90/10). The desired fractions were collected and the solvent was evaporated. The residue was dried (vacuum, 50 °C). Yield : 0.266 g of final compound 80.

Example B4

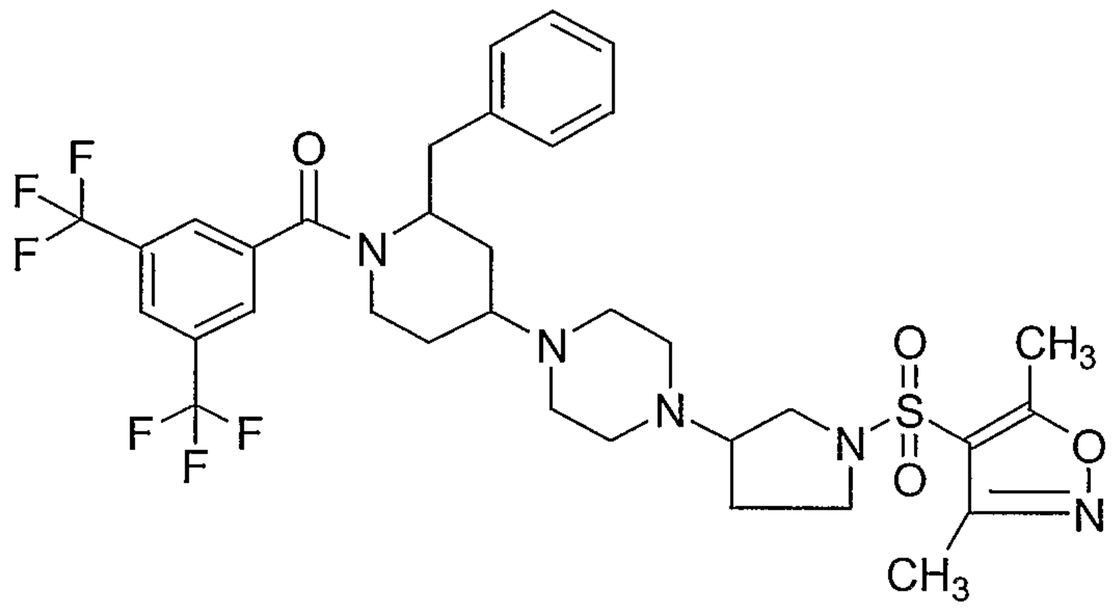
Preparation of final compound 5



A mixture of final compound 2 (0.003 mol), 2-chloropyrimidine (0.0033 mol) and Na_2CO_3 (0.004 mol) in ethanol p.a. (50 ml) was stirred and refluxed for 8 hours. The solvent was evaporated and the residue was taken up in H_2O/CH_2Cl_2. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 and the organic layer was washed with H_2O, dried ($MgSO_4$) and filtered. The solvent was evaporated and 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 and the solvent was evaporated. Yield: 1.378 g of final compound 5.

Example B5

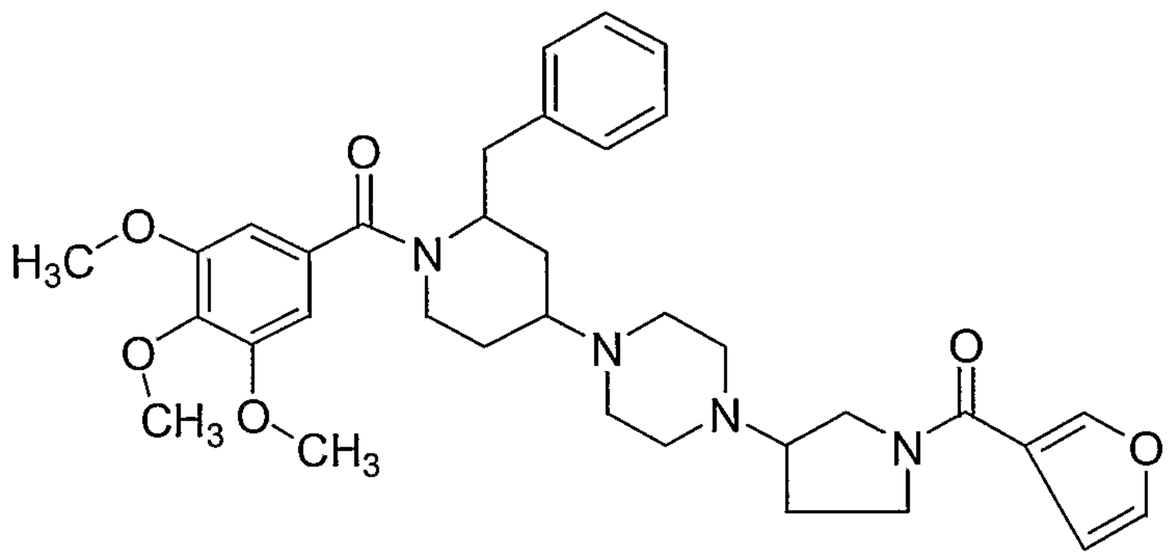
Preparation of final compound 79



A mixture of final compound 2 (0.002 mol), 3,5-dimethylisoxazole-4-sulfonylchloride (0.002 mol),Na_2CO_3 (0.005 mol) and CH_2Cl_2 (50 ml) was stirred at room temperature overnight. 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 residu was dried at 50 °C. Yield : 0.98 g of final compound 79.

Example B6

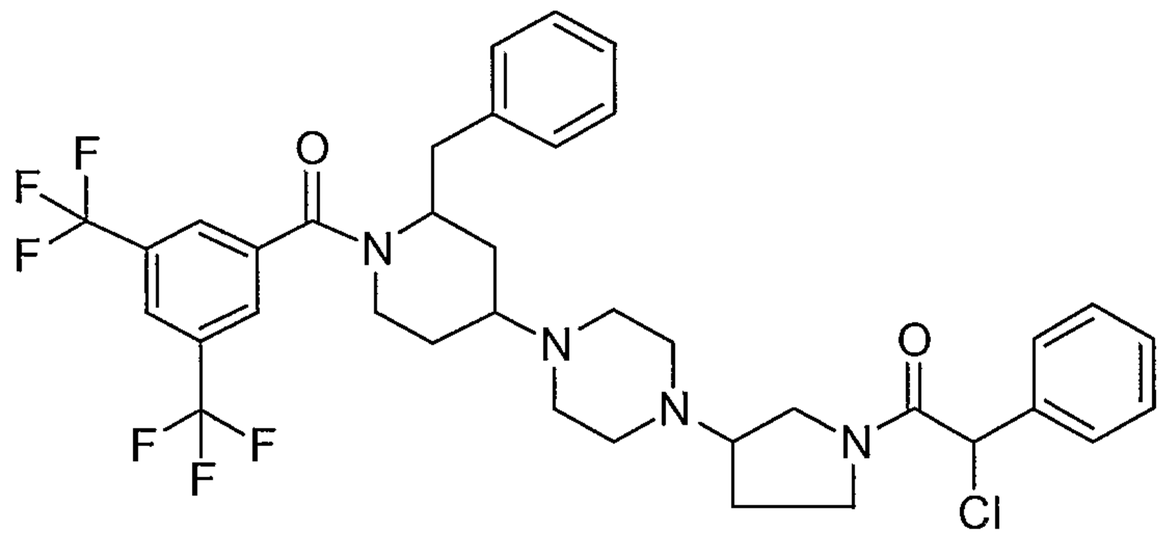
Preparation of final compound 81



A mixture of intermediate compound 9 (prepared according to A2e) (0.0005 mol) in CH_2Cl_2 (25 ml), 3,4,5-trimethoxybenzoylchloride (0.0006 mol) and Et_3N (1 ml) was stirred for 3 hours. The reaction mixture was washed with diluted NaOH during 30 minutes, washed with H_2O, dried and the solvent was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/MeOH 98/2; 90/10). The desired fractions were collected and the solvent evaporated. Yield: 0.114 g of final compound 81.

Example B7

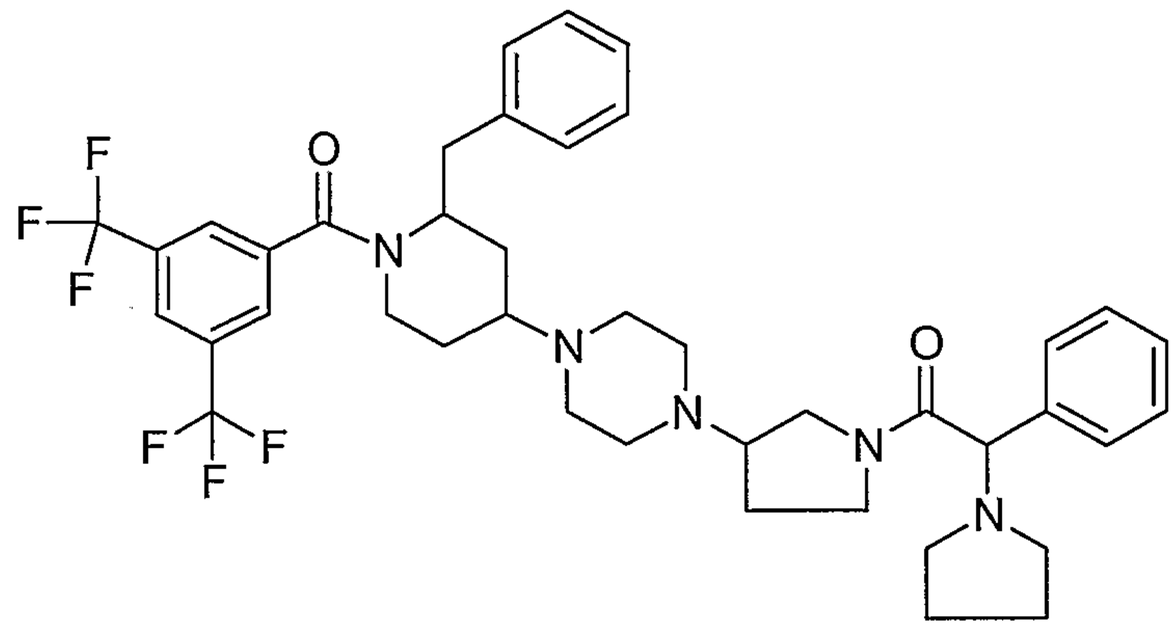
Preparation of final compound 104



Final compound 2 was dissolved in CH_2Cl_2 (100 ml). Alpha-chlorobenzeneacetyl chloride (0.01 mol) was added and the mixture was stirred for 18 hours at room temperature. The reaction mixture was washed with aqueous Na_2CO_3. The organic layer was separated, dried and the solvent evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/MeOH 100/0 to 90/10). The desired fractions were collected and the solvent evaporated. Yield : 6 g of final compound 104.

Example B8

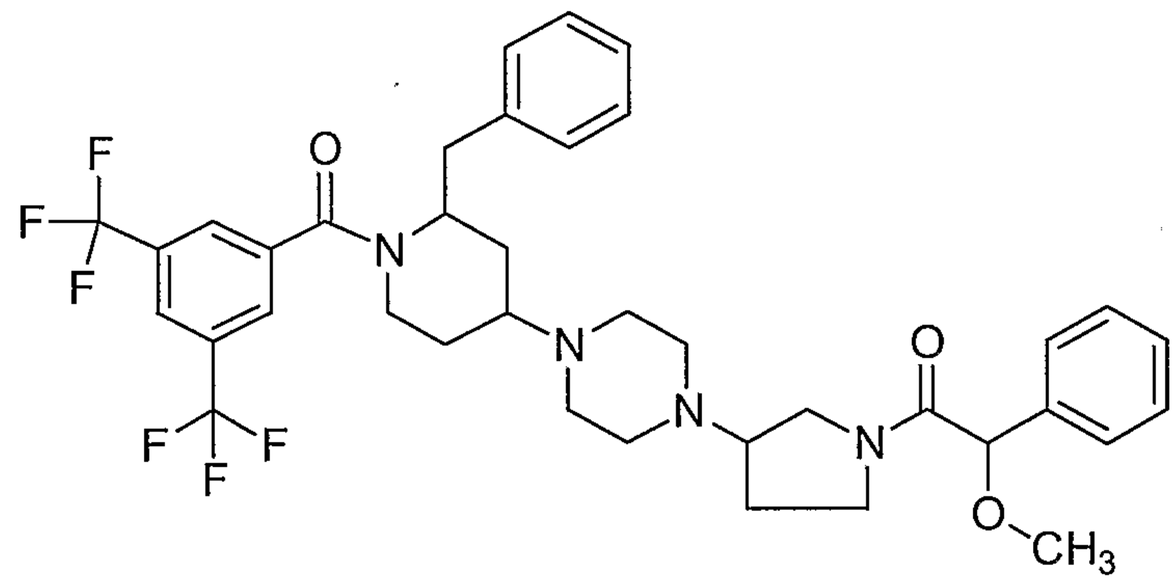
Preparation of final compound 108



A mixture of final compound 104 (prepared according to B7) (0.001 mol) and pyrrolidine (0.5g) was stirred overnight at a bath temperature of 85°C. The excess pyrrolidine was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/MeOH 100/0 to 80/20). The desired fractions were collected and the solvent evaporated. Yield : 0.194g of final compound 108.

Example B9

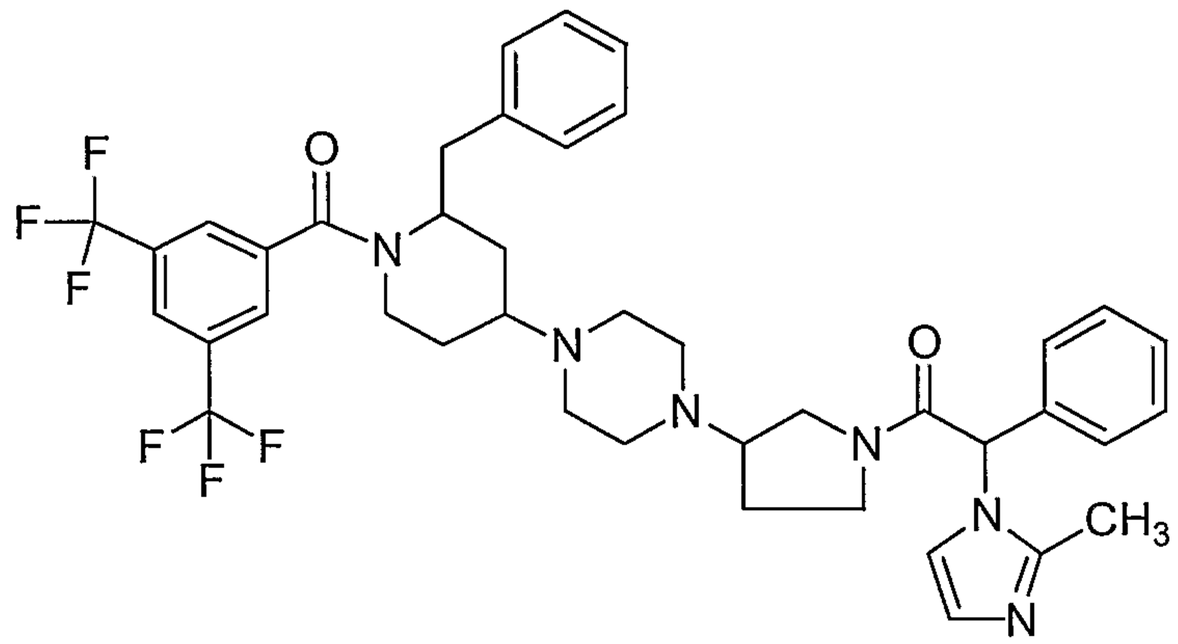
Preparation of final compound 109



Final compound 104 (prepared according to B7) (0.001 mol) was dissolved in methanol (5 ml). $NaOCH_3$ (0.002 mol) was added and the mixture was stirred and refluxed for 48 hours. After 24 hours of stirring and refluxing once more $NaOCH_3$ (0.002 mol) was added. The reaction mixture was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/MeOH 100/0 to 90/10). The desired fractions were collected and the solvent evaporated. Yield : 0.310 g of final compound 109.

Example B10

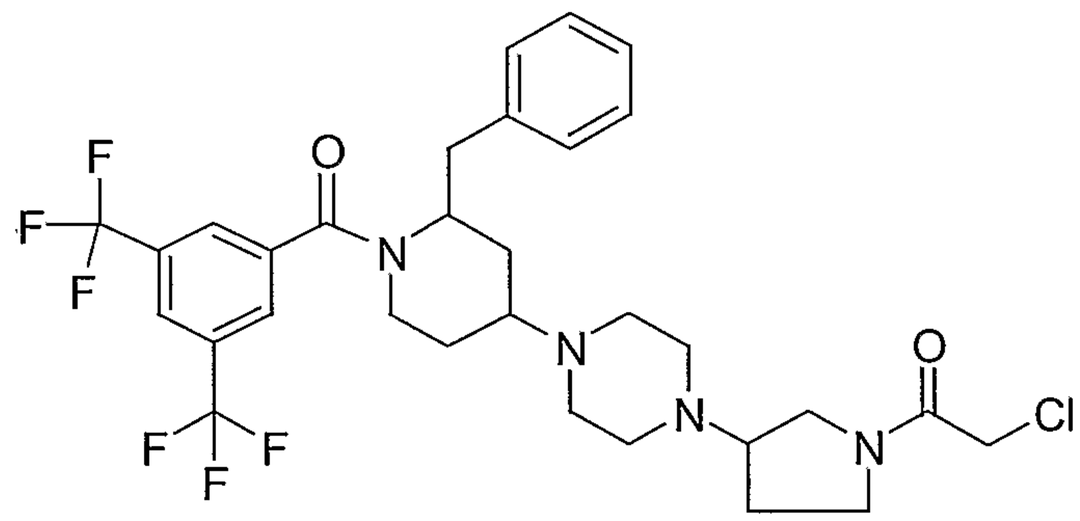
Preparation of final compound 110



NaH (0.002 mol) was added to 2-methylimidazole (0.002 mol) in DMF (10 ml). To the mixture final compound 104 (prepared according to B7) (0.001 mol) diluted in DMF (5 ml) was added and stirred at room temperature for 1 hour. The mixture was stirred for 18 hours at a temperature of 100 °C. The solvent was evaporated. The residue was taken up in H_2O/CH_2Cl_2. The organic layer was separated, dried and evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/MeOH 100/0 to 80/20). The desired fractions were collected and the solvent evaporated. The residue was suspended in petroleum ether, filtered off and dried. Yield : 0.190 g of final compound 110.

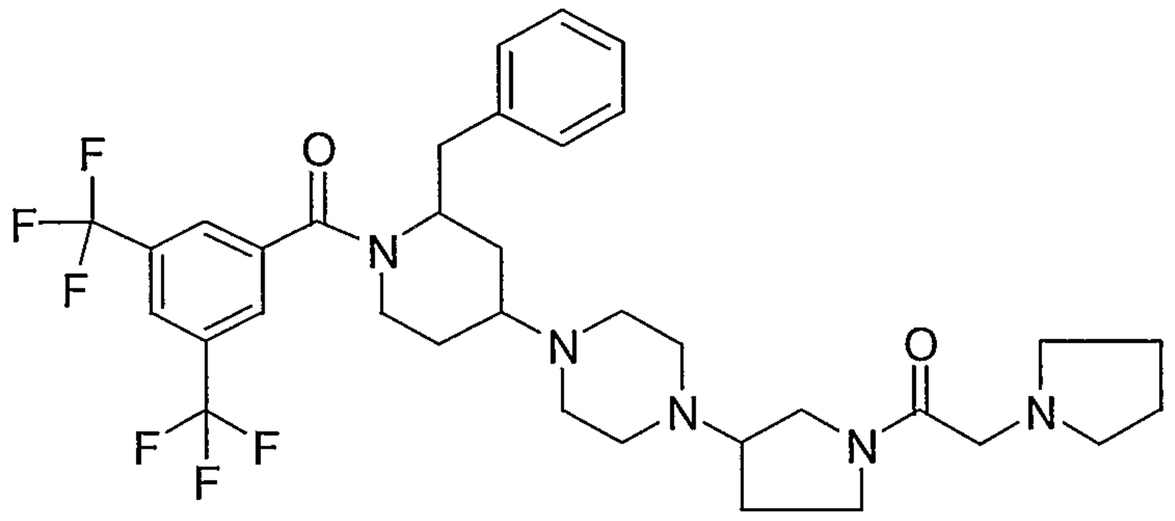
Example B11

a. Preparation of final compound 230



Chloroacetyl chloride (0.01 mol) was added to a solution of final compound 2 (prepared according to B1.b) (0.01 mol) in CH_2Cl_2 (75 ml), Et_3N (3 ml) was added and the reaction mixture was stirred for 4 hours at room temperature. The mixture was washed with a basic NaOH solution, dried and the solvent was evaporated (< 35°C). DIPE was added and the solvent was evaporated again. Yield: 5 g of final compound 230 (77.5%)

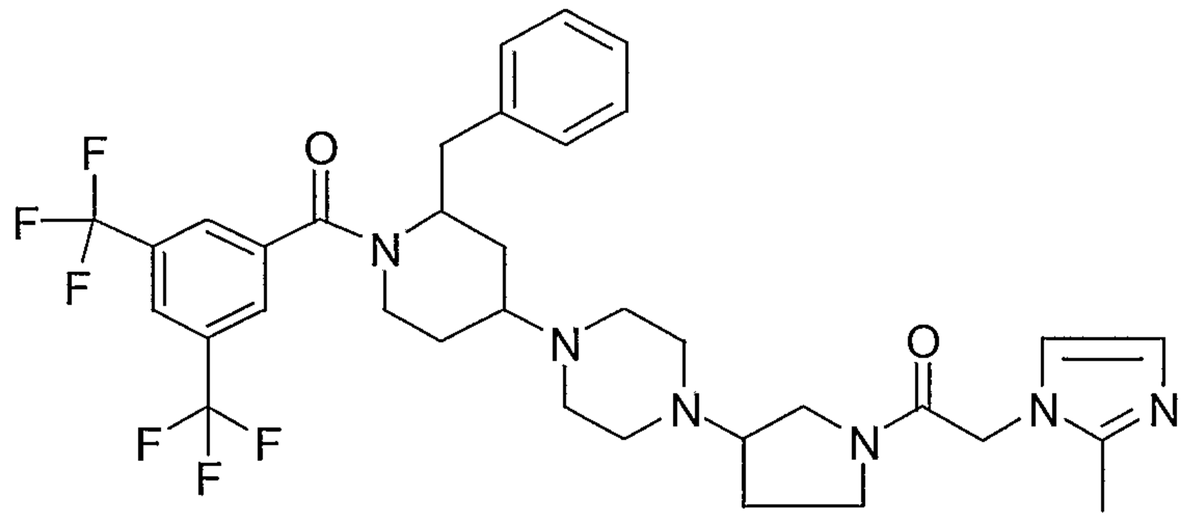
b. Preparation of final compound 196



Final compound 230 (prepared according to B11.a) (0.001 mol) was taken up in pyrrolidine (1 ml) and the reaction mixture was stirred for 2 hours at 60 °C , the solvent was evaporated and the residue was purified by column chromatography (gradient eluent: CH_2Cl_2/(CH_3OH/NH_3) 100/0 - 90/10). The product fractions were collected and the solvent was evaporated. Yield: 0.257 g of final compound 196.

Example B12

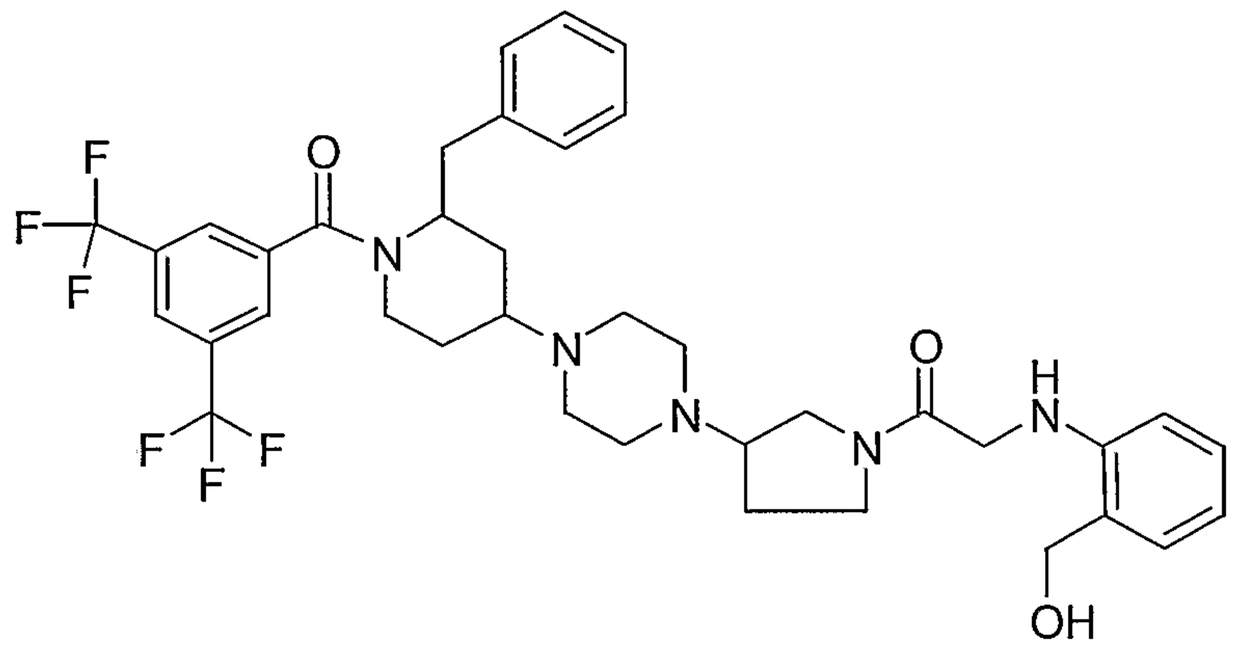
Preparation of final compound 209



NaH (0.001 mol) was added to a solution of 2-methylimidazole (0.001 mol) in DMF (20 ml) and the resulting mixture was stirred for 1 hour and warmed to 40 °C. Final compound 230 (prepared according to B11.a) (0.001 mol) was added and the reaction mixture was stirred for 18 hours at 50 °C. The solvent was evaporated till dryness and the residue was taken up in CH_2Cl_2/H_2O. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 85/15). The product fractions were collected and the solvent was evaporated. Yield: 0.305 g of final compound 209.

Example B13

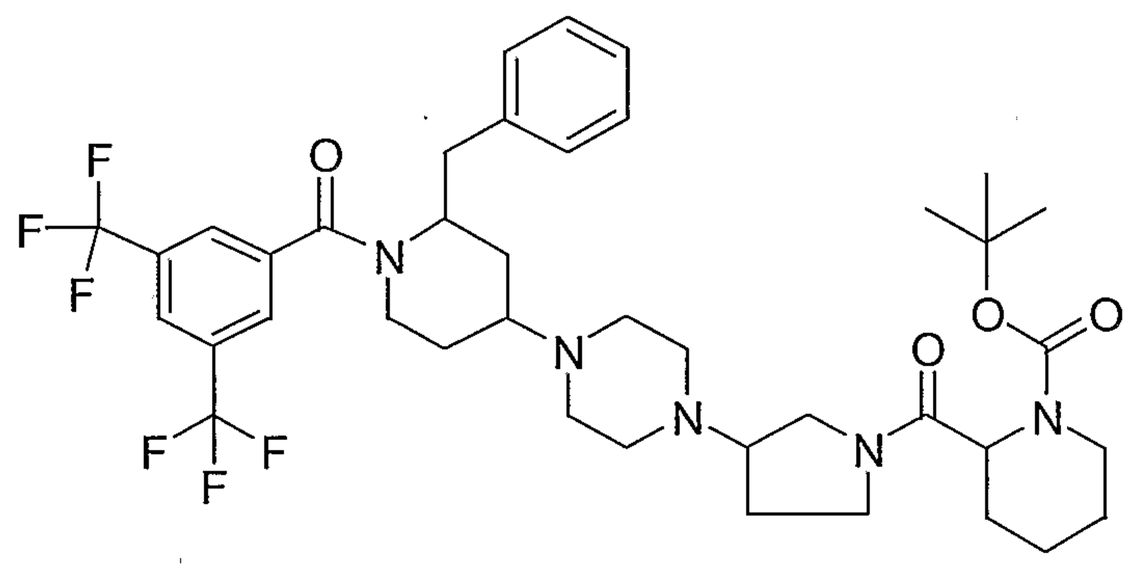
Preparation of final compound 207



Final compound 230 (prepared according to B11.a) (0.001 mol) and Na_2CO_3 (0.5 g) were added to a mixture of 2-aminobenzenemethanol (0.001 mol) in DMF (20 ml) and the reaction mixture was stirred for 18 hours at 50 °C. The solvent was evaporated till dryness and the residue was taken up in CH_2Cl_2/H_2O. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 85/15). The desired product fractions were collected and the solvent was evaporated. Yield: 0.043 g of final compound 207.

Example B14

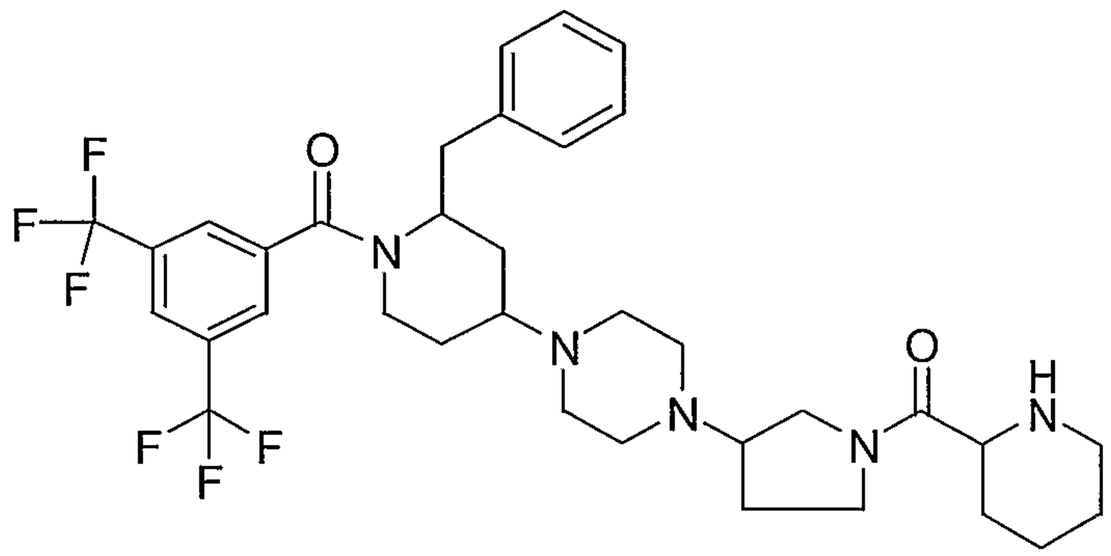
a. Preparation of final compound 206



1-Hydroxy-1*H*-benzotriazole (0.004 mol) and Et_3N (0.004 mol) were added to a solution of 1-(1,1-dimethylethyl)-1,2-piperidinedicarboxylic acid ester (0.004 mol) in CH_2Cl_2, p.a. (50 ml) and the mixture was stirred at room temperature, *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine (0.004 mol) was added and the reaction mixture was stirred for 10 min. at room temperature. A mixture of final compound 2 (prepared according to B1.b) (0.003 mol) in CH_2Cl_2, p.a. (20 ml) was added and the reaction mixture was stirred overnight at room temperature. The mixture was washed with $H_2O/NaHCO_3$ and with H_2O. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by

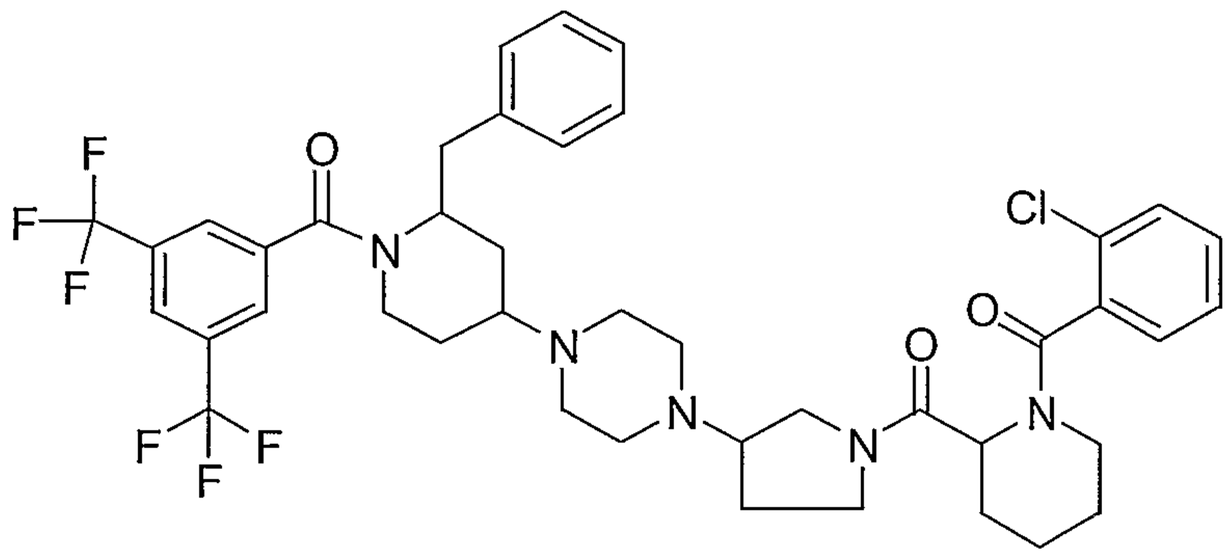
column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 80/20). The product fractions were collected and the solvent was evaporated. Yield: 1.3 g of final compound 206.

b. Preparation of final compound 294



2-propanol/HCl (3 ml) was added to a solution of final compound 206 (prepared according to B14.a) (0.0017 mol) in 2-propanol (30 ml) and the reaction mixture was stirred and refluxed for 2 hours. The solvent was evaporated and the residue was suspended in DIPE. The resulting precipitate was filtered off, taken up in H_2O and washed with DIPE. The aqueous layer was alkalised and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated till dryness. Yield: 1.0 g of final compound 294.

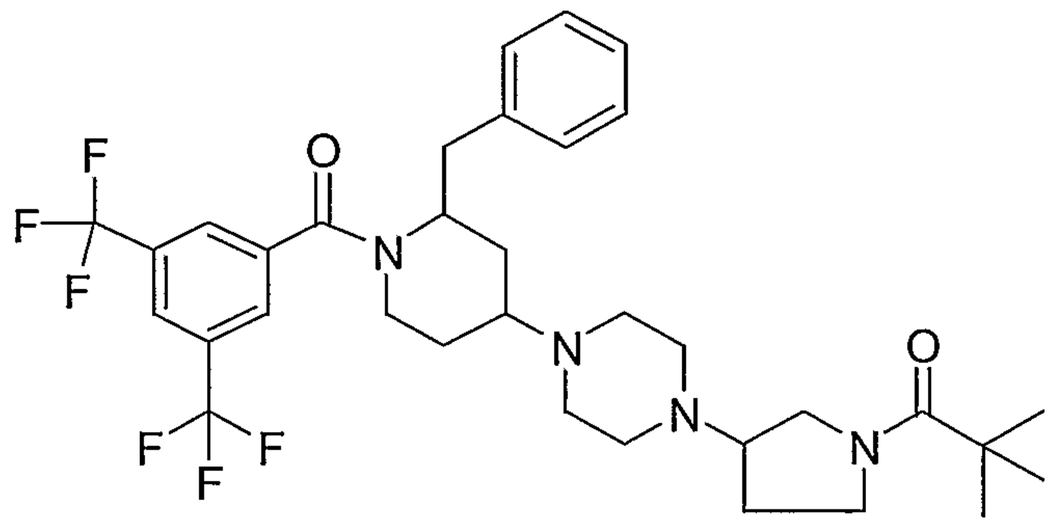
c. Preparation of final compound 295



2-Chlorobenzoyl chloride (0.0004 mol) was added to a solution of final compound 294 (prepared according to B14.b) (0.0004 mol) in CH_2Cl_2, p.a. (15 ml), Na_2CO_3 (0.3 g) was added and the reaction mixture was stirred overnight. The crude mixture was filtered over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10). The product fractions were collected and the solvent was evaporated and the residue was dried. Yield: 0.250 g of final compound 295.

Example B15

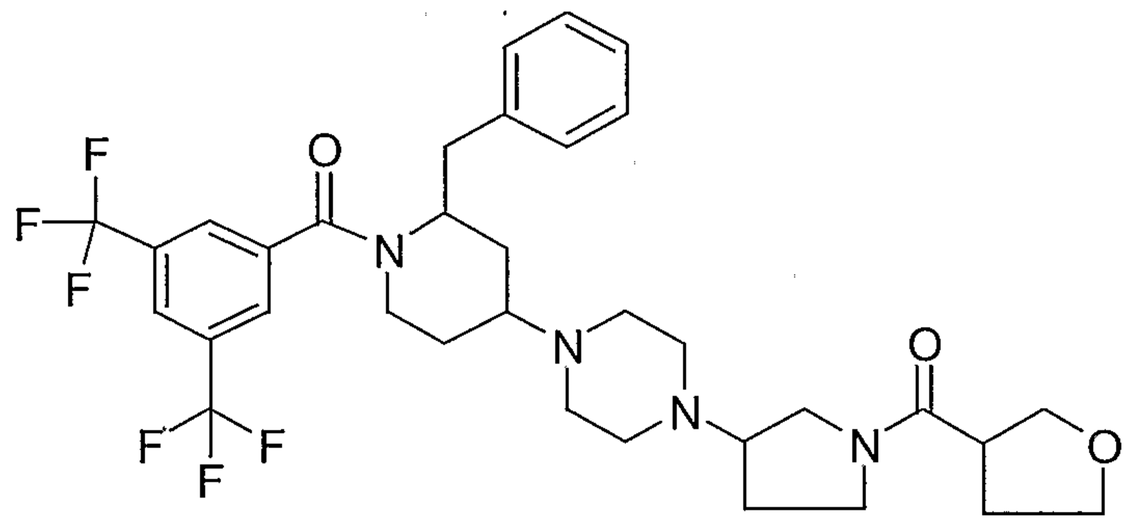
Preparation of final compound 167



2,2-Dimethylpropanoyl chloride (0.001 mol) and Na_2CO_3 (0.5 g) were added to a solution of final compound 2 (prepared according to B1.b) (0.001 mol) in CH_2Cl_2 (25 ml) and the reaction mixture was stirred for 2 hours. The mixture was filtered over a glass filter (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10). The product fractions were collected and the solvent was evaporated and the residue was dried. Yield: 0.448 g of final compound 167.

