(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2005 (29.12.2005)

PCT

(10) International Publication Number
WO 2005/123081 A2

(51) International Patent Classification[7]: A61K 31/496, A61P 25/18

(21) International Application Number: PCT/EP2005/052887

(22) International Filing Date: 21 June 2005 (21.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04102885.3 22 June 2004 (22.06.2004) EP

(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)*: **LESAGE, Anne, Simone, Josephine** [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **ASHTON, David** [GB/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **JANSSENS, Frans, Eduard** [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

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

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *of inventorship (Rule 4.17(iv)) for US only*

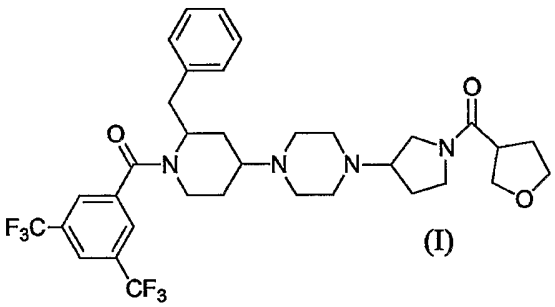
**Published:**

— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 2005/123081 A2

(54) Title: (2-BENZYL-4-{4-[1-(TETRAHYDROFURAN-3-CARBONYL)-PYRROLIDIN-3-YL]-PIPERAZIN-1-YL}-PIPERIDIN-1-YL)-(3,5-TRIFLUOROMETHYL-PHENYL))-METHANONE FOR THE TREATMENT OF SCHIZOPHRENIA




(I)

and prodrugs thereof.

(57) Abstract: This invention concerns the use of 2-benzyl-4-{4-[1-(tetrahydrofuran-3-carbonyl)pyrrolidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-trifluoromethyl-phenyl)-methanone and its derivatives having neurokinin antagonistic activity, in particular a combined $NK_1/NK_2/NK_3$ antagonistic activity and to modulate the activity of dopaminergic pathways in the brain, as a medicine for the prophylactic and/or therapeutic treatment of schizophrenia. 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

# (2-BENZYL-4-{4-[1-(TETRAHYDROFURAN-3-CARBONYL)-PYRROLIDIN-3-YL]-PIPERAZIN-1-YL}-PIPERIDIN-1-YL)-(3,5-TRIFLUOROMETHYL-PHENYL)-METHANONE FOR THE TREATMENT OF SCHIZOPHRENIA

## Field of the Invention

This invention concerns the use of (2-benzyl-4-{4-[1-(tetrahydrofuran-3-carbonyl)-pyrrolidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-trifluoromethyl-phenyl)-methanone and its derivatives having neurokinin antagonistic activity, in particular a combined $NK_1/NK_2/NK_3$ antagonistic activity and to modulate the activity of dopaminergic pathways in the brain, as a medicine for the prophylactic and/or therapeutic treatment of schizophrenia.

## Background of The Invention

The ascending dopaminergic pathway arising in the ventral tegmental area innervates a number of structures, including the nucleus accumbens in the striatum. This pathway has been shown to be overactive in schizophrenia (Laruelle *et al.*, *Proc Natl Acad Sci* 93: 9235-9240, 1996). $NK_3$ mRNA is found in human substantia nigra and striatum, as well as in frontal, temporal and parietal cortex, hypothalamus, and hippocampus (Buell *et al.*, *FEBS* 299 : 90-95, 1992). $NK_3$ receptors were more difficult to detect, and were found across all cortical layers, at the pial surface of the prefrontal cortex and in the hypothalamus, especially the paraventricular nucleus (Mileusnic *et al.*, *Neurobiol Aging* 20: 19-35, 1999 ; Koutcherov *et al.*, *NeuroReport* 11: 3127-3131, 2000 ; Tooney *et al.*, *Clin Exp Pharmacol Phys* 27: 947-949, 2000). Microinjection of the selective $NK_3$ agonist senktide or NKB into the substantia nigra or ventral tegmental area were shown to excite dopaminergic neurons and evoke DA release in the striatum of rat or guinea-pig (Humpel *et al.*, *Eur J Pharmacol* 195: 107-114, 1991 ; Marco *et al.*, *Neuropeptides* 32: 481-488, 1998). Microinjection of senktide into the substantia nigra and VTA also evokes dopamine-mediated hyperlocomotion (Stoessl *et al.*, *Brain Res* 565 : 254-262, 2003). The $NK_3$ antagonist osanetant (SR142801) was able to reduce the activity of dopaminergic neurons in the ventral tegmental area and the substantia nigra pars compacta (Marco *et al.*, *Neuropeptides* 32: 481-488, 1998 ; Gueudet *et al.*, *Synapse* 33: 71-79, 1999). These data suggest a beneficial effect of an $NK_3$ antagonist on the hyperactive dopaminergic state in schizophrenia. The first successful phase II trial with an $NK_3$ antagonist in schizophrenic patients was the meta-trial of Sanofi-Synthelabo, conducted and reported in a full paper just recently (Meltzer *et al.*, *Am J Psychatry* 161: 975-981, 2004). Osanetant (200 mg/day, 6 weeks) showed

