Title: COMBINATION THERAPY WITH 5-HT\textsubscript{1A} AND 5-HT\textsubscript{1B} RECEPTOR ANTAGONISTS

Abstract: A compound having 5-HT\textsubscript{1A} antagonist activity is useful for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract in combination with the prior, concurrent or post-administration of a compound having 5-HT\textsubscript{1B} antagonist activity. Alternatively a single compound having both 5HT\textsubscript{1A} and 5-HT\textsubscript{1B} antagonist activity is useful for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract.
TITLE
Combination Therapy with 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} Receptor Antagonists

DESCRIPTION

Background of the Invention

The invention is directed to treatment of disease of the lower urinary tract using a combination of HT\textsubscript{1A} and HT\textsubscript{1B} serotonin receptor antagonists.

In mammals, micturition (urination) is a complex process that requires the integrated action of the bladder, its internal and external sphincters, the musculature of the pelvic floor and neurological control over these muscles at three levels (in the bladder wall or sphincter itself, in the autonomic centres of the spinal cord and in the central nervous system at the level of the pontine micturition centre (PMC) in the brainstem (pons) under the control of the cerebral cortex) (De Groat, *Neurobiology of Incontinence*, Ciba Foundation Symposium 151:27, 1990). Micturition results from contraction of the detrusor muscle, which consists of interlacing smooth-muscle fibres, under the control of the parasympathetic autonomic system originating from the sacral spinal cord. A simple voiding reflex is triggered by sensory nerves for pain, temperature and distension that run from the bladder to the sacral spinal cord.

However, sensory tracts from the bladder reach the PMC too, generating nerve impulses that normally suppress the sacral spinal suppression of cortical inhibition of the reflex arc, and relaxing the muscles of the pelvic floor and external sphincter. Finally, the detrusor muscle contracts and voiding occurs. Abnormalities of lower-urinary tract function, e.g., dysuria, incontinence and enuresis, are common in the general population. Dysuria includes urinary frequency, nocturia and urgency, and may be caused by cystitis (including interstitial cystitis), prostatitis or benign prostatic hyperplasia (BPH) (which affects about 70% of elderly males), or by neurological disorders. Incontinence syndromes include stress incontinence, urgency incontinence, overflow incontinence and mixed incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

Previously, treatment of neuromuscular dysfunction of the lower urinary tract involved administration of compounds that act directly on the bladder muscles, such as flavoxate, a spasmolytic drug (Ruffman, *J. Int. Med. Res.* 16: 317, 1988) which is also active on the PMC (Guarneri *et al.*, *Drugs of Today*, 30: 91, 1994), or
anticholinergic compounds such as oxybutynin (Andersson, Drugs 36: 477, 1988) and
tolterodine (Nilvebrant, Life Sci. 68: 2549, 2001). The use of α₁-adrenergic receptor
antagonists for the treatment of BPH is common too, but is based on a different
mechanism of action (Lepor, Urology, 42: 483, 1993). However, treatments that
involve direct inhibition of the pelvic musculature (including the detrusor muscle)
may have unwanted side effects, such as incomplete voiding or accommodation
paralysis, tachycardia and dry mouth (Andersson, Drugs 35: 477, 1988). Thus, it
would be preferable to utilize compounds that act via the central nervous system to
affect, for example, the sacral spinal reflex and/or the PMC inhibition pathways in a
manner that restores normal functioning of the micturition mechanism.

The descending bulospsinal pathway to the urinary bladder is essentially an

At least 15 different populations of 5-HT receptors have been identified.
These receptor types belong to 5-HT receptor families 5-HT₁ to 5-HT₇, and several of
the families are composed of subpopulations. For example, 5-HT₁ receptors are a
family of 5-HT receptors that are negatively coupled to adenylate cyclase and consist
of 5-HT₁₅, 5-HT₁₆, 5-HT₁₁, 5-HT₁₂ and 5-HT₁₃ subtypes (Gerhardt van Heerikhuitzen,

Of particular interest to the present invention are the 5-HT₁₅ and 5-HT₁₆ receptors. Animal and human 5-HT₁₅ receptors act as somatodendritic and
presynaptic receptors on nerve cells thus modulating neural firing, and at the
postsynaptic level where they mediate inhibitory functions. Certain rodent species,
including rat and mouse, possess 5-HT₁₅ receptors that serve primarily as terminal
autoreceptors. In humans, the corresponding receptors that function in a similar
manner were initially termed 5-HT₁₁ (Weinshank et al., Proc. Natl. Acad. Sci. USA
89: 3630, 1992; Artig et al., Mol. Pharmacol. 41: 1, 1992). Rat 5-HT₁₆ receptors and
human 5-HT₁₁ receptors are considered species homologues, and there is >90% transmembrane sequence homology between them. It has been recommended that
human 5-HT₁₁ receptors be termed h5-HT₁₆ receptors (Hartig et al., Trends
Pharmacol. Sci. 17: 103, 1996). Most agents that bind at rat 5-HT₁₆ receptors also
bind at human cloned 5-HT$_{1B}$ receptors.

In the central nervous system, several independent serotonergic cell clusters located in the raphe nuclei have been identified, possessing differential projection patterns. Serotonin within the dorsal horn of spinal cord arises primarily from neurons in the pontomedullary nucleus raphe magnus (NRM) (Bowker et al. *Brain Res* 226: 187, 1981).


Neutral antagonists at somatodendritic 5-HT$_{1A}$ receptors therefore, by increasing the firing of NRM neurons, lead to an increase of spinal 5-HT thus inhibiting the micturition reflex (Testa et al. *J Pharmacol. Exp. Ther* 290: 1258, 1999). The release of 5-HT is inhibited by the stimulation of presynaptic 5-HT$_{1B}$ receptors (induced by the 5-HT itself) which are located on the synaptic terminals of serotonergic neurons (Bolanos-Jimenex et al., *Eur. J. Pharmacol.* 294: 531, 1995).

The 5-HT$_{1B}$ subtype receptor has been localized in all laminae in the spinal cord, where they represent approximately 18% of all 5-HT binding sites. Most of these 5-HT$_{1B}$ receptors are located on the terminals of descending pathways from raphe nuclei (Gjerstad et al., *Eur. J. Pharmacol.* 335: 127, 1997).
The use of 5-HT$_{IA}$ receptor antagonists in treatment of urinary incontinence or overactive bladder is disclosed in US 6399614, US 6271234, US 6071920 and US 5990114. Additional compounds that are 5-HT$_{IA}$ receptor antagonists are disclosed in US 6514976, US 6358958 and US 6239135. Although the compounds are disclosed as useful for treatment of urinary incontinence, the documents provide no experimental support for treatment of urinary incontinence either in human patients or in an animal model for lower urinary tract disease.

WO 99/05134, WO 99/14207, WO 99/14212 and WO 99/14213 disclose compounds as useful for the treatment of different diseases, including urinary incontinence. The compounds are disclosed as 5-HT$_{IB}$ receptor antagonists. None of these documents, however, provide experimental support for 5-HT$_{IB}$ receptor binding, or treatment of urinary incontinence, either in human patients or in an animal model for lower urinary tract disease.

WO 95/31988 discloses combinations of 5-HT$_{IA}$ and 5-HT$_{ID}$ antagonists and their methods of use in treating CNS disorders. This document does not disclose the use of a combination of 5-HT$_{IA}$ and 5-HT$_{ID}$ antagonists for the treatment of urinary incontinence, either in human patients or in an animal model for lower urinary tract disease.

WO 99/13876 discloses the use of the combination of one class of ronalotan-like 5-HT$_{IA}$ antagonists and one class of 5-HT$_{IB}$ antagonists or partial agonists for treatment of different diseases, including urinary incontinence. The reference does not, however, provide experimental support for treatment of urinary incontinence, either in human patients or in an animal model for lower urinary tract disease.

The aforementioned patent publications, therefore, disclose 5-HT$_{IA}$ and/or 5-HT$_{IB}$ receptor antagonists in combination. None of the references, however, provide support for treatment of urinary incontinence, either in human patients or in an animal model for lower urinary tract disease.

Patients with lower urinary tract conditions often respond to certain classes or subclasses of therapeutic agents. Furthermore, patients may respond initially to a therapeutic agent, but become non-responsive to the agent over time. Additionally, patients may exhibit undesirable side effects when therapeutic agents are administered in concentrations required to treat lower urinary tract conditions. These side effects may be overcome by administering lower dosages of two or more therapeutic agents to achieve a therapeutic effect, wherein one or more of the lower dosages would not
be sufficient to have a therapeutic when the respective therapeutic agent is used in monotherapy.

Accordingly, one of ordinary skill in the art will appreciate a continuing need to identify new treatment regimens for treatments of lower urinary tract disease(s). The new treatment regimens may include, for example, combination therapies that target two or more receptors involved in lower urinary tract conditions.

The Invention

The invention is based on the finding that administration of a combination of compounds at least one of which is endowed with antagonistic activity at 5-HT\textsubscript{1A} and at least one of which is endowed with antagonist activity at 5-HT\textsubscript{1B} receptors, or a compound that has both 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} antagonistic activity, produces a synergistic effect which is useful in the treatment of neuromuscular dysfunction of the lower urinary tract in mammals and in particular provides a very potent inhibition of the micturition reflex.

Accordingly the invention provides the use of a compound having 5-HT\textsubscript{1A} antagonist activity (or of a pharmaceutically acceptable salt, enantiomer, diastereomer, N-oxide, crystalline form, hydrate, solvate, active metabolite or prodrug of such a compound) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract in combination with the prior, concurrent or post-administration of a compound having 5-HT\textsubscript{1B} antagonist activity (or of a pharmaceutically acceptable salt, enantiomer, diastereomer, N-oxide, crystalline form, hydrate, solvate, active metabolite or prodrug of such a compound).

In another aspect, the invention provides the use of a compound having both 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} antagonist activity (or of a pharmaceutically acceptable salt, enantiomer, diastereomer, N-oxide, crystalline form, hydrate, solvate, active metabolite or prodrug of such a compound) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract.

In jurisdictions in which claims to methods of treatment of human beings and/or other mammals are patentable, the invention extends to the use of the aforesaid medicaments for the treatment of neuromuscular dysfunction of the lower urinary tract.

In a preferred embodiment, the compound having 5-HT\textsubscript{1A} antagonist activity has a structure represented by one of the formulae A to K set out in claim 2.

The compounds of Formula B are disclosed in US 6271234. Preferred compounds of Formula B are those wherein

n is 1 or 2,
Het represents a pyridyl group,
R represents a cycloalkyl or a monocyclic heteroaryl group having 5 or 6 ring atoms of which 1 or 2 are heteroatoms selected from N, O and S,
R^3 represents a hydrogen atom or a lower alkyl group,
Z represents a -CH_2- group,
B represents (a) a monocyclic heteroaryl group having 5 or 6 ring atoms of which 1 or 2 are heteroatoms selected from N, O and S or (b) a substituted phenyl group of the formula

wherein R^1 represents a halogen atom or an alkoxy, nitro, amino, acetylamino, pivaloylamino, butanoylamino, phenylacetylamino, formylamino, alkylamino or alkylsulphonylamino group, and R^2 represents a halogen atom or an alkoxy, polyfluoroalkoxy, cyano or aminocarbonyl group.

The compounds of Formula C are disclosed in US 6514976.