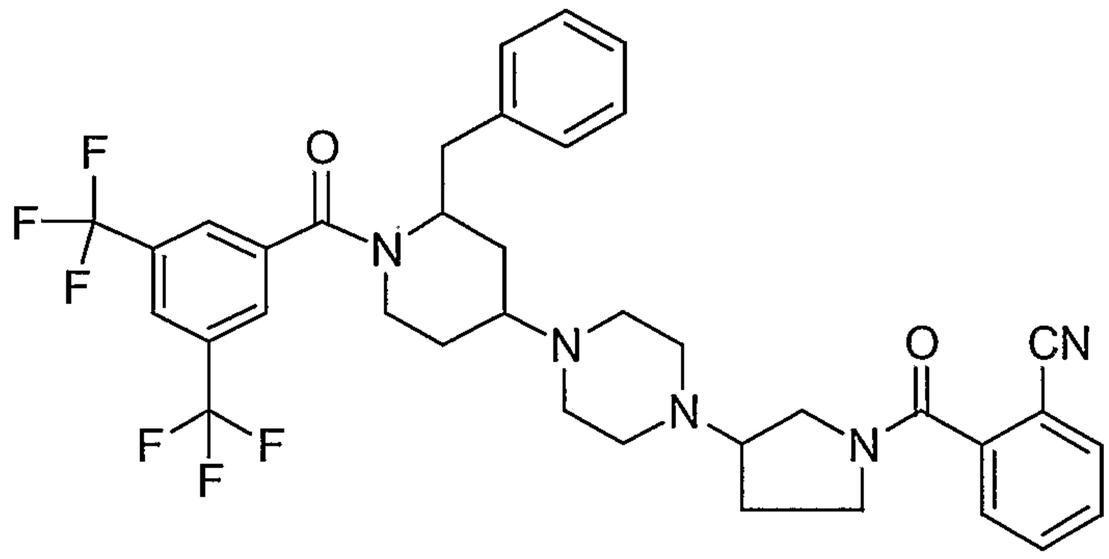
Example B16

a. Preparation of final compound 216



CH_2Cl_2 (50 ml) was added to tetrahydro-3-furancarboxylic acid (0.0012 mol) and 1,1'-carbonylbis-1*H*-imidazole (0.0012 mol) was added. The mixture was stirred for 45 min. at 40 °C and stirred for 3 hours at room temperature. Final compound 2 (0.001 mol) was added and the reaction mixture was stirred overnight at room temperature. The mixture was washed with a basic NaOH solution, the organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 80/20). The product fractions were collected and the solvent was evaporated and the residue was dried. Yield: 0.480 g of final compound 216.

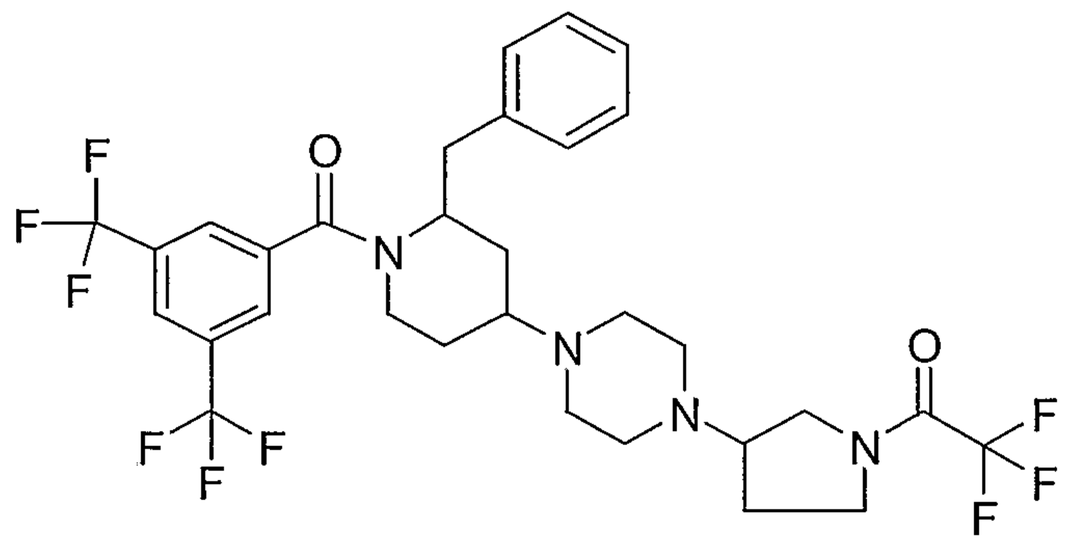
b. Preparation of final compound 195



2-Cyanobenzoic acid (0.001 mol) was taken up in CH_2Cl_2 (30 ml) and 1,1'-carbonylbis-1*H*-imidazole (0.001 mol) was added. The resulting mixture was stirred for 2 hours at 40 °C and was cooled to room temperature. Final compound 2 (prepared according to B1.b) (0.001 mol) was added and the reaction mixture was stirred overnight at room temperature and was left to stand over the weekend. The mixture was washed with a basic NaOH solution, the organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was filtered over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10). The product fractions were collected and the solvent was evaporated and the residue was dried. Yield: 0.272 g of final compound 195.

Example B17

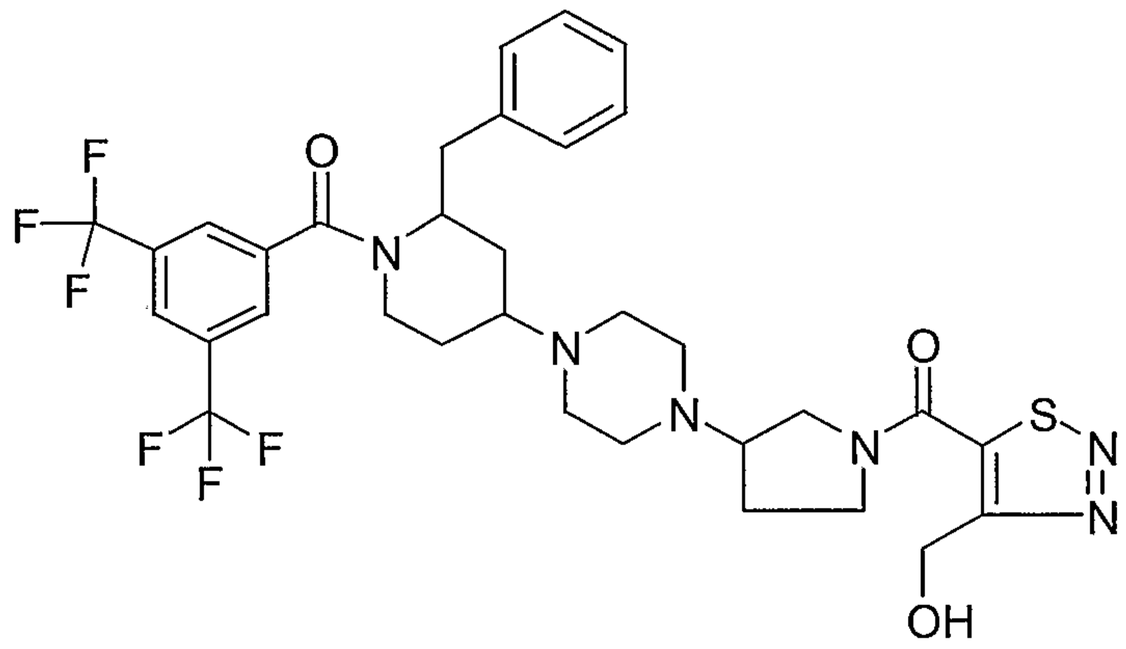
Preparation of final compound 203



Trifluoromethanecarbonic acid anhydride (0.001 mol) and Na_2CO_3 (0.5 g) were added to a solution of final compound 2 (prepared according to B1.b) (0.001 mol) in CH_2Cl_2 (15 ml) and the reaction mixture was stirred for 2 hours. The mixture was filtered on a glass filter over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10). The product fractions were collected and the solvent was evaporated and the residue was dried. Yield: 0.276 g of final compound 203.

Example B18

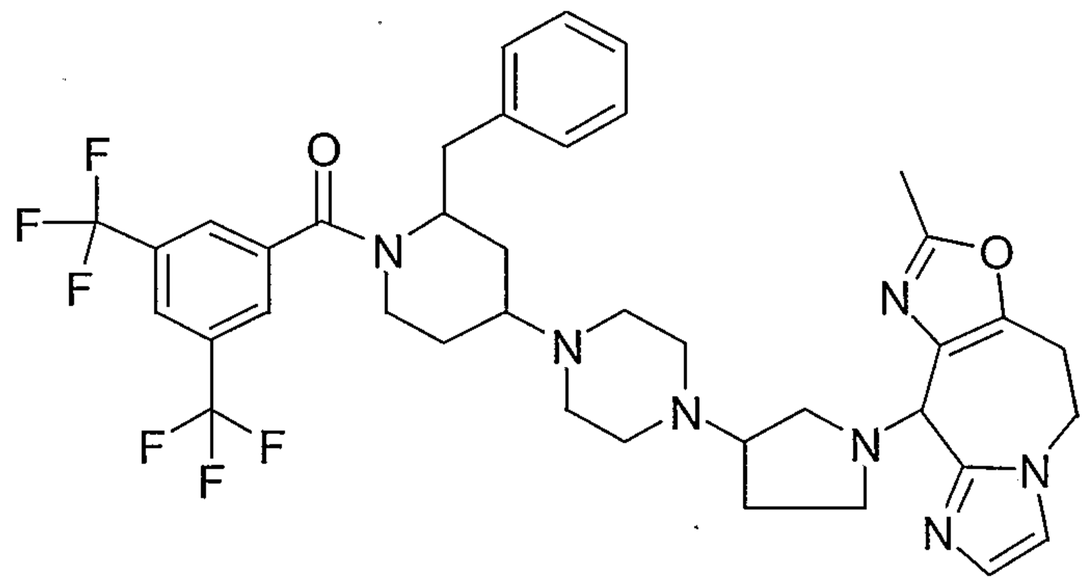
Preparation of final compound 166



A mixture of 4-[(acetyloxy)methyl]-1,2,3-thiadiazole-5-carboxylic acid methyl ester (0.002 mol) and final compound 2 (prepared according to B1.b) (0.004 mol) in CH_3OH (25 ml) was stirred over the weekend at room temperature and the reaction mixture was filtered over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10). The product fractions were collected and the solvent was evaporated and the residue was dried. Yield: 0.600 g of final compound 166.

Example B19

Preparation of final compound 375

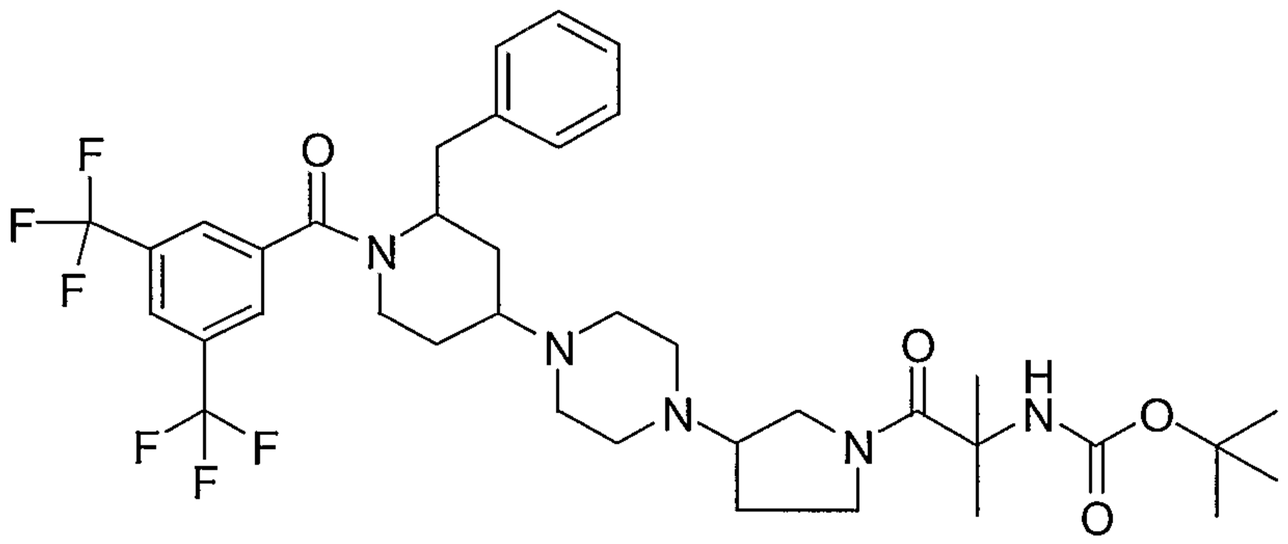


A mixture of final compound 2 (prepared according to B1.b) (0.001 mol), intermediate compound 15 (prepared according to A3.d) (0.001 mol) and titanium, tetrakis(2-propanolato) (1 ml) in CH_3OH (50 ml) was hydrogenated at 50 °C with Pd/C 10 % (0.1 g) as a catalyst in the presence of thiophene soln. (0.1 ml). After uptake of H_2 (1 eq.), the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in H_2O/CH_2Cl_2, dicalite was added and the resulting mixture was filtered over dicalite. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography (gradient eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 99/1 - 80/20). The product fractions were collected and the

solvent was evaporated and the residue was dried. Yield: 0.017 g of final compound 375.

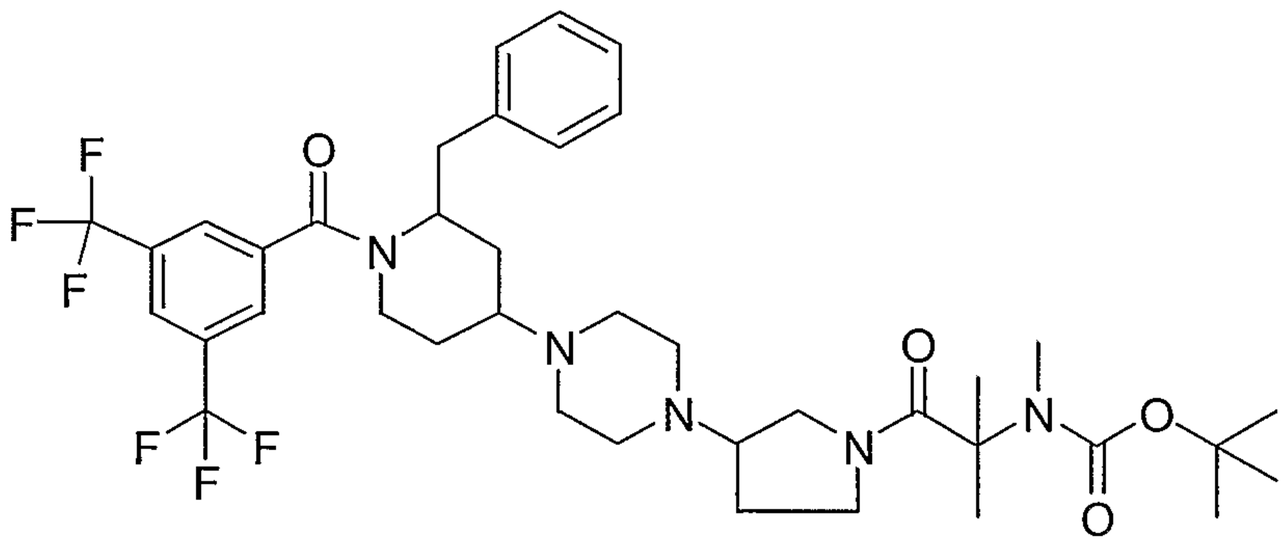
Example B20

a. Preparation of final compound 205



1-Hydroxy-1*H*-benzotriazole (0.004 mol) and Et_3N (0.004 mol) were added to a solution of *N*-[(1,1-dimethylethoxy)carbonyl]-2-methylalanine (0.004 mol) in CH_2Cl_2 (50 ml) and the mixture was stirred at room temperature, *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine (0.004 mol) was added and the reaction mixture was stirred for 10 min. at room temperature. A mixture of final compound 2 (prepared according to B1.b) (0.003 mol) in CH_2Cl_2 (20 ml) was added and the reaction mixture was stirred overnight at room temperature. The mixture was washed with $H_2O/NaHCO_3$ and with H_2O. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 80/20). The product fractions were collected and the solvent was evaporated. Yield: 0.414 g of final compound 205.

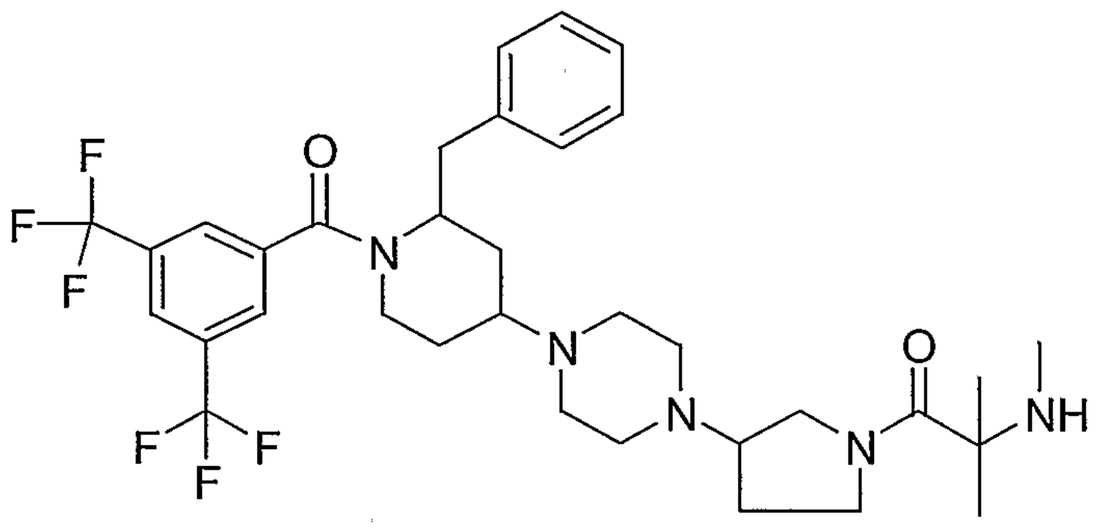
b. Preparation of final compound 304



50% NaH (0.0015 mol) was added to a solution of final compound 205 (prepared according to B20.a) (0.0013 mol) in DMF p.a. (25 ml) and the resulting mixture was slowly (35 min.) heated to 45 °C. CH_3I (0.0015 mol) was added and the reaction mixture was stirred for 4 hours at 50 °C and stirred overnight at room temperature. The solvent was evaporated and the residue was taken up in H_2O and the mixture was

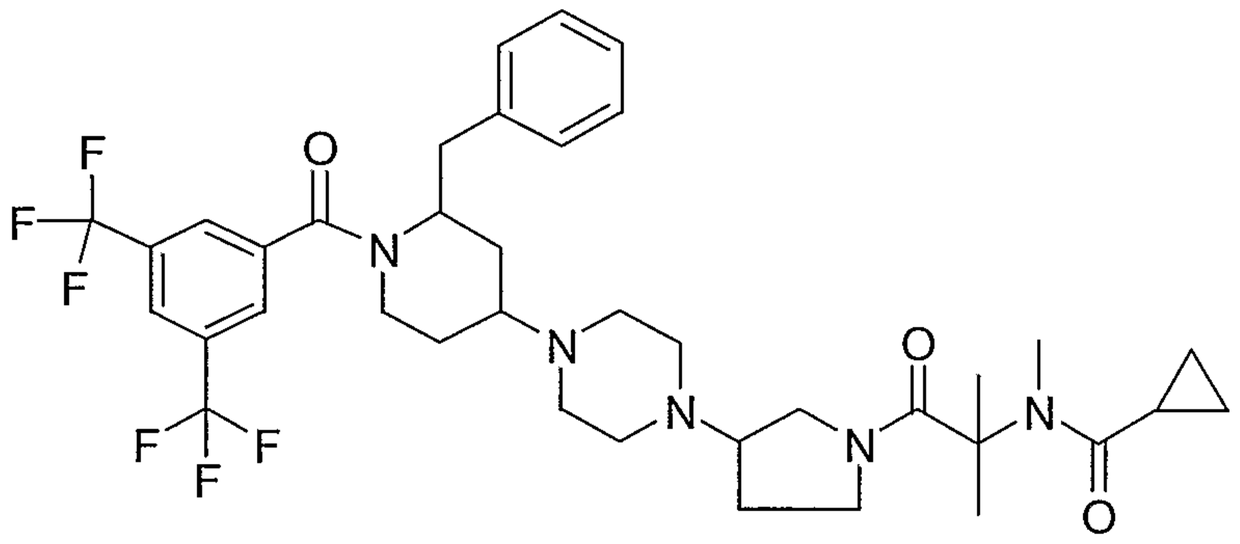
extracted with CH_2Cl_2. The organic layer was separated, dried (over $MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10). The product fractions were collected and the solvent was evaporated and the residue was dried. Yield: 0.47 g of final compound 304.

c. Preparation of final compound 309



2-Propanol/HCl (2 ml) was added to a solution of final compound 304 (prepared according to B20.b) (0.00061 mol) in 2-propanol (20 ml) and the reaction mixture was stirred and refluxed for 90 min. The solvent was evaporated and the residue was taken up in H_2O and washed with DIPE. The aqueous layer was alkalised and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered off and the solvent was evaporated. Yield: 0.320 g of final compound 309.

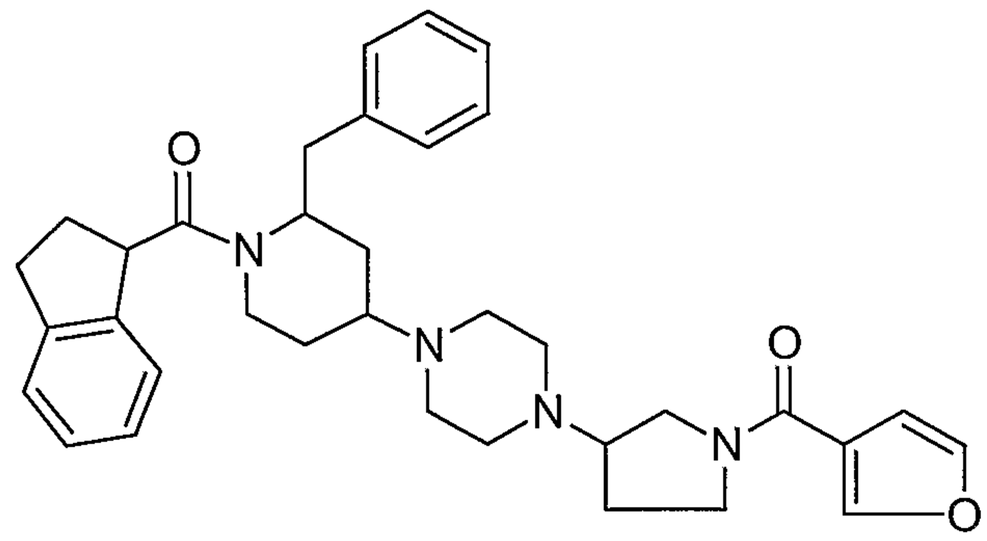
d. Preparation of final compound 310



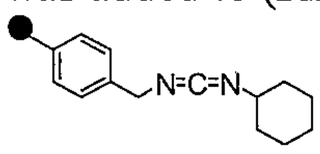
Cyclopropanecarbonyl chloride (0.0005 mol) was added to a solution of final compound 309 (prepared according to B20.c) (0.00048 mol) in CH_2Cl_2 (20 ml), Na_2CO_3 (0.5 g) was added and the reaction mixture was stirred for 2 hours at room temperature. The crude mixture was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 - 90/10). The desired product fractions were collected and the solvent was evaporated and the residue was dried. Yield: 0.080 g of final compound 310.

Example B21

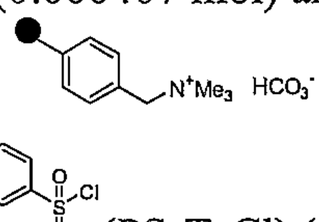
Preparation of final compound 147



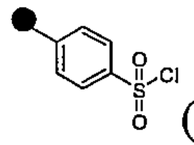
CH_2Cl_2 (10 ml) was added to intermediate compound 9 (prepared according to A2.e) (0.000177 mol) and the mixture was stirred to give solution (I). Solution (I) (10 ml) was added to (RS) 2,3-dihydro-1*H*-indene-1-carboxylic acid (0.000266 mol),



(Novabiochem 01-64-0211)(0.000531 mol; 1.90 mmol/g) and 1-hydroxy-1*H*-benzotriazole (0.000407 mol) and the reaction mixture was stirred for 16 hours at room temperature.



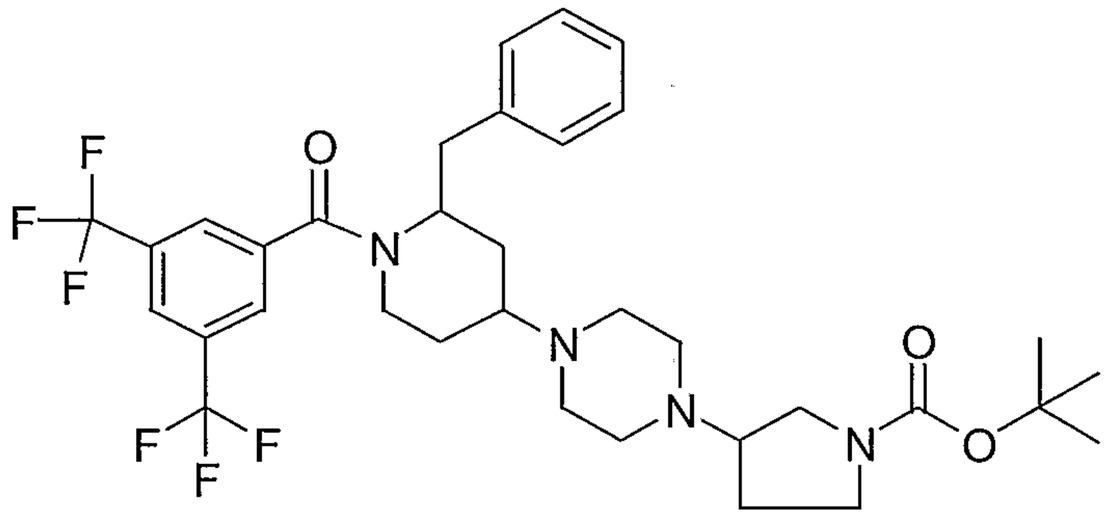
(Novabiochem 01-64-0419) (0.001221 mol; 5.80 mmol/g) and



(PS-TsCl) (0.000266 mol; 1.97 mmol/g) were added and the mixture was stirred for 16 hours at room temperature. The scavengers were filtered off and the filtrate was evaporated. Yielding final compound 147.

Example B22

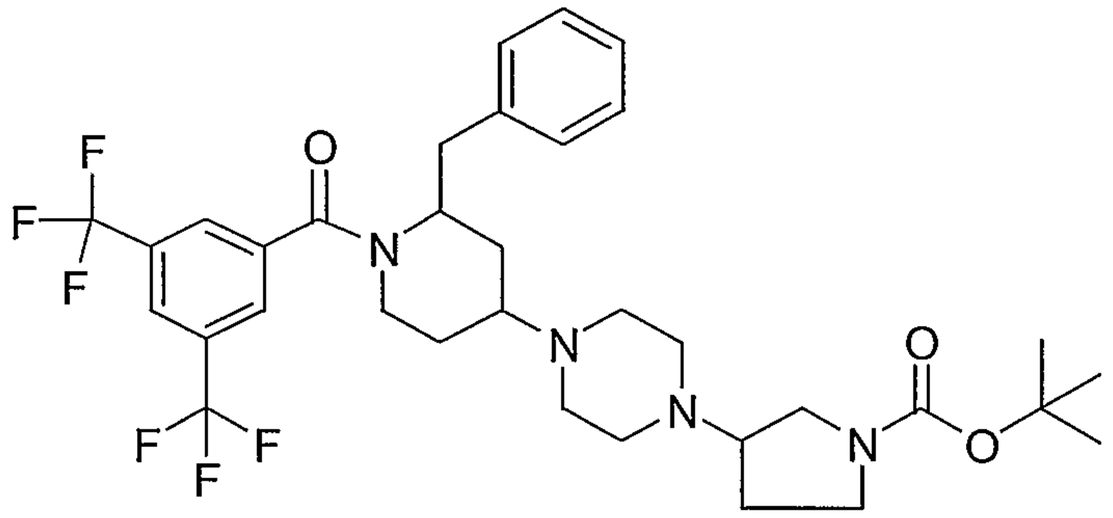
a. Preparation of final compound 130



A mixture of final compound 2 (prepared according to B1.b) (0.002 mol) in CH_2Cl_2, p.a. (50 ml) was stirred at room temperature. A solution of bis(1,1-dimethylethyl)dicarbonic acid ester (0.002 mol) in CH_2Cl_2 was added dropwise and the reaction mixture was stirred for 1 hour at room temperature. The solvent was evaporated and 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 and the solvent was evaporated. Yield: 1.039 g of final compound 130 (78 %).

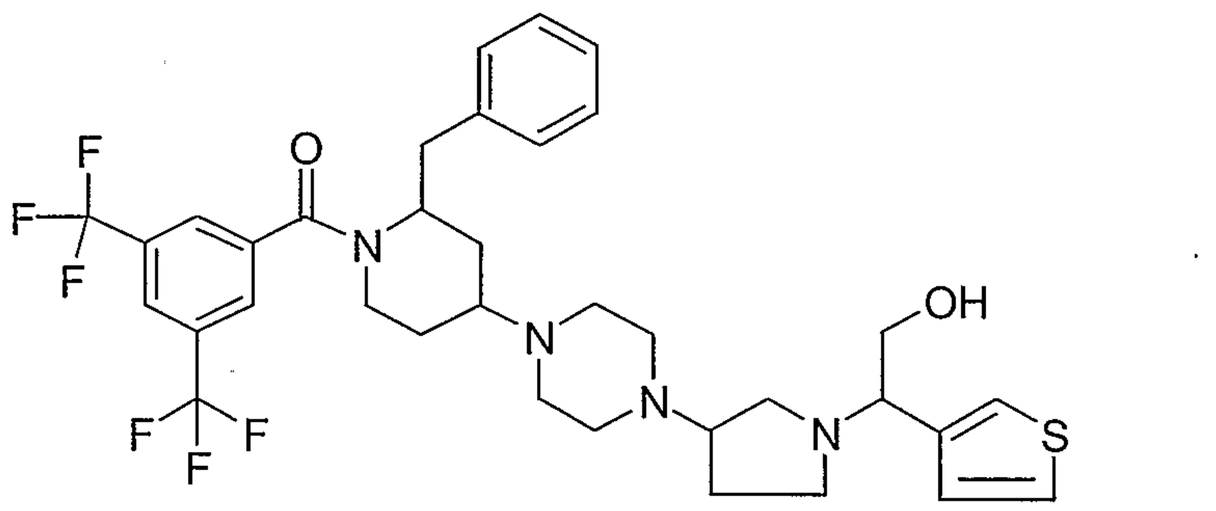
b. Preparation of final compound 150 and 151



A mixture of intermediate compound 4 (prepared according to A1.d) (0.15 mol) and 1,1-dimethylethyl-1-pyrrolidinecarboxylic acid ester (0.165 mol) in CH_3OH (500 ml) was hydrogenated overnight at 50°C with Pd/C 10% (5 g) as a catalyst in the presence of thiophene (4 ml). After uptake of H_2 (1 equiv.), the catalyst was filtered off and the filtrate was evaporated. The residue was crystallised from DIPE, the resulting precipitate was filtered off, giving solid S and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH from 100/0 to 95/5) The product fractions were collected and the solvent was evaporated. This residue and solid S were combined. This fraction was separated into its enantiomers by Chiral separation (AD, eluent: Hexane/2-propanol 90/10). Two product fractions were collected and the solvent was evaporated. Yield fraction 1: 46 g of final compound 150 ([2R-[2α,4β(S*)]]) (46 %) and yield fraction 2: 39 g of final compound 151 ([2R-[2α,4β(R*)]]) (39 %)

Example B23

Preparation of final compound 349

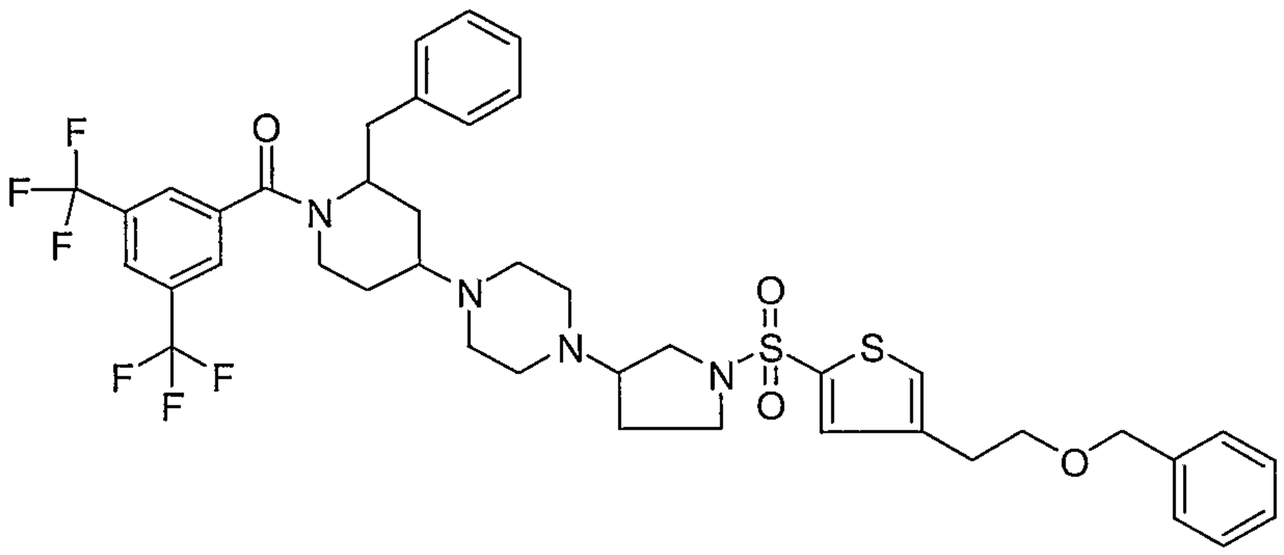


A mixture of final compound 2 (prepared according to B1.b) (0.001 mol, 0.5 g), 1,4-dioxane-2,5-diol (0.001 mol, 0.113 g) and 3-thiophene boronic acid (0.001 mol, 0.106 g) in ethanol (5 ml) was stirred at room temperature for 18 hours . This was followed by addition of solution of K_2CO_3 (10 %) and extracted with ethyl acetate. The

combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The residue (0.6 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 93/07/0.5) and the product fractions were concentrated. Yield: 0.075 g (12 %) of final compound 349.

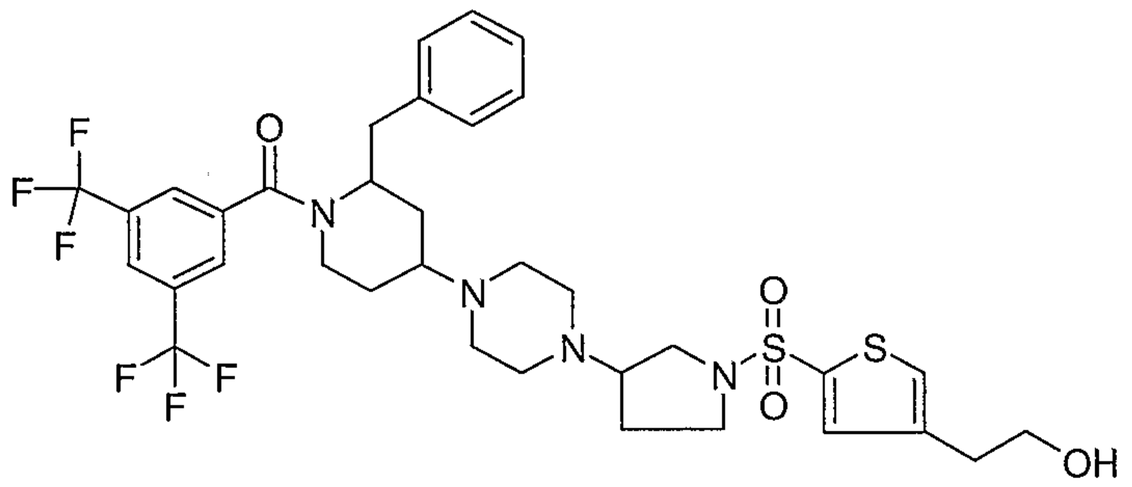
Example B24

a. Preparation of final compound 335



Intermediate compound 17 (prepared according to A4.b) (0.002 mol, 0.67 g) was added portionwise to a solution of final compound 2 (prepared according to B1.b) (0.002 mol, 1.0 g) in CH_2Cl_2 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 (1.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/MeOH 98/2) and the product fractions were concentrated. Yield : 1.1 g (73 %) of final compound 335.

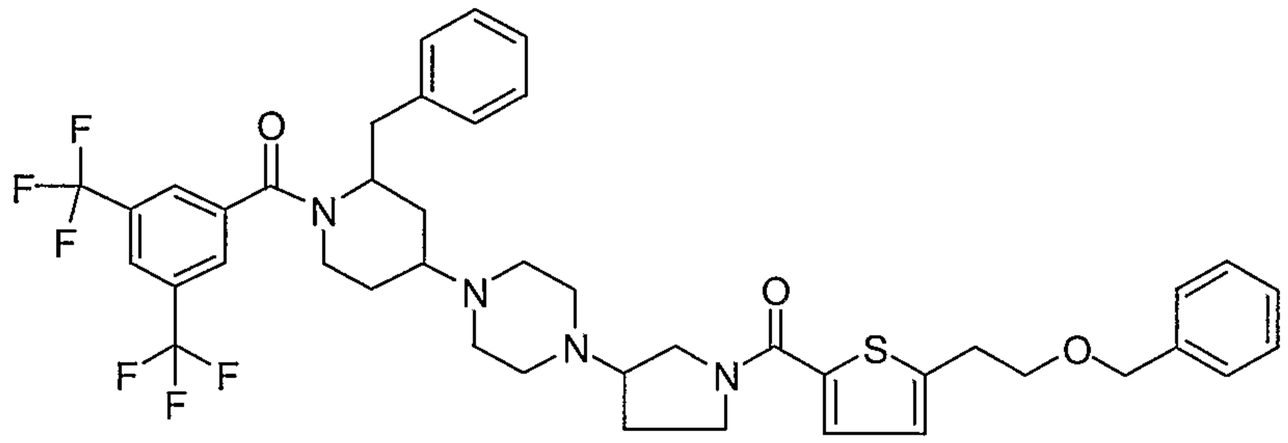
b. Preparation of final compound 342



BBr_3 (1M in CH_2Cl_2) (0.004 mol, 3.6 ml) was slowly added to a mixture of final compound 335 (prepared according to B24.a) (0.001 mol, 0.6 g) in CH_2Cl_2 (6 ml) at -70 °C under N_2 flow. The reaction was allowed to warm up slowly to -50 °C and stirred at -50 °C during 1 hour. The mixture was hydrolyzed with K_2CO_3 (10 %), extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. The crude product (0.65 g) was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/MeOH/NH_4OH 96/4/0.1 to 92/8/0.5) and the product fractions were concentrated. Yield: 0.113 g of final compound 342 (21 %).