a significantly greater improvement over baseline than the group receiving placebo as measured by the PANSS total score, the CGI severity of illness score and the BPRS psychosis cluster score. Even though osanetant was effective against positive symptoms, no effect on negative symptoms was observed. Also recently, a second positive phase II trial was reported by Glaxo for the selective $NK_3$ antagonist talnetant (SB223412). Talnetant (200 mg, 6 weeks) was reported to be efficacious against psychosis as measured on the PANSS total scale, with a magnitude of effect that was less pronounced than for risperidone. Talnetant showed superior tolerability and no prolactin release, no weight gain, and no extrapyramidal symptoms (Ratti, http://www.gsk.com/financial/presentations_2003_archive.htm, 2003).

$NK_2$ receptors are found mainly at low levels in discrete regions of human central nervous system, including prefrontal cortex, caudate putamen, substantia nigra, hippocampus and caudate nucleus (Bensaid *et al.*, *Neurosci lett* 303: 25-28, 2001). The endogenous $NK_2$ agonist NKA and NKA binding sites are found in close proximity of dopaminergic cell bodies in the ventral tegmental area and substantia nigra (Ljungdahl et al., *Neurosci* 3: 954-976, 1978 ; Somogyi et al., *Cell. Tisue Res* 223 : 469-486, 1982 ; Kalivas et al., *Neurosci Lett* 57: 241-246, 1985 ; Lee et al., *Brain Res* 371: 152-154, 1986 ; Burns et al., *Pharmacol. Biochem Behavior* 31 : 255-263, 1988). NKA was shown to excite dopaminergic neurons in the substantia nigra in rat (Innes et al., *Brain Res.* 335: 381-383, 1985) and to evoke dopamine release in striatum (Baruch et al., *Neurosci.* 25: 889-898, 1988). Microinjection of the selective $NK_2$ agonist (bAla8)-NKA(4-10) into the ventral tegmental area also increased locomotor activity and rearing, a behaviour that was blocked by haloperidol, suggesting that it is mediated via dopaminergic neurons (Burns et al., *Pharmacol. Biochem Behavior* 31 : 255-263, 1988). As activation of $NK_2$ receptors evokes an excitation of mesolimbic and nigrostriatal dopaminergic pathways, it can be expected that $NK_2$ receptor antagonists will modulate the mesolimbic, mesocortical and/or nigrostriatal dopaminergic system.

In human, $NK_1$ is highly expressed in locus coeruleus, caudate, putamen and hypothalamus, and moderately highly expressed in hippocampus, amygdala and frontal and cingulate cortex (Caberlotto *et al.*, *Eur J Neurosci* 17 : 1736-1746, 2003 ; Tooney *et al.*, *Clin Exp Pharmacol Phys* 27: 947-949, 2000 ; Hargreaves, *J Clin Psychiatry* 63: 18-24, 2002). The endogenous agonist Substance P (SP) is found in close proximity of dopaminergic cell bodies in the ventral tegmental area and substantia nigra (Ljungdahl et al., *Neurosci* 3: 954-976, 1978 ; Somogyi et al., *Cell. Tisue Res* 223 : 469-486, 1982 ; Kalivas et al., *Neurosci Lett* 57: 241-246, 1985 ; Lee et al., *Brain Res* 371: 152-154, 1986). Microinjection of SP into the ventral tegmental area causes behavioural changes

such as psychomotor activation, attributed to dopaminergic activation and dopamine release in the nucleus accumbens (Stinus et al., *Nature* 276 : 616-618, 1978 ; Kelley et al., *Neurosci Lett* 11: 335-339, 1979). $NK_1$ receptor blockade with the $NK_1$ antagonist LY306740 (20 and 35 nmol intrastriatal) decreases amphetamine-induced behaviour in rat (Gonzales-Nicolini et al., *Brain Res* 931: 41-49, 2002). $NK_1$ receptor blockade in striatum with L-733,060 attenuated cocaine-evoked DA overflow in the striatum (Loonam et al., *Life Sci* 73: 727-739, 2003). And $NK_1$ blockade with GR 205171 also evoked an elevation of frontal cortex but not striatal dopamine levels in rat (Lejeune et al., *Brain Res* 935: 134-139, 2002).