The compounds of Formula D are disclosed in US Application 10/463196. As referred to in the definition of R_6, aryl, heteroaryl, arlyloxy, heteroaryloxy, arylalkoxy and heteroarylalkoxy group may be optionally substituted with one or more substituents selected from the group consisting of (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylthio, hydroxy, halo, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_1-C_6)-haloalkyl, (C_1-C_6)-haloalkoxy, (C_1-C_6)-hydroxyalkyl, alkoxyalkyl, nitro, amino, (C_1-C_6)aminoalkyl, (C_1-C_6)alkylamino(C_1-C_6)-alkyl, (C_1-C_6)-alkylamino, di(C_1-C_6)-alkylamino, acylamino, (C_1-C_6)alkylsulphonylamino, aminosulphonyl, (C_1-C_6)alkylaminosulphonyl, cyano, aminocarbonyl, N-(C_1-C_6)alkylaminocarbonyl, N,N-di-(C_1-C_6)alkylaminocarbonyl, (C_1-C_6)-alkylaminocarbonyl, (C_1-C_6)-alkoxy carbonyl, (C_1-C_6)-alkylcarbonyl, formyl, alkylcarbonylalkyl, alkanoyloxyalkyl, (C_1-C_6)-alkylaminocarbonylamino, (C_1-C_6)-
alkylsulphinyl, (C₁-C₆)-alkylsulphonyl, and N, N-di-(C₁-C₆)-alkylaminosulphonyl
groups.

The compounds of Formula E are disclosed in US Application 10/463222.
The compounds of Formula F are disclosed in US Application 10/463221.
The compounds of Formula G are disclosed in US 2003/0181446 and US 2003/0162777. The term “substituted” for Formula G without further description refers to the instance where one or more hydrogen atoms on a radical are replaced independently with one or more atoms or groups selected from halogen, hydroxyl, oxo, nitro, cyano, alkyl, haloalkyl, polyhaloalkyl, alkylthio, alkoxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, alkoxy, alkenyloxyl, alkynyloxyl, cycloalkoxy, aryloxyl, substituted aryloxyl, cycloalkenyloxyl, cycloalkynylloxyl, arylalkoxy, acyloxyl, alkylaminocarbonoxyl, sulphonyloxyl, polyhaloalkylsulphonyloxyl, acyl, ureido, amino, alkylnitro, dialkylamine, acrylamino, diacrylamino, N-alkyl-N-aroxyamine, N-arylcycl-N- alkylsulphonylamino, alkylsulphonylamino, alkenyloxylamino, dialkenylamino, aminino, diarylamino, alkoxyxcarbonamino, alkoxyxcarbonyl, acyloxylamino, acylalkylamino, sulphonylalkylamino, cyanoamino, arylsulfoxyl, alkylarylssulphonyl, sulphamoyl, substituted sulphamoyl, aryl, substituted aryl, arylalkylamino, substituted arylalkylamino, heterocycle, substituted heterocycle, analkyl, aryloxyalkyl,

heterocycloxyalkyl, heterocyclicalkyl, wherein the terms substituted heterocycle, substituted aryl, substituted aryloxyl and substituted arylalkylamino refer respectively to a heterocyclic, aryl, aryloxyl or arylalkylamino group wherein one or more of the hydrogen atoms on a ring of the heterocyclic, aryl, aryloxyl or arylalkylamino group is replaced by one or more of the substituents recited herein, with the proviso that if variable A or B is substituted with a first substituted heterocycle, substituted aryl, substituted aryloxyl or substituted arylalkylamino and said first substituted heterocycle, substituted aryl, substituted aryloxyl or substituted arylalkylamino is substituted with a second substituted heterocycle, substituted aryl, substituted aryloxyl and substituted arylalkylamino, said second substituted heterocycle, substituted aryl,

substituted aryloxyl and substituted arylalkylamino may not be substituted with a third substituted heterocycle, substituted aryl, substituted aryloxyl and substituted arylalkylamino,

The compounds of Formula H are disclosed in US Application 09/127059. A preferred compound of formula H is 1-[3-hydroxy-3-bis-(2-pyridyl)-propyl]-4-(4-
indolyl)-piperazine.

The compounds of Formula I are disclosed in WO 94/21610.

The compounds of Formula J are disclosed in US 6127357.

The compounds of Formula K are disclosed in US 5462942. A preferred
compound of formula K is 2-{4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-
piperazin-1-yl]-butyl}1-2-benzisothiazol-3(2H)-one 1,1-dioxide.

In preferred embodiments, a compound having 5-HT$_{1B}$ antagonist activity has
a structure represented by formulae L to S as defined in claim 4.

The compounds of Formula L are disclosed in GB 2276163. A preferred
compound of formula L is 3-[3-(dimethylamino)-propyl]-4-hydroxy-N-[4-(4-
pyridinyl)-phenyl]-benzamide.

The compounds of Formula M are disclosed in US 5968954. Additional
compounds of formula M are disclosed in WO 02/074764.

The compounds of Formula N are disclosed in WO 97/17350.

The compounds of Formula O are disclosed in WO 97/17351.

The compounds of Formula P are disclosed in WO 01/23374.

The compounds of Formula Q are disclosed in WO 02/074768.

The compounds of Formula R are disclosed in US 5801170. A preferred
compound of formula R is N-[3-[2-(dimethylamino)-ethoxy]-4-methoxyphenyl-
2-methyl-4p-(5-methyl-1,2,4-oxadiazol-3-yl)]-[1,1p-biphenyl]-4-carboxamide.

The compounds of Formula S are disclosed in US 5972951. A preferred
compound of formula S is 1p-methyl-5-[2p-methyl-4p-(5-methyl-1,2,4-oxadiazol-3-
yl)biphenyl-4-yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-]indole-3,4p-piperidine.

In preferred embodiments, a compound having both 5-HT$_{1A}$ and 5-HT$_{1B}$
antagonist activities has a structure represented by formulae T, U, V or W as defined
in claim 7.

The compounds of Formula T are disclosed in WO 98/14433 and US
6472388. A preferred compound of formula T is (Z)-4-(3,4-dichlorophenyl)-2-[2-(4-
methylpiperazin-1-yl)benzylidene]thiomorpholin-3-one (elzasonan).

The compounds of Formula U are disclosed in US 6222034.

The compounds of Formula V are disclosed in US 6355647.

The compounds of Formula W are disclosed in US 6414157.
The following definitions and preferences apply throughout the formulae A to W, unless otherwise specified. Alkyl groups preferably have from 1 to 6, and more preferably from 1 to 4, carbon atoms. Lower alkyl groups have from 1 to 6, and preferably from 1 to 4, carbon atoms. The most preferred alkyl and lower alkyl groups are methyl and ethyl. Preferred polyfluoroalkyl groups are trifluoromethyl and 2,2,2-trifluoroethyl, with preferred polyfluoroalkoxy groups being trifluoromethoxy and 2,2,2-trifluoroethoxy. Alkenyl and alkynyl groups preferably have from 2 to 6, and more preferably from 2 to 4, carbon atoms. Cycloalkyl, cycloalkenyl and cycloalkynyl groups preferably have from 3 to 10, and more preferably from 5 to 8, carbon atoms in the ring. The most preferred cycloalkyl group is cyclohexyl. Monocyclic aryl groups preferably have from 5 to 7 carbon atoms, and bicyclic aryl groups preferably have from 9 to 12 carbon atoms. The most preferred monocyclic aryl group is phenyl and the most preferred bicyclic aryl group is naphthyl. Monocyclic heteroaryl or heterocyclic groups preferably have from 5 to 7 ring atoms of which up to 3 are heteroatoms selected from O, N and S. Bicyclic heteroaryl or heterocyclic groups preferably have from 9 to 12 ring atoms of which up to 3 are heteroatoms selected from O, N and S. Where the number of rings is unspecified, aryl, heteroaryl and heterocyclic groups preferably have from 5 to 12 ring atoms. In the case of heteroaryl and heterocyclic groups, up to three of these ring atoms may be selected from O, N and S. The foregoing definitions and preferences apply equally when any of the terms is used as part of a more complex group, such as (but non-exhaustively) alkylamino, alkylcarbonyl, alkylsulphonyl, alkoxy, alkanoyl, aralkyl, aralkoxy, aryloxy, heteroaryloxy, heteroarylcarbonyl, haloalkyl, hydroxyalkyl and haloalkoxy. The preferred acyl groups are formyl, alkylcarbonyl groups and arylcarbonyl groups, with the most preferred acyl groups being formyl, acetyl and benzoyl groups.

The medicament prepared according to the invention may be intended for reducing the frequency of bladder contractions due to bladder distention, for increasing urinary bladder capacity or for ameliorating at least one condition among urinary urgency, overactive bladder, increased urinary frequency, decreased urinary compliance (decreased bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder.

For treating the above disorders, the compounds of the invention may be administered in combination with known antimuscarinic drugs such as oxybutynin,
tolterodine, darifenacin and tamsulosin. Analogously, the compounds of the invention may be associated to \( \alpha_1 \)-adrenergic antagonists such as prazosin, doxazosin, terazosin, alfuzosin and tamsulosin, for the therapy of lower urinary tract symptoms, whether or not these are associated with BPH.

Treatment may be effected by delivering to the environment of 5-HT\(_{1A} \) and 5-HT\(_{1B} \) serotonergic receptor, for example to the extracellular medium, (or by systemically or locally administering to a mammal possessing such receptor) an amount of a compound of the invention effective to increase the duration of bladder quiescence with no contractions. The present invention refers to a method of administering a compound of the above formula with the previously-disclosed substituent patterns and combinations of such substituents.

Combination therapy with 5-HT\(_{1A} \) and 5-HT\(_{1B} \) antagonists may further include an \( \alpha_1 \)-adrenergic antagonist, for the therapy of lower urinary tract symptoms, whether or not these are associated with BPH. Preferred \( \alpha_1 \)-adrenergic antagonists suitable for administration in combination with a selective 5-HT\(_{1A} \) and/or 5-HT\(_{1B} \) antagonist are, prazosin, doxazosin, terazosin, alfuzosin, and tamsulosin. Additional \( \alpha_1 \)-adrenergic antagonists suitable for administration in combination with 5-HT\(_{1A} \) and 5-HT\(_{1B} \) antagonists are described in US 5990114, US 6306861, US 6365591, US 6387909 and US 6403594.

Examples of 5-HT\(_{1A} \) antagonists are found in Leonardi et al., *J. Pharmacol. Exp. Ther.* 299: 1027-1037, 2001(e.g., Rec 15/3079), U.S. Patents No.6,071,920, 6,399,614, 6,271,234, 5,990,114, incorporated herein by reference in their entirety. Other phenylpiperazine derivatives are described in WO 99/06383 and pending U.S. Patent Applications Serial No. 10/266,088 and 10/266,104 filed on October 7, 2002.

Additional 5-HT\(_{1A} \) antagonists include 2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yI)piperazin-1-yl]butyl]-1,2-benzisothiazol-3-(2H)-one-1,1\( \_ \)dioxide and related compounds described in U.S. Patent No. 5,462,942 and robalzotan and related compounds described in WO 95/11891, incorporated herein by reference in their entireties.

Compounds having 5-HT\(_{1A} \) antagonist activity and \( \alpha_1 \) adrenergic receptor activity are described in U.S. Patents Nos. 5,605,896, 5,474,994, and 5,403,842, 5,462,942, 6,127,357, incorporated herein by reference in their entireties. Preferred 5-HT\(_{1A} \) compounds of the invention are N-[2-[4-(2-methoxyphenyl)piperazin-1-
yl]-N-(2-pyridyl)cyclohexanecarboxamide, 2-[4-[4-(7-chloro-2,3-dihydro-1,4-
benzodioxin-5-yl)piperazin-1-yl]butyl]-1,2-benzisothiazol-3-(2H)-one-1,1,1-
N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-
methoxyphenyl)piperazine, 1-[3-hydroxy-3,3 bis-(2-pyridyl)propyl]-4-(4-
indolyl)piperazine.