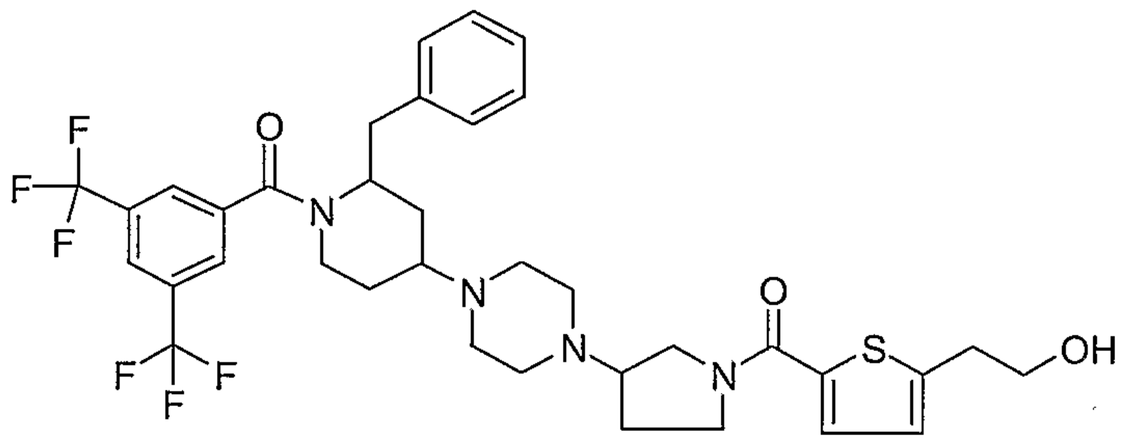
Example B25

a. Preparation of final compound 356



1-(3-Dimetylaminopropyl)-3-ethylcarbodiimide.hydrochloride (0.002 mol, 0.33g) was added portionwise to a solution of final compound 2 (prepared according to B1.b) (0.002 mol, 1g) , intermediate compound 19 (prepared according to A5.b) (0.002 mol, 0.56g) , 1-hydroxybenzotriazole (0.002 mol, 0.29g) and triethylamine (0.003 mol, 0.37 ml) in CH_2Cl_2 (10 ml) 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 (1.65g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 96/4/0.5) and the product fractions were concentrated. Yield: 0.62 g (43%) of final compound 356.

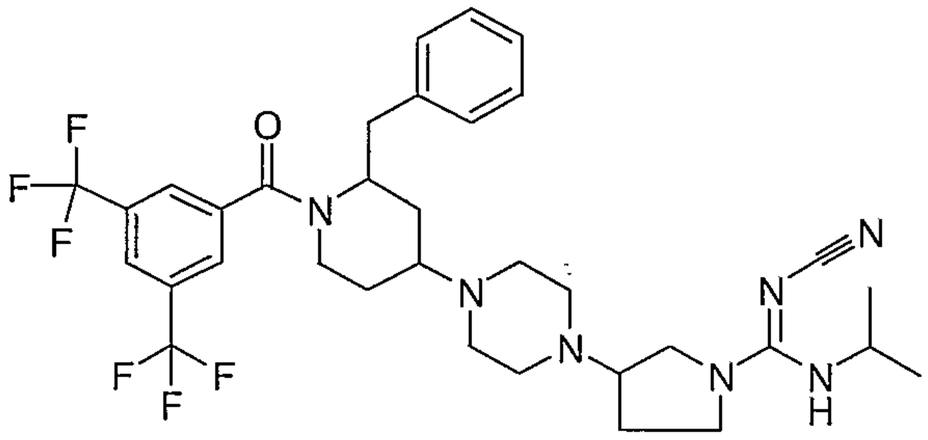
b. Preparation of final compound 359



The same procedure as described in Example B24.b but instead of the use of final compound 334 (prepared according to B24.a), final compound 356 (prepared according to B25.a) was used.

Example B26

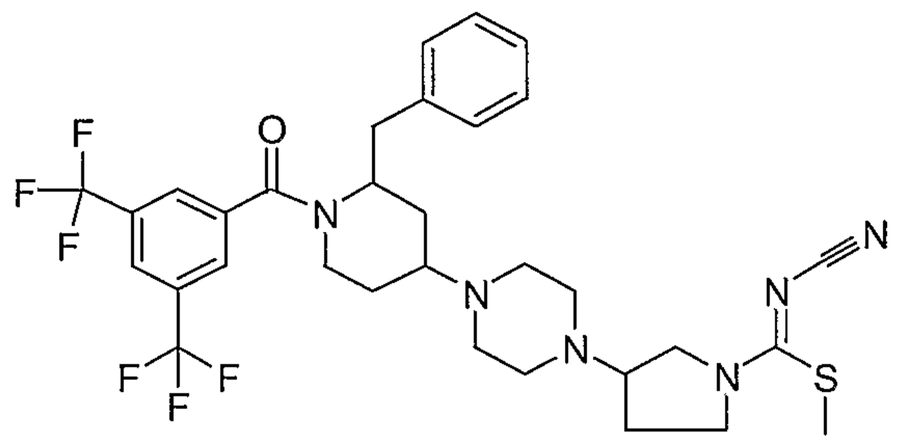
Preparation of final compound 344



A mixture of dimethyl-*N*-cyanodithioiminocarbonate (1g; 6.8 mmol) and isopropylamine (0.6 ml; 6.8 mmol) in acetonitrile (10 ml) 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; 6.8 mmol) and 3N sodium hydroxide solution (2.3 ml; 6.8 mmol) were added. The mixture was stirred for 5 minutes and a solution of 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 and 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 (15-40 mm, eluent: CH_2Cl_2/MeOH/NH_4OH 95/5/0.5). The pure fractions were collected and evaporated. Yield: 1.9 g of of final compound 344 (41%).

Example B27

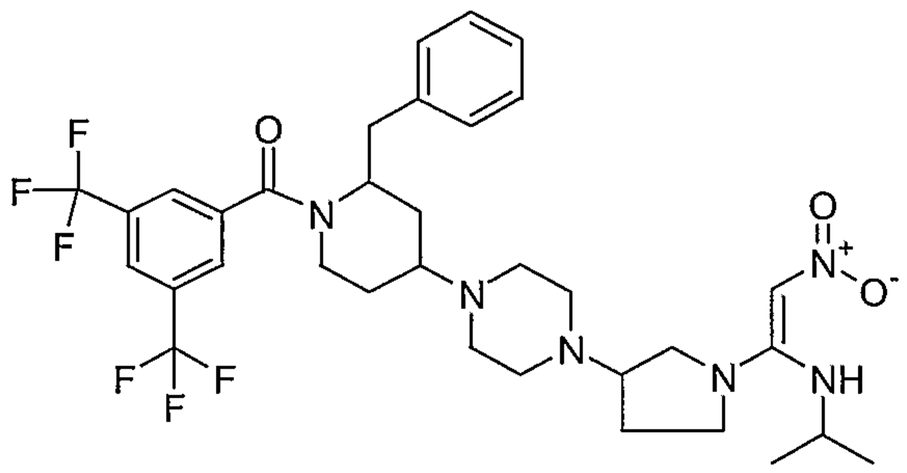
Preparation of final compound 301



Dimethyl-*N*-cyanodithioiminocarbonate (0.001 mol) was added to a mixture of final compound 2 (prepared according to B1.b) (0.0009 mol) in *i*PrOH (25ml). The mixture was stirred and refluxed for 20 hours. H_2O was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (0.52g) 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: 0.27g of final compound 301.

Example B28

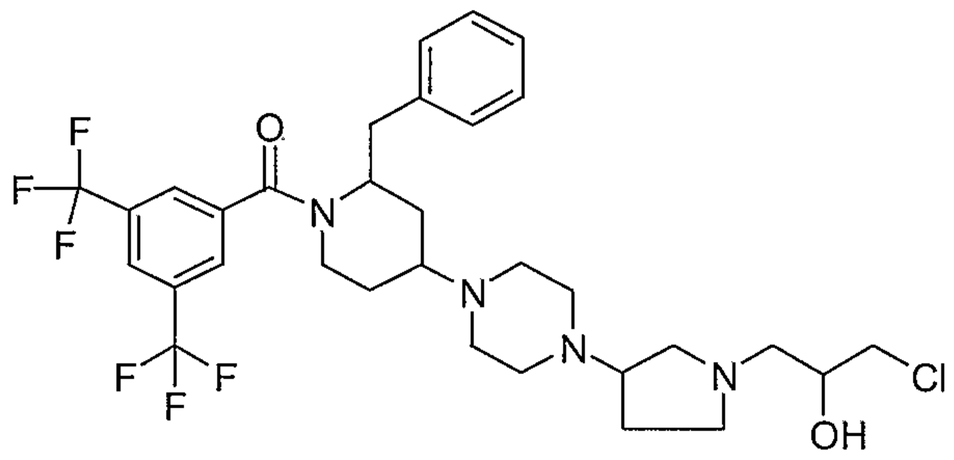
Preparation of final compound 354



A mixture of 1,1-bis(methylthio)-2-nitroethylene (0.15 g; 0.9 mmol) and isopropylamine (0.08 ml; 0.9 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) (0.512 g; 0.9 mmol) and 3N NaOH solution (0.9 ml; 0.9 mmol) were 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 for 2 hours at 0 °C, and stirred overnight at room temperature. 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 mm, eluent: CH_2Cl_2/MeOH/NH_4OH 96/4/0.1). The pure fractions were collected and evaporated. Yield: 0.267 g of final compound 354 (43 %).

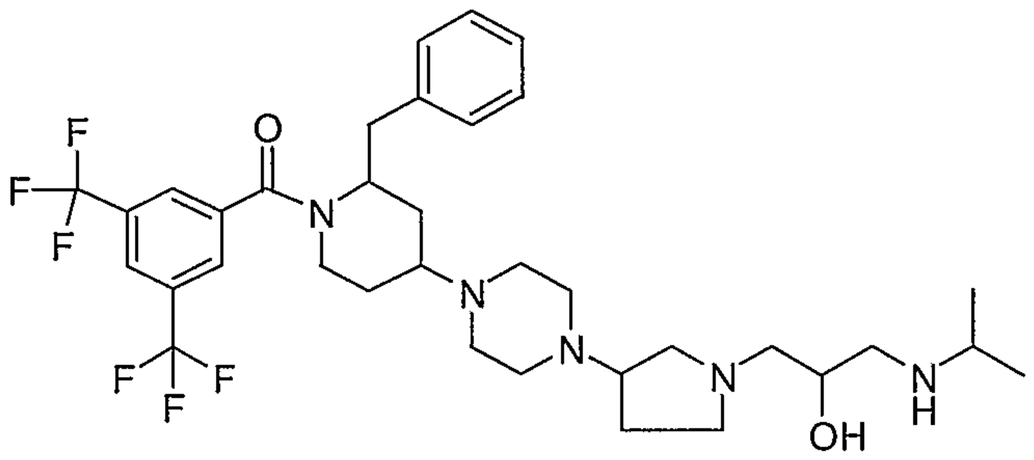
Example B29

a. Preparation of final compound 383



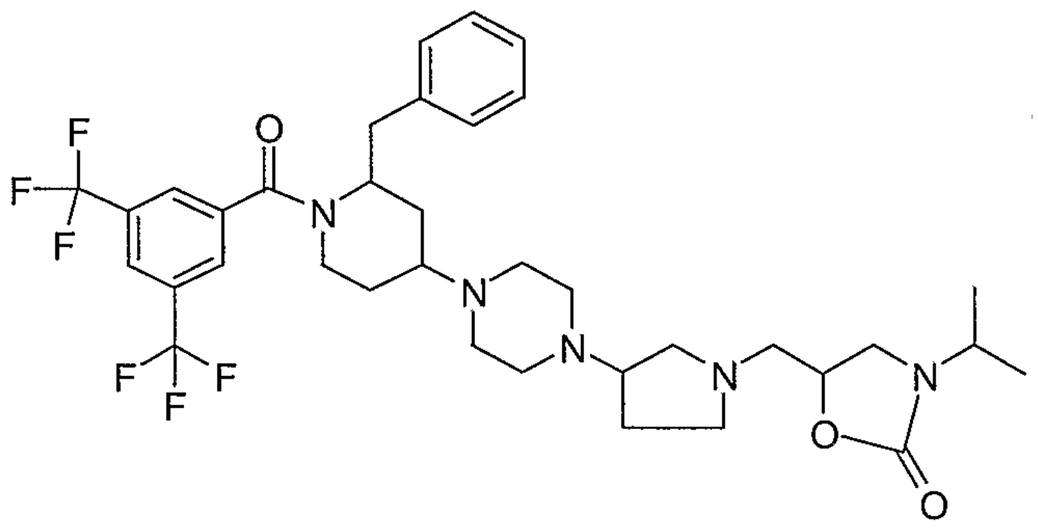
A mixture of final compound 2 (prepared according to B1.b) (2 g; 3.5 mmol) and 2-chloromethyloxirane (0.70 ml; 8.9 mmol) in methanol (20 ml) was stirred at room temperature overnight. The solvent was evaporated and the residue was taken up in methylene chloride. The solvent was evaporated and the residue was purified by column chromatography over silica gel (15-40 mm, eluent: CH_2Cl_2/MeOH/NH_4OH 92/8/0.5). The pure fractions were collected and evaporated. Yield: 0.23 g of final compound 383 (10 %).

b. Preparation of final compound 384



A mixture of final compound 383 (0.230 g; 0.35 mmol), isopropylamine (0.033 ml; 0.38 mmol) and potassium carbonate (0.072 g; 0.52 mmol) in acetonitrile (5 ml) were heated under reflux overnight. The reaction mixture was filtered and the solvent was evaporated. Yield: 0.225 g of final compound 384 (95 %).

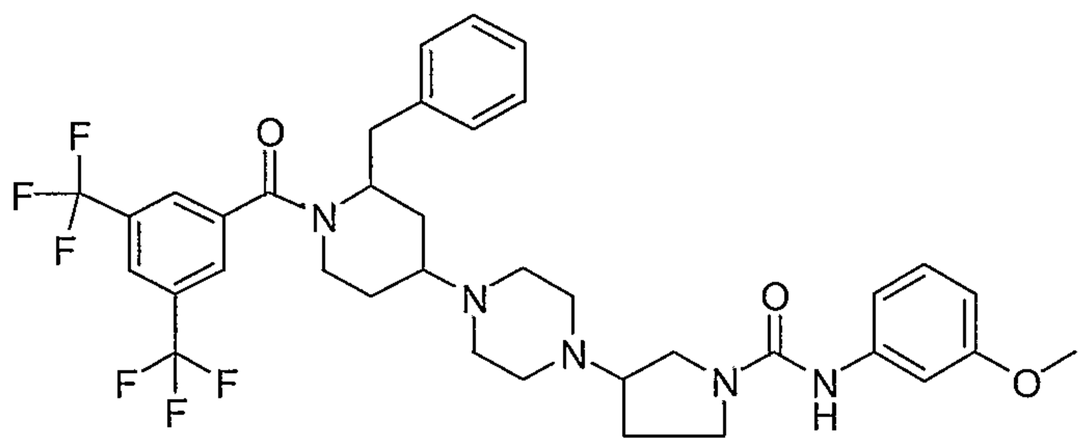
c. Preparation of final compound 385



A mixture of final compound 384 (0.220 g; 0.29 mmol) and 1,1'-carbonyldiimidazole (0.071 g; 0.44 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by column chromatography over silica gel (Kromasil 10 mm, eluent: CH_2Cl_2/MeOH/NH_4OH 95/5/0.5). The pure fractions were collected and evaporated. Yield: 0.118 g of final compound 385 (52 %).

Example B30

Preparation of final compound 343

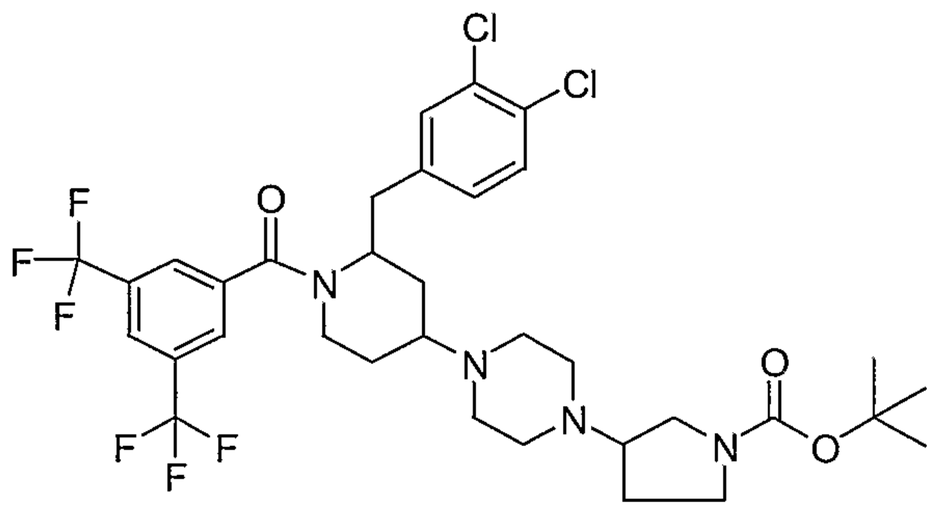


A mixture of final compound 2 (prepared according to B1.b) (1.0 g; 1.76 mmol) and 3-methoxyphenyl isocyanate (0.25 ml; 1.93 mmol) in THF (10 ml) was stirred at room

temperature overnight. The reaction mixture was poured onto ice-water and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography over silica gel (40 mm, eluent: CH_2Cl_2/MeOH/NH_4OH 97/3/0.5). The pure fractions were collected and evaporated. Yield: 1.3 g of final compound 343 (100 %).

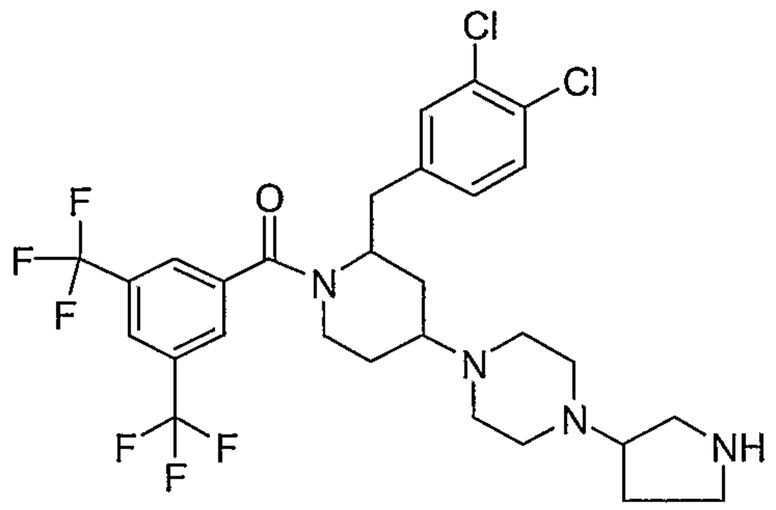
Example B31

a) Preparation of final compound 243



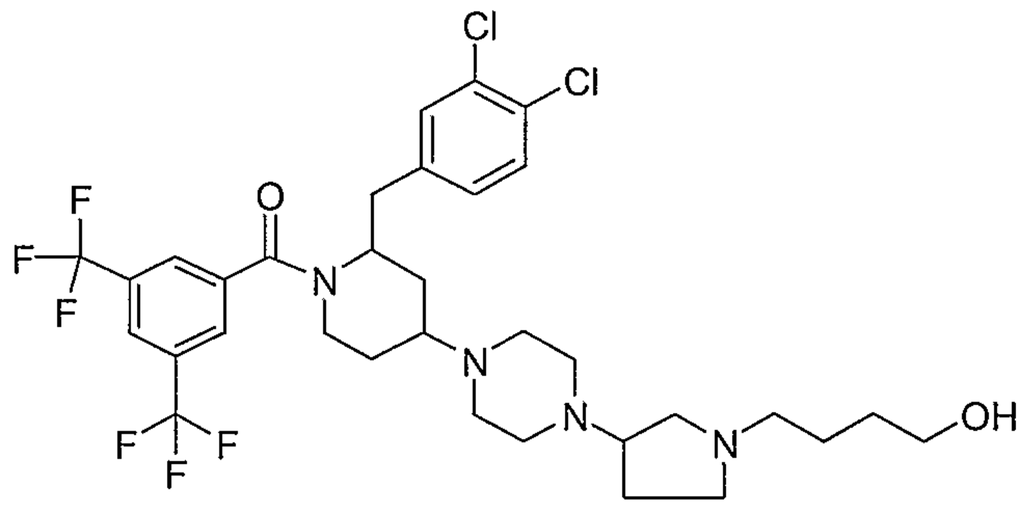
A mixture of intermediate compound 23 (prepared according to A6.d) (0.02 mol), intermediate compound 30 (prepared according to A8) (0.02 mol) and Pt/C 5% (3 g) in thiophene solution (2 ml) and CH_3OH (250 ml) was stirred at 50°C under H_2 (gas), titanium, tetrakis(2-propanolato) (15 g) was added and the reaction mixture was filtered. The filtrate was evaporated and the residue was taken up in CH_2Cl_2/H_2O. The biphasic mixture was stirred for 15 min. and filtered through dicalite. The organic filtrate was separated, dried and the solvent was evaporated. The residue was separated by column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH 100/0 -> 90/10). The product fractions were collected and the solvent was evaporated. The purification was repeated, two product fractions were collected and the solvent was evaporated. The desired fraction was crystallised from petroleum ether and the resulting solids were collected. Yield: 1.8 g of final compound 243.

b) Preparation of final compound 244



HCl/2-propanol (5 ml) was added to a solution of final compound 243 (0.0046 mol) in 2-propanol (50 ml) and the reaction mixture was stirred and refluxed for 2 hours. The resulting precipitate was filtered off and washed with DIPE/2-propanol. The solids were taken up in H_2O. The mixture was alkalised and extracted with CH_2Cl_2. The organic layer was separated, dried and the solvent was evaporated. Yield: 2.1 g of final compound 244 (72%).

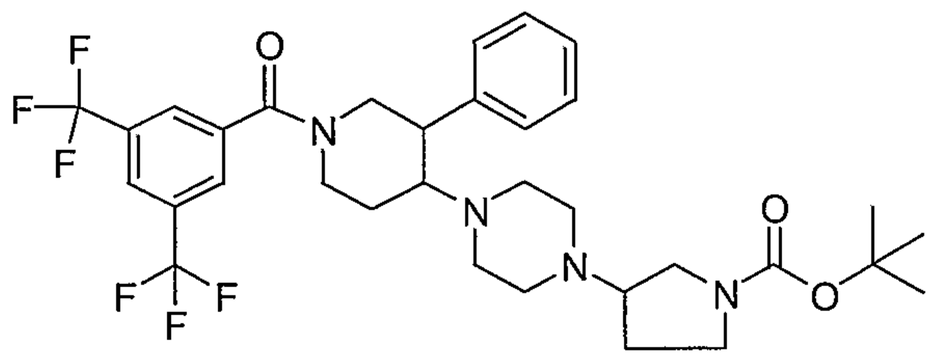
c) Preparation of final compound 393



A mixture of final compound 298 (prepared according to B31.a) (1.47 g) in a 5 to 6N HCl/isopropanol solution (40 ml) and THF (5 ml) was stirred at room temperature for 4 hours. The reaction mixture was concentrated, poured onto a 10% sodium carbonate solution and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 85/15/1). The pure fractions were collected and evaporated. The residue was taken up with diisopropylether, filtered and dried. Yield: 0.273 g of final compound 393 (19%).

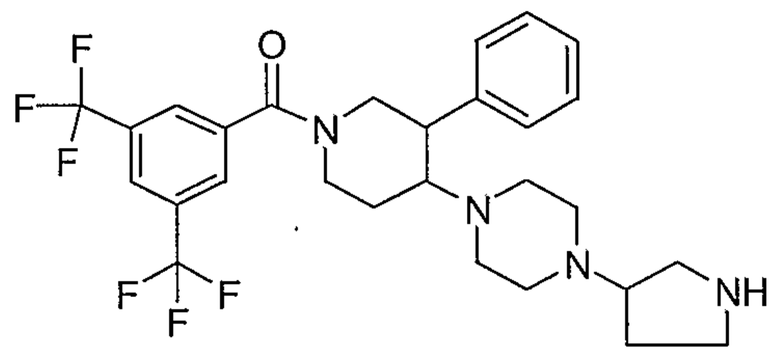
Example B32

a) Preparation of final compound 405



3,5-bis(trifluoromethyl)benzoylchloride (0.005 mol) was added to a solution of intermediate compound 29 (prepared according to A7.d) (0.0048 mol) in CH_2Cl_2 (20 ml) and the mixture was briefly stirred, Et_3N (1 ml) was added and the reaction mixture was stirred for 18 hours. The mixture was washed with a diluted NaOH solution and with H_2O, dried and the solvent was evaporated. Yield: 2.8 g of final compound 405.

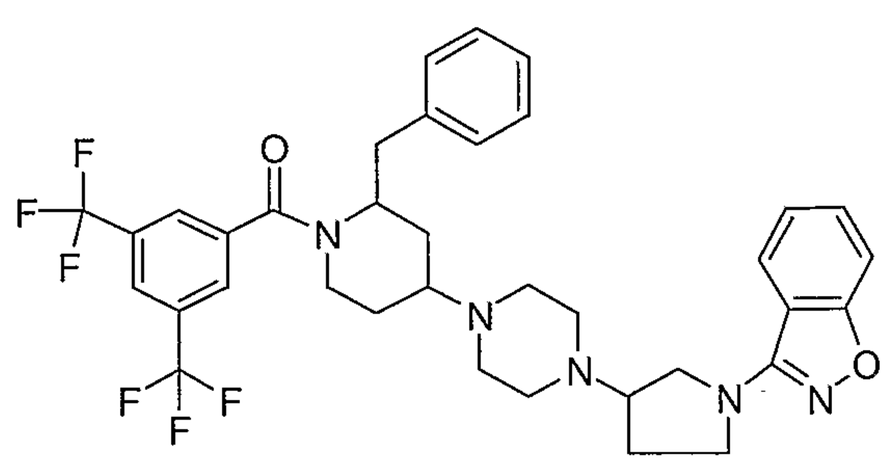
b) Preparation of final compound 406



Final compound 405 (0.0043 mol) was taken up in HCl/2-propanol (5 ml) and 2-propanol (50 ml) was added (precipitation occurred), the reaction mixture was stirred and refluxed for 2 hours. The mixture was cooled and the resulting precipitate was filtered off. The precipitate was taken up in H_2O, alkalised with a basic NaOH solution and extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified over silica gel on a glass filter (gradient eluent: CH_2Cl_2/(CH_3OH/NH_3) 99/1 -> 90/10). The product fractions were collected and the solvent was evaporated. Yield: 1.5 g of final compound 406.

Example B33

Preparation of final compound 204

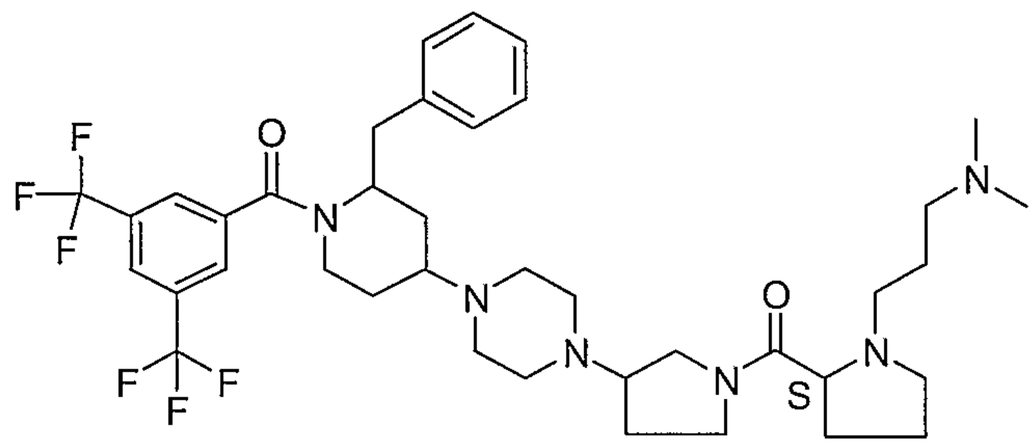


A mixture of final compound 2 (prepared according to B1.b) (0.0014 mol), 3-chloro-1,2-benzoisoxazole (0.0015 mol), Na_2CO_3 (0.0014 mol) and KI (0.0014 mol) in 4-

methylpentanone (20 ml, p.a.) was stirred under N_2 in autoclave at 160°C over the weekend. The reaction mixture was cooled and the solvent was evaporated. The residue was partitioned between H_2O/CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: CH_2Cl_2/CH_3OH from 100/0 to 90/10). The product fractions were collected and the solvent was evaporated. Yield: 0.783 g of final compound 204 (82 %).

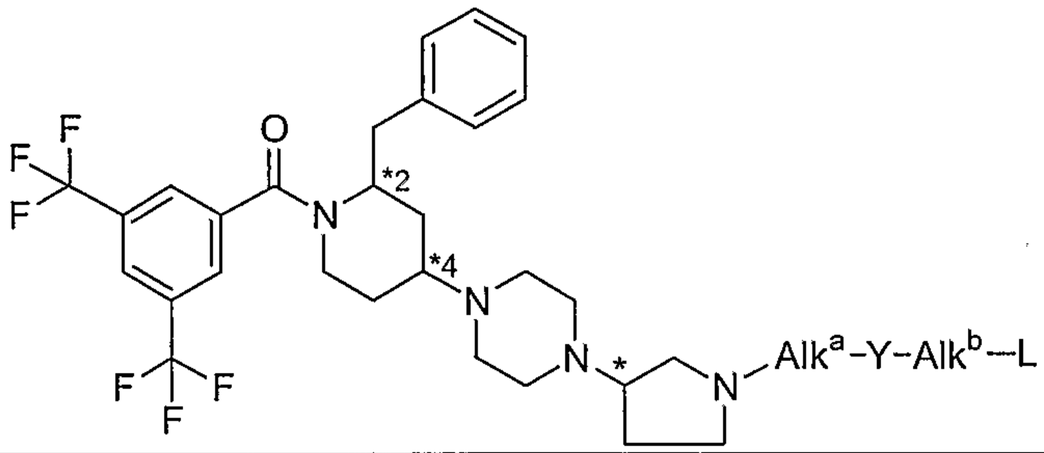
Example B34

Preparation of final compound 185



A mixture of final compound 144 (prepared according to B14.b) (0.00096 mol), 2-chloro-*N,N*-dimethylethanamine (0.00098 mol) and Na_2CO_3 (0.0029 mol) in 2-butanol (5 ml) was stirred under microwave irradiation (45 min. at 175°C). The mixture was evaporated under vacuum and the residue was suspended in CH_2Cl_2, then isocyanate-resin (0.125 g, scavenger) was added and the reaction mixture was stirred for 5 hours at room temperature. The mixture was filtered off, the filter residue was washed with CH_2Cl_2 and the solvent was evaporated. The residue was purified by column chromatography over silica gel (gradient eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ (7N) from 100/0 to 80/20). The product fractions were collected, the solvent was evaporated and the residue was dried (vac., 50°C) for 48 hours. Yield: 0.056 g of final compound 185 (8%).

Table 1:



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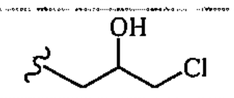
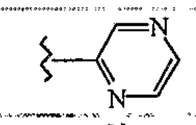
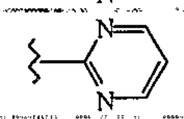
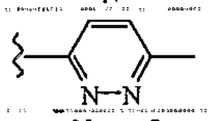
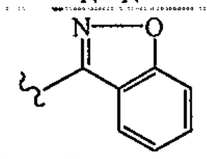
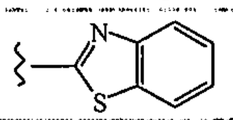
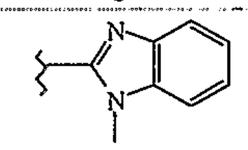
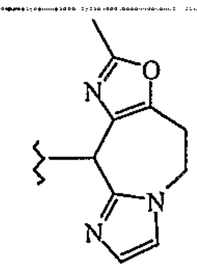
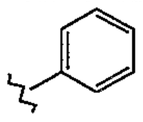
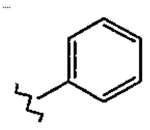
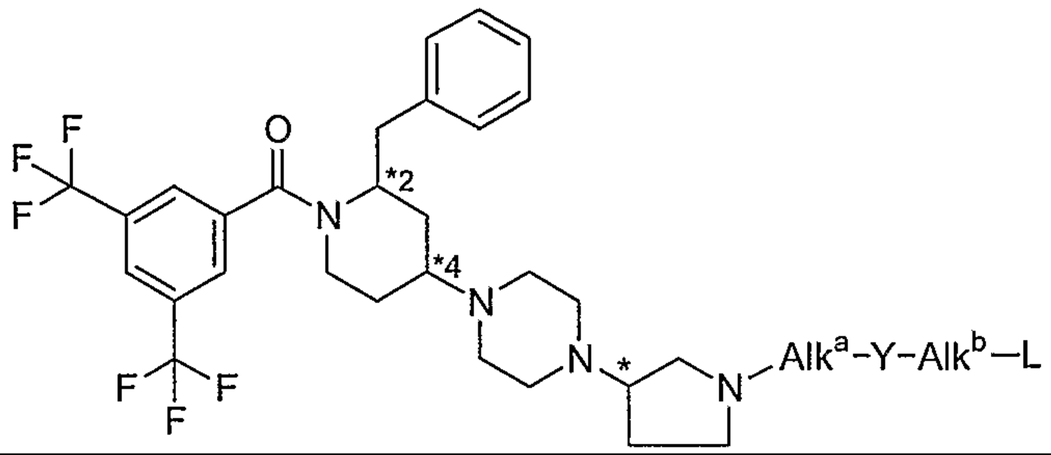
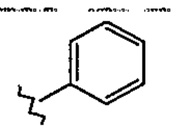
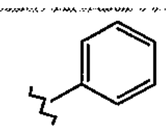
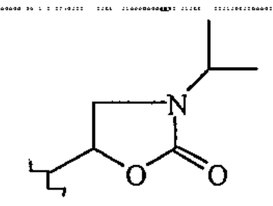
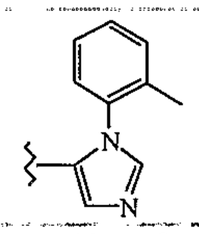
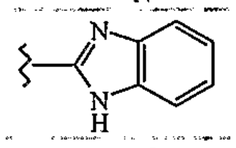
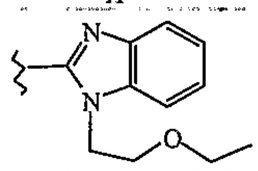
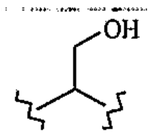
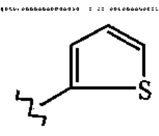
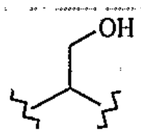
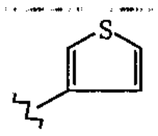
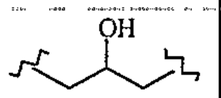
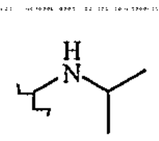
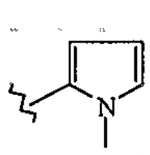
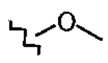
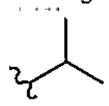
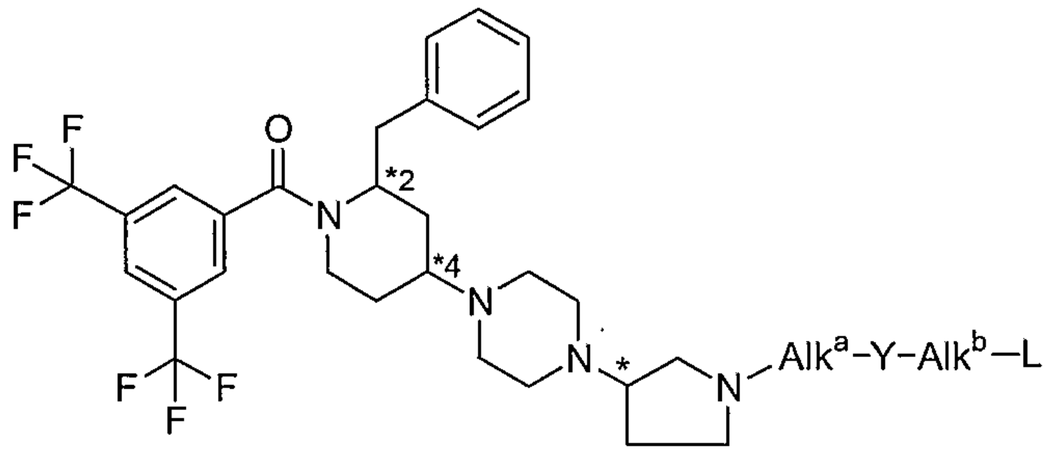
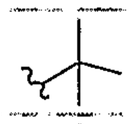
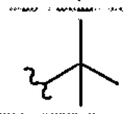
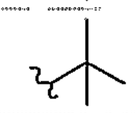
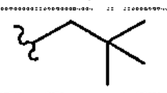
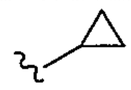
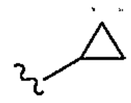
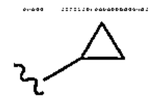
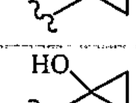
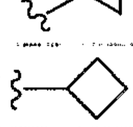
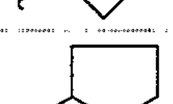
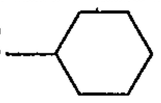
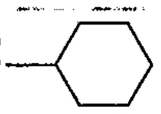
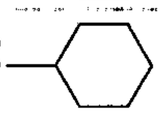
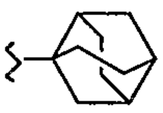
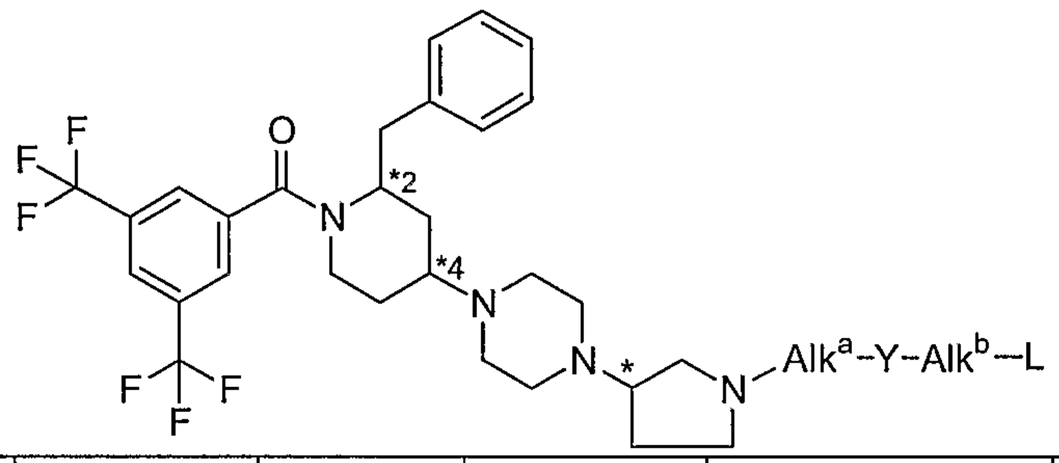
149	B31.b	cb	cb	cb	H	[2R-[2α,4β(R)]]
116	B1b	cb	cb	cb	H	2S-trans
117	B1b	cb	cb	cb	H	2R-cis
118	B1b	cb	cb	cb	H	2S-cis
383	B29.a	cb	cb	cb		2R-trans
4	B4	cb	cb	cb		2R-trans
5	B4	cb	cb	cb		2R-trans
6	B4	cb	cb	cb		2R-trans
204	B33	cb	cb	cb		2R-trans
7	B4	cb	cb	cb		2R-trans
8	B4	cb	cb	cb		2R-trans
375	B19	cb	cb	cb		2R-trans
1	B1a	$-CH_2-$	cb	cb		2R-trans
112	B1a	$-CH_2-$	cb	cb		2R-cis