These modulations of the dopaminergic pathways observed with neurokinin $NK_1$, $NK_2$, or $NK_3$ agonists and/or antagonists would allow that a mixed $NK_{1,2,3}$ antagonist also modulates dopaminergic signalling in the brain.

Background prior art

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

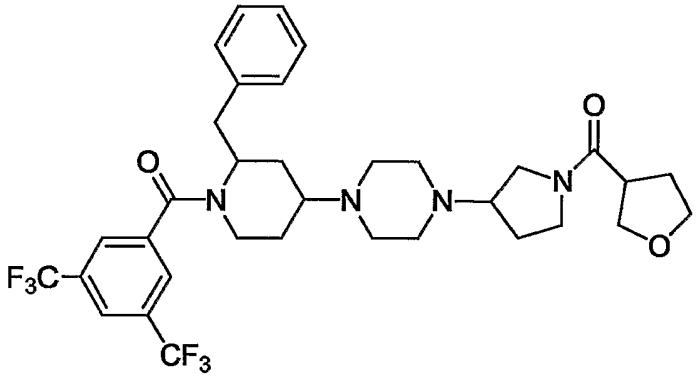
The compounds of the present invention differ from the compounds of the prior art in the substitution of the piperazinyl moiety, being a substituted pyrrolidinyl moiety, in their activity as a dopamine receptor modulator, as well as in their improved ability as potent, orally and centrally active neurokinin antagonists with therapeutic value, especially for the prophylactic and/or therapeutic treatment of schizophrenia.

The compounds of the present invention, as part of a series of substituted 1-piperidin-4-yl-4-pyrrolidin-3-yl-piperazine derivatives, have been published in WO2004/056799 (published 8 July 2004), further directed to their use as neurokinin antagonists, 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.. The present invention is directed to specific compounds for use in the

prophylactic and/or therapeutic treatment of schizophrenia. These compounds surprisingly have been found to modulate not only the $NK_{1,2,3}$-activity, but also the activity of dopaminergic pathways in the brain.

Description of the Invention

The present invention relates to the use of a compound according to the general Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, for the manufacture of a medicament for the prophylactic and/or therapeutic treatment of schizophrenia.

More in particular, the invention relates to the use of a compound according to the invention with the chemical name (2-benzyl-4-{4-[1-(tetrahydrofuran-3-carbonyl)-pyrrolidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-trifluoromethyl-phenyl)-methanone.

More in particular, the invention relates to the use of a compound according to the invention, wherein the stereoconfiguration is [2R-[2α,4β(S(R))]].

In the framework of this application, with "compound 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.

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, mandelic 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.

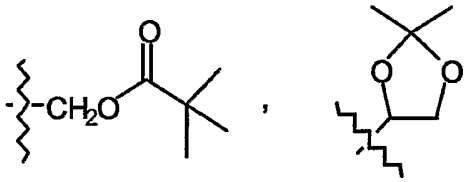
Following CAS nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. R* and S* each indicate optically 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

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 mixed neurokinin $NK_{1,2,3}$ antagonists. The binding affinity of the present compounds for the human, rat, guinea-pig, ferret and gerbil neurokinin $NK_1$, $NK_2$ and $NK_3$ receptors may also be determined *in vitro* in a receptor binding test using $^3$H-substance-P, [$^3$H]-SR-48968 or [$^3$H]-SR-142801 as radioligand. The potency with which the compounds of the present invention antagonize $NK_1$, $NK_2$ and $NK_3$ activity may also be measured *in vitro*. The test may be based on receptor-activated signal transduction and may be based on the measurement of compound-evoked inhibition of agonist-induced receptor-mediated $Ca^{++}$ mobilization. All compounds of the present invention showed an excellent $NK_1$, $NK_2$ and $NK_3$ antagonist potency, and therefore are potent $NK_{1,2,3}$ antagonists.