Preferred 5-HT_{1B} compounds of the invention are N-[3-[3-
(dimethylamino)ethoxy]-4-methoxyphenyl-2′p-methyl-4′p-(5-methyl-1,2,4-
oxadiazol-3-yl)-[1,1p-biphenyl]-4-carboxamide, 1p-methyl-5-[(2p-methyl-4p-(5-
methyl-1,2,4-oxadiazol-3-yl)piphenyl-4-yl]carbonyl]-2,3,6,7-
tetrahydrospiro[ furan2,3.-f]indole,3,4p-piperidine, 3-[3-dimethylamino)propyl]-4-
hydroxy-N-[4-(4-pyridinyl)phenyl benzamide. A preferred compound having both 5-
HT_{1A} and 5-HT_{1B} activity is (Z)-4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-
yl)benzyllidene]thiomorpholin-3-one.

Pharmacological blocking of the 5-HT_{1A} and/or 5-HT_{1B} receptor leads to
positive effects in the management of neuromuscular dysfunction of the lower urinary
tract. An antagonist of the 5-HT_{1A} and/or 5-HT_{1B} receptor is a substance which
diminishes or abolishes the effect of a ligand (agonist) which typically activates the 5-
HT_{1A} and/or 5-HT_{1B} receptor. The antagonist may be, for example, a chemical
antagonist, a pharmacokinetic antagonist, an antagonist by receptor block, a non-
competitive antagonist or a physiological antagonist.

A chemical antagonist is a substance wherein the antagonist binds the ligand
in solution so the effect of the ligand is lost. A pharmacokinetic antagonist is one
which effectively reduces the concentration of the active ligand at its site of action,
for example, by increasing the rate of metabolic degradation of the active ligand.

Antagonism by receptor-block involves two important mechanisms: reversible
competitive antagonism and irreversible, or non-equilibrium competitive antagonism.
Reversible competitive antagonism occurs when the rate of dissociation of the
antagonist molecules is sufficiently high such that, on addition of the ligand,
displacement of chemical antagonist molecules from the receptors effectively occurs.

Of course the ligand cannot evict a bound antagonist molecule, or vice versa.
Irreversible or non-equilibrium competitive antagonism occurs when the antagonist
dissociates very slowly, or not at all, from the receptor with the result that no change
in the antagonist occupancy takes place when the ligand is applied. Thus, the
antagonism is insurmountable. Non-competitive antagonism describes the situation where the antagonist blocks at some point in the signal transduction pathway leading to the production of a response by the ligand.

Physiological antagonism is a term used loosely to describe the interaction of two substances whose opposing actions in the body tend to cancel each other out. An antagonist can also be a substance which diminishes or abolishes expression of functional 5-HT$_{1A}$ and/or 5-HT$_{1B}$ receptor. Thus an antagonist can be, for example, a substance which diminishes or abolishes expression of the gene encoding either the 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor, diminishes or abolishes translation of either the 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor RNA, diminishes or abolishes post-translational modification of either the 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor protein or diminishes or abolishes the insertion of either the 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor into the cell membrane.

An inverse agonist of either the 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor is a substance which preferentially binds to the inactive state of the receptor (in contrast to the agonists that bind preferentially to the active state of the receptor), and therefore avoids the stimulation of the receptor by the agonist.

In general, the in vivo activity of inverse agonists is similar to that of antagonists and for the sake of clarity inverse agonists will be defined as antagonists in the present application.

5-HT$_{1A}$ or 5-HT$_{1B}$ antagonists have the following properties.

(1) **Significant 5-HT$_{1A}$ or 5-HT$_{1B}$ antagonist activity.** Useful compounds preferably exhibit antagonist potency (measured as IC$_{50}$ or Ki) between 1000 and 0.1 nM. Without limiting the present disclosure, as described in more detail below, potency may be measured by determining the antagonist activity of compounds in vivo or in vitro, including cell extracts or fractions of extracts. Inhibitory potency may also be determined using, as non-limiting examples, native or recombinant 5-HT$_{1A}$ or 5-HT$_{1B}$ receptors, that are expressed constitutively or that have been induced, and that have expressed in native or non-native species and/or cell types (Barnes NM and Sharp T. Neuropharmacology 38: 1083-1152, 1999).

Preferably, the compounds of the method of the present invention have a selectivity toward one or both of 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors that is at least ten-fold compared to other 5-HT receptor subtypes, e.g., 5-HT$_{2}$, 5-HT$_{3}$, 5-HT$_{4}$.

The commonly used in vitro assays for assessing antagonist activity for 5-HT$_{1A}$ or 5-HT$_{1B}$ receptors are found in Pauwels PJ et al., Neuropharmacology 36:
499-512, 1997. In preferred embodiment, measurement of antagonist activity at either a 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor is performed using one or more of the assays described in the examples set forth below. Using one or more of said assays, the antagonist activity at either a 5-HT$_{1A}$ or 5-HT$_{1B}$ receptor of a test compound can be measured, and the concentration inhibiting binding by 50% (IC$_{50}$) can be calculated using regression analysis, or equivalent computational methods that are well-known in the art (Tallarida et al., Manual of Pharmacologic Calculations. Springer-Verlag, pp. 10-12, 1981.).

Once a compound is identified as a 5-HT$_{1A}$ or 5-HT$_{1B}$ antagonist, its pharmacological activity can be confirmed using one or more animal model systems for neuromuscular dysfunction of the lower urinary tract.

A useful animal model system for measuring such pharmacological activity is, without limitation, volume-induced rhythmic bladder voiding contractions in anesthetized rats. In this method, the urinary bladder is catheterized through the external urethra with a polyethylene tubing filled with physiological saline. The external urethra is then ligated and connected to a pressure recording device. The bladder is then filled with saline until reflex voiding contractions occur, after which the frequency of the voiding contractions is measured for 15 min. Test compounds are then administered intravenously and their effect evaluated for the following 60 min. This method is described in more detail in Example 3 below. This model has been validated by the use of different reference standards (Guarneri et al., Pharmacol. Res. 27:173-187, 1993).

Other animal models useful to assess activity of the selective 5-HT$_{1A}$ or 5-HT$_{1B}$ antagonists on the lower urinary tract are based on cystometric recording of bladder activity in conscious rats instrumented in order to measure bladder pressure during constant infusion of the bladder with saline or very diluted acetic acid. Velasco C. et al., J. Urol. 166: 1962-1968, 2001. These methods are widely used and accepted by researchers skilled in this field and foresee a period of infusion of about five hours after administration of test compounds with continuous monitoring of bladder performance and assessment of intervals between micturitions and peak micturition pressure.

A metabolite of a compound disclosed herein is a derivative of a compound which is formed when the compound is metabolised. The term “active metabolite” refers to a biologically active derivative of a compound which is formed when the
compound is metabolised.

The term “metabolised” refers to the sum of the processes by which a particular substance is changed in the living body. In brief, all compounds present in the body are manipulated by enzymes within the body in order to derive energy and/or to remove them from the body. Specific enzymes produce specific structural alterations to the compound. For example, cytochrome P450 catalyses a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyse the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphhydryl groups. Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996), pages 11-17.

Metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells *in vitro* and analysis of the resulting compounds. Both methods are well known in the art.

A “prodrug” of a compound disclosed herein is an inactive substance that converts into an active form of the disclosed compounds *in vivo* when administered to a mammal.

Medicaments prepared according to the invention may include optional additives, such as a pharmaceutically acceptable carrier or diluent, a flavouring, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrator, an excipient, a diluent, a lubricant, an absorption enhancer, a bactericide and the like, a stabiliser, a plasticizer, an edible oil, or any combination of two or more of said additives.

Suitable pharmaceutically acceptable carriers or diluents include ethanol, water, glycerol, aloe vera gel, allantoin, glycerine, vitamin-A and E oils, mineral oil, phosphate buffered saline, PPG2 myristyl propionate, magnesium carbonate, potassium phosphate, vegetable oil, animal oil and solketal.

Suitable binders include starch, gelatine, natural sugars such as glucose, sucrose and lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, vegetable gum, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like.

Suitable disintegrators include starch such as corn starch, methyl cellulose, agar, bentonite, xanthan gum and the like.
Suitable lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

A suitable suspending agents is bentonite.

Suitable dispersing and suspending agents include synthetic and natural gums such as vegetable gum, tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone and gelatine.

Suitable edible oils include cottonseed oil, sesame oil, coconut oil and peanut oil.

Examples of additional additives include sorbitol, talc, stearic acid and dicalcium phosphate.

Medicaments prepared according to the invention may be formulated as unit dosage forms, such as tablets, pills, capsules, boluses, powders, granules, sterile parenteral solutions, sterile parenteral suspensions, sterile parenteral emulsions, elixirs, tinctures, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories. The unit dosage forms may be used for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation, transdermal patches, and a lyophilized composition. In general, any delivery of active ingredients that results in systemic availability of such ingredients can be used. Preferably the unit dosage form is an oral dosage form, most preferably a solid oral dosage; therefore the preferred dosage forms are tablets, pills and capsules. However, parenteral preparations are preferred too.

Solid unit dosage forms may be prepared by mixing the active agents of the present invention with a pharmaceutically acceptable carrier and any other desired additives as described above. The mixture is typically mixed until a homogeneous mixture of the active agents of the present invention is obtained and the carrier and any other desired additives are formed, i.e., the active agents are dispersed evenly throughout the composition. In this case, the composition can be formed as dry or moist granules.

Tablets or pills can be coated or otherwise prepared so as to form a unit dosage form that has delayed and/or sustained action, such as controlled release and delayed release unit dosage forms. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of a layer or envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component
to pass intact into the duodenum or to be delayed in release.

Biodegradable polymers for controlling the release of the active agents include, but are not limited to, polylactic acid, polyeptilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polycetals, polydihydropyranos, polycyanoacrylates and crosslinked or amphiphatic block copolymers of hydrogels.

For liquid dosage forms, the active substances or their physiologically acceptable salts are dissolved, suspended or emulsified, optionally with the usually employed substances such as solubilizers, emulsifiers or other auxiliaries. Solvents for the active combinations and the corresponding physiologically acceptable salts can include water, physiological salt solutions or alcohols, e.g., ethanol, propanediol or glycerol. Additionally, sugar solutions such as glucose or mannitol solutions may be used. A mixture of the various solvents mentioned may be used in the present invention too.

A transdermal dosage form is contemplated by the present invention too. Transdermal forms may be a diffusion transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system. Other transdermal dosage forms include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and iontophoretic (electrical diffusion) delivery systems. Transdermal dosage forms may be used for delayed release and sustained release of the active agents of the present invention.

The medicaments and unit dosage forms of the present invention for parenteral administration, and in particular by injection, typically include a pharmaceutically acceptable carrier, as described above. A preferred liquid carrier is vegetable oil. Injection may be, for example, intravenous, epidural, intrathecal, intramuscular, intraluminal, intratracheal or subcutaneous.

The active agents can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The active agents of the present invention may also be coupled with soluble polymers such as targetable drug carriers. Such polymers include, but are not limited to, polyvinylpyrrolidone, pyran copolymers, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol, and polyethylenoxypolylysine substituted with palmitoyl residues.
Medicaments prepared according to the invention may include or their unit dosage forms may be administered by a variety of routes, such as the oral and enteral, intravenous, intramuscular subcutaneous, transdermal, transmucosal (including rectal and buccal) and by inhalation routes. Preferably, the oral or transdermal route is used (i.e., with solid or liquid formulations or skin patches, respectively).

The pharmaceutical composition or unit dosage forms comprising an effective amount of the present invention may be administered to an animal, preferably a human, in need of treatment of neuromuscular dysfunction of the lower urinary tract described by E. J. McGuire in “Campbell’s UROLOGY”, 5th Ed. 616-638, 1986, W.B. Saunders Company, and patients affected by any physiological dysfunction related to impairment of 5-HT_{1A} and 5-HT_{1B} receptor function.