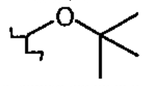
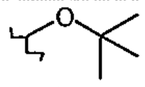
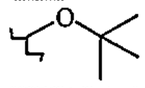
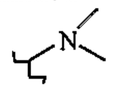
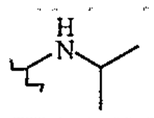
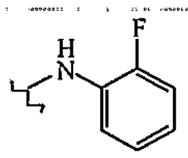
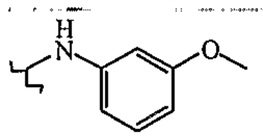
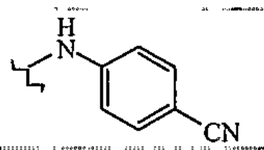
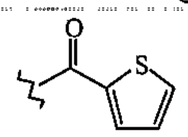
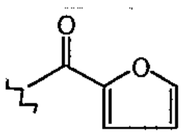
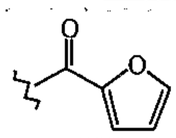
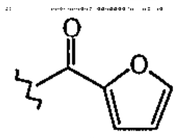
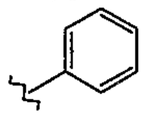
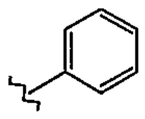
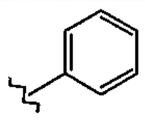
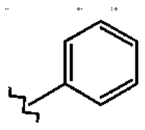


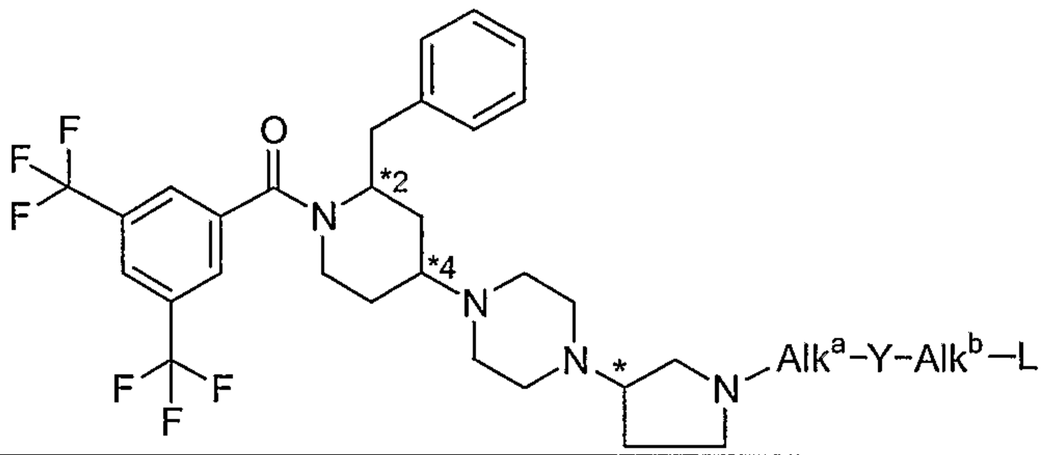
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
113	B1a	-CH_2-	cb	cb		2S-trans
114	B1a	-CH_2-	cb	cb		2S-cis
385	B29.c	-CH_2-	cb	cb		2R-trans
9	B4	-CH_2-	cb	cb		2R-trans
10	B4	-CH_2-	cb	cb		2R-trans
11	B4	-CH_2-	cb	cb		2R-trans
319	B23		cb	cb		2R-trans
349	B23		cb	cb		2R-trans
384	B29.b		cb	cb		2R-trans
103	B5	-CH_2-	C=O	cb		2R-trans
80	B3	-CH_2CH_2-	C=O	cb		2R-trans
198	B15	cb	C=O	cb	-CH_3	2R-trans
230	B11	cb	C=O	cb	-CH_2Cl	2R-trans
203	B17	cb	C=O	cb	-CF_3	2R-trans
199	B15	cb	C=O	cb		2R-trans

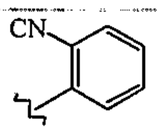
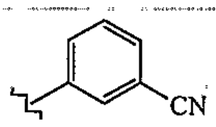
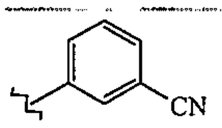
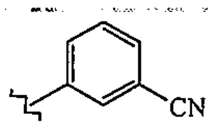
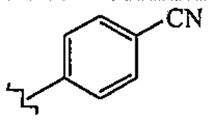
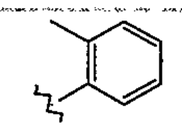
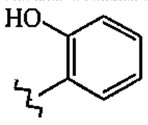
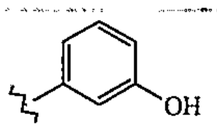
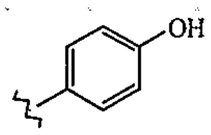
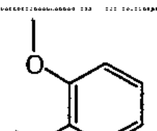
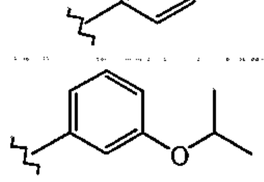
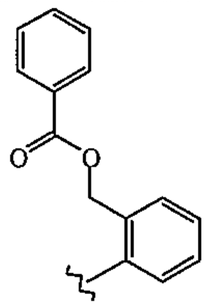


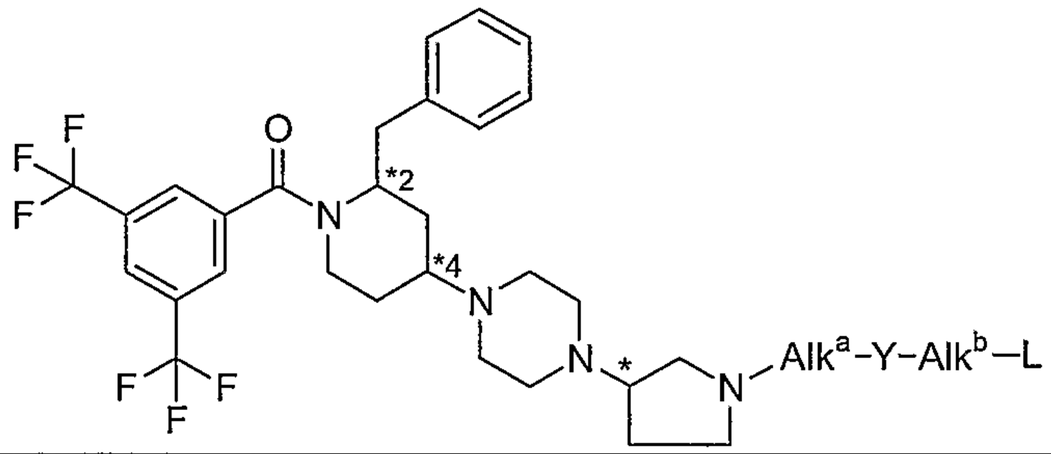
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
167	B15	cb	C=O	cb		2R-trans
305	B15	cb	C=O	cb		[2R-[2α,4β(R)]]
306	B15	cb	C=O	cb		[2R-[2α,4β(S)]]
200	B15	cb	C=O	cb		2R-trans
70	B2	cb	C=O	cb		[2R-[2α,4β(R*)]]
71	B2	cb	C=O	cb		[2R-[2α,4β(S*)]]
72	B2	cb	C=O	cb		2R-trans
182	B2	cb	C=O	cb		2S-cis
126	B2	cb	C=O	cb		2S-trans
137	B2	cb	C=O	cb		2R-cis
73	B2	cb	C=O	cb		2R,trans
276	B14	cb	C=O	cb		2R,trans
179	B15	cb	C=O	cb		2R-trans
74	B2	cb	C=O	cb		2R-trans
178	B15	cb	C=O	cb		2R-trans
402	B15	cb	C=O	cb		[2R-[2α,4β(R*)]]
403	B15	cb	C=O	cb		[2R-[2α,4β(S*)]]
220	B15	cb	C=O	cb		2R-trans

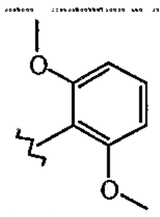
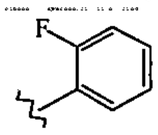
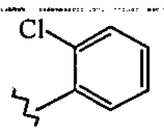
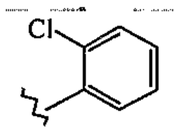
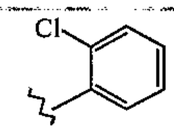
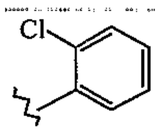
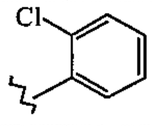
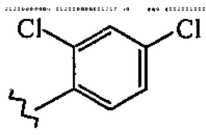
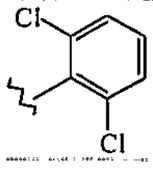
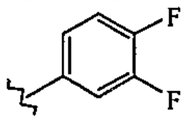
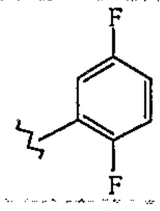
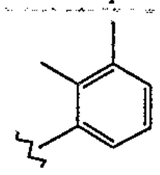
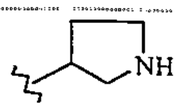


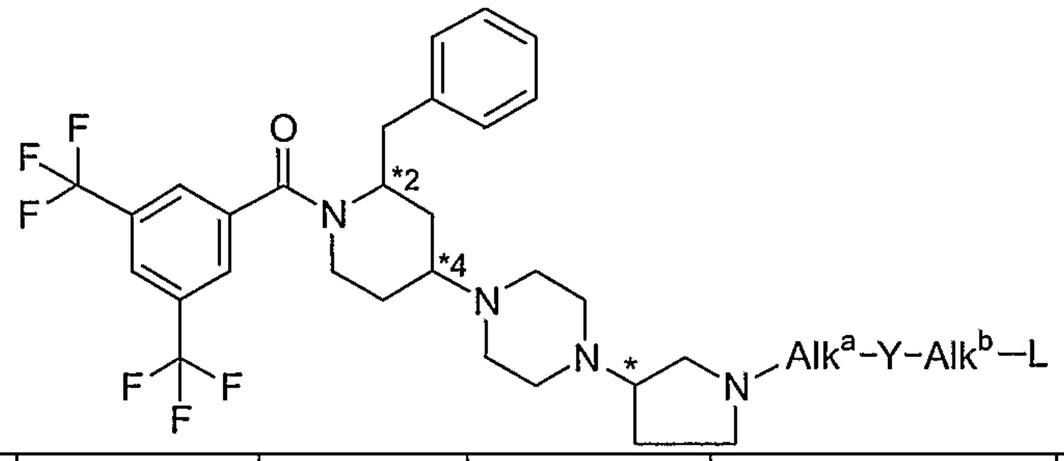
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
130	B2	cb	C=O	cb		2R-trans
150	B22.b	cb	C=O	cb		[2R-[2α,4β(S*)]]
151	B22.b	cb	C=O	cb		[2R-[2α,4β(R*)]]
145	B2	cb	C=O	cb		2R-trans
293	B30	cb	C=O	cb		2R-trans
284	B30	cb	C=O	cb		2R-trans
343	B30	cb	C=O	cb		2R-trans
283	B30	cb	C=O	cb		2R-trans
188	B16	cb	C=O	cb		2R-trans
64	B2	cb	C=O	cb		2R-trans
190	B14	cb	C=O	cb		[2R-[2α,4β(S*)]]
191	B14	cb	C=O	cb		[2R-[2α,4β(R*)]]
136	B2	cb	C=O	cb		2R-cis
3	B2	cb	C=O	cb		2R-trans
180	B2	cb	C=O	cb		2S-cis
127	B2	cb	C=O	cb		2S-trans

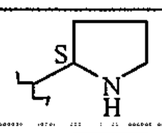
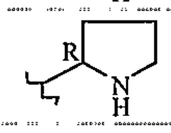
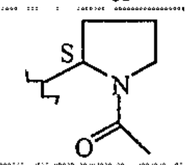
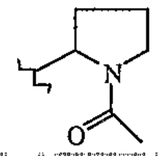
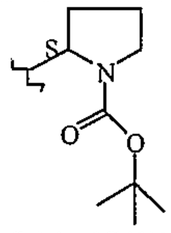
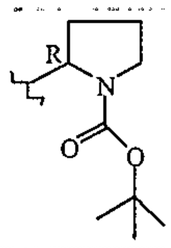
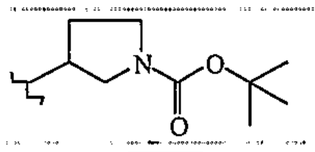
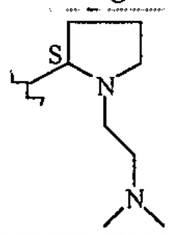
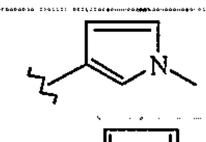
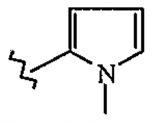
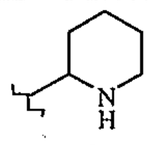
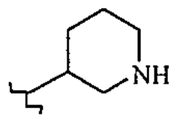


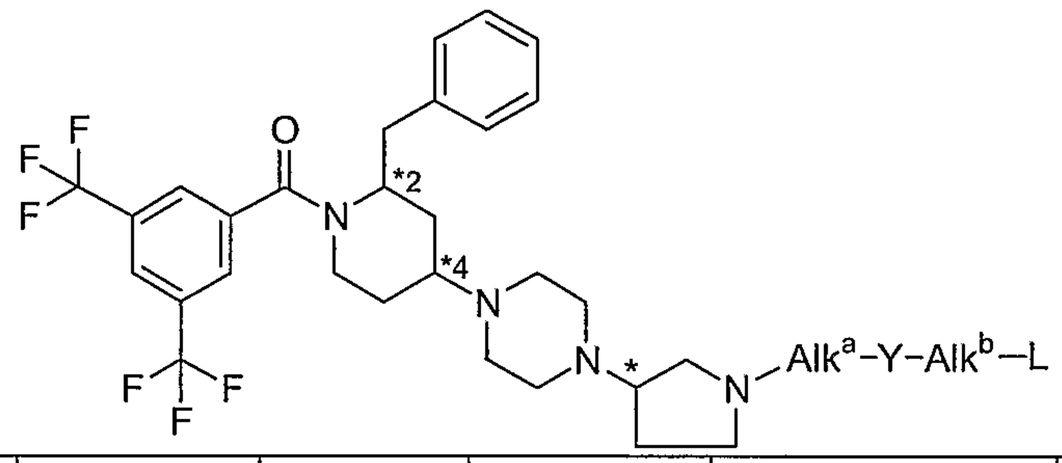
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
195	B16	cb	C=O	cb		2R-trans
12	B2	cb	C=O	cb		2R-trans
192	B2	cb	C=O	cb		[2R-[2α,4β(S*)]]
193	B2	cb	C=O	cb		[2R-[2α,4β(R*)]]
271	B14	cb	C=O	cb		2R-trans
13	B2	cb	C=O	cb		2R-trans
327	B14	cb	C=O	cb		2R-trans
332	B14	cb	C=O	cb		2R-trans
341	B14	cb	C=O	cb		2R, trans
14	B2	cb	C=O	cb		2R-trans
15	B2	cb	C=O	cb		2R-trans
346	B14	cb	C=O	cb		2R-trans

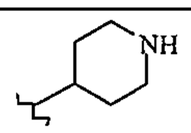
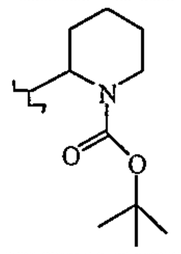
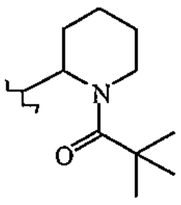
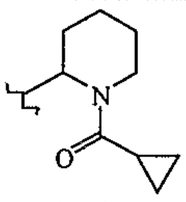
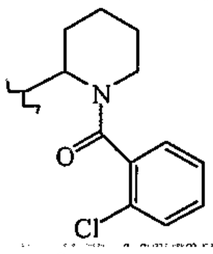
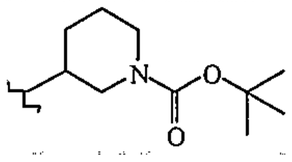
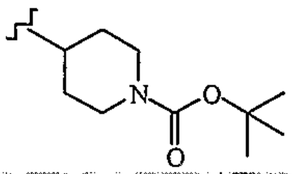
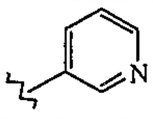
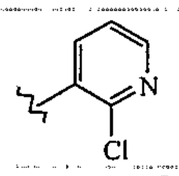
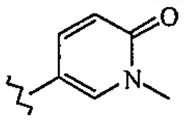
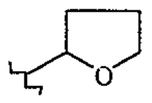


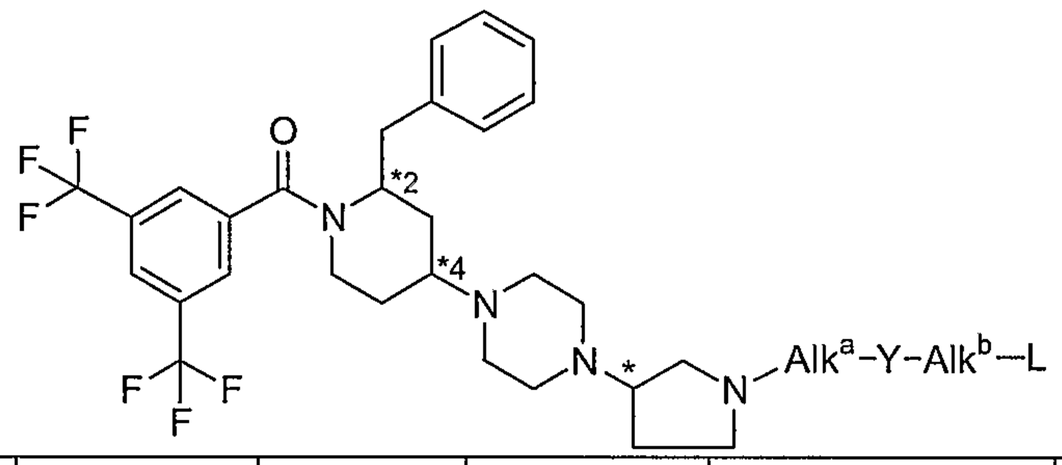
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
18	B2	cb	C=O	cb		2R-trans
16	B2	cb	C=O	cb		2R-trans
17	B2	cb	C=O	cb		2R-trans
181	B2	cb	C=O	cb		2S-cis
87	B2	cb	C=O	cb		2R-cis
159	B2	cb	C=O	cb		[2R-[2α,4β(S*)]]
160	B2	cb	C=O	cb		[2R-[2α,4β(R*)]]
22	B2	cb	C=O	cb		2R-trans
169	B2	cb	C=O	cb		2R-trans
20	B2	cb	C=O	cb		2R-trans
21	B2	cb	C=O	cb		2R-trans
19	B2	cb	C=O	cb		2R-trans
235	B14.b	cb	C=O	cb		2R-trans

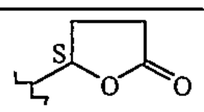
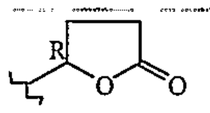
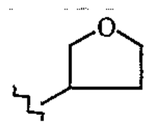
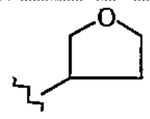
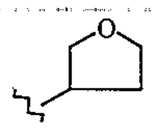
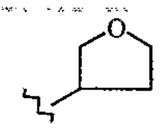
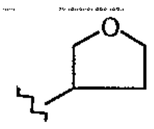
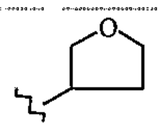
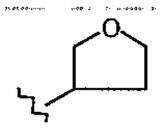
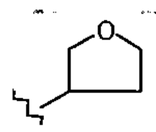
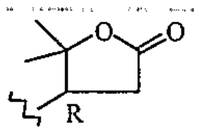
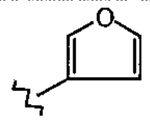
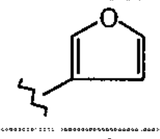
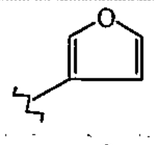
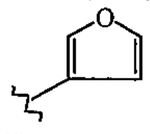


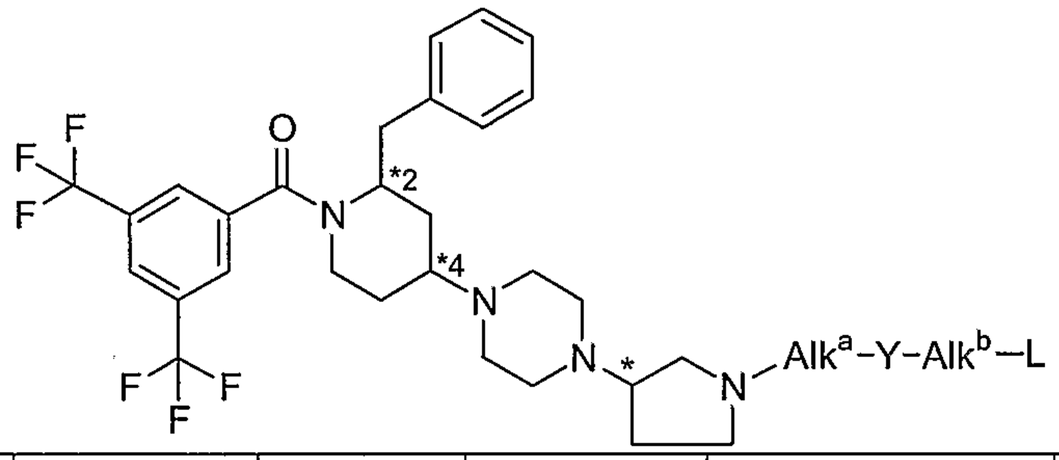
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
144	B14.b	cb	C=O	cb		2R-trans
213	B14.b	cb	C=O	cb		2R-trans
186	B14.b	cb	C=O	cb		2R-trans
187	B14.a	cb	C=O	cb		2R-trans
115	B2	cb	C=O	cb		2R-trans
189	B14	cb	C=O	cb		2R-trans
228	B14	cb	C=O	cb		2R-trans
185	B34	cb	C=O	cb		2R-trans
23	B2	cb	C=O	cb		2R-trans
24	B2	cb	C=O	cb		2R-trans
294	B14.b	cb	C=O	cb		2R-trans
240	B14.b	cb	C=O	cb		2R-trans

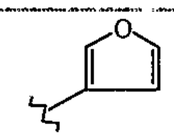
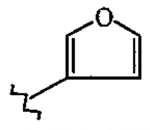
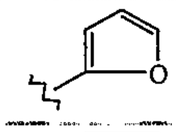
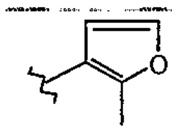
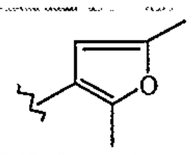
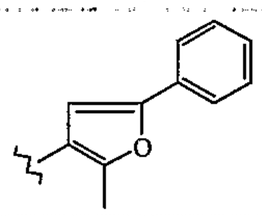
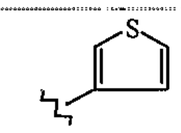
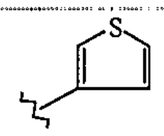
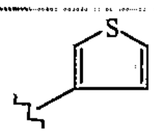
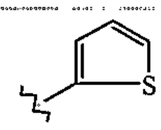
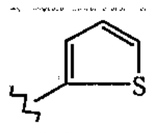
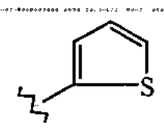
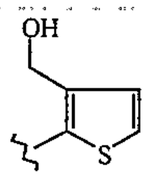
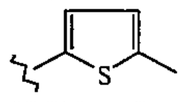


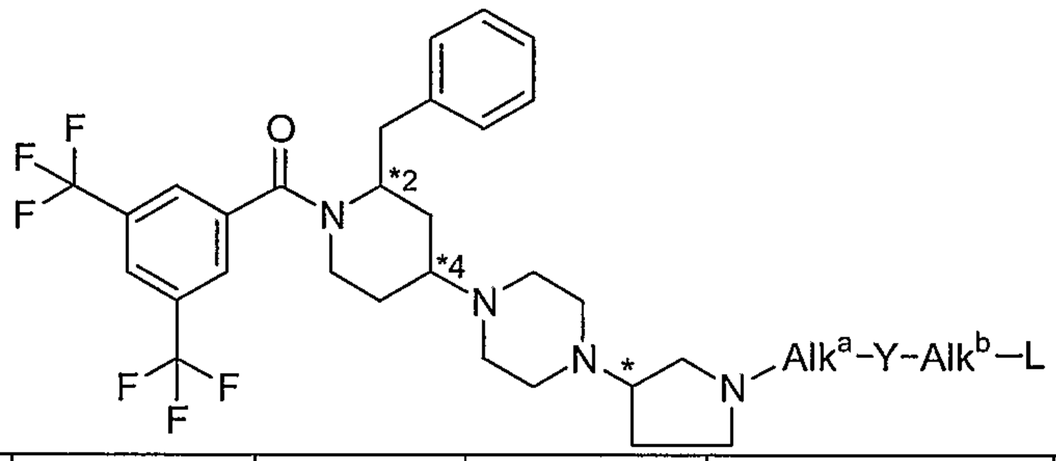
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
241	B14.b	cb	C=O	cb		2R-trans
206	B14.a	cb	C=O	cb		2R-trans
297	B14.c	cb	C=O	cb		2R-trans
296	B14.c	cb	C=O	cb		2R-trans
295	B14.c	cb	C=O	cb		2R-trans
229	B14	cb	C=O	cb		2R-trans
210	B14	cb	C=O	cb		2R-trans
28	B2	cb	C=O	cb		2R-trans
168	B15	cb	C=O	cb		2R-trans
29	B2	cb	C=O	cb		2R-trans
97	B2	cb	C=O	cb		2R-trans

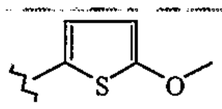
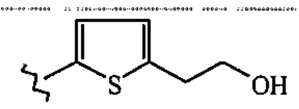
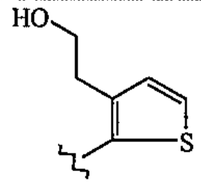
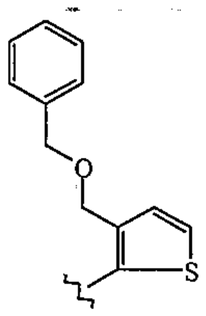
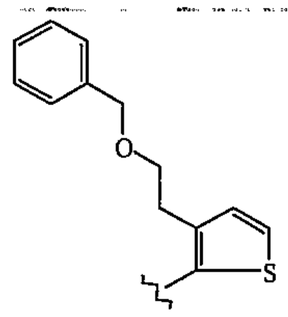
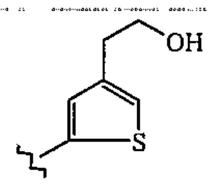
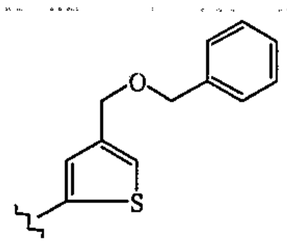
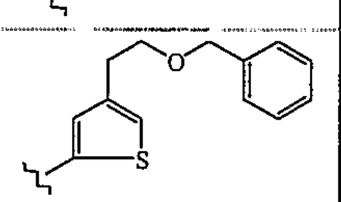


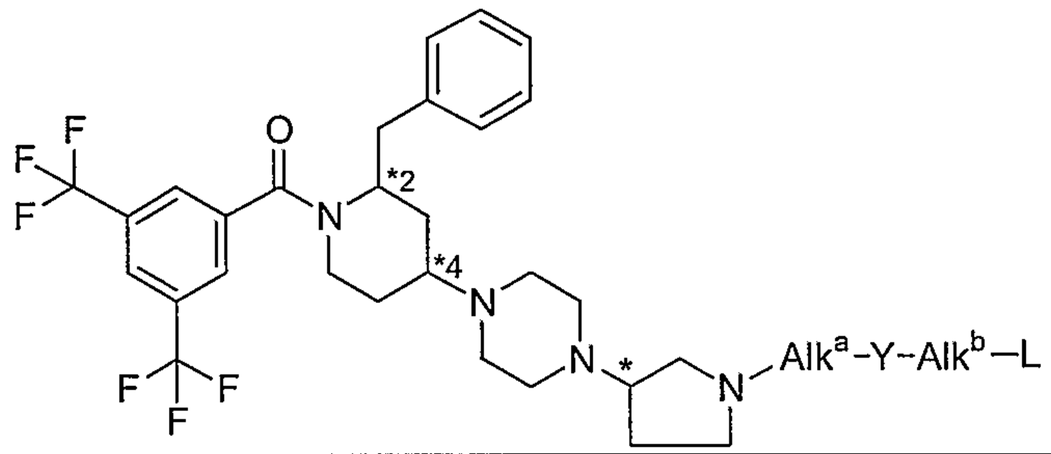
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
386	B14	cb	C=O	cb		2R-trans
387	B14	cb	C=O	cb		2R-trans
31	B16	cb	C=O	cb		2R-trans
184	B16	cb	C=O	cb		2S-cis
129	B16	cb	C=O	cb		2S-trans
139	B16	cb	C=O	cb		2R-cis
216	B16	cb	C=O	cb		[2R-[2α,4β(S(S))]]
217	B16	cb	C=O	cb		[2R-[2α,4β(R(S))]]
219	B16	cb	C=O	cb		[2R-[2α,4β(R(R))]]
218	B16	cb	C=O	cb		[2R-[2α,4β(S(R))]]
404	B20	cb	C=O	cb		2R-trans
32	B2	cb	C=O	cb		2R-trans, R*
33	B2	cb	C=O	cb		2R-trans, S*
34	B2	cb	C=O	cb		2R-trans
183	B2	cb	C=O	cb		2S-cis

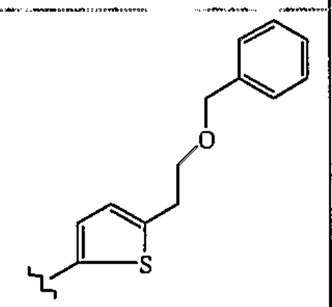
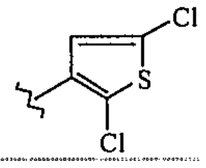
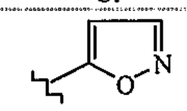
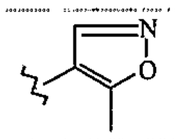
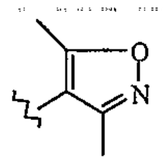
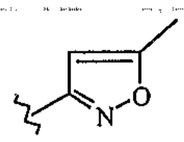
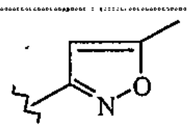
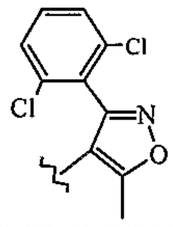
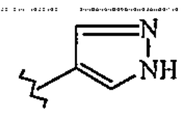
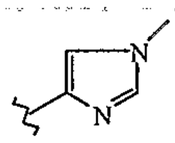
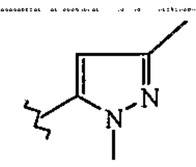


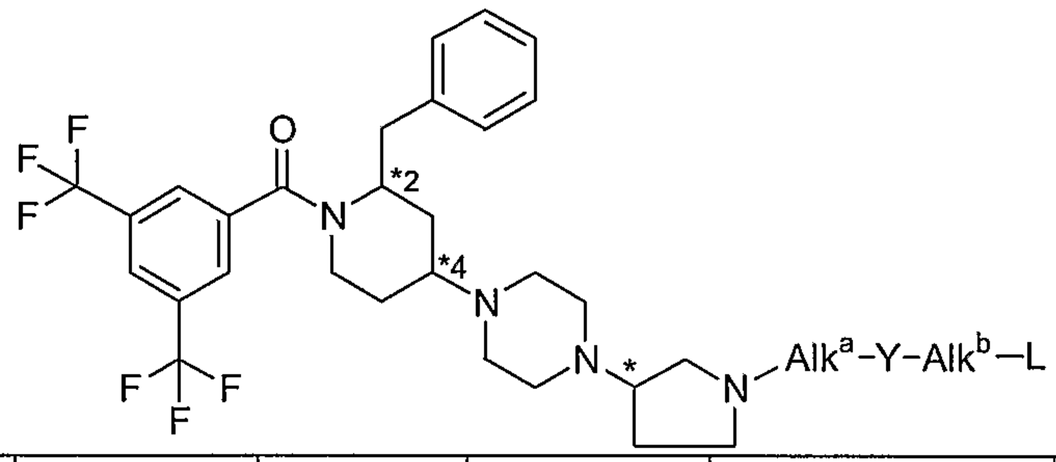
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
128	B2	cb	C=O	cb		2S-trans
138	B2	cb	C=O	cb		2R-cis
35	B2	cb	C=O	cb		2R-trans
36	B2	cb	C=O	cb		2R-trans
37	B2	cb	C=O	cb		2R-trans
38	B2	cb	C=O	cb		2R-trans
39	B2	cb	C=O	cb		2R-trans, R*
40	B2	cb	C=O	cb		2R-trans, S*
41	B2	cb	C=O	cb		2R-trans
42	B2	cb	C=O	cb		2R-trans
321	B2	cb	C=O	cb		[2R-[2α,4β(R)]]
322	B2	cb	C=O	cb		[2R-[2α,4β(S)]]
360	B25	cb	C=O	cb		2R-trans
43	B2	cb	C=O	cb		2R-trans

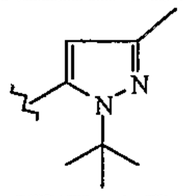
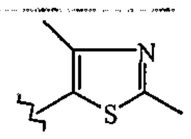
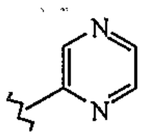
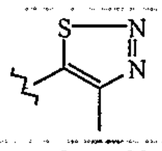
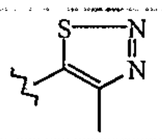
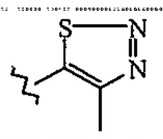
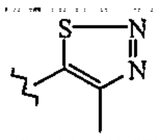
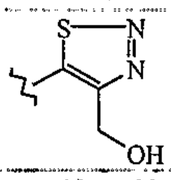
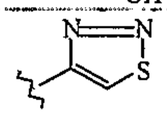
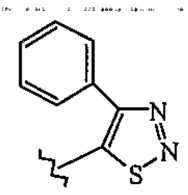
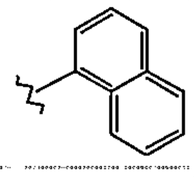
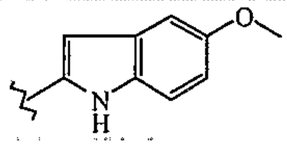
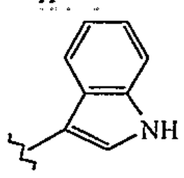


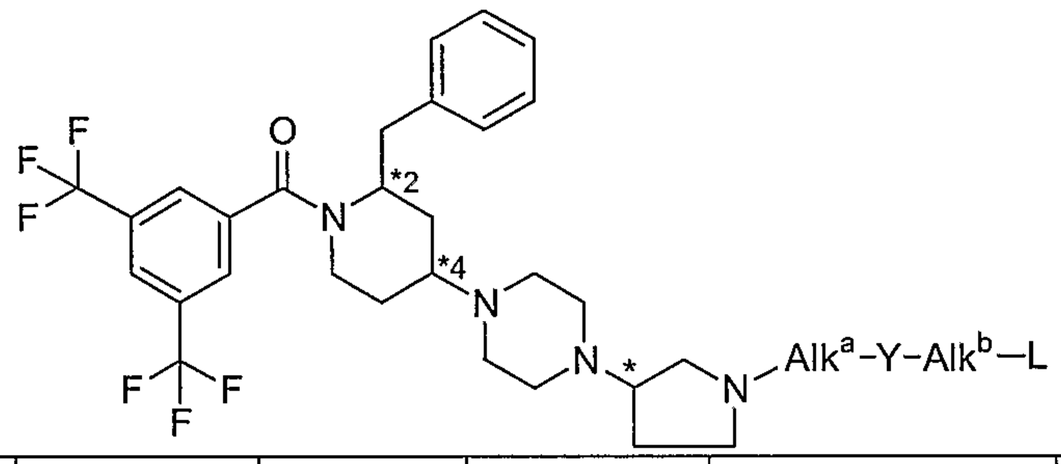
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
350	B25	cb	C=O	cb		2R-trans
359	B25	cb	C=O	cb		2R-trans
369	B25	cb	C=O	cb		2R-trans
353	B25	cb	C=O	cb		2R-trans
361	B25	cb	C=O	cb		2R-trans
363	B25	cb	C=O	cb		2R-trans
352	B25	cb	C=O	cb		2R-trans
362	B25	cb	C=O	cb		2R-trans