The subject compounds also show substance-P antagonistic activity *in vivo* as may be evidenced by, for instance, the antagonism of substance P-induced thumping behavior in gerbil or antagonism of drug-induced emesis in ferrets (Megens *et al.*, 2002).

In the course of our experiments, we observed that the specific $NK_3$ receptor agonist senktide greatly reduced rearing in gerbils. We performed dose- and time-response curves for senktide-induced inhibition of rearing. This effect was antagonized by selective $NK_3$ antagonists and by the reference $NK_3$ antagonist SR-142801. We

therefore introduced this as a possible screening test to determine the *in vivo* potency of test compounds to antagonise activation of central $NK_3$ receptors. The compounds of this invention potently attenuated $NK_3$ receptor activation-induced behaviour.

The compounds of the invention were also found active in several models of peripheral $NK_1$, $NK_2$ or $NK_3$ receptor activity, including substance P-induced plasma protein extravasation in guinea pig, senktide-induced miosis in rabbits, and [$\beta$ALA$^8$]-neurokinin A (4-10)- induced lethality in guinea-pigs.

The compounds of the present invention are also found to regulate dopamine release as can e.g. be determined using competition binding experiments using e.g. [$^{11}$C]fallypride in in vitro and in in vivo setups (Slifstein M, Hwang D-R, Huang Y, Guo N, Sudo Y, Narendran R, Talbot P, and Laruelle M. (2004). In vivo affinity of [$^{18}$F]fallypride for striatal and extrastriatal dopamine D2 receptors in nonhuman primates. *Psychopharmacology* - In press).

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, and in view of their ability to modulate the activity of dopaminergic pathways, the compounds according to the invention are useful as orally active, centrally penetrating medicines for use in the prophylactic and/or therapeutic treatment of neurokinin- and/or dopamine regulated diseases, in particular schizophrenia.

The present invention also relates to a method for the prophylactic and/or therapeutic treatment of schizophrenia, 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 prodrugs 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

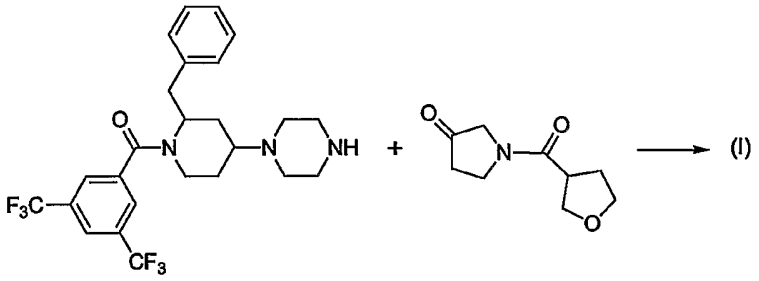
particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions 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.

Preparation

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

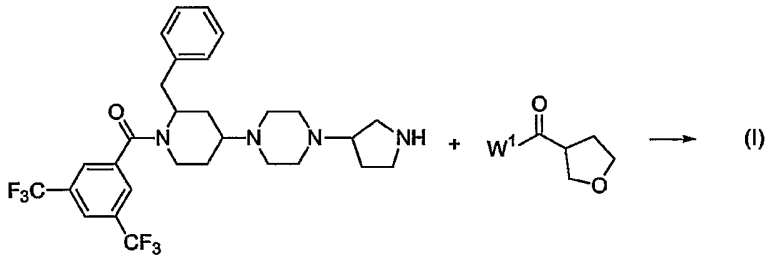
The final compounds of Formula (I) are conveniently prepared by reductively *N*-alkylating an intermediate compound of Formula (II) with an intermediate compound of Formula (III) . Said reductive *N*-alkylation may be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol or toluene or a mixture thereof, and in the presence of an appropriate reducing agent such as, for example, a borohydride, e.g. sodium borohydride, sodium cyanoborohydride or triacetoxy borohydride. In case a borohydride is used as a reducing agent, it may be convenient to use a complex-forming agent such as, for example, titanium(IV)isopropylate as described in J. Org. Chem, 1990, *55*, 2552-2554. Using said complex-forming agent may also result in an improved *cis/trans* ratio in favour of the *trans* isomer. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal or platinum-on-charcoal. In case hydrogen is used as reducing agent, it may be advantageous to add a dehydrating agent to the reaction mixture such as, for example, aluminium *tert*-butoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene or quinoline-sulphur. Stirring and optionally elevated temperatures and/or pressure may enhance the rate of the reaction.