As used herein, the term “effective amount” refers to an amount that results in measurable amelioration of at least one symptom or parameter of a specific disorder. In a preferred embodiment, the compound treats disorders of the urinary tract, such as urinary urgency, overactive bladder, increased urinary frequency, reduced urinary compliance (reduced bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder.

The pharmaceutical composition or unit dosage form of the present invention may be administered according to a dosage and administration regimen defined by routine testing in the light of the guidelines given above in order to obtain optimal activity while minimising toxicity or side effects for a particular patient. However, such fine tuning of the therapeutic regimen is routine in the light of the guidelines given herein.

The dosage of the active agents of the present invention may vary according to a variety of factors such as underlying disease conditions, the individual’s condition, weight, sex and age, and the mode of administration. An effective amount for treating a disorder can easily be determined by empirical methods known to those of ordinary skill in the art, for example by establishing a matrix of dosages and frequencies of administration and comparing a group of experimental units or subjects at each point in the matrix. The exact amount to be administered to a patient will vary depending on the state and severity of the disorder and the physical condition of the patient. A measurable amelioration of any symptom or parameter can be determined by a person skilled in the art or reported by the patient to the physician. It will be understood that
any clinically or statistically significant attenuation or amelioration of any symptom or parameter of urinary tract disorders is within the scope of the invention. Clinically significant attenuation or amelioration means perceptible to the patient and/or to the physician.

For example, a single patient may suffer from several symptoms of dysuria simultaneously, such as, for example, urgency and excessive frequency of urination or both, and these may be reduced using the methods of the present invention. In the case of incontinence, any reduction in the frequency or volume of unwanted passage of urine is considered a beneficial effect of the present method of treatment.

The amount of the agent to be administered can typically range between about 0.01 and about 25 mg/kg/day, preferably between about 0.1 and about 10 mg/kg/day and most preferably between 0.2 and about 5 mg/kg/day. It will be understood that the pharmaceutical formulations of the present invention need not necessarily contain the entire amount of the agent that is effective in treating the disorder, as such effective amounts can be reached by administration of a plurality of doses of such pharmaceutical formulations.

In a preferred embodiment of the present invention, the compounds are formulated in capsules or tablets, preferably containing 50 to 200 mg of the compounds of the invention, and are preferably administered to a patient at a total daily dose of 50 to 400 mg, preferably 150 to 250 mg and most preferably about 200 mg, for relief of urinary incontinence and dysfunctions under treatment with 5-HT\textsubscript{1A} and/or 5-HT\textsubscript{1B} receptor ligand.

A pharmaceutical composition for parenteral administration contains from about 0.01% to about 100% by weight of the active agents of the present invention, based upon 100% weight of total pharmaceutical composition.

Generally, transdermal dosage forms contain from about 0.01% to about 100% by weight of the active agents versus 100% total weight of the dosage form.

The pharmaceutical composition or unit dosage form may be administered in a single daily dose, or the total daily dosage may be administered in divided doses. In addition, co-administration or sequential administration of another compound for the treatment of the disorder may be desirable. For example, the combinations of the invention may be administered in combination with known antimuscarinic drugs such as oxybutynin, tolterodine, darifenacin and temiverine. Analogously, the
combinations of the invention may be associated to α₁-adrenergic antagonists, such as prazosin, doxazosin, terazosin, alfuzosin and tamsulosin for the therapy of the lower urinary tract symptoms.

For combination treatment where the compounds are in separate dosage formulations, the compounds can be administered concurrently, or each can be administered at separate staggered times. For example, the compound of the invention may be administered in the morning and the antimuscarinic compound may be administered in the evening, or vice versa. Additional compounds may be administered at specific intervals too. The order of administration will depend upon a variety of factors including age, weight, sex and medical condition of the patient; the severity and etiology of the disorders to be treated, the route of administration, the renal and hepatic function of the patient, the treatment history of the patient, and the responsiveness of the patient. Determination of the order of administration may be fine-tuned and such fine-tuning is routine in the light of the guidelines given herein.

Uses- Methods for Treatment

Without wishing to be bound by theory, it is believed that co-administration of 5-HT₁A and 5-HT₁B receptor antagonists prevents unwanted activity of the sacral reflex and/or cortical mechanisms that control micturition. Thus, it is contemplated that a wide range of neuromuscular dysfunctions of the lower urinary tract can be treated using the compounds of the present invention, including without limitation dysuria, incontinence and enuresis (overactive bladder). Dysuria includes urinary frequency, nocturia, urgency, reduced urinary compliance (reduced bladder storage capacity), difficulty in emptying the bladder, i.e., a suboptimal volume of urine is expelled during micturition. Incontinence syndromes include stress incontinence, urgency; incontinence and enuresis incontinence, as well as mixed forms of incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

Example 1: Radioligand binding to recombinant 5-HT₁A receptors

A. Method

Genomic clone G-21 coding for the human 5-HT₁A-serotonergic receptor was stably transfected in a human cell line (HeLa). HeLa cells were grown as monolayers
in Dulbecco's modified Eagle medium (DMEM), containing 10% fetal bovine serum, gentamicin (10 mg/ml) and 5% carbon dioxide, at 37°C. The cells were detached from the growth flask at 95% confluence by a cell scraper and were lysed in cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4). The homogenates were centrifuged at 40000 x g x 20 minutes and the pellets were resuspended in a small volume of cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4) and immediately frozen and stored at –70°C until use. On the day of experiment, the cell membranes were resuspended in incubation buffer: 50 mM Tris HCl (pH 7.4), 2.5 mM MgCl₂, 10 mM pargyline (Fargin et al., *Nature* 335, 358, 1988). The membranes were incubated in a final volume of 1 ml for 30 minutes at 30°C with 1 nM [³H]8-OH-DPAT, in the absence or presence of the test compounds. Non-specific binding was determined in the presence of 10 µM 5-HT. Incubation was stopped by addition of cold Tris-HCl buffer and rapid filtration through a 0.2%-polyethyleneimine-pretreated Whatman-GF/B or Schleicher-&-Schuell-GF52 filter.

**B. Results**

The affinity of the tested compounds was evaluated as inhibition of specific binding of the radioligand to 5-HT₁A receptors (IC₅₀) by using the non-linear curve-fitting program Allfit (De Lean et al., *Am. J. Physiol.* 235: E97, 1978). The IC₅₀ value was converted to an affinity constant (Ki) by the equation of Cheng & Prusoff (*Biochem. Pharmacol.* 22: 3099, 1973). The results are reported in Table 1.
TABLE 1

Binding affinity at 5-HT_{1A} receptors. Data are expressed as Ki (nM)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Affinity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>carboxamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-cyclohexyl-4-[4-(2-methoxyphenyl)piperazine-1-yl]-3-(2-pyridyl)butan-1-one</td>
<td>0.68</td>
<td>Recordati data on file</td>
</tr>
<tr>
<td>1-cyclohexyl-4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-2-pyridin-2-yl-butan-1-one</td>
<td>0.15</td>
<td>Recordati data on file</td>
</tr>
<tr>
<td>1-[3-hydroxy-3,3 bis-(2-pyridyl)propyl]-4-(4-indolyl)piperazine</td>
<td>4.75</td>
<td>Recordati data on file</td>
</tr>
</tbody>
</table>

Example 2: Radioligand binding to recombinant 5-HT_{1B} receptors

A. Method

C6-gliarial cells stably transfected with a pcDNA3/h5-HT_{1B} plasmid were prepared as monoclonal cell lines cultured (Pauwels et al., Naunyn-Schmied. Arch. Pharmacol. 353: 144, 1996), and used for radioligand binding experiments. On the day of experiments, the cell membrane expressing h5-HT_{1B}-receptors were resuspended in incubation buffer containing 50 mM Tris-HCl pH 7.7, 4 mM CaCl_2, 10 μM pargyline and 0.1% ascorbic acid. Membrane (20-80 μg protein), were incubated in a final volume of 0.5 ml for 30 min at 25°C, with 0.5 nM of [³H]corboxamidotryptamine, in absence or presence of competing drugs. Non-specific binding was determined in the presence of 10 μM serotonin. The incubation was stopped by addition of 3 ml ice-cold 50 mM Tris-HCl buffer pH 7.7 and rapid filtration over Whatman GF/B glass fibre filters using a Brandel harvester, washed and the radioactivity was counted by liquid scintillation spectrometry.

B. Results

The affinity of the tested compounds was evaluated as inhibition of specific binding of the radioligand to 5-HT_{1B} receptors (IC_{50}) and converted to an affinity constant (Ki) as in the Example 1. The results are reported in Table 2.
### TABLE 2
Binding affinity at 5-HT_{1B} receptors. Data are expressed as $K_i$ (nM)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Affinity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-[3-[3-(dimethylamino)ethoxy]-4-methoxyphenyl-2′p-methyl-4p-(5-methyl-1,2,4-oxadiazol-3-yl)]-[1,1p-biphenyl]-4-carboxamide</td>
<td>1</td>
<td>Naunyn. Schmied. Arch. Pharmacol. 356(3): 312, 1997</td>
</tr>
<tr>
<td>1p-methyl-5-[(2p-methyl-4p-(5-methyl-1,2,4-oxadiazol-3-yl) bipheny1-4-yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4p-piperidine</td>
<td>10</td>
<td>Br. J. Pharmacol. 114: 1107, 1995</td>
</tr>
</tbody>
</table>

#### Example 3: Effect on rhythmic bladder-voiding contractions induced by bladder filling in anaesthetised rats

**A. Method**

Female Sprague-Dawley rats weighing 225-275 g (Crl: CDo Br, Charles River Italia) were used. The animals were housed with free access to food and water and maintained on a forced 12-hour alternating light-dark cycle at 22-24°C for at least one week, except during the experiment. The activity on rhythmic bladder voiding contractions was evaluated according to the method of Dray J., Pharmacol. Methods, 13:157, 1985, with some modifications as in Guarneri (Guarneri, Pharmacol. Res. 27:173, 1993). Briefly, the rats were anaesthetised by subcutaneous injection of 1.25 g/kg (5 ml/kg) urethane, after which the urinary bladder was catheterised via the urethra using PE 50 polyethylene tubing filled with physiological saline. The catheter was tied in place with a ligature around the external urethral orifice and was connected to conventional pressure transducers (Statham P23 ID/P23 XL). The intravesicle pressure was displayed continuously on a chart recorder (Battaglia Rangoni KV 135 with DC1/TF amplifier). The bladder was then filled via the recording catheter by incremental volumes of warm (37°C) saline until reflex bladder-voiding contractions occurred (usually 0.8-1.5 ml). For intravenous injection of bioactive compounds, PE 50 polyethylene tubing filled with physiological saline was inserted into the jugular vein. Tested compounds were administered or co-administered in solution in a final volume of 0.5 ml/kg.
From the cystometrogram, the number of contractions recorded 15 minutes before (basal values) and after treatment, as well as the mean amplitude of these contractions (mean height of the peaks in mmHg), was evaluated.

Since most compounds produced an effect that was relatively rapid in onset and led to a complete cessation of bladder contractions, bioactivity was conveniently estimated by measuring the duration of bladder quiescence (i.e., the length of the time in minutes during which no contractions occurred: disappearance time = DT).

The administered doses (alone or in combination) of the tested compounds were chosen on the basis of previously published results obtained with the same compounds in the utilized model (Testa et al., *J. Pharmacol. Exp. Ther.* 290: 1258, 1999; Leonardi et al., *J. Pharmacol. Exp. Ther.* 299: 1027, 2001; Testa et al., *BJU Int.* 87: 256, 2001) or of their affinity for the 5-HT\textsubscript{1A} or 5-HT\textsubscript{1B} receptor.