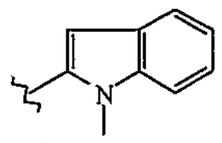
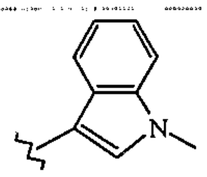
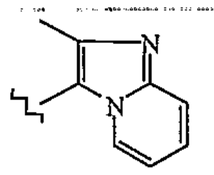
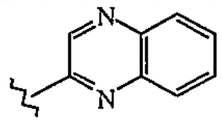
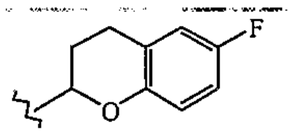
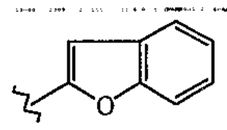
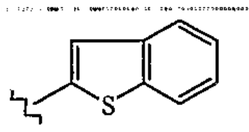
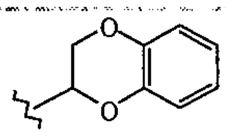
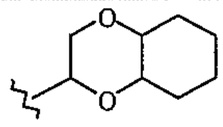
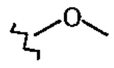
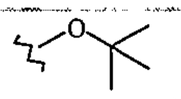
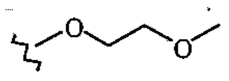
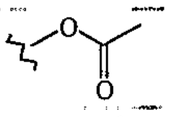
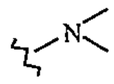
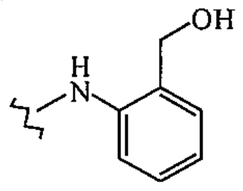


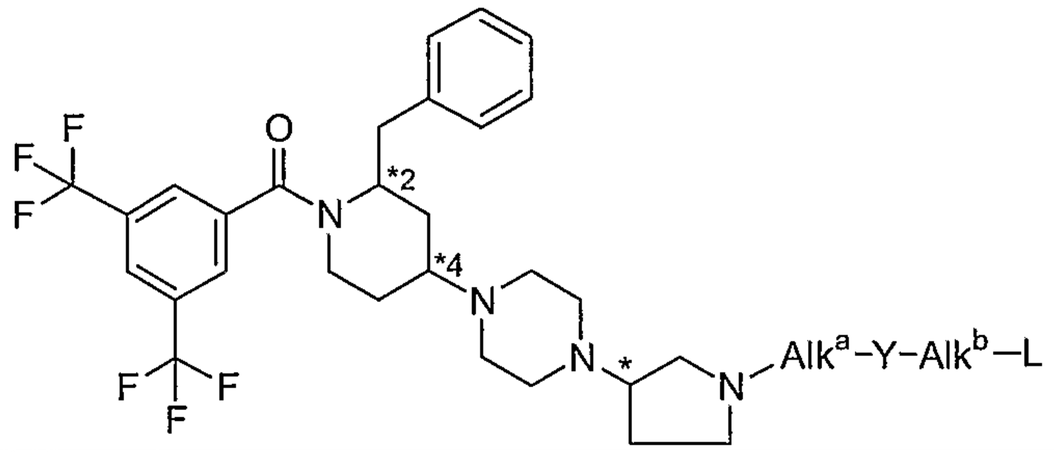
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
356	B25.a	cb	C=O	cb		2R-trans
44	B2	cb	C=O	cb		2R-trans
68	B2	cb	C=O	cb		2R-trans
45	B2	cb	C=O	cb		2R-trans
48	B2	cb	C=O	cb		2R-trans
46	B2	cb	C=O	cb		2R-trans
47	B2	cb	C=O	cb		2R-trans
49	B2	cb	C=O	cb		2R-trans
25	B2	cb	C=O	cb		2R-trans
282	B14	cb	C=O	cb		2R-trans
26	B2	cb	C=O	cb		2R-trans

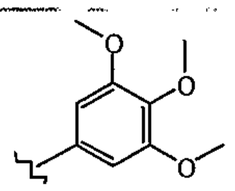
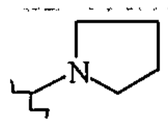
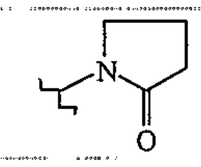
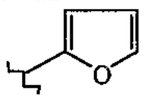
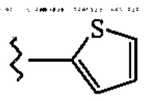
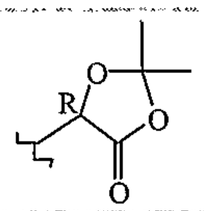
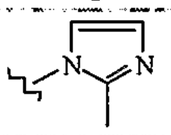
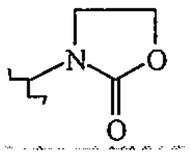
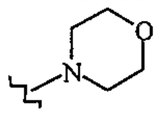
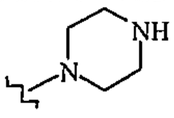
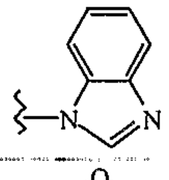
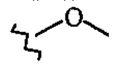
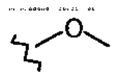
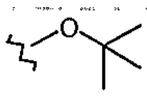
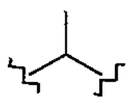
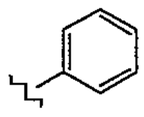


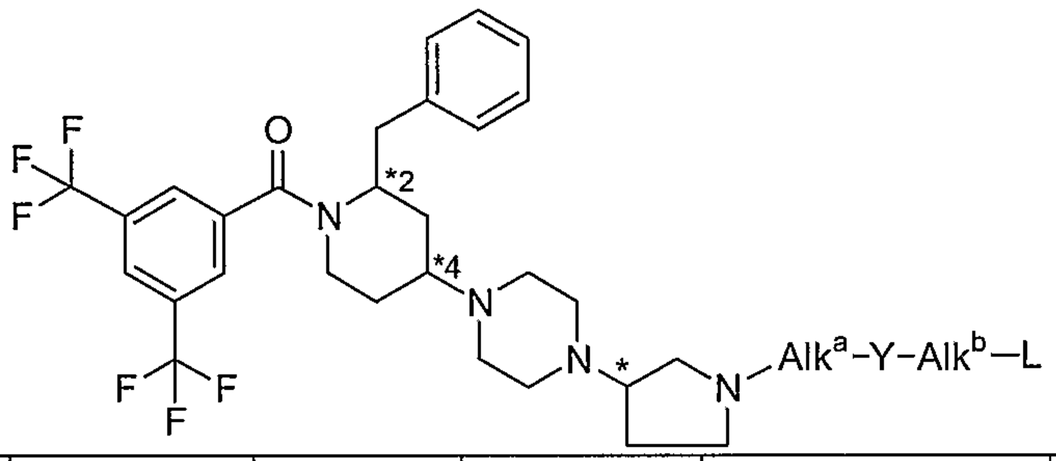
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
27	B2	cb	C=O	cb		2R-trans
50	B2	cb	C=O	cb		2R-trans
30	B2	cb	C=O	cb		2R-trans
51	B2	cb	C=O	cb		2R-trans
125	B2	cb	C=O	cb		2S-trans
380	B15	cb	C=O	cb		[2R-[2α,4β(S*)]]
381	B15	cb	C=O	cb		[2P-[2α,4β(R*)]]
166	B18	cb	C=O	cb		2R-trans
52	B2	cb	C=O	cb		2R-trans
53	B2	cb	C=O	cb		2R-trans
54	B2	cb	C=O	cb		2R-trans
55	B2	cb	C=O	cb		2R-trans
56	B2	cb	C=O	cb		2R-trans

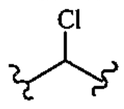
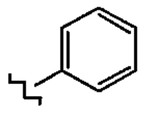
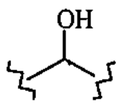
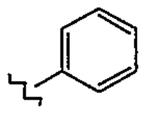
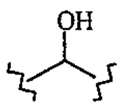
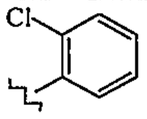
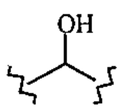
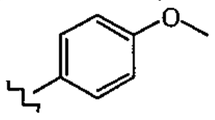
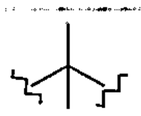
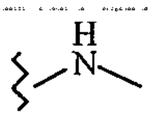
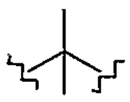
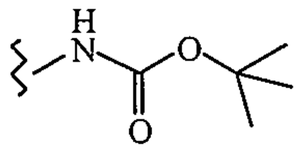
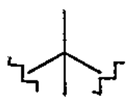
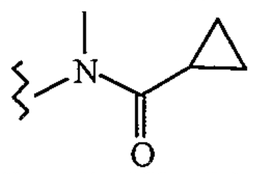
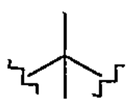
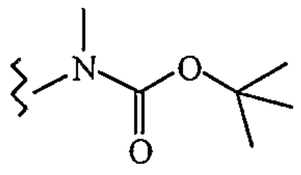
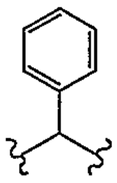
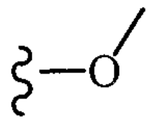
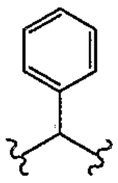
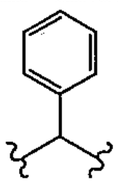
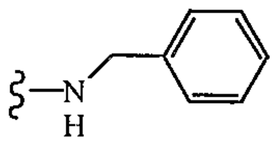


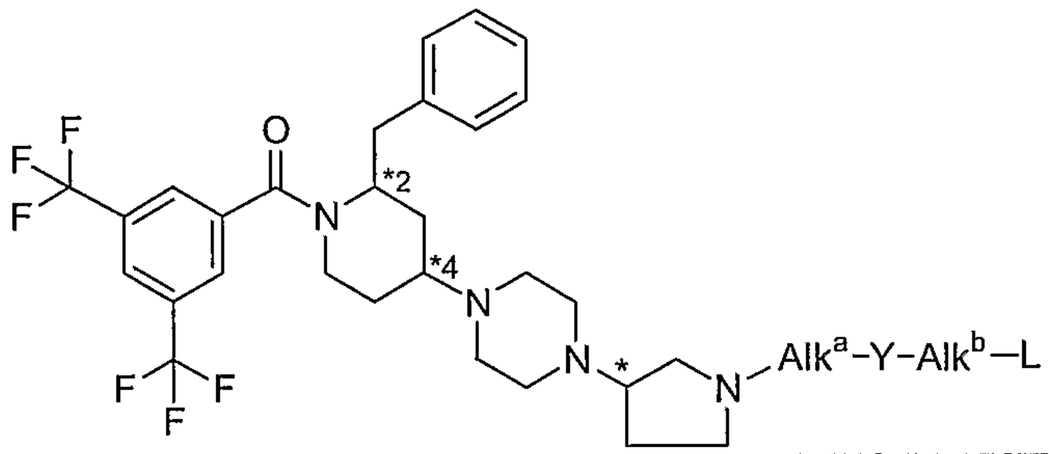
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
57	B2	cb	C=O	cb		2R-trans
58	B2	cb	C=O	cb		2R-trans
59	B2	cb	C=O	cb		2R-trans
60	B2	cb	C=O	cb		2R-trans
61	B2	cb	C=O	cb		2R-trans
62	B2	cb	C=O	cb		2R-trans
63	B2	cb	C=O	cb		2R-trans
98	B2	cb	C=O	cb		2R-trans
99	B2	cb	C=O	cb		2R-trans
177	B15	cb	C=O	-CH_2-		2R-trans
388	B14	cb	C=O	-CH_2-		2R-trans
390	B14	cb	C=O	-CH_2-		2R-trans
389	B14	cb	C=O	-CH_2-		2R-trans
202	B11.b	cb	C=O	-CH_2-		2R-trans
207	B13	cb	C=O	-CH_2-		2R-trans

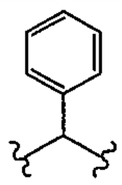
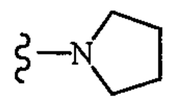
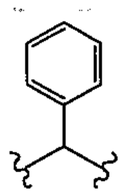
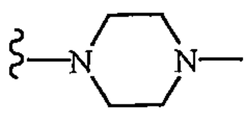
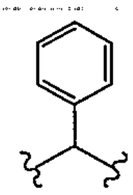
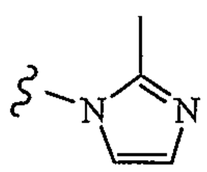
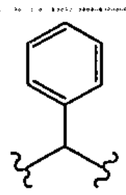
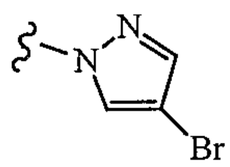
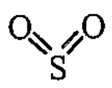
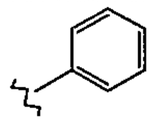
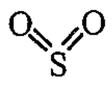
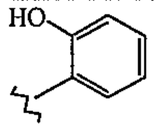
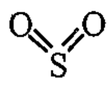
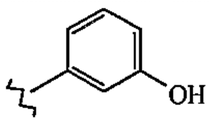
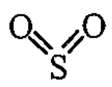
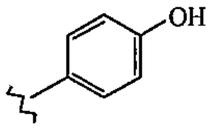
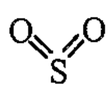
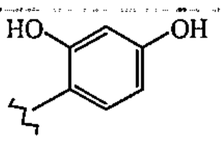
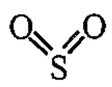
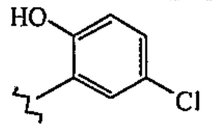
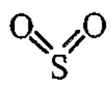
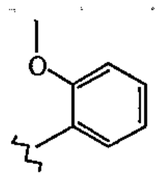
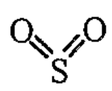
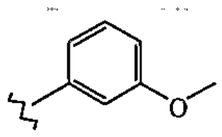


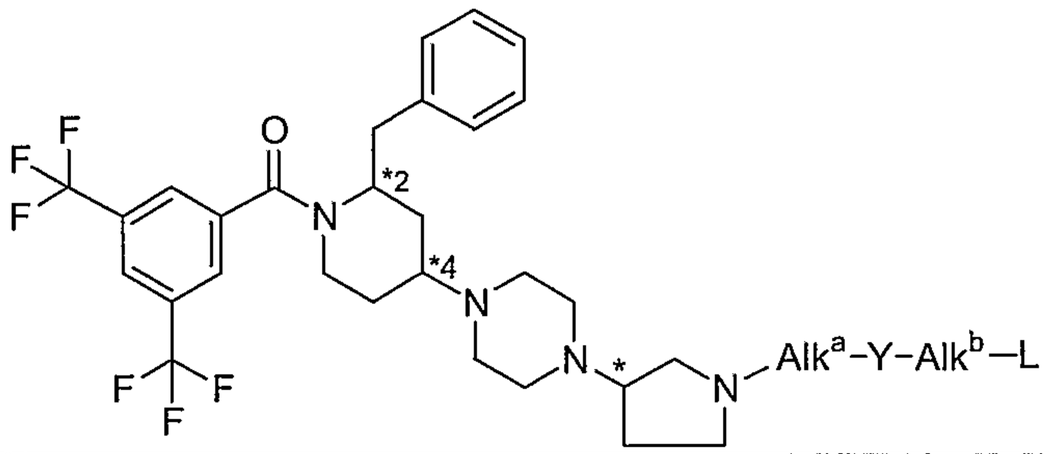
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
65	B2	cb	C=O	-CH_2-		2R-trans
196	B11.b	cb	C=O	-CH_2-		2R-trans
214	B14	cb	C=O	-CH_2-		2R-trans
66	B2	cb	C=O	-CH_2-		2R-trans
67	B2	cb	C=O	-CH_2-		2R-trans
392	B14	cb	C=O	-CH_2-		2R-trans
209	B12	cb	C=O	-CH_2-		2R-trans
215	B14	cb	C=O	-CH_2-		2R-trans
197	B11.b	cb	C=O	-CH_2-		2R-trans
201	B11.b	cb	C=O	-CH_2-		2R-trans
208	B12	cb	C=O	-CH_2-		2R-trans
413	B14	cb	C=O	-CH_2- CH_2-		2R-trans, S
414	B14	cb	C=O	-CH_2- CH_2-		2R-trans, R
391	B14	cb	C=O	-CH_2- CH_2-		2R-trans
69	B2	cb	C=O			2R-trans

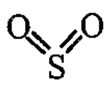
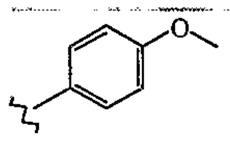
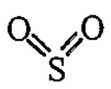
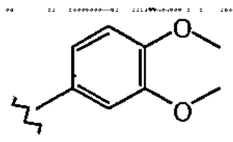
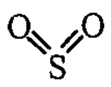
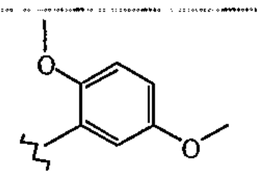
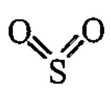
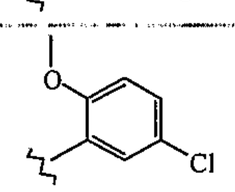
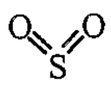
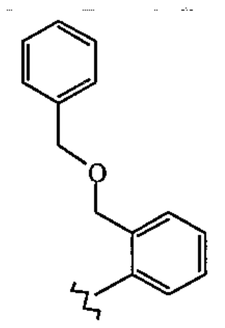
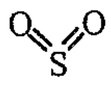
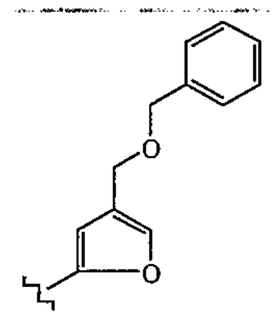
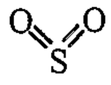
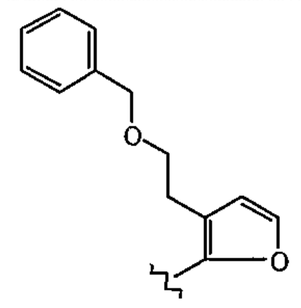
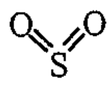
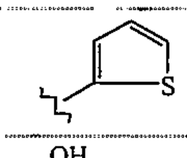
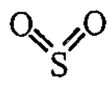
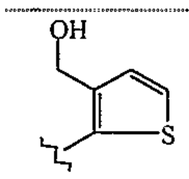


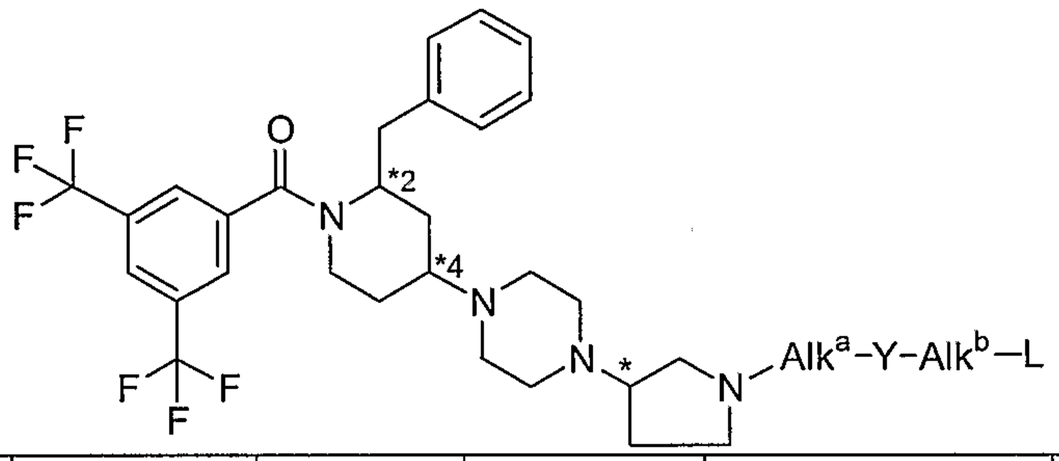
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
104	B7	cb	C=O			2R-trans
275	B14	cb	C=O			2R-trans
334	B14	cb	C=O			2R-trans
333	B14	cb	C=O			2R-trans
309	B20.c	cb	C=O			2R-trans
205	B20.a	cb	C=O			2R-trans
310	B20.d	cb	C=O			2R-trans
304	B20.b	cb	C=O			2R-trans
109	B9	cb	C=O			2R-trans
106	B8	cb	C=O			2R-trans
107	B8	cb	C=O			2R-trans

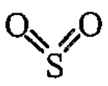
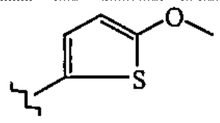
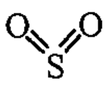
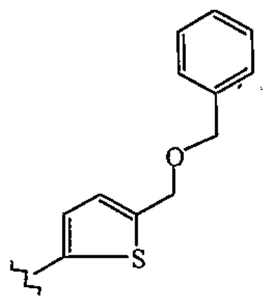
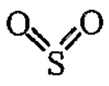
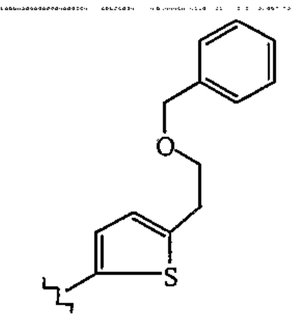
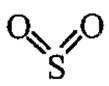
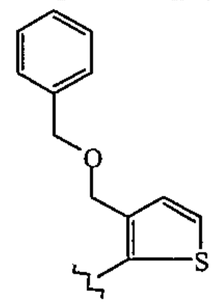
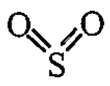
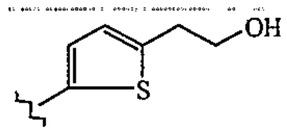
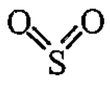
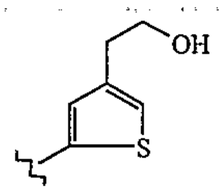
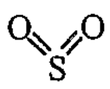
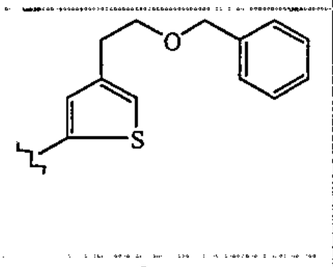
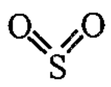
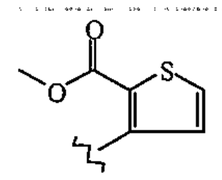


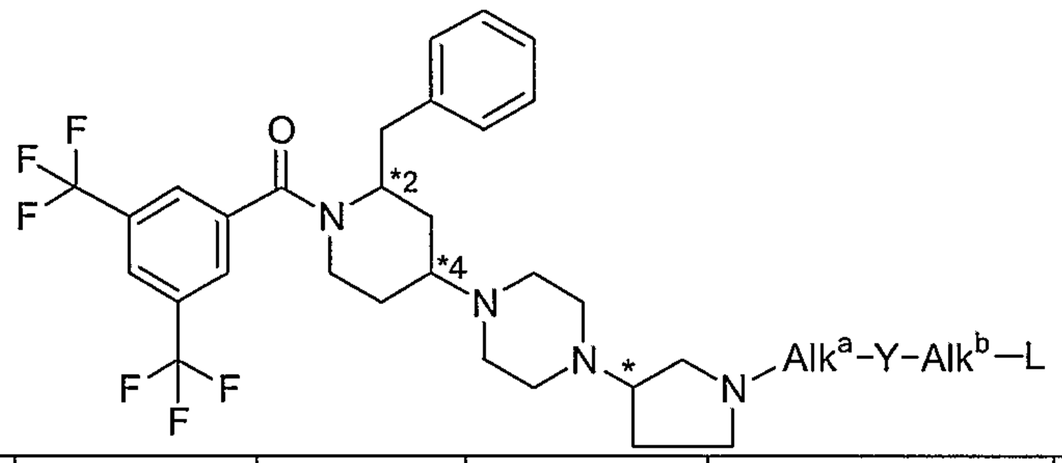
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
108	B8	cb	C=O			2R-trans
105	B8	cb	C=O			2R-trans
110	B10	cb	C=O			2R-trans
111	B10	cb	C=O			2R-trans
75	B5	cb		cb		2R-trans
307	B24.b	cb		cb		2R-trans
348	B24.b	cb		cb		2R-trans
303	B24.b	cb		cb		2R-trans
415	B24.b	cb		cb		2R-trans
416	B24.b	cb		cb		2R-trans
300	B24.a	cb		cb		2R-trans
347	B24.a	cb		cb		2R-trans

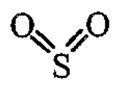
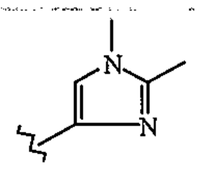
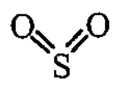
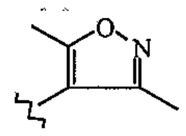
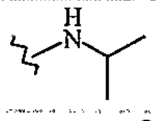
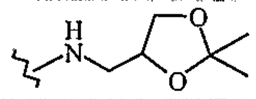
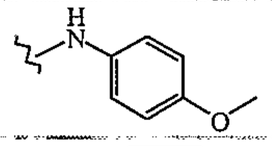
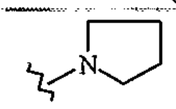
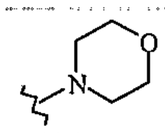
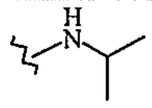
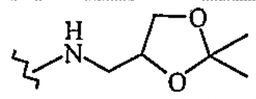
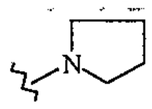


Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
280	B24.a	cb		cb		2R-trans
378	B24.a	cb		cb		2R-trans
411	B24.a	cb		cb		2R-trans
412	B24.a	cb		cb		2R-trans
401	B24.a	cb		cb		2R-trans
394	B24.a	cb		cb		2R-trans
410	B24.a	cb		cb		2R-trans
76	B5	cb		cb		2R-trans
308	B24.b	cb		cb		2R-trans



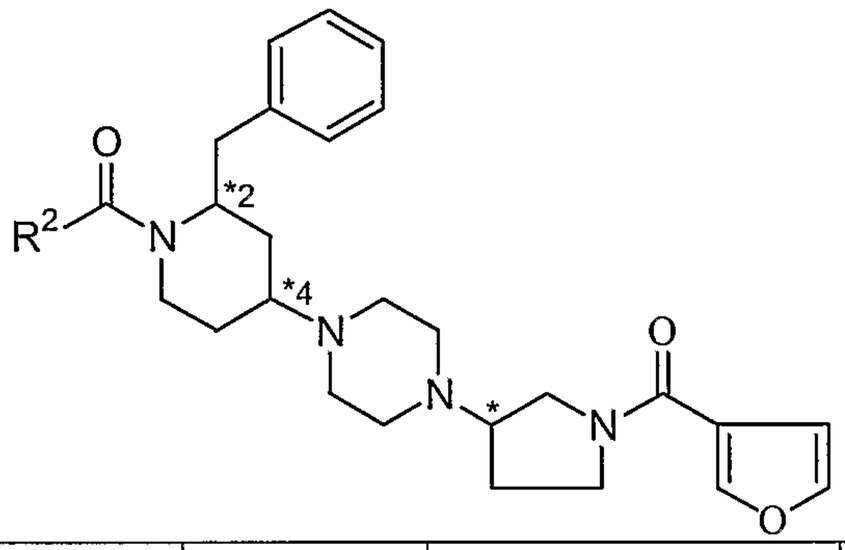
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
328	B5	cb		cb		2R-trans
345	B24.a	cb		cb		2R-trans
336	B24.a	cb		cb		2R-trans
292	B24.a	cb		cb		2R-trans
351	B24.b	cb		cb		2R-trans
342	B24.b	cb		cb		2R-trans
335	B24.a	cb		cb		2R-trans
77	B5	cb		cb		2R-trans

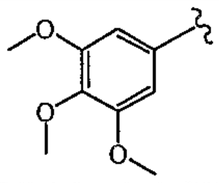
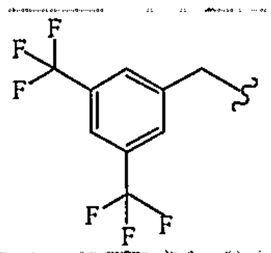
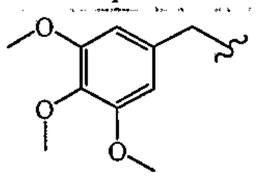
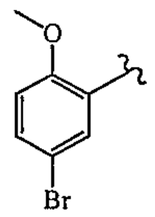
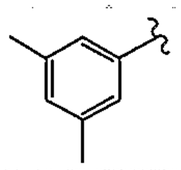
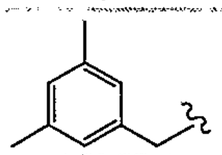
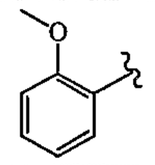
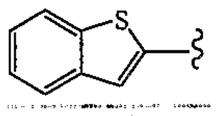
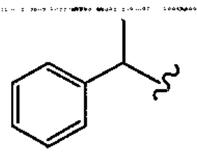
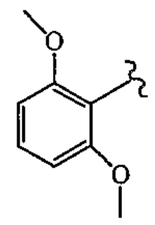


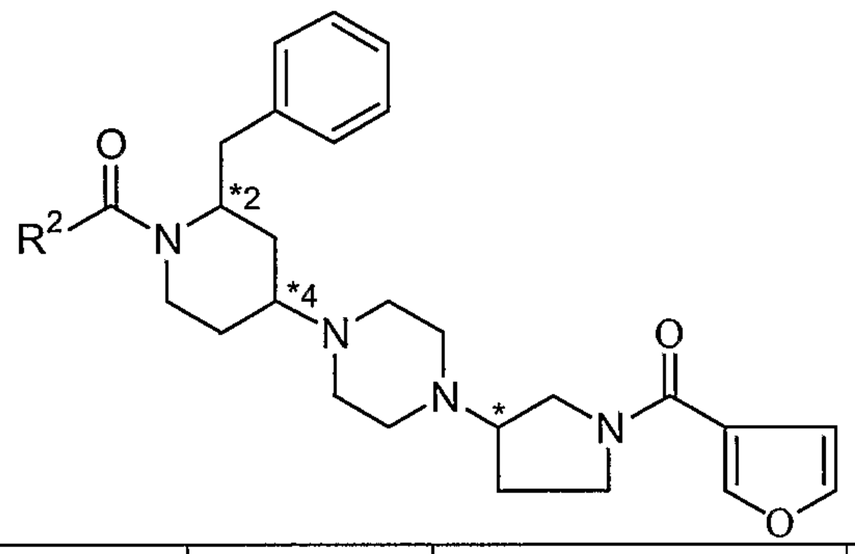
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
78	B5	cb		cb		2R-trans
79	B5	cb		cb		2R-trans
301	B27	cb	C=N-CN	cb	-SCH_3	2R-trans
344	B27	cb	C=N-CN	cb		2R-trans
370	B27	cb	C=N-CN	cb		2R-trans
355	B27	cb	C=N-CN	cb		2R-trans
302	B27	cb	C=N-CN	cb		2R-trans
371	B27	cb	C=N-CN	cb		2R-trans
354	B28	cb	C=C-NO_2	cb		2R-trans
376	B28	cb	C=C-NO_2	cb		2R-trans
377	B28	cb	C=C-NO_2	cb		2R-trans

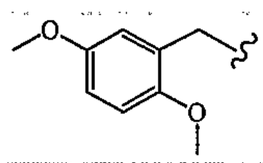
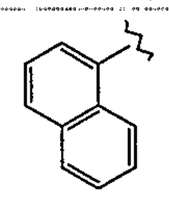
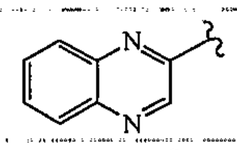
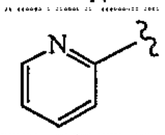
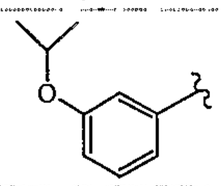
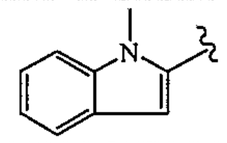
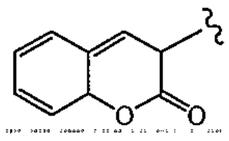
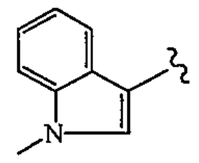
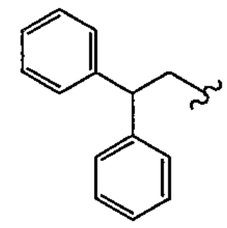
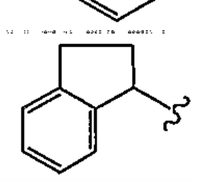
cb=covalent bond

Table 2:



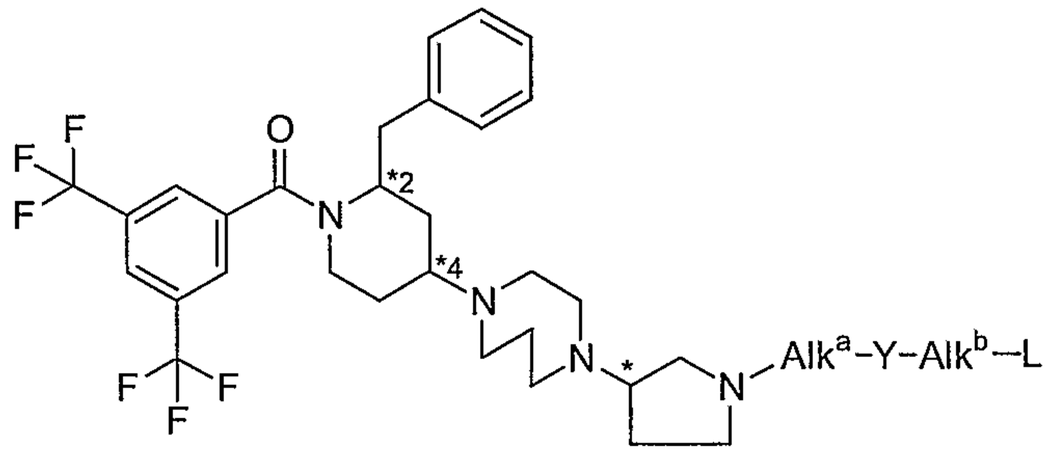
Co. No.	Exp. No.	R^2-	Stereo descriptors
81	B6		2R-trans
82	B6		2R-trans
83	B6		2R-trans
84	B6		2R-trans
85	B6		2R-trans
86	B6		2R-trans
88	B6		2R-trans
89	B6		2R-trans
90	B6		2R-trans
91	B6		2R-trans

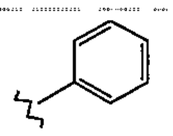
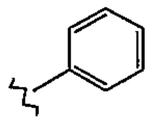
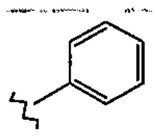
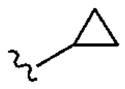
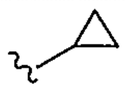
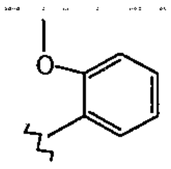
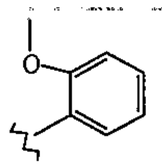
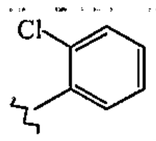
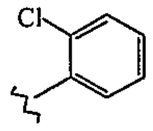
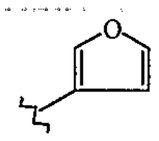
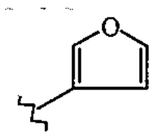
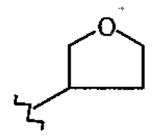


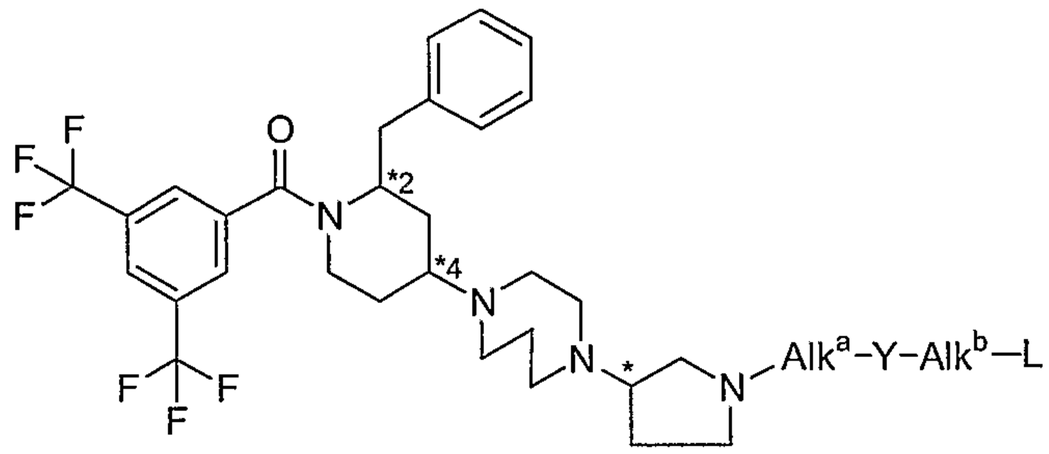
Co. No.	Exp. No.	R^2-	Stereo descriptors
92	B6		2R-trans
93	B6		2R-trans
94	B6		2R-trans
95	B6		2R-trans
96	B6		2R-trans
100	B6/B21		2R-trans
101	B6/B21		2R-trans
102	B6/B21		2R-trans
146	B21		2R-trans
147	B21		2R-trans

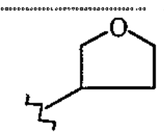
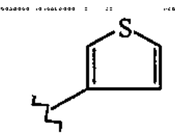
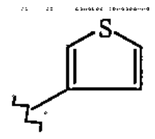
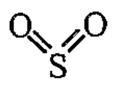
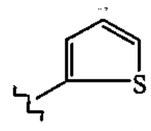
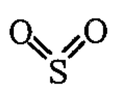
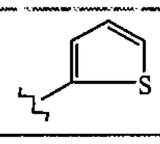
cb=covalent bond

Table 3:



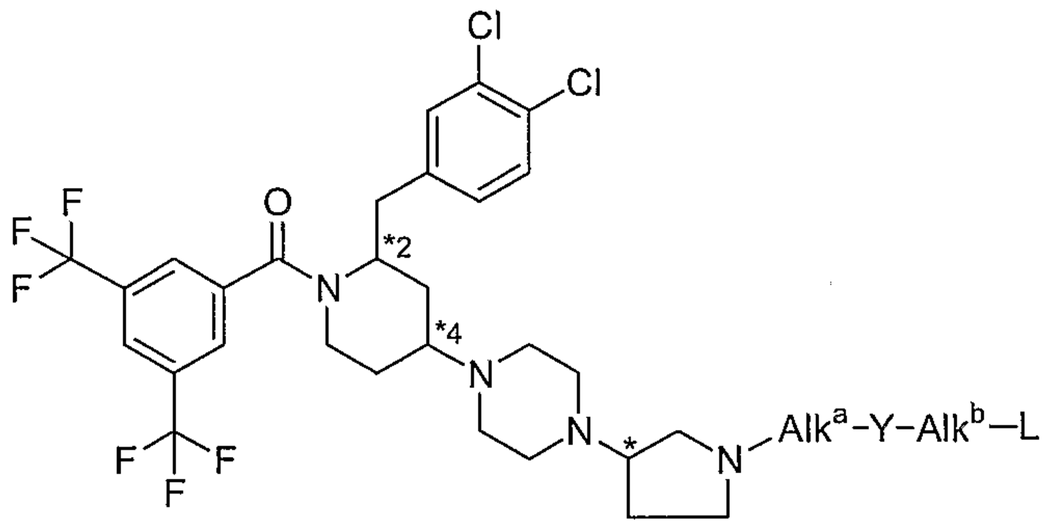
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
120	B1b	cb	cb	cb	H	2S-trans
123	B1b	cb	cb	cb	H	2R-cis
133	B1b	cb	cb	cb	H	2R-cis+trans
119	B1a	$-CH_2-$	cb	cb		2R-trans
132	B1a	$-CH_2-$	cb	cb		2R-cis+trans
140	B1a	$-CH_2-$	cb	cb		2R-cis
154	B15	cb	C=O	cb		2R-cis
156	B15	cb	C=O	cb		2R-trans
134	B2	cb	C=O	cb		2R-cis
135	B2	cb	C=O	cb		2R-trans
157	B15	cb	C=O	cb		2R-cis
158	B15	cb	C=O	cb		2R-trans
121	B2	cb	C=O	cb		2R-trans
131	B2	cb	C=O	cb		2R-cis
152	B14	cb	C=O	cb		2R-cis