(II) (III)

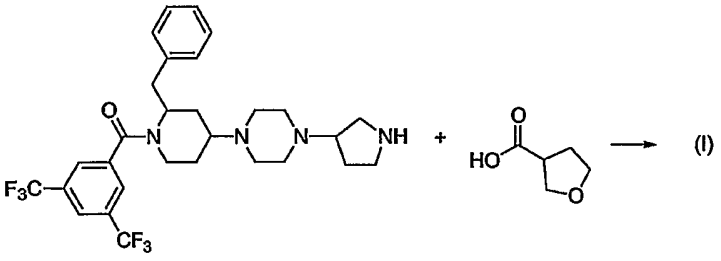
In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

Alternatively, the final compounds of Formula (I) can be prepared by reacting a compound of Formula (IV) 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.



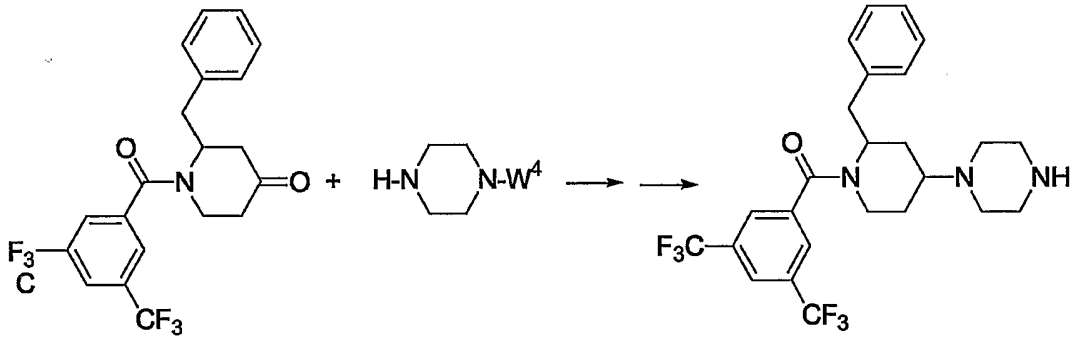
(IV) (V)

Alternatively, the final compounds of Formula (I) can also be prepared by reacting a final compound of Formula (IV) 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 (carbonyl-diimidazole) 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.



(IV) (VI)

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)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.




(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.

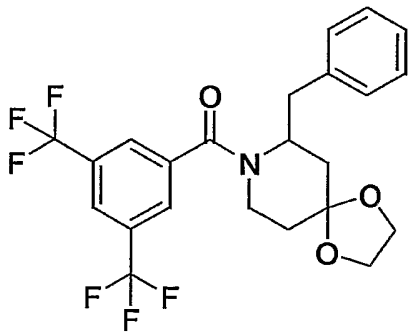
Experimental Part

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

A. Preparation of the intermediate compounds

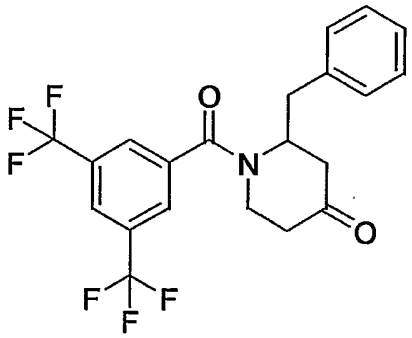
Example A1

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.

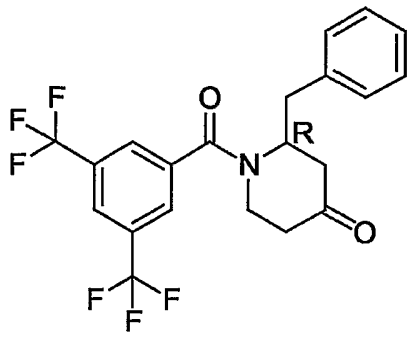
b. Preparation of intermediate compound 2



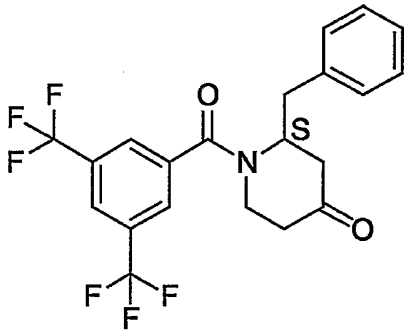
HCl cp (300 ml) was added to a mixture of intermediate compound 1 (0.5 mol) in ethanol (300 ml) and $H_2O$ (300 ml). The reaction mixture was stirred at 60 °C for 20

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).

c. Preparation of intermediate compound 3R and intermediate compound 3S.