B. Results

The rapid distension of the urinary bladder in urethane-anaesthetised rats produced a series of rhythmic bladder-voiding contractions whose characteristics have been described (Maggi et al., *Brain Res.* 380:83, 1986; Maggi et al., *J. Pharmacol. Exp. Ther.,* 230: 500, 1984).

The intravenous administration of vehicle did not block the bladder contractions.

The selective 5-HT\textsubscript{1A} antagonists: a) N-[2-[4-(2-methoxyphenyl)-piperazin-1-yl]-ethyl]-N-(2-pyridyl)-cyclohexane carboxamide hydrochloride (WAY 100635) (0.01 mg/kg), b) 1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)piperazine mesylate (Rec 15/3079) (0.03 mg/kg), c) 2-[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]butyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide dihydrochloride (Rec 0/0311) (0.01 mg/kg), and d) 1-[3-hydroxy-3,3 bis-(2-pyridyl)propyl]-4-(4-indolyl)piperazine (Rec 27/0206) (0.1 mg/kg) alone blocked the bladder contractions for 10.39 ± 1.45, 2.26 ± 0.51, 6.96 ± 1.05 and 9.29 ± 0.80 min, respectively.

The co-administration of the above selective 5-HT\textsubscript{1A} antagonists and 3-[3-(dimethylamino)-propyl]-4-hydroxy-N-[4-(4-pyridinyl)-phenyl]-benzamide (GR 55562) induced a block of bladder contractions (D.T. = 17.7 ± 1.83, 12.45 ± 1.9) 3, 14.6 ± 1.85, and 13.31 ± 1.67 min, respectively) significantly higher than that observed after administration of the selective antagonists alone (see Figures 1 to 4).
Similar results were obtained when the selective 5-HT\textsubscript{1B} antagonist 1'-
methyl-5-[(2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]carbonyl]-
2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4'-piperidine hydrochloride (SB 224289)
(1.0 mg/kg) was administered alone (DT = 2.40 ± 0.46 min) or in combination with 2-
[4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]butyl]-1,2-
benzisothiazol-3(2H)-one 1,1-dioxide dihydrochloride (Rec 0/0311) (0.01 mg/kg),
giving a DT of 13.69 ± 2.05 min (p<0.01, see Figure 5), and in combination with 1-
[3-hydroxy-3,3 bis-(2-pyridyl)propyl]-4-(4-indolyl)piperazine (Rec 27/0206) (0.1
mg/kg), giving a DT of 13.23 ± 1.41 min (p<0.05, see Figure 6).

Furthermore, the selective 5-HT\textsubscript{1B} antagonist N-[3-[2-
(dimethylamino)ethoxy]-4-methoxyphenyl-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-
yl)-[1,1'-biphenyl]-4-carboxamide hydrochloride (SB 216641) (0.3 mg/kg) when
administered alone gave a DT of 1.50 ± 0.28 min, and when co-administered with 1-
[3-hydroxy-3,3 bis-(2-pyridyl)propyl]-4-(4-indolyl)piperazine (Rec 27/0206) (0.1
mg/kg) and 1-cyclohexyl-4-[4-(2-methoxy-phenyl)piperazin-1-yl]-2-pyridin-2-yl-
butan-1-one (Rec 0/0277) (0.01 mg/kg) gave DT values of 14.58 ± 1.62 (see Figure
7) and 10.2 ± 1.68 (see Figure 8), respectively, both significantly (p<0.01) higher than
the DT values observed after the administration of the 5-HT\textsubscript{1A} antagonists alone (see
Figures 7 and 8).

Example 4: Effect on cystometric parameters in conscious rats after intravenous
administration

A. Method

Male Sprague-Dawley rats [Crl: CD° (SD) BR] of 300-400 g supplied by
Charles River Italia were used. The animals were housed with free access to food and
water and maintained on a forced 12-hour-light/12-hour-dark cycle at 22-24°C of
temperature, except during the experiment. To quantify urodynamic parameters in
conscious rats, cystometrographic studies were performed according to the procedure

Briefly, the rats were anaesthetized by intraperitoneal administration of 3
ml/kg of Equithensin solution (pentobarbital 30 mg/kg and chloral hydrate 125
mg/kg) and placed in a supine position. An approximately-10-mm-long midline
incision was made in the shaved and cleaned abdominal wall. The urinary bladder was gently freed from adhering tissues, emptied and then cannulated via an incision in the bladder body, using a polyethylene cannula (0.58-mm internal diameter, 0.96-mm external diameter) which was permanently sutured with silk thread. The cannula was exteriorised through a subcutaneous tunnel in the retroscapular area, where it was connected to a plastic adapter in order to avoid the risk of removal by the animal. For drug testing, the rats were utilised one day after implantation.

On the day of the experiment, the rats were placed in modified Bollman cages, i.e., restraining cages that were large enough to permit the rats to adopt a normal crouched posture, but narrow enough to prevent turning around. After a stabilisation period of about 20 minutes, the free tip of the bladder cannula was connected through a T-shaped tube to a pressure transducer (Statham P23XL) and to a peristaltic pump (Gilson minipuls 2) for continuous infusion of a warm (37°C) saline solution into the urinary bladder, at a constant rate of 0.1 ml/minute. The intraluminal-pressure signal during infusion of saline into the bladder was continuously recorded on a polygraph (Rectigraph-8K San-ei with BM614/2 amplifier from Biomedica Mangoni) and, from the cystometrogram, two urodynamic parameters were evaluated: bladder volume capacity (BVC) and micturition pressure (MP). BVC (in ml) is defined as the volume of saline infused into the bladder necessary to induce detrusor contraction followed by micturition. MP (in mmHg) is defined as the maximal intravesical pressure caused by contraction during micturition. Basal BVC and MP values were evaluated as mean of the values observed in the cystometrograms recorded in an initial period of 30-60 minutes. At this point in the assay the test compounds were administered intravenously under continuous infusion of the bladder, and changes in BVC and MP were evaluated from the cystometrograms observed during 1, 2, 3, 4 and 5 hours after treatment. The compounds were administered in a volume of 2 ml/kg and groups of control animals received the same amount of vehicle.

**Statistical analysis**

Data were expressed as mean ± standard error. To compare the effects of the different treatments, for each rat the theoretical and practical AUC were evaluated. The theoretical AUC was the area under the curve having as abscissa the observation times and as ordinate the basal value of the considered parameter. The practical AUC
was the area under the curve having as abscissa the observation times and as ordinate
the observed value (at each time) of the considered parameter. For each animal, the Δ
value “practical AUC - theoretical AUC” was evaluated. The difference between
vehicle and active-treatments effect was evaluated by ONE WAY ANOVA followed
by Tukey’s test for multiple comparisons.

B. Results

The effects of the administered doses of the tested 5-HT\textsubscript{1A} antagonist N-[2-[4-
(2-methoxyphenyl)-piperazin-1-yl]-ethyl]-N-(2-pyridyl)-cyclohexane carboxamide
hydrochloride (WAY 100635) and the tested 5-HT\textsubscript{1B} antagonist 3-[3-(dimethylamino)-propyl]-4-hydroxy-N-[4-(4-pyridinyl)-phenyl]-benzamide (GR
55562) on the Δ values of BVC are shown in Fig. 9. The combination of the two
antagonists induced an increase of BVC that was significantly (p<0.05) different from
that induced by all the other treatments. Administration of the single antagonists
alone induced changes of BVC that were not significantly different from those
observed in the control group (animals treated with the vehicle). The changes induced
by all the treatment on MP were not significant and practically the same observed in
the control group.
CLAIMS

1. Use of a compound having 5-HT$_{1A}$ antagonist activity (or of a pharmaceutically acceptable salt, enantiomer, diastereomer, N-oxide, crystalline form, hydrate, solvate, active metabolite or prodrug of such a compound) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract in combination with the prior, concurrent or post-administration of a compound having 5-HT$_{1B}$ antagonist activity (or of a pharmaceutically acceptable salt, enantiomer, diastereomer, N-oxide, crystalline form, hydrate, solvate, active metabolite or prodrug of such a compound).

2. Use according to claim 1 in which the compound having 5-HT$_{1A}$ antagonist activity is a compound of one of the following formulae A to K:

![Formula A](image)

wherein
R represents a hydrogen atom, an alkylcarbonyl group, an unsubstituted cycloalkylcarbonyl group or a cycloalkylcarbonyl group substituted with one or more lower alkyl or acyl group(s), or a monocyclic heteroarylcarbonyl group,
R$^1$ represents a hydrogen atom or a lower alkyl group,
R$^2$ represents a halogen atom or an alkoxy, phenoxy, nitro, cyano, acyl, amino, acylamino, alkylsulphonylamino, alkoxy carbonyl, aminocarbonyl, N-alkylaminocarbonyl, N,N-dialkylaminocarbonyl, N-acylaminocarbonyl, trifluoromethyl or polyfluoroalkoxy group,
B represents (a) a mono- or bicyclic aryl group, each optionally substituted with one or more lower alkyl, lower alkoxy, polyhaloalkoxy, halogen, hydroxyl, nitro, cyano, amido, amino, alkylamino, acylamino, alkylsulphonylamino, lower
acyloxy, lower N-alkylaminocarbonyloxy, N, N-dialkylaminocarbonyloxy or acyl groups, (b) a mono- or bicyclic heteroaryl group, each optionally substituted with one or more alkyl, alkoxy, halogen, nitro, cyano, amido, amino, alkylamino, acylamino, alkylsulphonylamino or acyl groups or (c) a benzyl group optionally substituted with one or more alkyl, alkoxy, halogen, nitro, cyano, amido, amino, alkylamino, acylamino, alkylsulphonylamino or acyl groups,
and n is 1 or 2

\[ \text{Formula B} \]

wherein

n is 1 or 2,

Het represents a monocyclic heteroaryl group,
R represents a cycloalkyl or a monocyclic heteroaryl group,
R\(^3\) represents a hydrogen atom or a lower alkyl group,
Z represents a bond, or a \(-\text{CH}_2\), \(-\text{CH}_2\text{CH}_2\), \(-\text{CH}_2\text{C(O)}\), \(-\text{CH}_2\text{CH(OH)}\), \(-\text{O}\), \(-\text{OCH}_2\) or \(-\text{C(O)}\) group, each of which is depicted with its left end being the end which attaches to the piperazine ring and its right end being the end which attaches to group B,
B represents (a) a mono- or bicyclic heteroaryl group having from 5 to 12 ring atoms of which one or more are heteroatoms selected from nitrogen, oxygen, and sulphur, (b) an unsubstituted aryl group or (c) a substituted phenyl group of the formula

\[ \text{wherein } R^1 \text{ represents a hydrogen or halogen atom or an alkoxy, nitro, amino, acylamino, alkylamino, dialkylamino or alkylsulphonylamino group, and } R^2 \text{ represents a halogen atom or an alkoxy, polyfluoroalkoxy, cyano or } \]