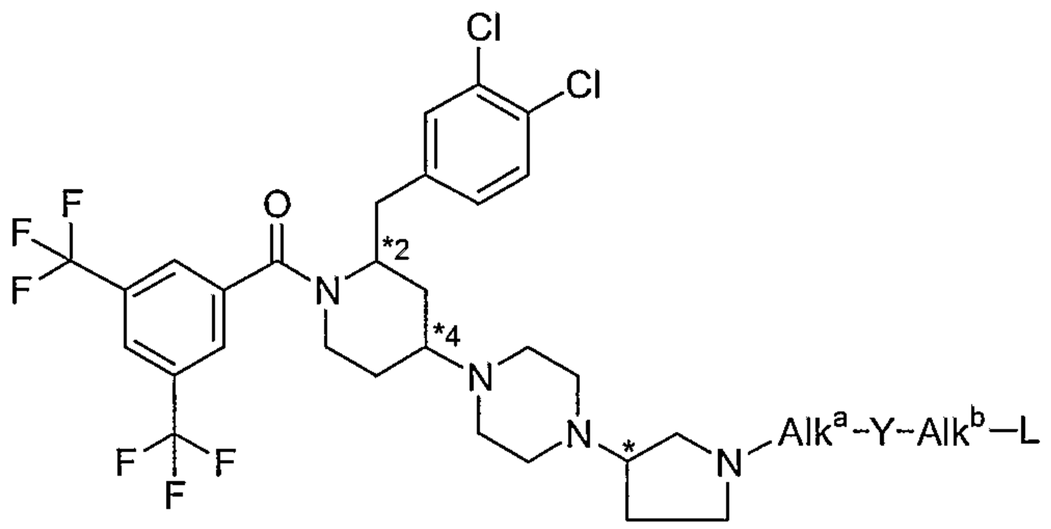
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
153	B14	cb	C=O	cb		2R-trans
122	B2	cb	C=O	cb		2R-cis
124	B2	cb	C=O	cb		2R-trans
155	B5	cb		cb		2R-trans
170	B5	cb		cb		2R-cis

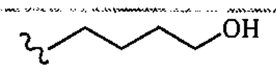
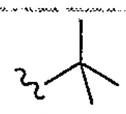
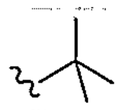
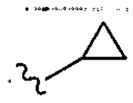
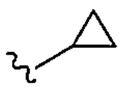
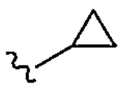
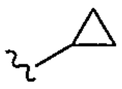
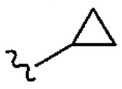
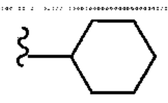
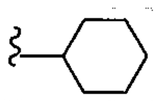
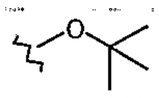
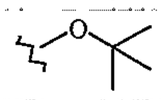
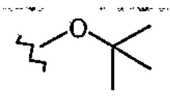
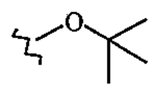
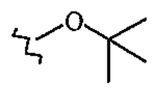
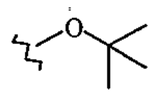
cb=covalent bond

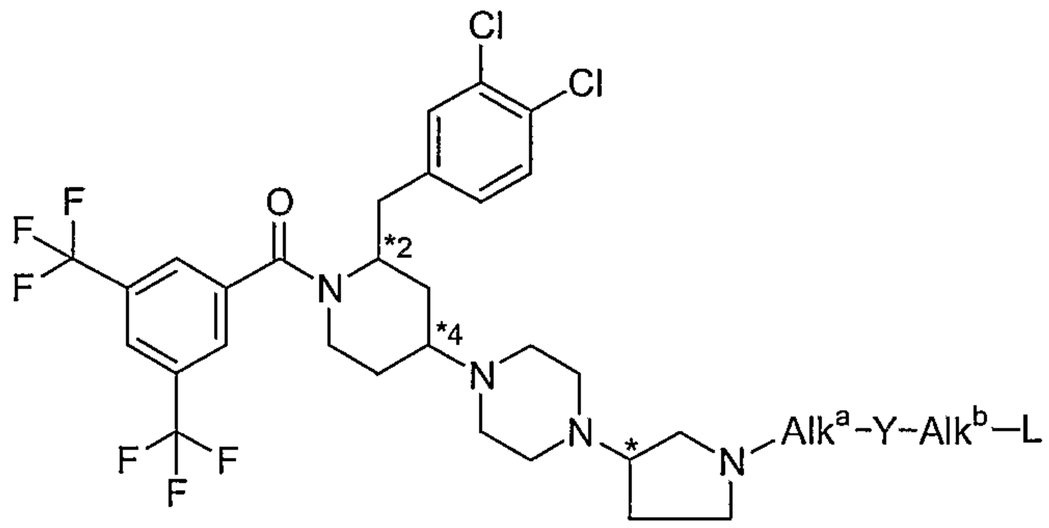
Table 4:

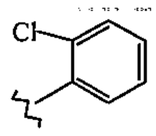
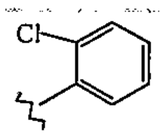
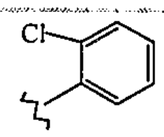
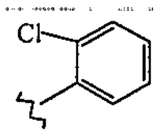
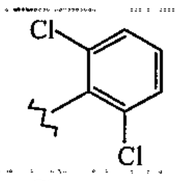
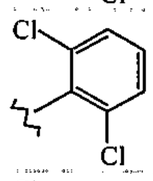
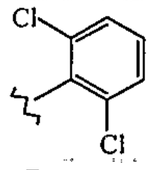
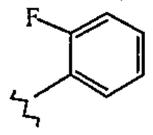
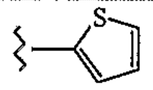
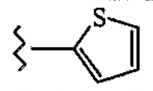
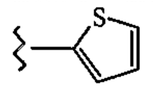
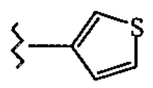
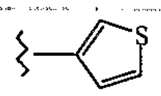
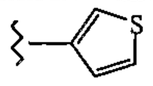
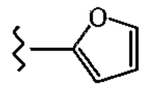


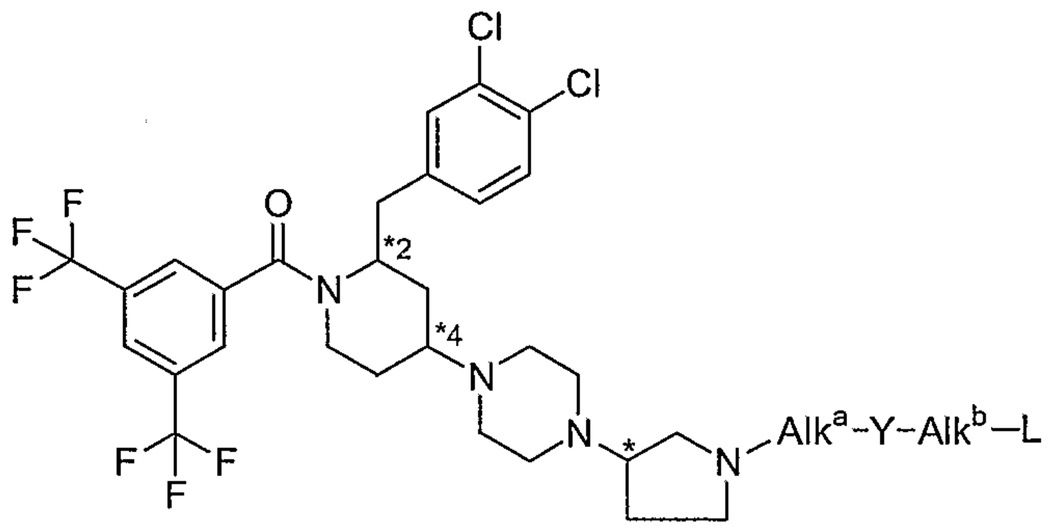
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
262	B31.b	cb	cb	cb	H	[(2R-trans),(R)]
244	B31.b	cb	cb	cb	H	[(2S-trans),(S)]
194	B31.	cb	cb	cb	H	trans

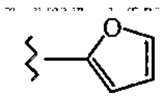
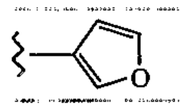
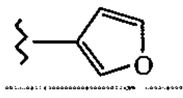
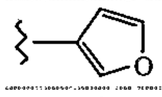
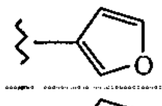
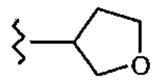
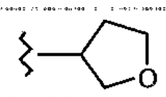
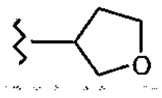
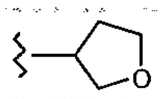
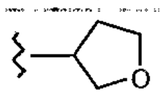
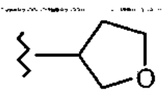
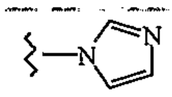
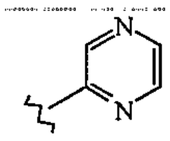
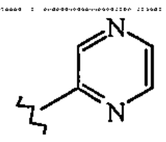
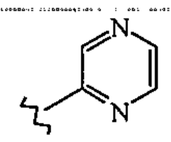
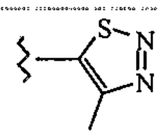
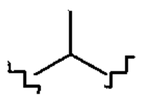
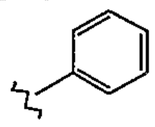
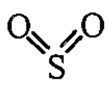
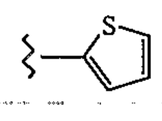


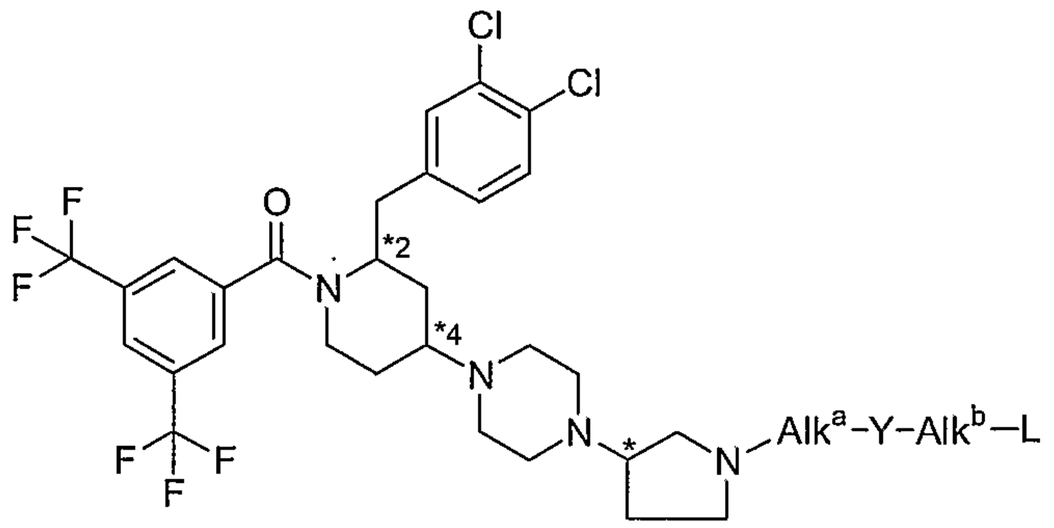
Co. No.	Exp. No. b	Alk[a]	Y	Alk[b]	L	Stereo descriptors
311	B31.b	cb	cb	cb	H	[(2R-trans),(S)]
393	B31.c	cb	cb	cb		[2R-[2α,4β(S)]]
247	B15	cb	C=O	cb		[(2S-trans),(S)]
289	B15	cb	C=O	cb		[(2R-trans),(R)]
313	B15	cb	C=O	cb		[(2R-trans),(S)]
143	B2	cb	C=O	cb		cis
162	B15	cb	C=O	cb		trans
245	B15	cb	C=O	cb		[(2S-trans),(S)]
263	B15	cb	C=O	cb		[(2R-trans),(R)]
312	B15	cb	C=O	cb		[(2R-trans),(S)]
299	B15	cb	C=O	cb		[(2R-trans),(R)]
314	B15	cb	C=O	cb		[(2R-trans),(S)]
243	B31.a	cb	C=O	cb		[(2S-trans),(S)]
261	B31.a	cb	C=O	cb		[(2R-trans),(R)]
329	B31.a	cb	C=O	cb		[(2R-cis),(R)]
248	B31.a	cb	C=O	cb		[(2S-cis),(S)]
165	B31.a	cb	C=O	cb		trans
298	B31.a	cb	C=O	cb		[(2R-trans),(S)]

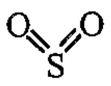
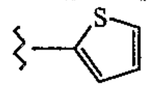
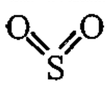
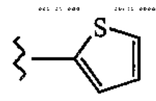


Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
141	B2	cb	C=O	cb		cis
164	B15	cb	C=O	cb		trans
266	B15	cb	C=O	cb		[(2R-trans),(R)]
315	B15	cb	C=O	cb		[(2R-trans),(S)]
246	B15	cb	C=O	cb		[(2S-trans),(S)]
265	B15	cb	C=O	cb		[(2R-trans),(R)]
316	B15	cb	C=O	cb		[(2R-trans),(S)]
174	B15	cb	C=O	cb		trans
264	B15	cb	C=O	cb		[(2R-trans),(R)]
175	B15	cb	C=O	cb		trans
318	B15	cb	C=O	cb		[(2R-trans),(S)]
287	B16	cb	C=O	cb		[(2R-trans),(R)]
251	B16	cb	C=O	cb		[(2S-trans),(S)]
325	B16	cb	C=O	cb		[(2R-trans),(S)]
267	B15	cb	C=O	cb		[(2R-trans),(R)]



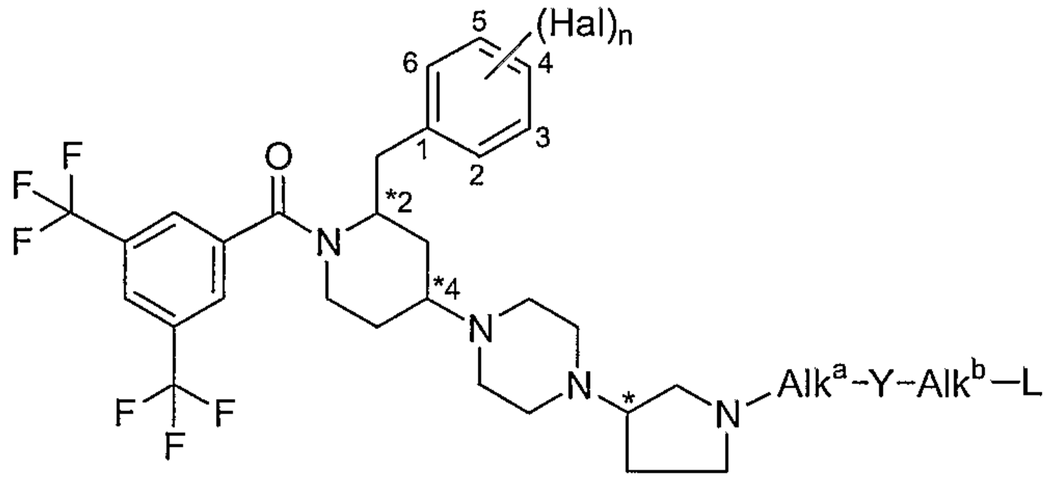
Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
317	B15	cb	C=O	cb		[(2R-trans),(S)]
173	B16	cb	C=O	cb		trans
250	B16	cb	C=O	cb		[(2S-trans),(S)]
288	B16	cb	C=O	cb		[(2R-trans),(R)]
326	B16	cb	C=O	cb		[(2R-trans),(S)]
172	B16	cb	C=O	cb		trans
249	B16	cb	C=O	cb		[(2S-trans),(S)]
290	B16	cb	C=O	cb		[(2R-trans),(R),(R)]
291	B16	cb	C=O	cb		[(2R-trans),(R),(S)]
330	B16	cb	C=O	cb		[(2R-trans),(S),(S)]
331	B16	cb	C=O	cb		[(2R-trans),(S),(R)]
324	B16	cb	C=O	cb		[(2R-trans),(S)]
171	B16	cb	C=O	cb		trans
286	B16	cb	C=O	cb		[(2R-trans),(R)]
323	B16	cb	C=O	cb		[(2R-trans),(S)]
161	B15	cb	C=O	cb		trans
176	B15	cb	C=O			trans
142	B5	cb		cb		cis

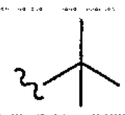
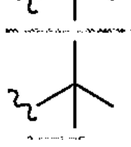
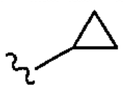
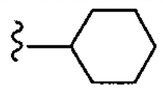
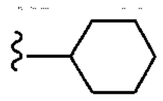


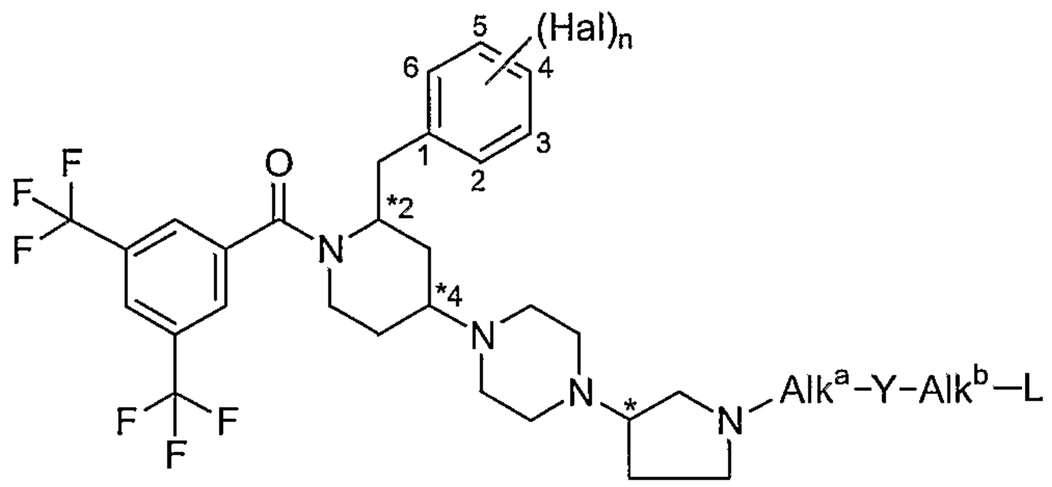
Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
163	B5	cb		cb		trans
268	B5	cb		cb		[(2R-trans),(R)]

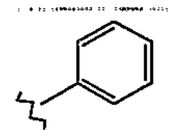
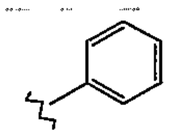
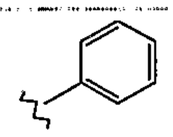
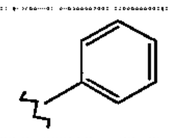
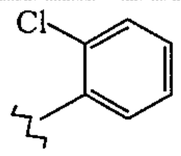
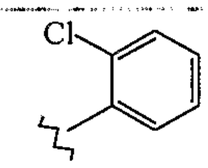
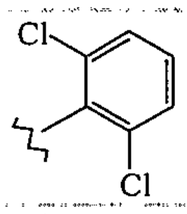
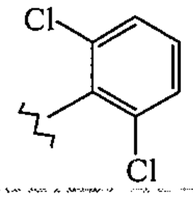
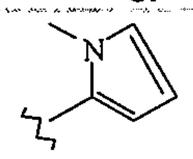
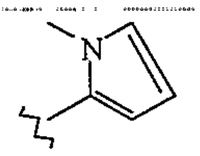
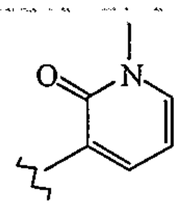
cb=covalent bond

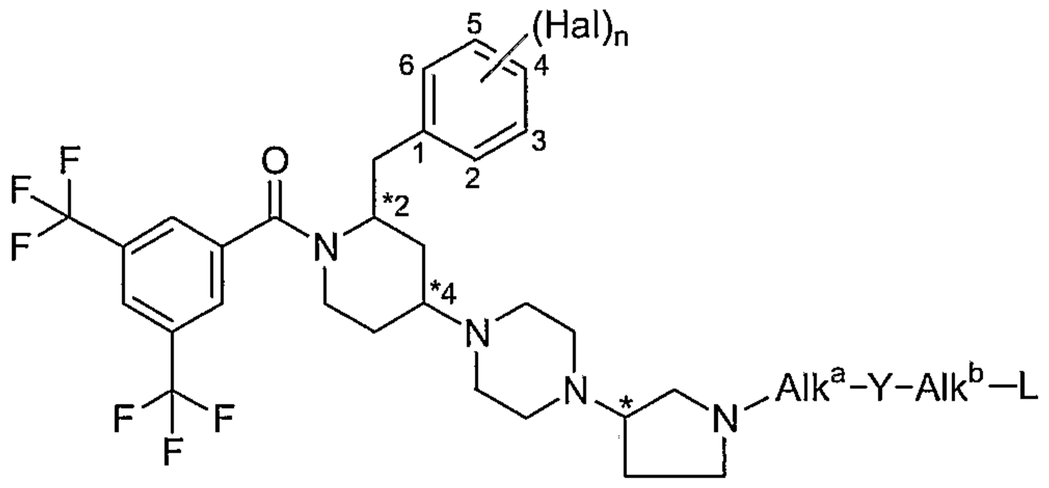
Table 5:

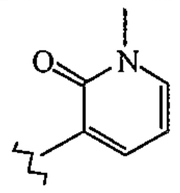
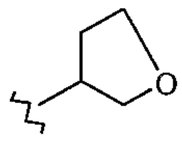
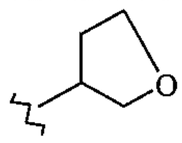
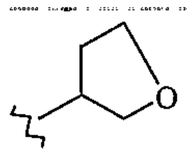
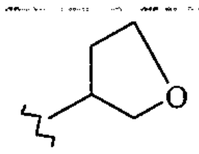
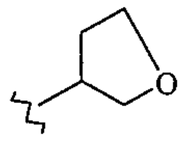
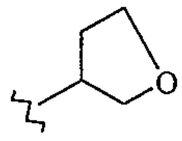
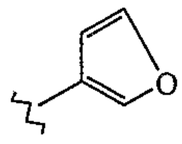
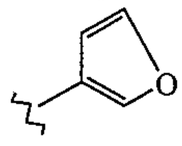
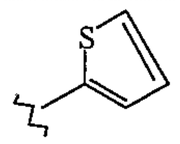
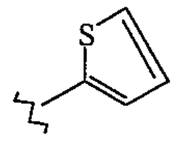
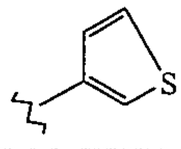


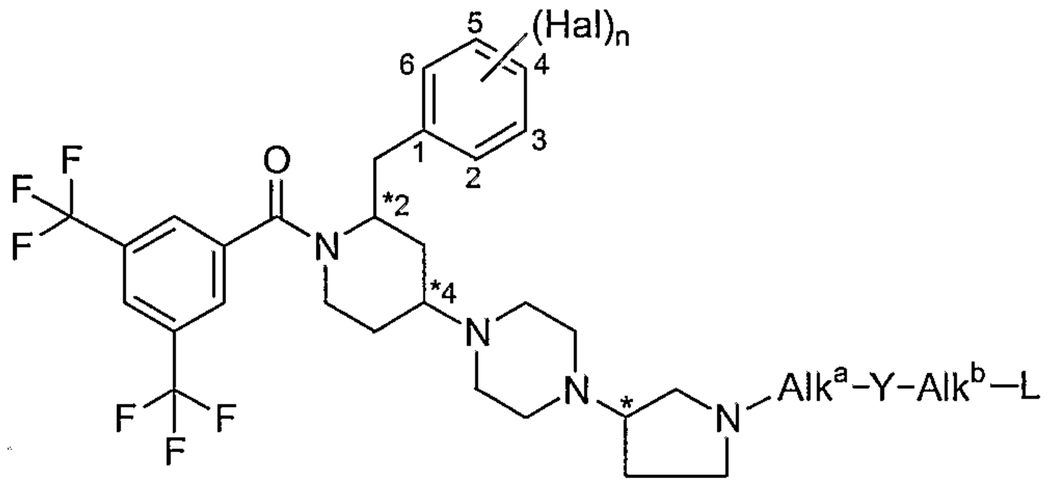
Co. No.	Exp. No.	$(Hal)_n$	Alk^a	Y	Alk^b	L	Stereo descriptors
225	B1.b	3-F, 4-F	cb	cb	cb	H	[2R-[2α,4β(R*)]]
212	B1.b	3-F, 4-F	cb	cb	cb	H	[2R-[2α,4α(S*)]]
364	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
365	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4α(S*)]]
231	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
252	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
357	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
358	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]

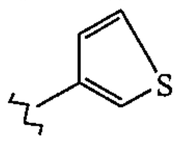
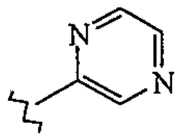
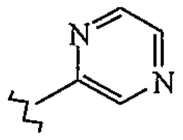
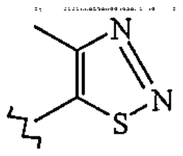
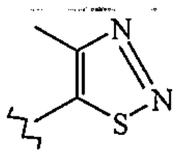
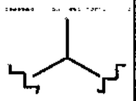
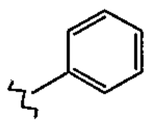
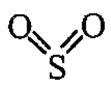
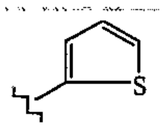
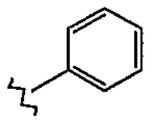
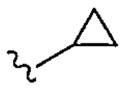
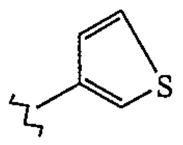
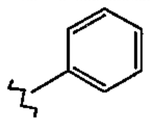
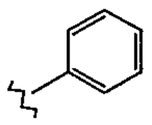


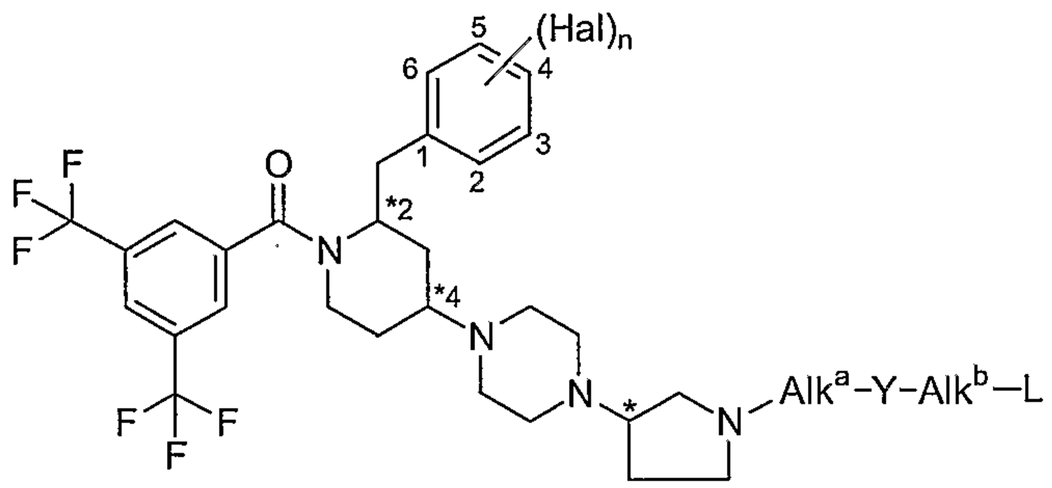
Co. No.	Exp. No.	$(Hal)_n$	Alk^a	Y	Alk^b	L	Stereo descriptors
221	B31	3-F, 4-F	-CH2-	cb	cb		[2R-[2α,4α(R*)]]
222	B31	3-F, 4-F	-CH2-	cb	cb		[2R-[2α,4β(R*)]]
224	B31	3-F, 4-F	-CH2-	cb	cb		[2R-[2α,4α(S*)]]
223	B31	3-F, 4-F	-CH2-	cb	cb		[2R-[2α,4β(S*)]]
211	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
255	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
239	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
256	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
366	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
367	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
260	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]

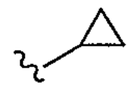
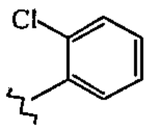
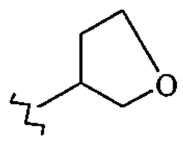
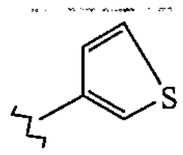


Co. No.	Exp. No.	$(Hal)_n$	Alk^a	Y	Alk^b	L	Stereo descriptors
368	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
227	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
269	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*(S*))]]
281	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*(S*))]]
285	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*(R*))]]
270	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*(R*))]]
242	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
226	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
258	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
254	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
232	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
238	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]



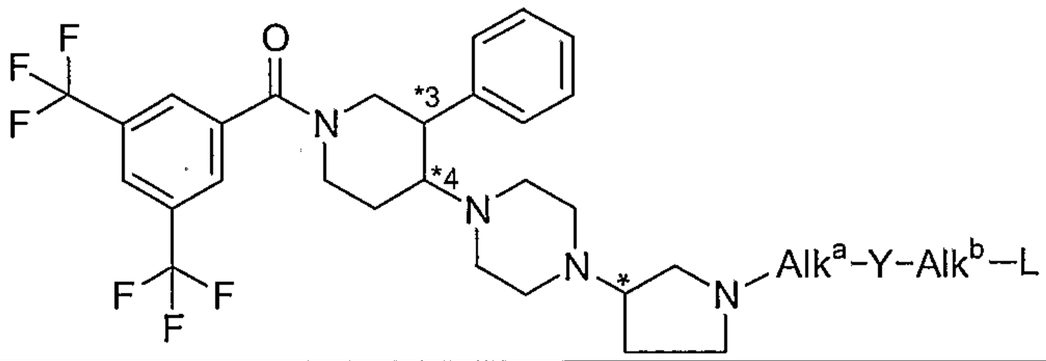
Co. No.	Exp. No.	$(Hal)_n$	Alk^a	Y	Alk^b	L	Stereo descriptors
257	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
237	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
259	B14	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
236	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(R*)]]
253	B15	3-F, 4-F	cb	C=O	cb		[2R-[2α,4β(S*)]]
233	B2	3-F, 4-F	cb	C=O			[2R-[2α,4β(R*)]]
234	B2	3-F, 4-F	cb		cb		[2R-[2α,4β(R*)]]
338	B1.b	3-F,5-F	cb	cb	cb	H	trans
339	B31	3-F,5-F	$-CH_2-$	cb	cb		trans
340	B2	3-F,5-F	cb	C=O	cb		trans
337	B14	3-F,5-F	cb	C=O	cb		trans
320	B31	3-Cl,5-Cl	$-CH_2-$	cb	cb		trans
273	B1.b	4-F	cb	cb	cb	H	trans
272	B31	4-F	-CH2-	cb	cb		trans

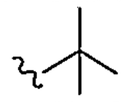
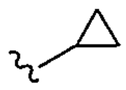
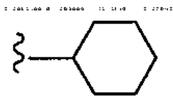
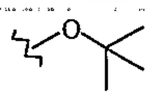
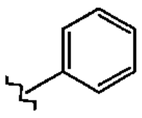


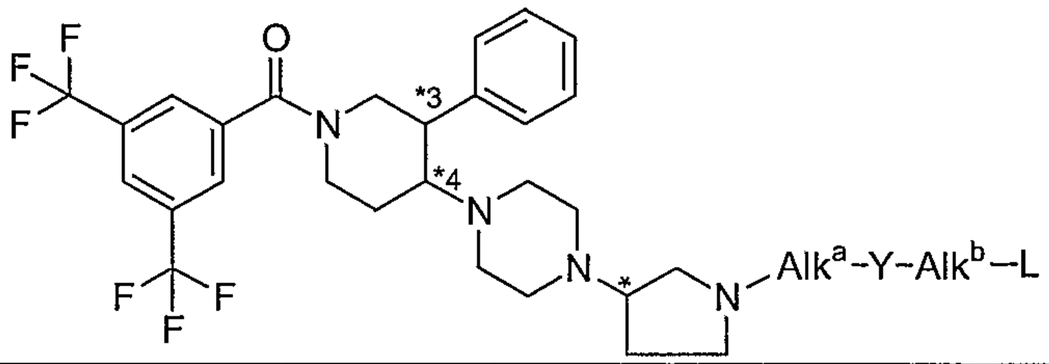
Co. No.	Exp. No.	$(Hal)_n$	Alk^a	Y	Alk^b	L	Stereo descriptors
277	B2	4-F	cb	C=O	cb		trans
279	B2	4-F	cb	C=O	cb		trans
274	B14	4-F	cb	C=O	cb		trans
278	B14	4-F	cb	C=O	cb		trans

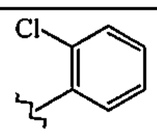
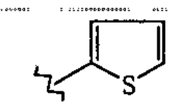
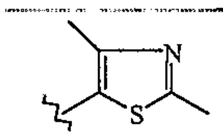
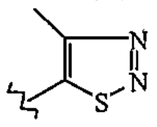
cb=covalent bond

Table 6:



Co. No.	Exp. No.	Alk^a	Y	Alk^b	L	Stereo descriptors
406	B32.b	cb	cb	cb	H	cis
395	B15	cb	C=O	cb		cis
396	B15	cb	C=O	cb		cis
397	B15	cb	C=O	cb		cis
405	B32.a	cb	C=O	cb		cis
398	B15	cb	C=O	cb		cis



Co. No.	Exp. No.	Alk[a]	Y	Alk[b]	L	Stereo descriptors
407	B15	cb	C=O	cb		cis
408	B1	cb	C=O	cb		cis
399	B16	cb	C=O	cb		cis
400	B15	cb	C=O	cb		cis

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 7 : Melting points for selected compounds.

Compound no.	Result (°C)
122	60-70
124	60-70
134	65-70
135	65-70
153	65
155	60-70
158	70
282	126
284	111

Compound no.	Result (°C)
287	138
292	158
293	106
302	100
307	92
308	100
334	120
402	89.2-98.5
403	89.7-99.2

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 ammoniumacetate + 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 3kV and the source temperature was maintained at 140°C . Nitrogen was used a 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 8 : LCMS parent peak and retention time for selected compounds.

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
2	569	5.01
1	659	6.16
28	674	5.45
3	673	5.84
20	709	5.95
12	698	6.05
29	704	5.33
32	663	5.68
33	663	6.05
31	667	5.5
69	701	6.09
41	679	6.13
80	655	5.66
51	695	5.68
70	637	5.95
71	637	5.68
72	637	5.68

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
34	663	5.67
13	687	5.96
35	663	5.70
42	679	5.83
14	703	5.83
26	691	5.67
44	747	6.28
78	727	5.49
79	728	5.97
30	675	5.55
67	693	5.84
52	681	5.68
36	677	5.83
43	693	6.21
59	663	5.31
56	712	5.74
64	691	5.67

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
66	677	5.72
45	677	5.76
23	676	5.61
85	555	5.24
86	569	5.42
68	664	6.11
37	691	6.00
74	665	6.01
47	678	5.80
24	676	6.26
81	617	4.44
82	677	5.80
83	631	4.54
11	771	6.26
84	635	5.15
16	691	5.86
17	707	5.96
19	701	6.09
54	723	6.10
49	822	6.10
22	741	6.22
7	702	6.36
8	699	6.00
5	647	5.83
6	661	5.69
10	699	5.81
9	739	6.10
21	709	5.88
73	651	5.76
61	747	6.07
15	731	6.15
65	777	5.76
90	555	5.14
88	557	4.70
91	587	5.08
92	601	4.92
93	673	5.17
94	579	4.62
89	583	5.25
95	528	4.43
96	585	5.22
97	667	5.68
98	731	6.01
99	737	6.00

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
103	690	6.16
104	721	6.39
105	785	5.71
106	746	5.64
107	792	6.26
108	756	5.87
109	717	5.9
110	767	5.81
111	831	6.21
112	659	6.75
113	659	6.62
114	659	6.82
115	766	6.39
116	569	5.24
119	673	6.15
121	677	4.43
130	669	6.23
131	677	5.87
140	673	6.26
141	775	6.39
142	783	6.34
143	705	6.21
144	666	5.14
145	640	5.65
152	681	5.67
154	651	5.87
156	651	5.73
157	721	6.16
159	707	5.96
161	763	5.99
162	705	6.00
163	783	6.61
164	775	6.20
165	737	6.75
166	711	5.84
167	653	6.36
168	708	5.61
169	741	6.04
170	729	6.13
171	745	5.89
172	735	5.85
173	731	5.98
174	759	6.13
175	747	6.54

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
176	769	6.31
177	641	5.69
178	679	6.56
179	651	6.24
180	673	6.21
181	707	6.32
182	637	6.05
183	663	5.84
184	667	5.68
185	737	5.70
186	708	5.41
187	708	5.41
188	707	5.87
189	766	6.00
190	749	5.66
191	691	5.67
192	698	5.87
193	698	5.89
194	637	5.53
195	698	6.04
196	680	5.26
197	696	5.73
198	611	5.44
199	639	5.75
200	667	6.09
201	695	5.11
202	654	5.35
203	665	6.29
204	686	6.52
205	754	6.10
206	780	6.54
207	732	5.74
208	727	5.76
209	691	5.34
213	666	5.14
214	694	5.38
215	696	5.32
216	667	5.49
217	667	5.49
218	667	5.49
219	667	5.51
220	703	5.76
221	695	6.31
222	695	6.08

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
223	695	6.06
224	695	6.32
225	605	5.02
226	699	5.61
227	703	5.45
228	766	6.03
229	780	6.15
210	780	6.05
211	743	5.87
212	605	5.02
231	673	5.63
232	715	5.77
233	737	6.01
234	751	5.85
235	666	5.05
236	731	5.62
237	711	5.50
238	715	5.73
239	777	5.97
240	680	5.09
241	680	5.03
242	703	5.43
243	737	6.42
244	637	5.51
245	705	5.98
246	809	6.26
247	721	6.19
248	737	7.11
249	735	5.82
250	731	5.97
251	747	6.06
252	673	5.61
253	731	5.62
254	715	5.76
255	743	5.88
256	777	5.98
257	715	5.72
258	699	5.60
259	711	5.50
260	740	5.28
261	737	6.42
262	637	5.72
263	705	5.98
264	747	6.09

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
265	809	6.26
266	775	6.18
267	731	5.98
268	783	6.14
269	703	5.45
270	703	5.45
281	703	5.43
283	713	5.76
285	703	5.21
286	743	5.63
287	747	5.75
288	731	5.66
289	721	5.85
290	735	5.87
291	735	5.86
294	680	5.22
295	818	6.09
296	748	5.86
297	764	6.15
298	737	6.45
299	747	6.38
302	690	4.40
304	768	6.09
305	653	5.96
306	653	5.95
310	736	5.76
311	637	5.49
312	705	6.34
313	721	6.98
314	747	7.11
315	775	6.96
316	809	7.04
317	731	6.77
318	747	6.87
321	679	5.82
322	679	5.82
323	743	6.61
324	731	6.54
325	747	6.78
326	731	6.68
329	679	5.75
330	735	5.85
331	735	5.86
332	689	5.57

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
336	849	6.41
337	715	5.76
340	673	5.67
341	689	5.51
342	759	5.71
343	718	5.83
344	678	5.68
345	835	6.37
346	807	6.26
347	739	6.04
348	725	5.75
349	695	5.73
350	709	5.91
351	759	5.70
352	799	6.28
353	799	6.28
354	697	5.44
355	742	5.70
356	813	6.36
357	715	6.05
358	715	6.06
359	723	5.57
360	709	5.61
361	813	6.34
362	813	6.34
363	723	5.55
364	689	5.87
365	689	5.88
366	712	5.78
367	712	5.79
368	740	5.27
369	723	5.66
370	750	5.66
371	706	5.51
374	651	5.59
375	756	5.70
376	769	5.49
377	709	5.27
378	769	5.89
379	677	5.59
380	695	5.68
381	695	5.68
382	693	5.72
385	710	5.71

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
386	681	5.39
387	681	5.38
388	683	5.85
389	669	5.48
390	685	5.47
391	697	5.98
392	725	5.67
393	709	5.61
394	833	6.43
395	653	6.84

Comp. no.	LCMS MS(MH+) Meth. A	Retention time
396	623	6.38
397	665	6.87
398	659	6.57
399	694	6.41
400	681	6.39
401	829	6.14
404	709	5.57
407	693	6.70
408	665	6.55

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 9 : LCMS parent peak and retention time for selected compounds.