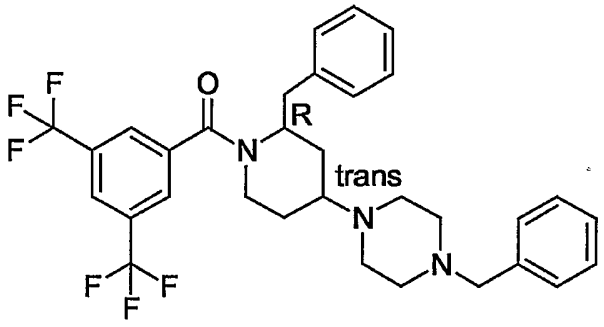
(3R)



(3S)

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 3R, and Fraction 2: 30.4 g of intermediate compound 3S.

d. Preparation of intermediate compound 4

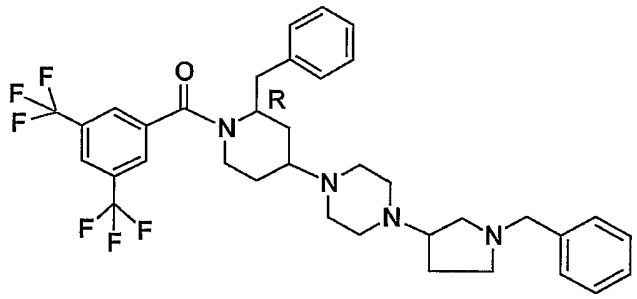


A mixture of intermediate compound 3R (0.046 mol), 1-(phenylmethyl)piperazine (0.051 mol) and Ti-isopropoxide (0.056 mol) was stirred for 2 hours at 40 °C. The

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 minutes. 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 4 (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 intermediate compound 3S 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.

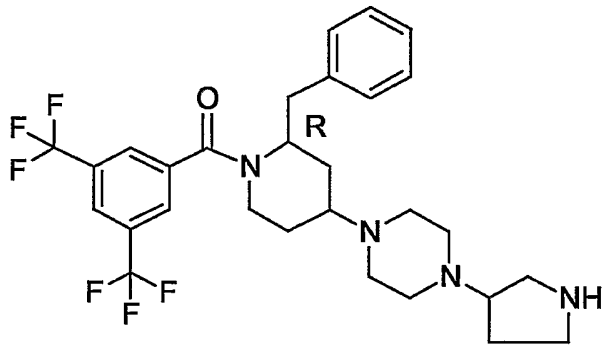
e. Preparation of intermediate compound 5




A mixture of (2R-trans) 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-(1-piperazinyl)piperidine [intermediate compound 4] (0.05 mol) and 1-(phenylmethyl)-3-pyrrolidinone (0.05 mol) in methanol (250 ml) 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 intermediate compound 5.

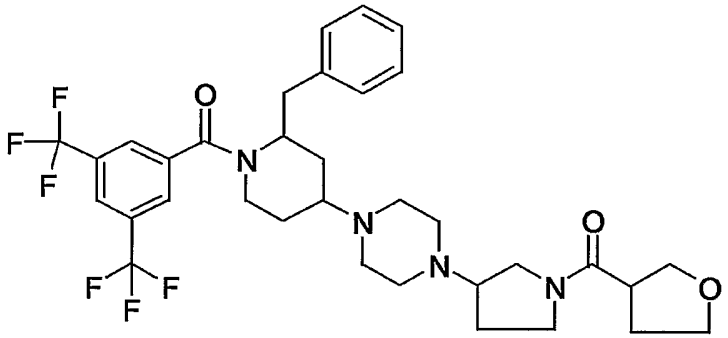
f. Preparation of intermediate compound 6




Intermediate compound 5 (0.022 mol) in methanol (250 ml) 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 intermediate compound 6.

B. Preparation of the final compounds

Example B1
Preparation of final compound 5




$CH_2Cl_2$ (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. Intermediate compound 6 (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 5.

The following stereochemical equivalens (Table 1) were made according to the above disclosed preparation.