-28-
aminocarbonyl group

\[ \text{Formula C} \]

\[ \text{wherein} \]
\[ \text{Ar}^1 \text{ represents a mono- or bicyclic aryl or heteroaryl group, each of which is} \]
\[ \text{unsubstituted or is substituted with from one to three substituents selected from} \]
\[ \text{halogen atoms and (C}_{1-6}\text{-alkyl), (C}_{1-6}\text{-alkoxy}, (C}_{1-6}\text{-alkythio}, (C}_{2-6}\text{-alkenyl, (C}_{2-6}\text{-alkynyl, (C}\text{)}_{1-6}\text{-alkylhalo, (C}_{3-8}\text{-cycloalkyl, (C}_{3-8}\text{-cycloalkenyl groups;}} \]
\[ \text{R}^1 \text{ represents a hydrogen atom or a (C}_{1-6}\text{-alkyl, (C}_{1-6}\text{-alkoxy or (C}\text{)}_{1-6}\text{-alkythio group;}} \]
\[ \text{R}^2 \text{ represents a phenyl, naphthyl or (C}_{3-12}\text{-cycloalkyl group, each of which is} \]
\[ \text{unsubstituted or is substituted with one or two substituents selected from} \]
\[ \text{halogen atoms and (C}_{1-6}\text{-alkyl, (C}_{1-6}\text{-alkoxy, (C}_{1-6}\text{-alkythio, (C}_{2-6}\text{-alkenyl, (C}_{2-6}\text{-alkynyl, (C}_{1-6}\text{-alkylhalo, (C}_{3-8}\text{-cycloalkyl, (C}_{3-8}\text{-cycloalkenyl groups;}} \]
\[ \text{R}^3 \text{ represents a hydrogen or halogen atom or a (C}_{1-6}\text{-alkyl, (C}_{1-6}\text{-alkoxy, (C}_{1-6}\text{-alkythio, (C}_{2-6}\text{-alkenyl, (C}_{2-6}\text{-alkynyl, (C}_{1-6}\text{-alkylhalo, (C}_{3-8}\text{-cycloalkyl or (C}_{3-8}\text{-cycloalkenyl group, and}\] \]
\[ \text{X denotes a -C(O)-, -CHOH- or -CH}_2\text{- group} \]
wherein
R represents a hydrogen atom or one or more substituents selected from halogen atoms and \( (C_1-C_6)\)-alkyl, \( (C_1-C_6)\)-alkoxy, \( (C_1-C_6)\)-alkythio, hydroxy, halo, \( (C_2-C_6)\)-alkenyl, \( (C_2-C_6)\)-alkynyl, \( (C_1-C_6)\)-haloalkyl, \( (C_1-C_6)\)-haloalkoxy, \( (C_1-C_6)\)-hydroxyalkyl, alkoxyalkyl, nitro, amino, \( (C_1-C_6)\)-aminoalkyl, \( (C_1-C_6)\)-alkylamino-(\(C_1-C_6\))-alkyl, \( (C_1-C_6)\)-alkylamino, di-(\(C_1-C_6\))-alkylamino, acylamino, \( (C_1-C_6)\)-alkylsulphonylamino, aminosulphonyl, \( (C_1-C_6)\)-alkylaminosulphonyl, cyano, aminocarbonyl, N-(\(C_1-C_6\))-alkylaminocarbonyl, N, N-di-(\(C_1-C_6\))-alkylaminocarbonyl, \( (C_1-C_6)\)-alkoxycarbonyl, \( (C_1-C_6)\)-alkylcarbonyl, alkylcarbonylalkyl, formyl, alkanoyloxyalkyl, \( (C_1-C_6)\)-alkylaminocarboxylamino, \( (C_1-C_6)\)-alkylsulphinyl, \( (C_1-C_6)\)-alkylsulphonyl, and N, N-di-(\(C_1-C_6\))-alkylaminosulphonyl groups;
R_1 represents a hydrogen atom or a cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heterocyclic, heterocycloxy, heterocycloalkyl or heterocycloalkoxy group, each of which is optionally substituted with one or more substituent R defined as above;
Q represents a \(-C(O)\), \(-CH(OH)\) or \(-CH(OR_2)\) group wherein R_2 represents (a) a \((C_1-C_6)\)-alkyl, \((C_2-C_6)\)-alkenyl, \((C_2-C_6)\)-alkynyl or cycloalkyl group, each of which is optionally substituted with one or more groups R_5 and R_6, R_5 representing a halogen atom or a \((C_1-C_6)\)-alkoxy, \((C_1-C_6)\)-haloalkoxy, cyano, \((C_1-C_6)\)-alkoxycarbonyl, \((C_1-C_6)\)-alkylcarbonyl, alkoxyalkyl, aminocarbonyl, N-(\(C_1-C_6\))-alkylaminocarbonyl or N,N-di-(\(C_1-C_6\))-alkylaminocarbonyl group and R_6 representing an aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy or heteroarylalkoxy group, each optionally substituted with a group R as defined above, or (b) a \(-C(O)-(C_1-C_6)\)-alkyl, \(-C(O)O-(C_1-C_6)\)-alkyl, \(-C(O)NR_7R_8\) or \(-C(S)NR_7R_8\) group wherein each of R_7 and R_8 independently represents a
hydrogen atom or a (C₁-C₆)-alkyl group;
R₃ represents a hydrogen atom or a (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, cycloalkyl, aryl or heterocycle group, each of which is optionally substituted with one or more substituent R or R₁ defined as above;
R₄ represents an aryl or heterocyclic group, each of which is optionally substituted with one or more substituent R defined as above;
A represents a bond or a group (CH₂)ₙ; and
n = 1 or 2

Formula E

wherein:
R¹ represents a halogen atom,
R³ represents a (C₃-C₆)-cycloalkyl group,
R⁴ represents a (C₁-C₄)-alkoxy or (C₁-C₄)-haloalkoxy group, and
each of m and n independently has the value 1 or 2

Formula F

wherein
R represents a hydrogen atom or one or more substituents selected from halogen atoms and alkyl, alkoxy, alkylthio, hydroxy, alkenyl, alkynyl, polyhaloalkyl, monohaloalkoxy, polyhaloalkoxy, hydroxyalkyl, alkoxyalkyl, nitro, amino, aminoaalkyl, alkylaminoalkyl, alkylamino, dialkylamino, acylamino, alkysulphonylamino, aminosulphonyl, alkylaminosulphonyl, cyano,
aminocarbonyl, N-alkylaminocarbonyl, N, N-dialkylaminocarbonyl, alkoxy carbonyl, alkyloxycarbonylalkyl, formyl, alkanoyloxyalkyl, alkylaminocarbonylamino, alkylsulphinyl, alkylsulphonyl and N, N-dialky laminosulphonyl groups;

$R_1$ represents a hydrogen atom or a cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heterocyclic, heterocycloxy, heterocycloalkyl or heterocycloalkoxy group, each of which is optionally substituted with one or more substituent $R$ as above defined;

$R_2$ represents a hydrogen atom or an alkyl, alkenyl, alkynyl or cycloalkyl group, each of which is optionally substituted with one or more groups $R_8$ and $R_9$, $R_8$ representing a halogen atom or an alkoxy, monohaloalkoxy, polyhaloalkoxy, cyano, alkoxy carbonyl, alkyl carbonyl, alkoxyalkyl, aminocarbonyl, N-alkylaminocarbonyl or N,N-dialkylaminocarbonyl group and $R_9$ representing an aryl, heteroaryl, aryloxy, heteroaryloxy, aryloxy or heteroarylkoxy group, each of which is optionally substituted with a group $R_1$ as defined above;

$R^3$ represents an alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted with one or more substituents $R$ and/or $R_1$ as above defined,

$R_4$ represents an aryl or heterocyclic group, each of which is optionally substituted with one or more substituents $R$ as above defined,

$A$ denotes CH or N,

$R_5$ represents a group of the formula

\[ -\bigg| \begin{array}{c} N \end{array} \bigg| - B \bigg| \begin{array}{c} R^6 \end{array} \]

or

\[ -\bigg| \begin{array}{c} N \end{array} \bigg| \begin{array}{c} R^7 \end{array} \bigg| \begin{array}{c} R^6 \end{array} \]

(where $R^6$ is bound to the right of each group)

$m$ and $n$ are independently 1 or 2,

$R^6$ represents a hydrogen atom or an alkyl group,

$R^7$ denotes O, S, NR$^6$ or CH$_2$;

$B$ denotes a bond, O, S, NR$^6$ or CH$_2$; and

------- is a single or double bond,
Formula G

wherein

W represents a group of the formula

\[ (i) \quad Z'' \quad \text{or} \quad (ii) \quad Z'' \]

\( R^1 \) represents a hydrogen atom or one or more substituents selected from halogen atoms and hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, nitro, aryl, substituted aryl, heterocycle, substituted heterocycle, alkenyl, substituted alkenyl, amino, alkylamino, dialkylamino, cyano, -SR\(^3\), -C(O)R\(^3\), -C(O)NR\(^3\)R\(^3\), -NR\(^3\)C(O)R\(^3\), -NR\(^3\)SO\(_2\)R\(^3\), -NR\(^3\)C(O)OR\(^3\) and -N(H)C(O)N(H)R\(^3\) groups;

each \( R^2 \) independently represents a hydrogen atom or an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycle or substituted heterocycle group;

\( R^2 \) represents a hydrogen atom or one or two substituents selected from halogen atoms and o xo, alkyl, substituted alkyl, alkenyl and substituted alkenyl groups;

Y represents a CH, CH\(_2\), CR\(_2\), CHR\(_2\) group or a bond;

Q represents a carbonyl, thiocarbonyl or sulphonyl group;

A represents an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heterocycle, substituted heterocycle, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, cyclic amino, substituted...
cyclic amino, arylamino, substituted arylamino, arylalkylamino or substituted arylalkylamino group;
n is 1 or 2;
m is 0, 1 or 2;
p is 1, 2 or 3;
each of a, b, c and d independently represents a carbon or nitrogen atom, or a CH, CH₂ or NH group, with the proviso that no more than two of a, b, c and d may simultaneously represent a nitrogen atom and/or a NH group,
X represents a bond, CH, CH₂, SO or SO₂ group or a carbon, nitrogen or sulphur atom and, when X is a nitrogen atom or CH group, the -Z-(CH₂)ₙ-B group is bound to said nitrogen atom or CH group, and when X is a carbon atom Z'' is not a hydrogen atom or oxo group and the Z-(CH₂)ₙ-B and Z'' groups are bound to said carbon;
Z represents a bond, an oxygen or sulphur atom or -CH(OH)-, -C(O)-NR³C(O)-, -NR³C(O)-NR³-, or -NR³- group;
Z' represents a bond or an oxygen or sulphur atom;
Z'' represents a hydrogen atom or hydroxy, oxo, alkylcarbonyl or cyano group,
B represents a monocyclic aryl, substituted monocyclic aryl, bicyclic aryl, substituted bicyclic aryl, monocyclic heterocycle, substituted monocyclic heterocycle, bicyclic heterocycle or substituted bicyclic heterocycle group; and
\[ \equiv \] represents a single or double bond and, when \( Y = \text{CH} \), the double bond is shifted so as to contain it

**Formula H**

```
    Ar
    \( \equiv \)CH₂\( \equiv \)CH-N
    Ar'
```

wherein

each of Ar and Ar' independently represents a phenyl or pyridyl group, each of which is optionally substituted by one or more alkyl, alkoxy, cyano, nitro, amino, alkylsulphonylamino and/or alkylamino groups,

Y represents a nitrogen atom or a CH, C-OH, C-CN or C-CONH₂ group,
R represents a hydrogen atom or a lower alkyl group, and 
B represents (a) a phenyl group substituted with one or more substituents 
selected from alkoxy, halogen, cyano, nitro, amino, alkylsulphonylamino and 
alkylamino groups, (b) a naphthyl group, optionally substituted with one or 
more substituents selected from halogen atoms and alkyl, alkoxy, cyano, nitro, 
amino, alkylsulphonylamino and alkylamino groups, (c) a benzodioxanyl group, 
or (d) an indolyl group

Formula I

\[
\begin{align*}
R^1 & \quad R^2 \\
R & \quad R^4
\end{align*}
\]

wherein
R represents a hydrogen atom, a lower alkyl group or two lower alkyl groups, 
the same as or different from each other, 
R\(^1\) represents a mono- or bicyclic aryl or heteroaryl group, 
R\(^2\) represents a hydrogen atom or a lower alkyl group, 
R\(^3\) represents a lower alkyl or cycloalkyl group, 
R\(^4\) represents a hydrogen atom or a lower alkyl group, 
A represents an alkylene chain of from 1 to 3 carbon atoms optionally 
substituted by one or more lower alkyl groups, and 
X represents a -CO-, -CHOH-, -CR\(^2\)OH- (R\(^5\) being a lower alkyl or cycloalkyl 
group), -S-, -SO- or -SO\(_2\)- group or, provided that R\(^3\) represents a cycloalkyl 
group, a bond or a -CH\(_2\)-or -CH\(_2\)CH\(_2\)- group