Compound no.	LCMS MS(MH+) Meth. B	Retention time
271	698	4.5
274	685	4.0
275	703	4.3
276	653	3.9
277	655	4.1
278	697	4.3
279	725	4.6
280	739	5.0
282	677	3.4
292	835	5.8
293	654	4.2
300	739	4.9
303	725	4.6

Compound no.	LCMS MS(MH+) Meth. B	Retention time
319	695	2.6
320	727	4.1
327	689	4.4
328	745	5.1
333	733	4.4
335	849	5.9

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 10 : Optical rotation data for selected compounds.

Compound No.	[α]	Wavelength (nm)
32	+15.14	589
33	-13.19	589
39	-18.3	589
40	+20.44	589
87	-17.97°	589
124	+29.34	365
125	+29.34°	365
126	+33.54°	365
127	+31.29°	365
128	+32.32	365
129	+31.33°	365
130	-35.9°	365
136	-18.71	589
137	-19.11	589
138	-19,02°	589
139	-19,03°	589
148	-45.59	365
149	-37.29	365

D. Pharmacological example

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

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

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

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

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

Example D.2 : Signal transduction (ST)

This test evaluates in vitro functional NK_1 antagonistic activity. For the measurements of intracellular Ca^{++} concentrations the cells were grown on 96-well (black wall/transparent bottom) plates from Costar for 2 days until they reached confluence. The cells were loaded with 2 µM Fluo3 in DMEM containing 0.1% BSA and 2.5 mM probenecid for 1 h at 37°C. They were washed 3x with a Krebs buffer (140 mM NaCl, 1 mM $MgCl_2x6H_2O$, 5 mM KCl, 10 mM glucose, 5 mM HEPES; 1.25 mM $CaCl_2$; pH 7.4) containing 2.5 mM probenecid and 0.1 % BSA (Ca^{++}-buffer). The cells were preincubated with a concentration range of antagonists for 20 min at RT and Ca^{++}-signals after addition of the agonists were measured in a Fluorescence Image Plate Reader (FLIPR from Molecular Devices, Crawley, England). The peak of the Ca^{++}-

transient was considered as the relevant signal and the mean values of corresponding wells were analysed as described below.

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

The pIC_{50} data for the signal transduction testing for a representative selection of compounds are presented in Table 11. The last colums indicates - without being limited thereto - for which action the compounds might be most suitable. Ofcourse, since for some neurokinin receptors no data was determined, it is obvious that these compounds might be attributed to another suitable use.

Table 11 : 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
227	8,5	n.d	5,8	NK_1
270	8,5	5,7	5,9	NK_1
305	8,5	5,8	5,8	NK_1
236	8,4	n.d	5,3	NK_1
269	8,4	5,6	5,2	NK_1
281	8,3	5,4	5,5	NK_1
332	8,3	5,8	5,5	NK_1
381	8,3	5,0	5,6	NK_1
393	8,3	5,0	5,0	NK_1
50	8,2	n.d	5,5	NK_1
166	8,2	n.d	5,8	NK_1
179	8,2	n.d	5,8	NK_1
231	8,2	n.d	5,5	NK_1
262	8,2	6,3	5,0	NK_1
271	8,2	5,3	5,7	NK_1
297	8,2	5,6	5,9	NK_1
303	8,2	6,2	5,5	NK_1
327	8,2	5,4	5,7	NK_1
328	8,2	6,2	5,2	NK_1
380	8,2	5,1	5,8	NK_1
404	8,2	5,3	7,1	NK_1
99	8,1	n.d	5,5	NK_1
219	8,1	5,4	5,5	NK_1
288	8,1	5,8	6,1	NK_1

Co. No	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
299	8,1	5,6	6,1	NK_1
302	8,1	5,6	6,0	NK_1
310	8,1	5,7	5,4	NK_1
364	8,1	5,7	6,2	NK_1
403	8,1	5,6	5,6	NK_1
73	8,0	n.d	5,8	NK_1
97	8,0	n.d	5,6	NK_1
199	8,0	n.d	5,8	NK_1
216	8,0	5,3	5,8	NK_1
234	8,0	n.d	5,5	NK_1
237	8,0	n.d	5,4	NK_1
242	8,0	n.d	5,6	NK_1
274	8,0	5,0	5,4	NK_1
275	8,0	5,6	5,3	NK_1
276	8,0	5,5	5,3	NK_1
277	8,0	5,0	5,6	NK_1
300	8,0	6,1	5,7	NK_1
311	8,0	5,6	5,0	NK_1
341	8,0	5,7	5,5	NK_1
348	8,0	6,5	5,7	NK_1
367	8,0	5,9	5,8	NK_1
368	8,0	5,5	5,5	NK_1
65	7,9	n.d	5,5	NK_1
98	7,9	n.d	5,3	NK_1
109	7,9	n.d	5,1	NK_1
145	7,9	n.d	5,7	NK_1
161	7,9	n.d	5,5	NK_1
282	7,9	5,4	5,4	NK_1
284	7,9	5,3	5,4	NK_1
350	7,9	5,3	5,3	NK_1
358	7,9	5,5	5,8	NK_1
359	7,9	5,6	5,7	NK_1
363	7,9	5,4	5,8	NK_1
375	7,9	5,0	5,4	NK_1
378	7,9	5,8	5,7	NK_1
48	7,8	n.d	5,6	NK_1
187	7,8	n.d	5,3	NK_1
190	7,8	n.d	5,7	NK_1
191	7,8	n.d	5,6	NK_1
208	7,8	n.d	5,6	NK_1
225	7,8	n.d	5,0	NK_1
210	7,8	n.d	5,1	NK_1
260	7,8	6,4	5,4	NK_1
278	7,8	5,4	5,7	NK_1
279	7,8	5,4	5,7	NK_1

Co. No	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
280	7,8	5,9	5,4	NK_1
293	7,8	5,2	5,3	NK_1
307	7,8	5,9	5,9	NK_1
355	7,8	5,3	5,2	NK_1
371	7,8	5,1	5,3	NK_1
377	7,8	5,0	5,2	NK_1
388	7,8	5,0	6,1	NK_1
389	7,8	5,0	5,2	NK_1
402	7,8	5,6	6,3	NK_1
25	7,7	5,3	5,3	NK_1
110	7,7	n.d	5,3	NK_1
196	7,7	n.d	5,0	NK_1
203	7,7	n.d	6,0	NK_1
207	7,7	n.d	5,4	NK_1
209	7,7	n.d	5,0	NK_1
213	7,7	n.d	5,8	NK_1
214	7,7	n.d	5,4	NK_1
294	7,7	5,1	5,0	NK_1
333	7,7	5,6	5,0	NK_1
344	7,7	5,4	5,0	NK_1
347	7,7	6,2	5,6	NK_1
370	7,7	5,2	5,1	NK_1
386	7,7	5,0	5,3	NK_1
387	7,7	5,0	5,3	NK_1
390	7,7	5,0	5,0	NK_1
391	7,7	5,0	5,5	NK_1
411	7,7	5,6	6,0	NK_1
18	7,6	n.d	5,6	NK_1
188	7,6	n.d	5,7	NK_1
197	7,6	n.d	5,0	NK_1
204	7,6	n.d	5,6	NK_1
228	7,6	n.d	5,2	NK_1
283	7,6	5,4	5,6	NK_1
376	7,6	5,0	5,4	NK_1
60	7,5	n.d	5,6	NK_1
46	7,5	5,4	5,9	NK_1
59	7,5	n.d	5,5	NK_1
85	7,5	n.d	5,0	NK_1
68	7,5	n.d	5,8	NK_1
16	7,5	5,3	5,6	NK_1
61	7,5	n.d	5,2	NK_1
15	7,5	n.d	5,7	NK_1
106	7,5	n.d	5,4	NK_1
108	7,5	n.d	5,6	NK_1
198	7,5	n.d	5,6	NK_1

Co. No	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
215	7,5	n.d	5,3	NK_1
229	7,5	n.d	5,6	NK_1
240	7,5	n.d	5,0	NK_1
241	7,5	n.d	5,0	NK_1
247	7,5	n.d	5,0	NK_1
319	7,5	5,3	5,5	NK_1
334	7,5	5,3	5,1	NK_1
343	7,5	5,5	5,1	NK_1
349	7,5	5,6	5,2	NK_1
354	7,5	5,0	5,0	NK_1
385	7,5	5,0	5,4	NK_1
413	7,5	5,0	5,7	NK_1
53	7,4	n.d	5,5	NK_1
37	7,4	n.d	5,7	NK_1
47	7,4	n.d	5,4	NK_1
9	7,4	n.d	5,9	NK_1
130	7,4	n.d	5,5	NK_1
143	7,4	n.d	5,5	NK_1
149	7,4	n.d	5,0	NK_1
202	7,4	n.d	5,2	NK_1
220	7,4	n.d	6,0	NK_1
235	7,4	n.d	5,0	NK_1
298	7,4	5,5	5,5	NK_1
337	7,4	5,5	5,9	NK_1
414	7,4	5,0	6,2	NK_1
28	7,3	5,6	n.d	NK_1
22	7,3	n.d	5,6	NK_1
185	7,3	n.d	5,0	NK_1
201	7,3	n.d	5,0	NK_1
222	7,3	n.d	5,2	NK_1
212	7,3	n.d	5,0	NK_1
245	7,3	n.d	5,0	NK_1
249	7,3	5,3	5,3	NK_1
251	7,3	5,2	5,3	NK_1
340	7,3	5,2	5,2	NK_1
410	7,3	5,9	5,0	NK_1
2	7,2	n.d	n.d	NK_1
51	7,2	n.d	5,4	NK_1
62	7,2	n.d	5,4	NK_1
6	7,2	5,0	5,6	NK_1
105	7,2	n.d	5,0	NK_1
148	7,2	n.d	5,0	NK_1
177	7,2	n.d	5,6	NK_1
346	7,2	5,8	5,9	NK_1
352	7,2	5,2	5,5	NK_1

Co. No	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
29	7,1	5,7	n.d	NK_1
111	7,1	n.d	5,2	NK_1
244	7,1	n.d	5,0	NK_1
412	7,1	5,6	5,3	NK_1
1	7,0	n.d	n.d	NK_1
80	7,0	n.d	n.d	NK_1
8	7,0	5,0	5,4	NK_1
10	7,0	n.d	5,2	NK_1
186	7,0	n.d	5,0	NK_1
250	7,0	5,2	5,3	NK_1
3	6,9	n.d	5,8	NK_1
20	6,9	n.d	5,3	NK_1
57	6,9	n.d	5,5	NK_1
63	6,9	n.d	5,5	NK_1
11	6,9	n.d	5,5	NK_1
118	6,9	n.d	5,0	NK_1
87	6,9	n.d	5,9	NK_1
138	6,9	n.d	5,2	NK_1
141	6,9	n.d	5,5	NK_1
144	6,9	n.d	5,0	NK_1
246	6,9	n.d	5,0	NK_1
356	6,9	5,0	5,4	NK_1
362	6,9	5,6	5,6	NK_1
137	6,8	n.d	5,2	NK_1
139	6,8	n.d	5,2	NK_1
223	6,8	n.d	5,8	NK_1
336	6,8	6,0	5,0	NK_1
38	6,7	n.d	5,1	NK_1
136	6,7	n.d	5,0	NK_1
243	6,7	n.d	5,0	NK_1
345	6,7	6,3	5,0	NK_1
129	6,6	n.d	5,0	NK_1
320	6,6	5,4	5,6	NK_1
392	6,6	5,0	5,1	NK_1
401	6,6	5,5	5,9	NK_1
55	6,5	n.d	5,1	NK_1
335	6,5	6,0	5,0	NK_1
331	8,5	5,7	6,6	$NK_1/NK_2/NK_3$
330	8,5	6,2	6,4	$NK_1/NK_2/NK_3$
313	8,4	6,2	6,6	$NK_1/NK_2/NK_3$
290	8,4	5,8	6,4	$NK_1/NK_2/NK_3$
291	8,4	5,9	6,4	$NK_1/NK_2/NK_3$
342	8,3	6,9	6,4	$NK_1/NK_2/NK_3$
253	8,3	6,4	6,3	$NK_1/NK_2/NK_3$
315	8,3	6,3	6,2	$NK_1/NK_2/NK_3$

Co. No	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
232	8,2	5,5	6,9	$NK_1/NK_2/NK_3$
238	8,2	5,9	6,8	$NK_1/NK_2/NK_3$
211	8,2	6,0	6,7	$NK_1/NK_2/NK_3$
171	8,2	6,1	6,6	$NK_1/NK_2/NK_3$
263	8,2	6,1	6,5	$NK_1/NK_2/NK_3$
286	8,2	6,0	6,4	$NK_1/NK_2/NK_3$
324	8,2	6,7	6,4	$NK_1/NK_2/NK_3$
226	8,2	5,9	6,3	$NK_1/NK_2/NK_3$
267	8,1	6,2	6,7	$NK_1/NK_2/NK_3$
308	8,1	6,7	6,6	$NK_1/NK_2/NK_3$
266	8,1	6,0	6,5	$NK_1/NK_2/NK_3$
172	8,1	6,1	6,4	$NK_1/NK_2/NK_3$
312	8,1	5,8	6,3	$NK_1/NK_2/NK_3$
206	8,0	6,1	6,6	$NK_1/NK_2/NK_3$
239	8,0	6,0	6,6	$NK_1/NK_2/NK_3$
323	8,0	5,9	6,5	$NK_1/NK_2/NK_3$
162	8,0	6,0	6,3	$NK_1/NK_2/NK_3$
252	8,0	6,0	6,3	$NK_1/NK_2/NK_3$
254	8,0	6,6	6,3	$NK_1/NK_2/NK_3$
257	8,0	6,5	6,2	$NK_1/NK_2/NK_3$
317	8,0	6,4	6,2	$NK_1/NK_2/NK_3$
351	8,0	6,6	6,0	$NK_1/NK_2/NK_3$
264	7,9	5,8	6,7	$NK_1/NK_2/NK_3$
287	7,9	5,9	6,6	$NK_1/NK_2/NK_3$
258	7,9	6,3	6,4	$NK_1/NK_2/NK_3$
69	7,9	6,2	6,3	$NK_1/NK_2/NK_3$
259	7,9	5,7	6,3	$NK_1/NK_2/NK_3$
306	7,9	5,5	6,0	$NK_1/NK_2/NK_3$
27	7,8	6,2	6,5	$NK_1/NK_2/NK_3$
164	7,8	7,1	6,4	$NK_1/NK_2/NK_3$
255	7,8	5,9	6,4	$NK_1/NK_2/NK_3$
318	7,8	6,5	6,4	$NK_1/NK_2/NK_3$
79	7,8	6,0	6,3	$NK_1/NK_2/NK_3$
314	7,8	5,9	6,3	$NK_1/NK_2/NK_3$
326	7,8	6,3	6,3	$NK_1/NK_2/NK_3$
325	7,8	6,4	6,2	$NK_1/NK_2/NK_3$
265	7,7	5,8	6,8	$NK_1/NK_2/NK_3$
76	7,7	5,9	6,7	$NK_1/NK_2/NK_3$
173	7,7	6,1	6,6	$NK_1/NK_2/NK_3$
316	7,7	6,1	6,2	$NK_1/NK_2/NK_3$
268	7,7	6,6	6,0	$NK_1/NK_2/NK_3$
75	7,6	6,0	6,4	$NK_1/NK_2/NK_3$
175	7,6	6,0	6,4	$NK_1/NK_2/NK_3$
78	7,5	6,4	6,6	$NK_1/NK_2/NK_3$
261	7,5	5,9	6,3	$NK_1/NK_2/NK_3$

Co. No	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
72	7,3	7,2	6,1	$NK_1/NK_2/NK_3$
361	7,1	6,0	6,2	$NK_1/NK_2/NK_3$
292	7,0	6,1	6,1	$NK_1/NK_2/NK_3$
366	8,2	5,7	7,0	NK_1/NK_3
285	8,2	5,5	6,2	NK_1/NK_3
296	8,2	5,8	6,1	NK_1/NK_3
40	8,1	5,6	6,9	NK_1/NK_3
189	8,1	5,0	6,6	NK_1/NK_3
14	8,1	5,3	6,5	NK_1/NK_3
200	8,1	5,0	6,4	NK_1/NK_3
168	8,1	5,0	6,3	NK_1/NK_3
193	8,1	5,0	6,3	NK_1/NK_3
365	8,1	5,6	6,3	NK_1/NK_3
167	8,1	5,7	6,2	NK_1/NK_3
322	8,1	5,4	6,2	NK_1/NK_3
217	8,1	5,5	6,1	NK_1/NK_3
289	8,1	5,7	6,1	NK_1/NK_3
26	8,0	5,8	6,8	NK_1/NK_3
304	8,0	5,8	6,8	NK_1/NK_3
178	8,0	5,7	6,6	NK_1/NK_3
205	8,0	5,5	6,6	NK_1/NK_3
31	8,0	5,6	6,4	NK_1/NK_3
160	8,0	5,0	6,4	NK_1/NK_3
192	8,0	5,0	6,2	NK_1/NK_3
218	8,0	5,4	6,1	NK_1/NK_3
357	8,0	5,5	6,1	NK_1/NK_3
360	8,0	5,4	6,0	NK_1/NK_3
32	7,9	5,3	6,7	NK_1/NK_3
70	7,9	5,0	6,3	NK_1/NK_3
21	7,9	5,3	6,4	NK_1/NK_3
169	7,9	5,6	6,6	NK_1/NK_3
195	7,9	5,0	6,4	NK_1/NK_3
321	7,9	5,5	6,6	NK_1/NK_3
369	7,9	5,4	6,2	NK_1/NK_3
33	7,8	5,4	6,3	NK_1/NK_3
39	7,8	5,5	6,4	NK_1/NK_3
41	7,8	5,8	6,7	NK_1/NK_3
17	7,8	5,1	6,6	NK_1/NK_3
103	7,8	5,3	6,4	NK_1/NK_3
295	7,8	5,7	6,5	NK_1/NK_3
71	7,7	5,3	6,1	NK_1/NK_3
34	7,7	5,5	6,5	NK_1/NK_3
77	7,7	5,6	6,3	NK_1/NK_3
45	7,7	5,2	6,8	NK_1/NK_3
74	7,7	5,0	6,3	NK_1/NK_3

Co. No	pIC_{50} NK_1	pIC_{50} NK_2	pIC_{50} NK_3	Suitable for
115	7,7	5,1	6,5	NK_1/NK_3
159	7,7	5,2	6,2	NK_1/NK_3
174	7,7	5,7	6,0	NK_1/NK_3
176	7,7	5,6	6,0	NK_1/NK_3
13	7,6	5,4	6,7	NK_1/NK_3
35	7,6	5,4	6,7	NK_1/NK_3
42	7,6	5,0	6,6	NK_1/NK_3
67	7,6	5,4	6,0	NK_1/NK_3
36	7,6	5,0	6,7	NK_1/NK_3
43	7,6	5,1	6,2	NK_1/NK_3
66	7,6	5,3	6,4	NK_1/NK_3
24	7,6	5,2	6,6	NK_1/NK_3
49	7,6	5,5	6,6	NK_1/NK_3
4	7,6	5,2	6,8	NK_1/NK_3
163	7,6	n.d	6,8	NK_1/NK_3
233	7,6	n.d	6,1	NK_1/NK_3
256	7,6	5,8	6,4	NK_1/NK_3
353	7,6	5,5	6,1	NK_1/NK_3
30	7,5	5,4	6,0	NK_1/NK_3
52	7,5	5,0	6,2	NK_1/NK_3
23	7,5	5,5	6,3	NK_1/NK_3
5	7,5	5,2	6,2	NK_1/NK_3
56	7,4	5,5	6,9	NK_1/NK_3
19	7,4	5,1	6,4	NK_1/NK_3
54	7,4	5,0	6,1	NK_1/NK_3
44	7,3	5,2	6,2	NK_1/NK_3
64	7,3	5,6	6,8	NK_1/NK_3
165	7,3	5,0	6,1	NK_1/NK_3
12	7,1	5,0	6,9	NK_1/NK_3
107	7,0	5,5	6,2	NK_1/NK_3
142	6,9	n.d	6,1	NK_1/NK_3
7	6,7	5,0	6,5	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

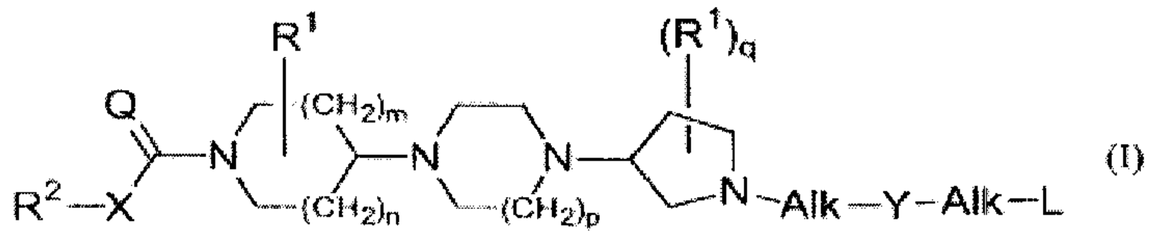
To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75 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.

WE CLAIM:

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



(I)

a pharmaceutically acceptable acid or base addition salt thereof, a stereochemically isomeric form thereof, or a N-oxide form thereof, wherein:

n	is an integer, equal to 0,1 or 2;
m	is 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 Ar^1, Ar^1alkyl or 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 H, 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 hydrogen, alkyl, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, alkyloxycarbonyl, mono- and di(alkyl)amino, mono- and di(alkyloxycarbonyl)amino, mono- and di(alkylcarbonyl)amino, mono- and di(Ar^3)amino, mono-and di(Ar^3alkyl)amino, mono- and di(Het^2)amino, mono- and di(Het^2alkyl)amino, alkylsulfanyl, adamantyl, Ar^3, Ar^3-oxy, Ar^3carbonyl, Het^2, Het^2-oxy or Het^2carbonyl;
Ar^1	is phenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other, halo, alkyl, cyano, aminocarbonyl or alkyloxy;
Ar^2	is naphthalenyl or phenyl, each optionally substituted with 1, 2 or 3 substituents, each independently from each other, halo, nitro, amino, mono- and di(alkyl)amino, cyano, alkyl, hydroxy, alkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl or mono- and d(alkyl)aminocarbonyl;

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

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

Het^2 is a monocyclic heterocyclic radical of pyrrolidinyl, dioxolyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 2H-pyrrolyl, pyrrolinyl, imidazolinyl, pyrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, dioxazolyl, oxazolidinyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl or triazinyl;
or a bicyclic heterocyclic radical 2,3-dihydro-benzo[1,4]dioxine, octahydro-benzo[1,4]dioxine, benzopiperidinyl, quinolinyl, quinoxalinyl, indolyl, isoindolyl, chromanyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl or benzothienyl;
or the tricyclic heterocyclic radical 8,9-dihydro-4*H*-1-oxa-3,5,7a-triaza-cyclopenta[f]azulenyl; each radical may optionally be substituted with one or more radicals of Ar^1, Ar^1alkyl, Ar^1alkyloxyalkyl, halo, hydroxy, alkyl, piperidinyl, pyrrolyl, thienyl, oxo, alkyloxy, alkylcarbonyl, Ar^1carbonyl, mono- and di(alkyl)aminoalkyl, alkyloxyalkyl or alkyloxycarbonyl; and

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

2. A compound according to claim 1 wherein:

n is an integer, equal to 1;

m is an integer, equal to 1;

p is an integer equal to 1 or 2;

q is an integer equal to 0;

Q is O

X is a covalent bond;

R^1 is Ar^1-alkyl;

R^2	is Ar^2, Ar^2-alkyl, di(Ar^2)alkyl or Het^1;
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 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 phenyl, halo and hydroxy radicals;
L	is hydrogen, alkyl, alkyloxy, alkyloxyalkyloxy, alkylcarbonyloxy, mono- and di(alkyl)amino, mono- and di(alkyloxycarbonyl)amino, mono- and di(alkylcarbonyl)amino, mono- and di(Ar^3)amino, mono-and di(Ar^3alkyl)amino, mono- and di(Het^2alkyl)amino, alkylsulfanyl, adamantyl, Ar^3, Het^2 or Het^2carbonyl;
Ar^1	is phenyl, optionally substituted with 1 or 2 halo radicals;
Ar^2	is naphthalenyl or phenyl, each optionally substituted with 1, 2 or 3 substituents, each independently from each other, halo, alkyl or alkyloxy;
Ar^3	is naphthalenyl or phenyl, optionally substituted with 1, 2 or 3 substituents, each independently from each other, alkyloxy, Ar^1alkyloxycarbonyl, Ar^1alkyloxyalkyl, alkyl, halo or cyano;
Het^1	is pyridinyl or a bicyclic heterocyclic radical of quinoxalinyl, indolyl, benzothienyl, indanyl or chromenyl; each heterocyclic radical may optionally be substituted on any atom by one or more radicals of oxo or alkyl;
Het^2	is a monocyclic heterocyclic radical of pyrrolidinyl, dioxolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuranyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, dioxazolyl, oxazolidinyl, isoxazolyl, thiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; or a bicyclic heterocyclic radical of 2,3-dihydro-benzo[1,4]dioxine, octahydro-benzo[1,4]dioxine, quinoxalinyl, indolyl, chromanyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, benzisoxazolyl, benzothiazolyl, benzofuranyl or benzothienyl; or the tricyclic heterocyclic radical 8,9-dihydro-4*H*-1-oxa-3,5,7a-triaza-cyclopenta[f]azulenyl; each radical may optionally be substituted with one or more radicals of Ar^1, Ar^1alkyloxyalkyl, halo, alkyl, oxo, alkyloxy, alkylcarbonyl, Ar^1carbonyl, mono- and di(alkyl)aminoalkyl, alkyloxyalkyl or alkyloxycarbonyl; and
alkyl	is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radicals having from 3 to 6 carbon atoms; optionally substituted on one or more carbon atoms with one or more radicals of phenyl, halo and hydroxy.

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

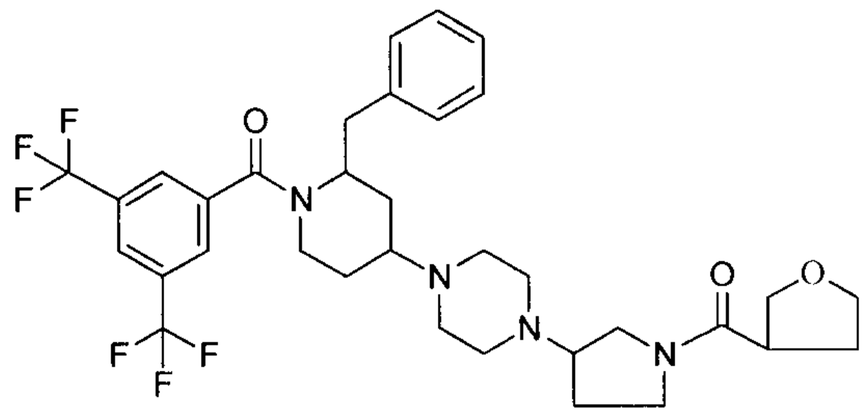
5. A compound according to any one of claims 1-4, characterized in that p is 1.

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

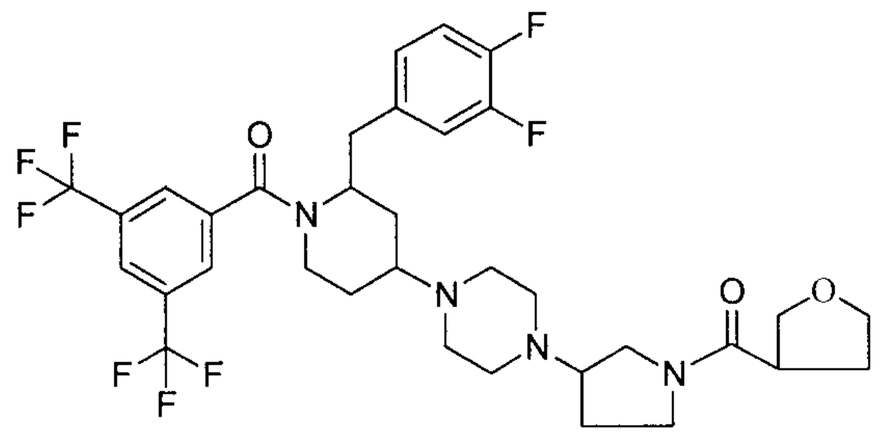
7. A compound according to any one of claims 1-6, characterized in that Alk is a covalent bond.

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

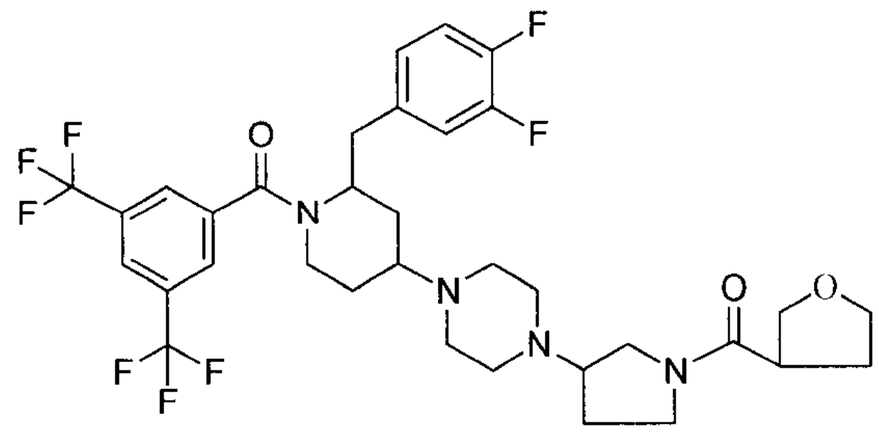
9. A compound according to claim 1, wherein the compound is:



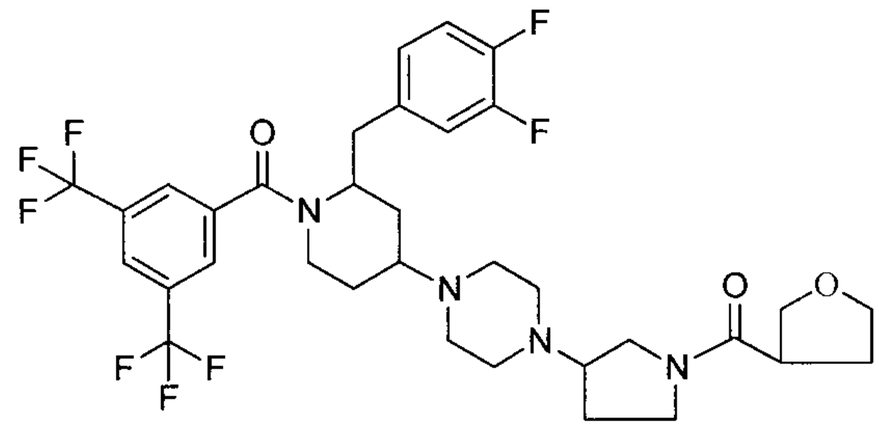
[2R-[2α,4β(R(R))]],



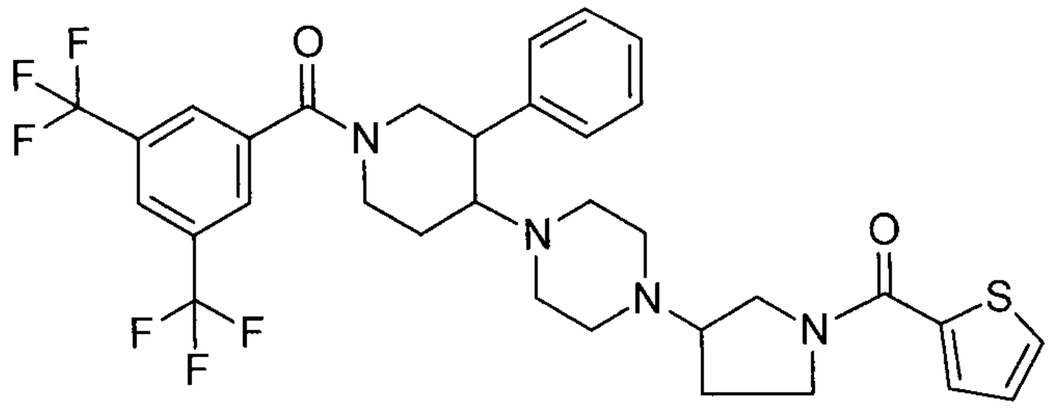
[2R-[2α,4β(R*(R*))]],



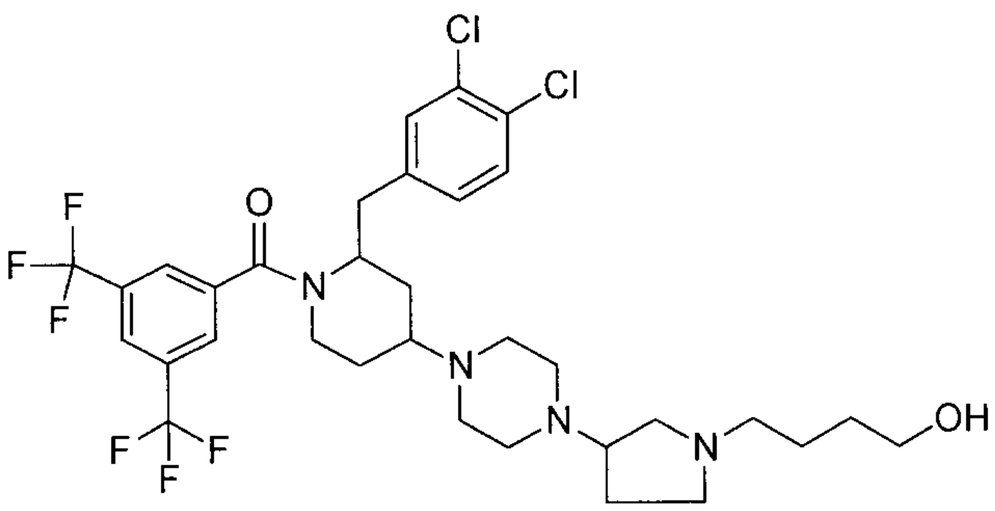
[2R-[2α,4β(R*(S*))]],



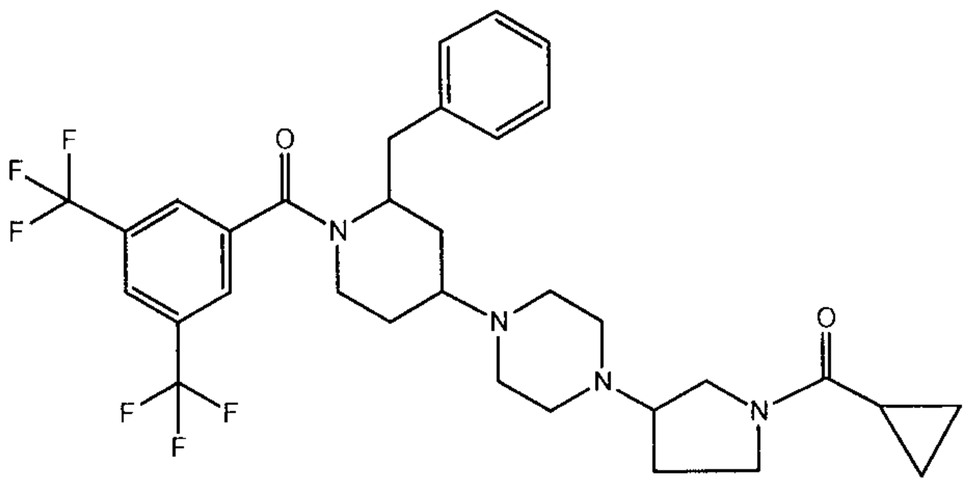
[2R-[2α,4β(S*(S*))]],



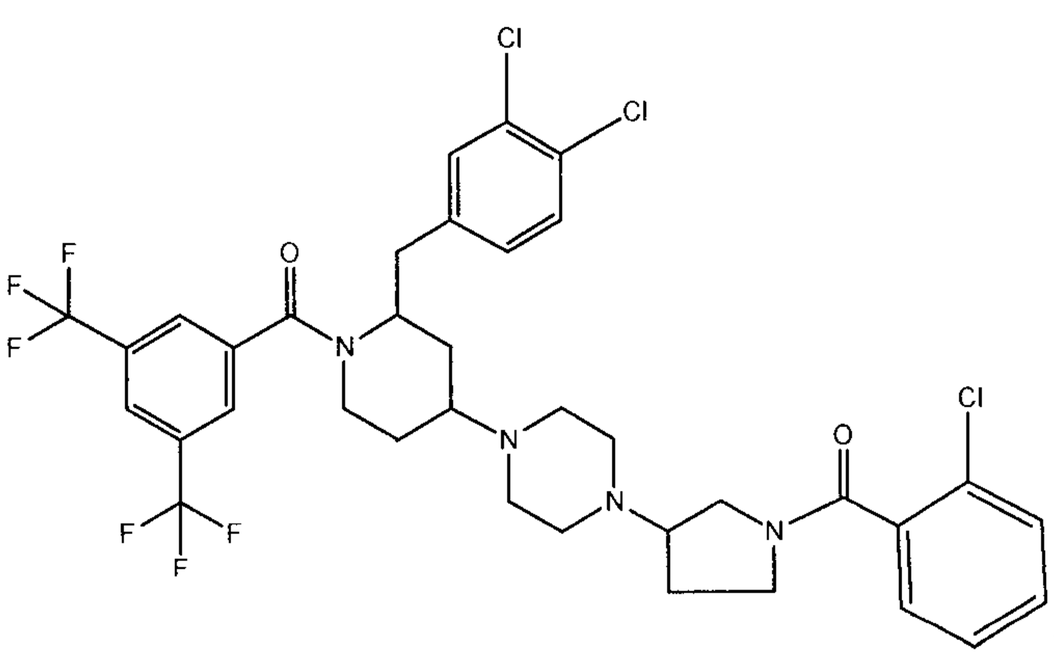
cis,



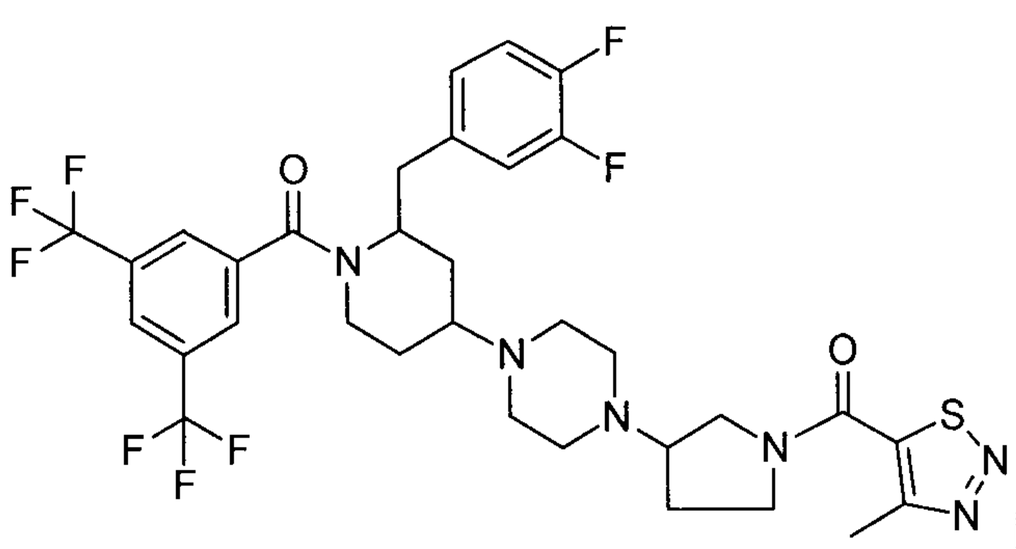
[2R-[2α,4β(S)]],



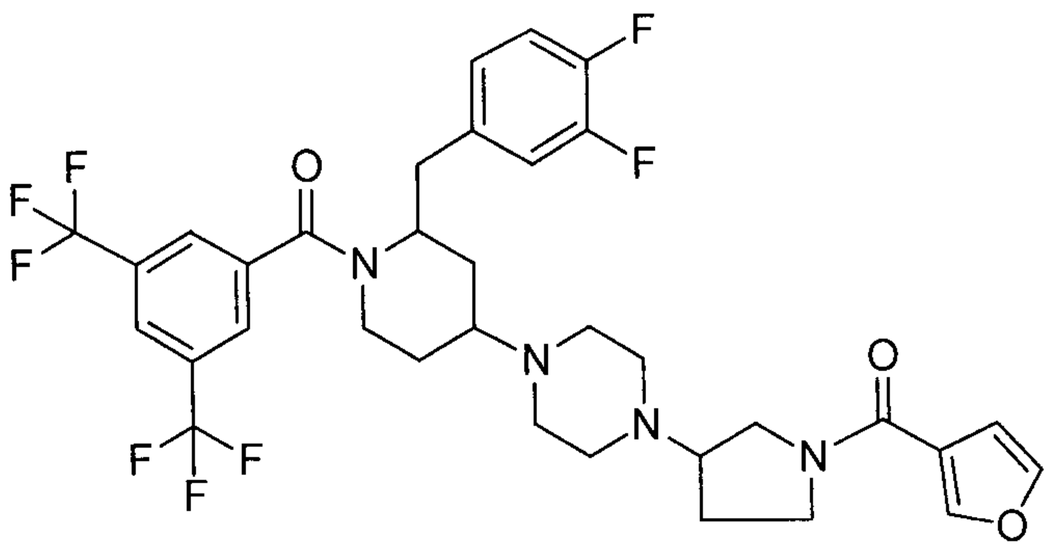
2R-trans,



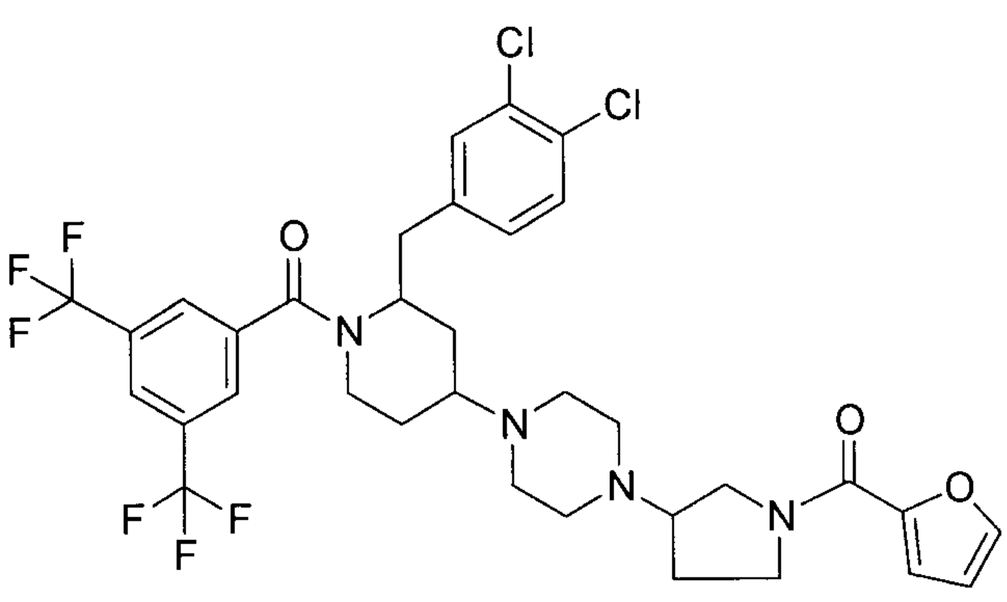
trans,



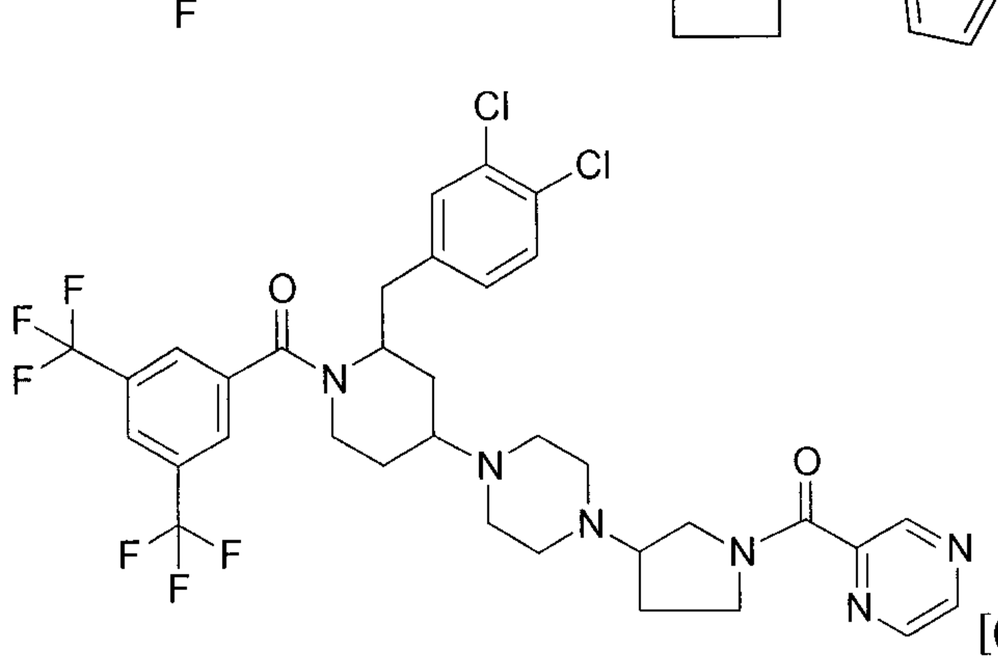
[2R-[2α,4β(S*)]],



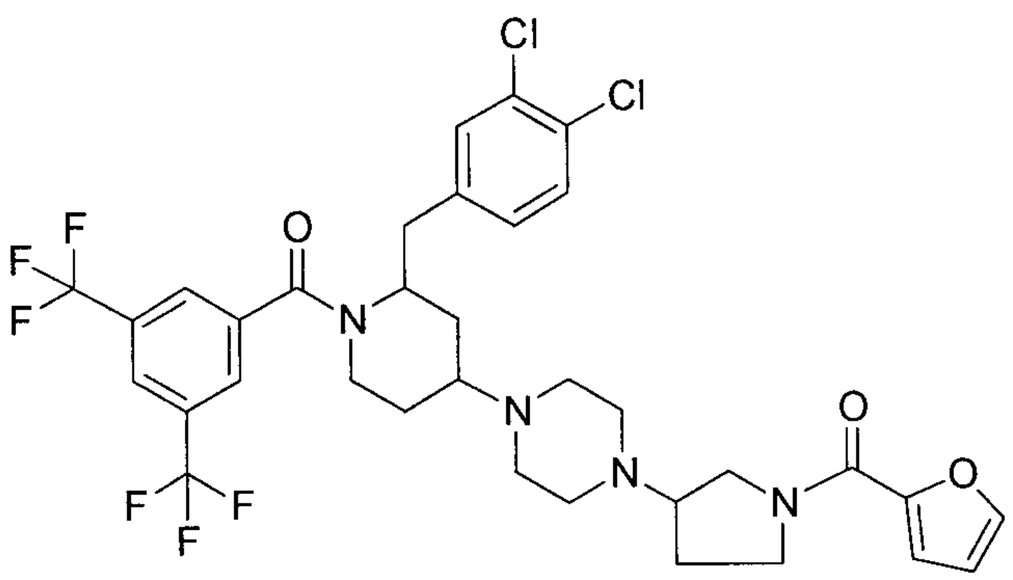
[2R-[2α,4β(S*)]],



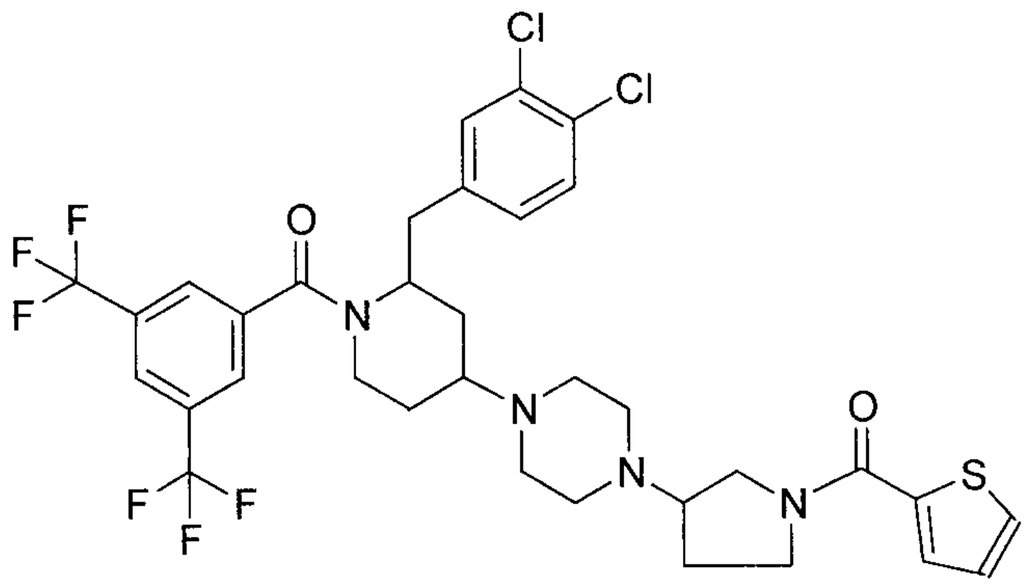
[(2R-trans),(R)],



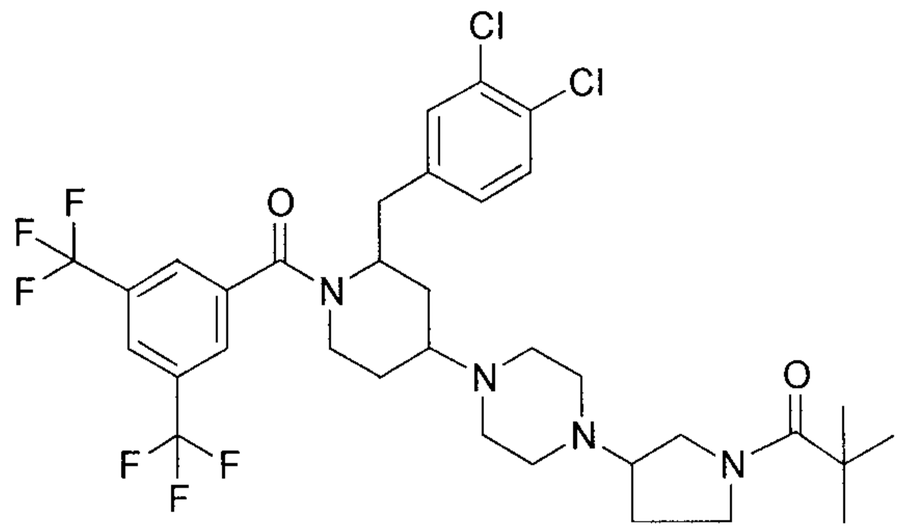
[(2R-trans),(R)],



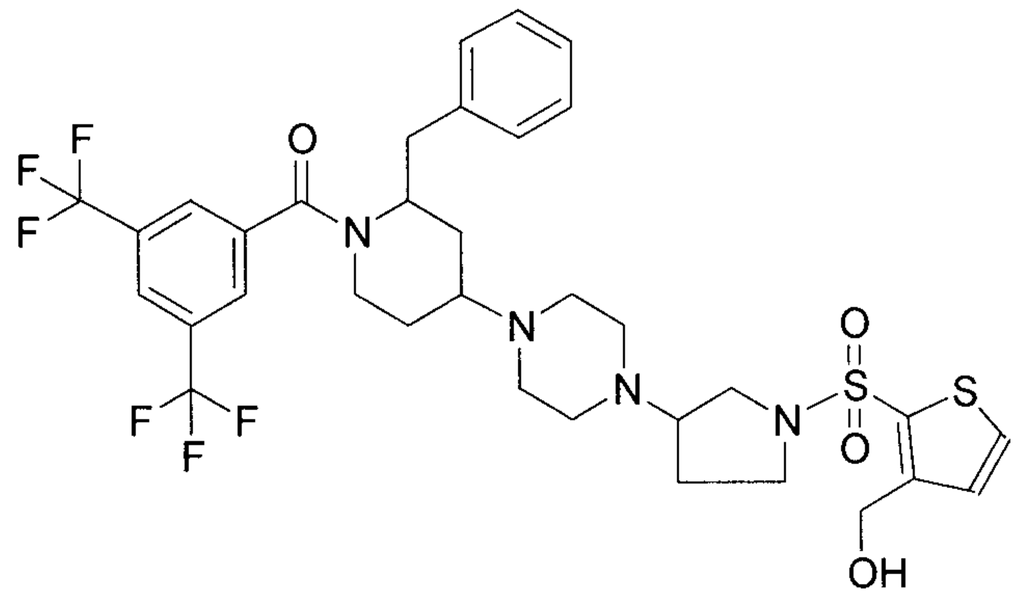
[(2R-trans),(S)],



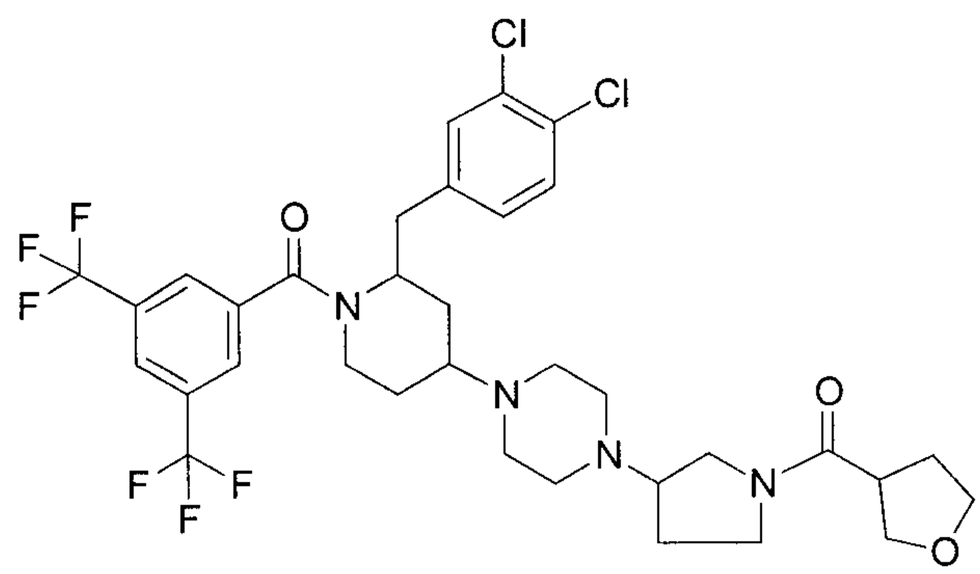
[(2R-trans),(S)],



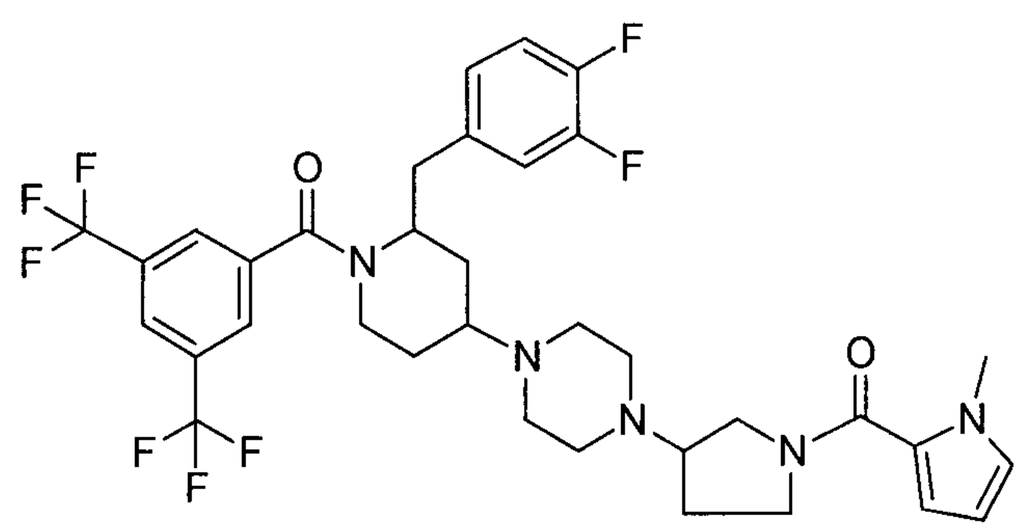
[(2R-trans),(S)],



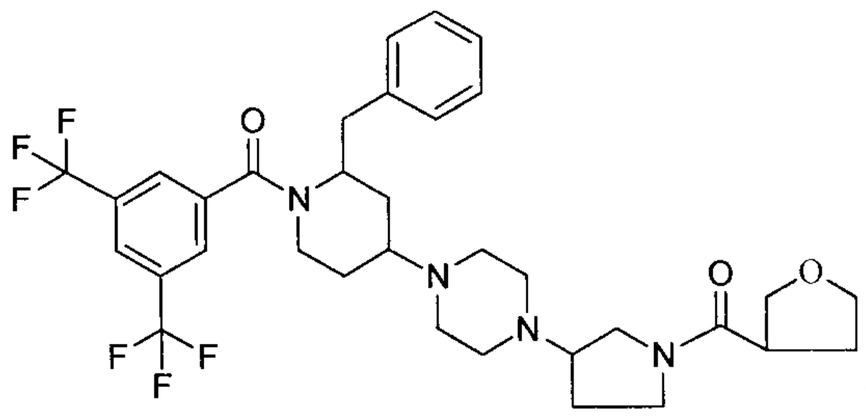
2R-trans,



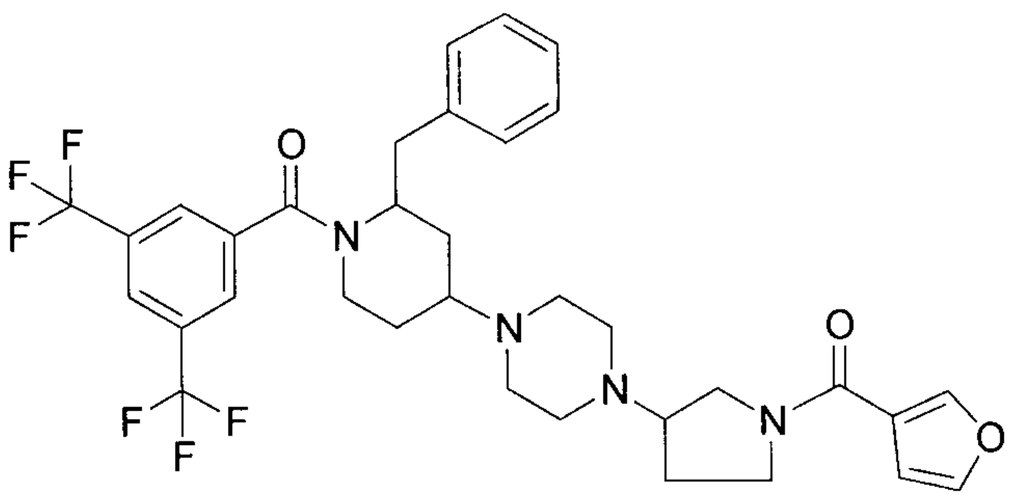
[(2R-trans),(S),(R)],



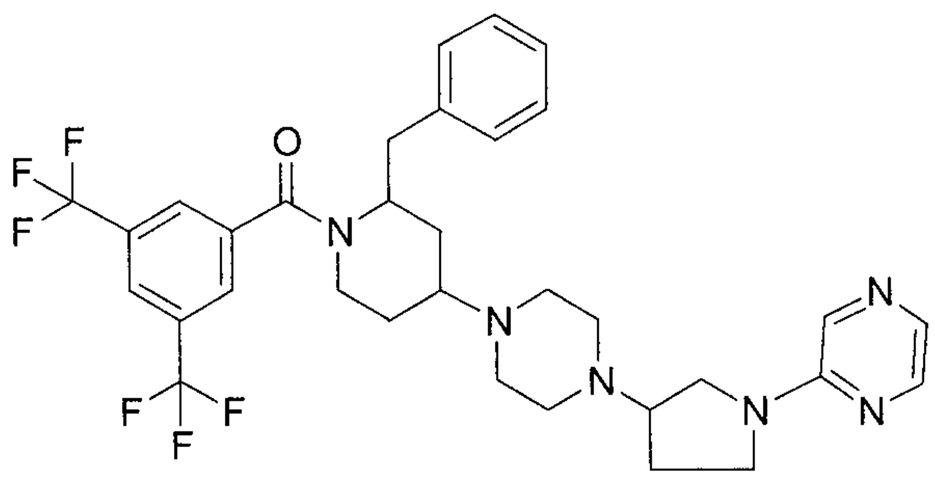
[2R-[2α,4β(R*)]],



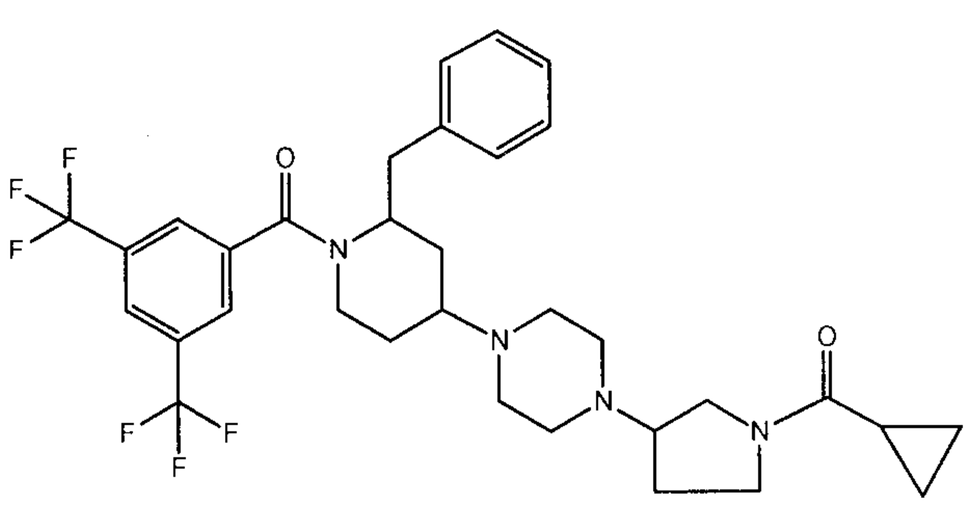
2R-trans,



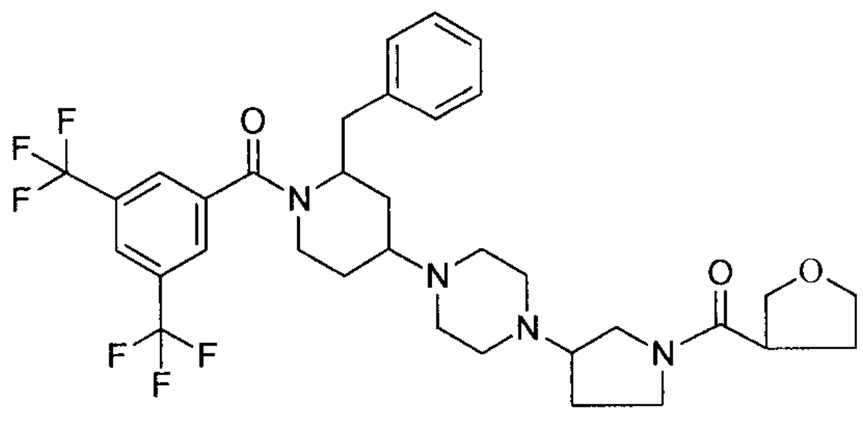
[2R-trans, R*],



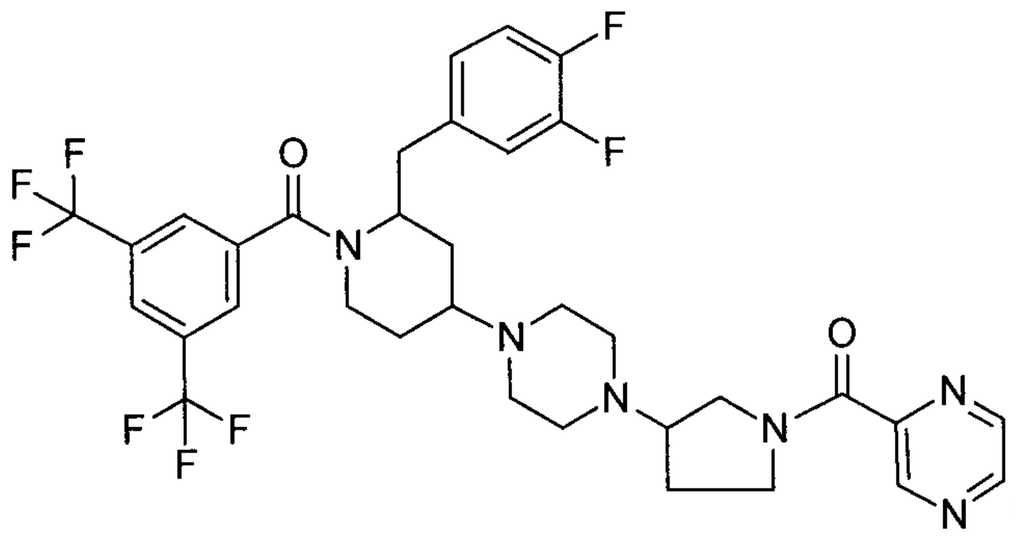
2R-trans,

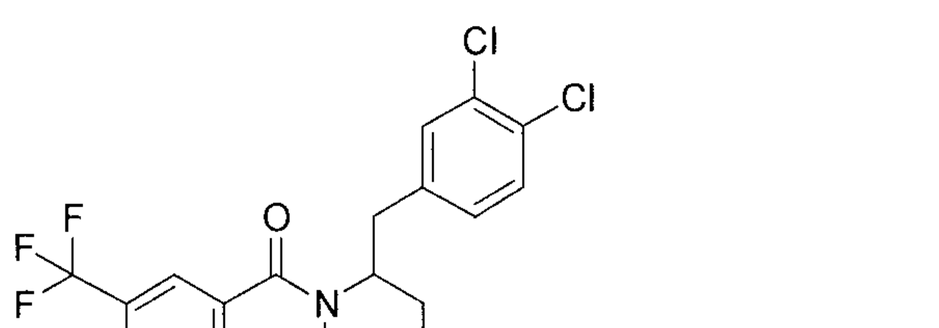


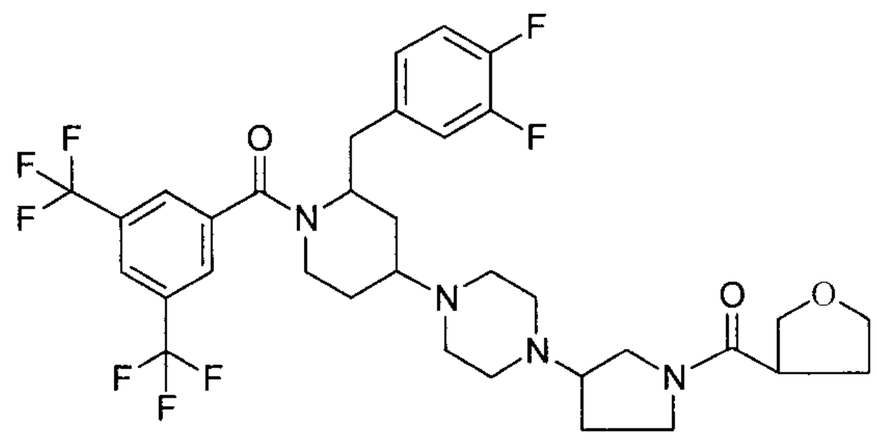
[2R-[2α,4β(S*)],

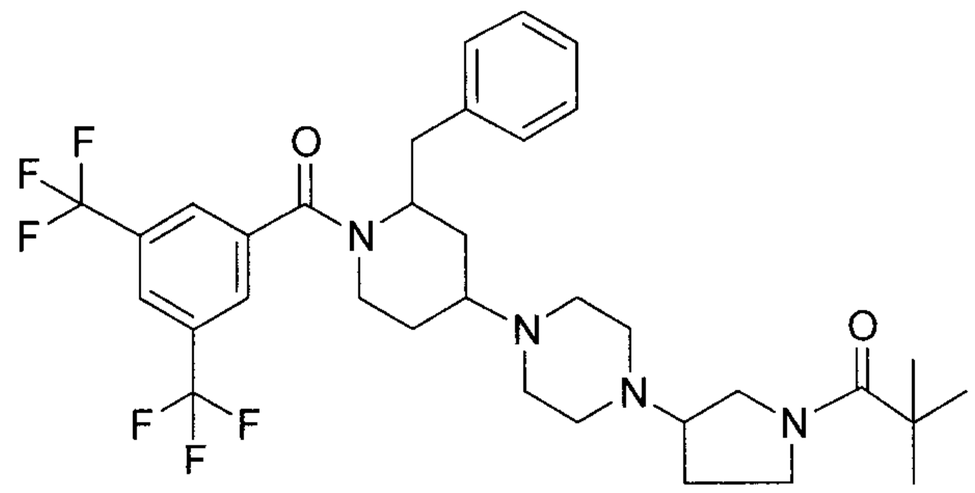


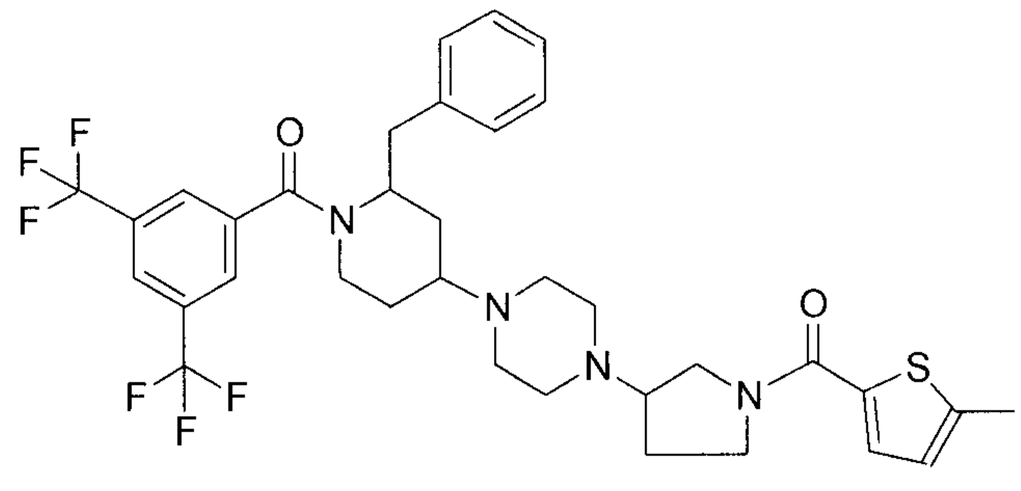
[2R-[2α,4β(S(R))]],


[2R-[2α,4β(S*)]],


[(2R-trans),(R)],


[2R-[2α,4β(S*(R*))]],


[2R-[2α,4β(S)]], or


[2R-[2α,4β(R)]].

10. The use of a compound as defined in any one of claims 1-9, for the manufacture of a medicament to inhibit neurokinin activity.

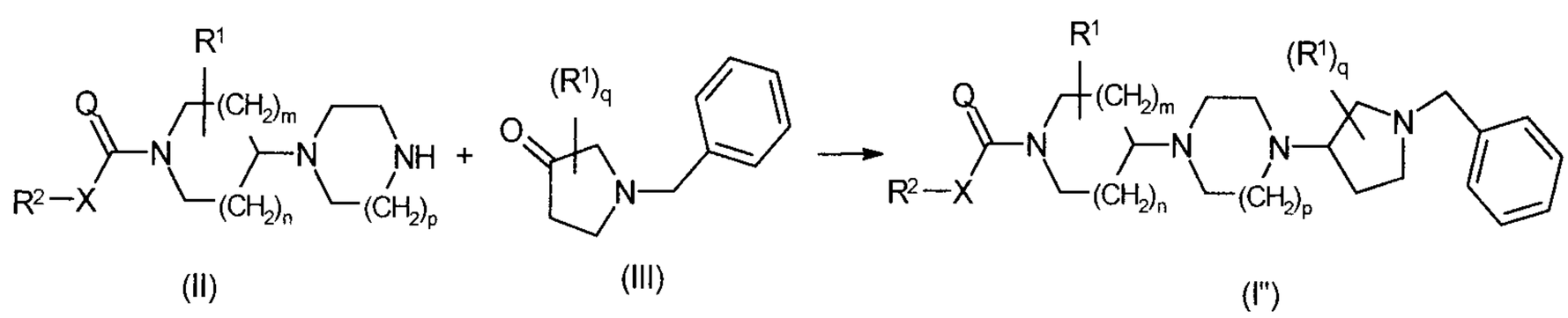
11. The use of a compound as defined in any one of claims 1-9, for the manufacture of a medicament for treating schizophrenia, emesis, anxiety, depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pain, neurogenic inflammation, asthma, micturition disorders.

12. The use of claim 11, wherein the micturition disorder is urinary incontinence or nociception.

13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a compound as defined in 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 compound as claimed in any one of claims 1-9.

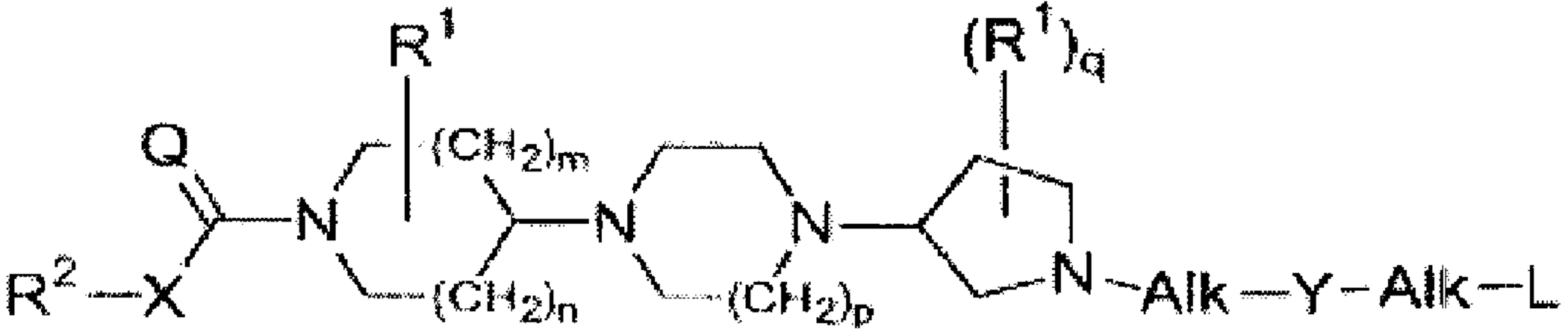
15. A process for the preparation of a compound of Formula (I") in which an intermediate compound of Formula (II) is reacted with an intermediate compound of Formula (III), wherein the radicals R^2, X, Q, R^1, m, n, p and q are as defined in claim 1



16. The use of a compound as defined in any one of claims 1-9, to inhibit neurokinin activity.

17. The use of a compound as defined in any one of claims 1-9, for treating schizophrenia, emesis, anxiety, depression, irritable bowel syndrome (IBS), circadian rhythm disturbances, pain, neurogenic inflammation, asthma, micturition disorders.

18. The use of claim 17, wherein the micturition disorder is urinary incontinence or nociception.



(I)