C. Analytical data

C1. Melting points

If possible, melting points (or ranges) were obtained with a Büchi apparatus, using a visual inspection.

C2. 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.

C3. LCMS conditions

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 1: Physico-chemical data for enantiomers 1 to 8.

| Co. No. | Stereo-descriptors | Optical rotation [α], (nm) | Melting Point (°C) | $pIC_{50}$ $NK_1$ | $pIC_{50}$ $NK_2$ | $pIC_{50}$ $NK_3$ |
|---|---|---|---|---|---|---|
| 1 | 2R-trans | -6.62°, 589 nm | - | 8,0 | 5,6 | 6,4 |
| 2 | 2S-cis | - | - | n.d | n.d | n.d |
| 3 | 2S-trans | +31.33°, 365 nm | - | 6,6 | n.d | 5,0 |
| 4 | 2R-cis | -19,03°,589 nm | - | 6,8 | n.d | 5,2 |
| 5 | [2R-[2α,4β(S(S))]] | -8.05°, 589 nm | - | 8,0 | 5,3 | 5,8 |
| 6 | [2R-[2α,4β(R(S))]] | +7.19°, 589 nm | - | 8,1 | 5,5 | 6,1 |
| 7 | [2R-[2α,4β(R(R))]] | - | - | 8,1 | 5,4 | 5,5 |
| 8 | [2R-[2α,4β(S(R))]] | -6.44°, 589 nm | 89.8 - 100.2 | 8,0 | 5,4 | 6,1 |

Table 2 : LCMS parent peak and retention time for selected compounds.

| Comp. no. | LCMS MS(MH+) Meth. A | Retention time |
|---|---|---|
| 1 | 667 | 5.5 |
| 2 | 667 | 5.68 |
| 5 | 667 | 5.49 |
| 6 | 667 | 5.49 |
| 7 | 667 | 5.51 |
| 8 | 667 | 5.49 |

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-$NK_1$, h-$NK_2$ and h-$NK_3$ receptors ranges for all compounds according to the invention between 10 and 5.5.

Example D.2 : Signal transduction (ST)

This test evaluates in vitro functional $NK_1$, h-$NK_2$ and h-$NK_3$ 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 (substance P, NKA, NKB) 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 1.

E. Composition examples

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

Example E.1 : ORAL DROPS

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

Example E.2 : ORAL SOLUTION

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

Example E.3 : FILM-COATED TABLETS

Preparation of tablet core

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

Coating

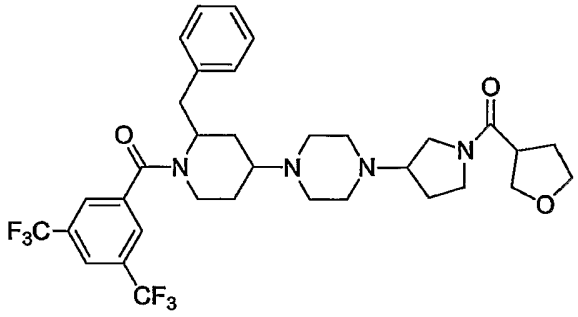
To a solution of 10 grams methyl cellulose in 75 ml of denaturated ethanol there was added a solution of 5 grams of ethyl cellulose in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 Grams of polyethylene glycol was molten and dissolved in 75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

Example E.4 : INJECTABLE SOLUTION

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

# CLAIMS

1. The use of a compound according to the general Formula (I)



(I)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the *N*-oxide form thereof and prodrugs thereof, for the manufacture of a medicament for the prophylactic and/or therapeutic treatment of schizophrenia.

2. The use of a compound according to claim 1 with the chemical name (2-benzyl-4-{4-[1-(tetrahydrofuran-3-carbonyl)-pyrrolidin-3-yl]-piperazin-1-yl}-piperidin-1-yl)-(3,5-trifluoromethyl-phenyl)-methanone.

3. The use of a compound according to any one of claims 1 to 2, characterized that the stereoconfiguration is [2R-[2α,4β(S(R))]].

4. The use of a compound according to any one of claims 1 to 3 for the manufacture of a medicament for the prophylactic and/or therapeutic treatment of neurokinin-regulated diseases, in particular schizophrenia.

5. The use of a compound according to any one of claims 1 to 3 for the manufacture of a medicament for the prophylactic and/or therapeutic treatment of dopamine regulated diseases, in particular schizophrenia.