Formula J

\[
\begin{align*}
R^1 & \quad R^2 \\
R & \quad CZR^3
\end{align*}
\]

wherein
A represents an alkylene chain of from 2 to 4 carbon atoms optionally substituted by one or more lower alkyl groups,
Z represents an oxygen or sulphur atom,
R represents a hydrogen atom or a lower alkyl group,
R\(^1\) represents a mono- or bicyclic aryl or heteroaryl group,
R\(^2\) represents a mono- or bicyclic heteroaryl group,
R\(^3\) represents (a) a hydrogen atom, (b) a lower alkyl, cycloalkyl, cycloalkenyl, cycloalkyl-(lower)alkyl, aryl, ary1-(lower)alkyl, heteroaryl or heteroaryl-(lower)alkyl group, (c) a group of formula -NR\(^4\)R\(^5\) wherein R\(^4\) represents a hydrogen atom or a lower alkyl, aryl or aryl-(lower)alkyl group and R\(^5\) represents a hydrogen atom or a lower alkyl, lower alkylcarbonyl, aryl, arylcarbonyl, ary1-(lower)alkyl, cycloalkyl or cycloalkyl-(lower)alkyl group or R\(^4\) and R\(^5\) together with the nitrogen atom to which they are attached represent a saturated heterocyclic ring which may contain a further hetero atom, or (d) a group of formula OR\(^6\) wherein R\(^6\) represents a lower alkyl, cycloalkyl, cycloalkyl-(lower)alkyl, aryl, aryl-(lower)alkyl, heteroaryl or heteroaryl-(lower)alkyl group

![Formula K](image)

wherein
R\(^1\) represents a halogen atom or a lower alkyl, lower alkoxy, hydroxy, trifluoromethyl or cyano group,
m has the value 1 or 2,
n has the value 0 or 1,
A represents a (C\(_2\)-C\(_6\))-alkylene chain which may be substituted with one or more lower alkyl and/or monocyclic (hetero)aryl group(s), and
B denotes -CH\(_2\)-, -CH\(_2\)CH\(_2\)-, -C(O)-, -S(O)-, -S(O)\(_2\)- or -S-. 
3. Use according to claim 1 in which the compound having 5-HT$_{1A}$ antagonist activity is

- N-[2-[4-(2-methoxyphenyl)piperazin-1-yl]-ethyl]-N-(2-pyridyl)-cyclohexanecarboxamide,
- 2-{4-[4-(7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]-butyl}-1,2-benzisothiazol-3-(2H)-one-1,1 dioxide,
- 1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminophenyl]-4-(2-methoxyphenyl)piperazine,
- 1-[3-hydroxy-3,3 bis-(2-pyridyl)-propyl]-4-(4-indolyl)piperazine, or
- 1-cyclohexyl-4-[4-(2-methoxyphenyl)piperazin-1-yl]-3-(2-pyridyl)-butan-1-one.

4. Use according to claim 1 in which the compound having 5-HT$_{1B}$ antagonist activity is a compound of one of the following formulae L to S:

```
Formula L
```

wherein

R$^1$ represents a hydrogen or halogen atom or a (C$_1$-C$_6$)-alkyl or (C$_1$-C$_6$)-alkoxy group;

each of R$^2$ and R$^3$ independently represents a hydrogen or halogen atom, a (C$_1$-C$_6$)-alkyl, hydroxy-(C$_1$-C$_6$)-alkyl, (C$_1$-C$_6$)-alkoxy-(C$_1$-C$_6$)-alkyl, (C$_1$-C$_6$)-alkoxy, hydroxy, cyano or nitro group, or a group of the formula -CO$_2$R$^5$, -COR$^5$, C(O)NR$^6$R$^7$ or -(CH$_2$)$_m$OC(O)-(C$_1$-C$_4$)-alkyl;

each of R$^4$ and R$^5$ independently represents a hydrogen or halogen atom or a hydroxy, (C$_1$-C$_6$)-alkyl or (C$_1$-C$_6$)-alkoxy group;

each of R$^6$ and R$^7$ independently represents a hydrogen atom or a (C$_1$-C$_6$)-alkyl group or R$^6$ and R$^7$ together with the nitrogen atom to which they are attached form a saturated heterocyclic ring having 5 or 6 ring atoms which, when there
are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom;
each of R\(^8\) and R\(^9\) independently represents a hydrogen atom or a (C\(_1\) - C\(_6\))-alkyl group;
X denotes -C(O)NH\(_2\), -NHC(O)\(_{-}\), -CH\(_2\)NH- or -NHCH\(_2\)-;
m represents zero or an integer from 1 to 3; and
p represents an integer from 2 to 4.

**Formula M**

![Formula M Diagram]

wherein
n denotes 1 or 2;
Ar represents
![Ar Representations Diagram]

wherein X represents a hydrogen or fluorine atom, or Ar represents
![Ar Representations Diagram]
R represents a hydrogen atom, a (C<sub>1</sub>-C<sub>3</sub>)-alkyl group or an aralkyl group, E represents a hydrogen atom or methyl group, and each of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> independently represents a hydrogen or halogen atom, a (C<sub>1</sub>-C<sub>3</sub>)-alkyl, (C<sub>1</sub>-C<sub>3</sub>)-alkoxy, trifluoromethyl, hydroxy, cyano or nitro group or a group of the formula -NR<sup>1</sup>R<sup>2</sup>, -C(O)NR<sup>1</sup>R<sup>2</sup>, -COOR<sup>3</sup>, -OC(O)R<sup>4</sup>,

wherein each of R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> independently represents a hydrogen atom or a (C<sub>1</sub>-C<sub>3</sub>)-alkyl group, and R<sup>4</sup> represents a (C<sub>1</sub>-C<sub>3</sub>)-alkyl group, and/or an adjacent pair of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> together with the carbon atoms of the phenyl nucleus to which they are attached form a 5-membered or 6-membered ring, which may include one or more oxygen and/or nitrogen and/or sulphur atoms

**Formula N**

wherein

R<sup>1</sup> represents (a) a hydrogen or halogen atom, (b) a (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, hydroxy, hydroxy-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, hydroxy-(C<sub>1</sub>-C<sub>6</sub>)-alkoxy, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy-(C<sub>1</sub>-C<sub>6</sub>)-alkoxy, acyl, nitro, trifluoromethyl or cyano group, (c) a group of the formula CO-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, SR<sup>8</sup>, SOR<sup>8</sup>, SO<sub>2</sub>R<sup>8</sup>,

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NR²CONR¹⁰R¹¹, NR¹⁰SO₂R¹¹, SO₂NR¹⁰R¹¹, CO₂R¹⁰, CONR¹⁰R¹¹, CO₂NR¹⁰R¹¹, 
CONR¹⁰(CH₂)aCO₂R¹¹, (CH₂)bNR¹⁰R¹¹, (CH₂)aCONR¹⁰R¹¹, (CH₂)bNR¹⁰COR¹¹, 
(CH₂)aCO₂C₁₋₆-alkyl, CO₂(CH₂)bOR¹⁰, NR¹⁰R¹¹, N=CNR₈NR¹⁰R¹¹, 
NR¹⁰CO(CH₂)bNR¹⁰R¹¹, NR¹⁰CO₂R¹¹, CONHNR¹⁰R¹¹, CR¹⁰=NOR¹¹, 
CR¹⁰=NOR¹¹ in which each of R², R¹⁰ and R¹¹ independently represents a 
hydrogen atom or a (C₁-C₆)-alkyl group and "a" is an integer from 1 to 4, or (d) 
a 5- to 7-membered heterocyclic ring containing from 1 to 4 ring heteroatoms 
selected from oxygen, nitrogen, and sulphur, optionally substituted with one or 
more substituents defined as R² or R³ below; 
each of R² and R³ independently represents a hydrogen or halogen atom, a (C₁- 
C₆)-alkyl, (C₃-C₆)-cycloalkyl, (C₃-C₆)-cycloalkenyl, (C₁-C₆)-alkoxy, hydroxy- 
(C₁-C₆)-alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl or cyano 
group or a group of the formula (C₁-C₆)-alkyl-O-(C₁-C₆)-alkyl, CO₂R¹⁰, 
CONR¹⁰R¹¹ or NR¹⁰R¹¹ wherein each of R¹⁰ and R¹¹ independently represents a 
hydrogen atom or a (C₁-C₆)-alkyl group; 
each of R⁴ and R⁵ represents a hydrogen atom or a (C₁-C₆)-alkyl group, or R₄ 
and R₅ together form a group (CR¹⁳R¹⁴)ᵢ or (CR¹³R¹⁴)ᵢ-D wherein q is 2, 3 or 4, 
r is 0, 1 or 2, each of R¹³ and R¹⁴ independently represents a hydrogen atom or a 
(C₁-C₆)-alkyl group and D represents an oxygen or sulphur atom or a CR¹³=CR¹⁴ 
group; 
R⁶ denotes -(CH₂)ₚ-OR¹⁶, -(CH₂)ₚ-SR¹⁶ or -(CH₂)ₚ-NR¹⁶R¹⁷ wherein each of R¹⁶ 
and R¹⁷ independently represents a hydrogen atom or a (C₁-C₆)-alkyl group; 
each of R⁷ and R⁸ independently represents a hydrogen atom or a (C₁-C₆)-alkyl 
group; 
B denotes O, CR¹⁸R¹⁹, NR¹⁹ or S(O)ₓ wherein each of R¹⁸ and R¹⁹ independently 
represents a hydrogen atom or a (C₁-C₆)-alkyl group and b is 1, 2, or 3; 
m is 1, 2, or 3; and 
n is 1, 2, or 3.
wherein each of R¹ and R² independently represents (a) a phenyl group, (b) a bicyclic aryl group, (c) a 5- to 7-membered heterocyclic ring containing from 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur or (d) a bicyclic heterocyclic ring containing from 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, save that P1 and P2 do not both represent phenyl groups; R¹ represents (a) a hydrogen or halogen atom, (b) a (C₁₋C₆)-alkyl, (C₃₋C₆)-cycloalkyl, (C₁₋C₆)-alkoxy, hydroxy, hydroxy-(C₁₋C₆)-alkyl, hydroxy-(C₁₋C₆)-alkoxy, (C₁₋C₆)-alkoxy-(C₁₋C₆)-alkoxy, acyl, nitro, trifluoromethyl or cyano group, (c) a group of the formula COC₁₋₆-alkyl, SR⁹, SOR⁹, SO₂R⁹, SO₂NR¹₀R¹₁, CO₂R¹₀, NR¹⁰SO₂R¹¹, CONR³R₁₁, CO₂NR¹⁰R¹¹, CONR¹⁰(CH₂)ₚCO₂R¹¹, (CH₂)ₚNR¹⁰R¹¹, (CH₂)ₚCONR¹⁰R¹¹, (CH₂)ₚNR¹⁰COR¹¹, CONR¹⁰(CH₂)ₚCO₂C₁₋₆-alkyl, CO₂(CH₂)ₚOR¹₀, CONHNR¹⁰R¹¹, NR¹⁰R¹¹, N=CNR⁹NR¹⁰R¹¹, NR¹⁰CO₂R¹¹, NR¹⁰CO(CH₂)ₚNR¹⁰R¹¹, NR¹⁰CONR¹⁰R¹¹, CR¹₀=NOR¹¹, CNR¹⁰=NOR¹¹, or NR¹²COR¹³, where each of R⁹, R¹₀ and R¹¹ independently represents a hydrogen atom or a (C₁₋C₆)-alkyl group, p is 1 to 4, R¹² is hydrogen, (C₁₋C₆)-alkyl or together with R² forms a group (CH₂)ₚₚ where q is 2, 3, or 4 and R¹³ is hydrogen, (C₁₋C₆)-alkyl, aryl, or aryl substituted with one or more substituents selected from R² and R³, as defined below; or (d) a 5- to 7-membered heterocyclic ring containing from 1 to 4 ring heteroatoms selected from oxygen, nitrogen and sulphur, optionally substituted with one or more substituents defined as R² or R³ below; each of R² and R³ independently represents a hydrogen or halogen atom, a (C₁₋C₆)-alkyl, (C₃₋C₆)-cycloalkyl, (C₃₋C₆)-cycloalkenyl, (C₁₋C₆)-alkoxy, hydroxy-(C₁₋C₆)-alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl or cyano group or a group of the formula (C₁₋C₆)-alkyl-O-(C₁₋C₆)-alkyl, CO₂R¹₀, CONR¹₀R¹¹ or NR¹⁰R¹¹ wherein each of R¹₀ and R¹¹ independently represents a hydrogen atom or a (C₁₋C₆)-alkyl group; or R² and R³ together form a group.
-(CH₂)ₙ-R¹⁴-(CH₂)ₚ- wherein R¹⁴ denotes O, S, CH₂, NH or N-(C₁-C₆)-alkyl and r and s are independently 0, 1, or 2;
A represents a group DR⁶-C(=B)- or a group -C(=B)-DR₆ where B denotes O or S, D denotes N, C or CH and R₆ represents a hydrogen atom or a (C₁-C₆)-alkyl group;
R⁷ represents a halogen atom or a (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy group, or R₆ and R⁷ together form a group (CR¹⁶R¹⁷)ₓ or (CR¹⁶R¹⁷)y-J where t is 1, 2, or 3, u is 0, 1 or 2, each of R¹⁶ and R¹⁷ independently represents a hydrogen atom or a (C₁-C₆)-alkyl group and J denotes O, S, CR¹⁶=CR¹⁷, CR¹⁶=N or N=N;
R⁸ represents a hydrogen atom or a (C₁-C₆)-alkyl group;
each of R⁹ and R¹⁰ independently represents a hydrogen atom,
E denotes O, CR¹⁸R¹⁹, NR²⁰ or S(O), wherein each of R¹⁸, R¹⁹ and R²⁰ independently represents a hydrogen atom or a (C₁-C₆)-alkyl group and v is 0, 1, or 2;
G denotes C=O or CR²¹R²² wherein each of R²¹ and R²² independently represents a hydrogen atom or a (C₁-C₆)-alkyl group
each of X and Y independently represents a group CR⁹R¹⁰ wherein R⁹ and R¹⁰ are defined as above; and
m is 1, 2, or 3

**Formula P**

\[ \text{Diagram of the molecule} \]

wherein

Rⁿ represents a group of the formula

\[ (R¹)ₙ \rightarrow P^i \quad \text{or} \quad (R²)ₙ \rightarrow P^i \quad A \rightarrow P^i \]

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P\(^1\) represents a phenyl, naphthyl or heteroaryl group;
P\(^2\) represents a phenyl, naphthyl or heteroaryl group or a 5- to 7-membered heterocyclic ring;
R\(^1\) represents a halogen atom, a (C\(_1\)-C\(_6\))-alkyl, (C\(_3\)-C\(_6\))-cycloalkyl, (C\(_1\)-C\(_6\))-alkoxy, hydroxy, hydroxy-(C\(_1\)-C\(_6\))-alkyl, nitro, trifluoromethyl or cyano group, or a group of the formula (C\(_1\)-C\(_6\))-alkyl-CO, SR\(^6\), SOR\(^6\), SO\(_2\)R\(^6\), SO\(_2\)NR\(^6\)R\(^7\), CO\(_2\)R\(^6\), CONR\(^6\)R\(^7\), OCONR\(^6\)R\(^7\), NR\(^6\)R\(^7\), NR\(^6\)CO\(_2\)R\(^7\), NR\(^6\)CONR\(^7\)R\(^8\) or CR\(^6\)=NOR\(^7\) in which each of R\(^6\), R\(^7\) and R\(^8\) are independently represents a hydrogen atom or a (C\(_1\)-C\(_6\))-alkyl group;
R\(^2\) is as defined above for R\(^1\) or is a heteroaryl group optionally substituted by a halogen atom or a (C\(_1\)-C\(_6\))-alkyl or (C\(_1\)-C\(_6\))-alkyl-CO group, or is a 5- to 7-membered heterocyclic ring optionally substituted by oxo;
R\(^3\) represents a halogen atom, a (C\(_1\)-C\(_6\))-alkyl, (C\(_3\)-C\(_6\))-cycloalkyl, (C\(_1\)-C\(_6\))-alkoxy, hydroxy, nitro, trifluoromethyl or cyano group, or a group of the formula (C\(_1\)-C\(_6\))-alkyl-CO, CO\(_2\)R\(^6\), CONR\(^6\)R\(^7\) or NR\(^6\)R\(^7\) where R\(^6\) and R\(^7\) are as defined above;
each of a, b and c is independently 0, 1, 2 or 3;
A denotes a bond, O, CO, CH\(_2\), NH or N-(C\(_1\)-C\(_6\))-alkyl;
Y denotes a single bond, CH\(_2\), O, NH or N-(C\(_1\)-C\(_6\))-alkyl;
W represents a group -CH=CH- or -(CR\(^9\)R\(^{10}\))- in which t is 2, 3, or 4 and each of R\(^9\) and R\(^{10}\) independently represents a hydrogen atom or a (C\(_1\)-C\(_6\))-alkyl group;
R\(^b\) represents a hydrogen or halogen atom or a hydroxy, (C\(_1\)-C\(_6\))-alkyl, trifluoromethyl, (C\(_1\)-C\(_6\))-alkyl-CO, cyano or (C\(_1\)-C\(_6\))-alkoxy group;
R\(^c\) represents a hydrogen atom or a (C\(_1\)-C\(_6\))-alkyl group and each of R\(^d\) and R\(^e\) independently represents a (C\(_1\)-C\(_4\))-alkyl group
wherein

R^8 represents a group of the formula

\[ (R^1)_b - p^1 \text{ or } (R^2)_b - p^2 - A - p^3 \]

P^1 represents a phenyl, naphthyl or heteroaryl group;
P^2 represents a phenyl, naphthyl or heteroaryl group or a 5- to 7-membered heterocyclic ring;
R^1 represents a halogen atom, a (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy, hydroxy, hydroxy-(C_1-C_6)-alkyl, nitro, halo-(C_1-C_6)-alkyl or cyano group, or a group of the formula (C_1-C_6)-alkyl-CO, SR^6,SOR^6,SO_2R^6,SO_2NR^6R^7,CO_2R^6,CONR^6R^7,OCONR^6R^7,NR^6R^7,NR^6CO_2R^7,NR^6CONR^7R^8 or CR^6=NOR^7 in which each of R^6, R^7 and R^8 are independently represents a hydrogen atom or a (C_1-C_6)-alkyl group;
R^2 is as defined above for R^1 or is a heteroaryl group optionally substituted by a halogen atom or a (C_1,C_6)-alkyl or (C_1-C_6)-alkyl-CO group, or is a 5- to 7-membered heterocyclic ring optionally substituted by oxo;
R^3 represents a halogen atom, a (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy, hydroxy, nitro, halo-(C_1-C_6)-alkyl or cyano group, or a group of the formula (C_1-C_6)-alkyl-CO, CO_2R^6, CONR^6R^7 or NR^6R^7 where R^6 and R^7 are as defined above;
each of a, b and c is independently 0, 1, 2 or 3;
Y denotes a single bond, CH_2 or NH;
X denotes O, S, NH or N-(C_1-C_6)-alkyl;
R^b represents a hydrogen or halogen atom or a (C_1-C_6)-alkyl, halo-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-CO or cyano group; and
$R^6$ represents a hydrogen atom or a (C$_1$-C$_6$)-alkyl group

**Formula R**

wherein

P represents a 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur,

each of $R^1$, $R^2$ and $R^3$ independently represents a hydrogen or halogen atom, a (C$_1$-C$_6$)-alkyl, (C$_3$-C$_6$)-cycloalkyl, (C$_3$-C$_6$)-cycloalkenyl, (C$_1$-C$_6$)-alkoxy, hydroxy-(C$_1$-C$_6$)-alkyl, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, or cyano group, or a group of the formula (C$_1$-C$_6$)-alkyl-O-(C$_1$-C$_6$)-alkyl, CO$_2$R$^9$, CONR$^{10}$R$^{11}$ or NR$^{10}$R$^{11}$ wherein each of $R^9$, $R^{10}$ and $R^{11}$ independently represents a hydrogen atom or a (C$_1$-C$_6$)-alkyl group;

each of $R^4$ and $R^5$ independently represents a hydrogen atom or a (C$_1$-C$_6$)-alkyl group;

$R^6$ represents a hydrogen or halogen atom or a hydroxy, (C$_1$-C$_6$)-alkyl or (C$_1$-C$_6$)-alkoxy group;

each of $R^7$ and $R^8$ independently represents a hydrogen atom, a (C$_1$-C$_6$)-alkyl group or an aralkyl group, or $R^7$ and $R^8$ together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen and sulphur;

A denotes CONH or NHCO;

B denotes O, S(O)$_p$, NR$^{12}$, CR$^4$=CR$^5$ or CR$^4$R$^5$ wherein $p$ is 0, 1 or 2, $R^{12}$ represents a hydrogen atom, a (C$_1$-C$_6$)-alkyl group or a phenyl-(C$_1$-C$_6$)-alkyl group, and each of $R^4$ and $R^5$ independently represents a hydrogen atom or a (C$_1$-C$_6$)-alkyl group;
m is an integer from 1 to 4; and
n is 1 or 2

wherein
R^1 represents (a) a hydrogen or halogen atom, (b) a (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkoxy, hydroxy, hydroxy-(C_1-C_6)-alkyl, hydroxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, acyl, nitro, trifluoromethyl or cyano group, (c) a group of the formula CO-(C_1-C_6)-alkyl, SR^2, SOR^2, SO_2R^2, SO_2NR^{10}R^{11}, CO_2R^{10}, NR^{10}SO_2R^{11}, CONR^{10}R^{11}, CO_2NR^{10}R^{11}, CONR^{10}(CH_2)_pCO_2R^{11}, (CH_2)_pNR^{10}R^{11}, (CH_2)_pCONR^{10}R^{11}, (CH_2)_pNR^{10}COR^{11}, (CH_2)_pCO_2C_1-salkyl, CO_2(CH_2)_pOR^{10}, CONHNR^{10}R^{11}, NR^{10}R^{11}, NR^{10}CO_2R^{11}, NR^{10}CO_2R^{11}, NR^{10}CO(CH_2)_pNR^{10}R^{11}, NR^{10}CONR^{10}R^{11}, CR^{10}CNOR^{11} or

CNR^{10}=NOR^{11} wherein each of R^9, R^{10} and R^{11} independently represents a hydrogen atom or a (C_1-C_6)-alkyl group and p is 1 to 4, or (d) an optionally substituted 5- to 7-membered heterocyclic ring containing from 1 to 4 ring heteroatoms selected from oxygen, nitrogen, and sulphur;

each of R^2 and R^3 independently represents a hydrogen or halogen atom, a (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_3-C_6)-cycloalkenyl, (C_1-C_6)-alkoxy, hydroxy-(C_1-C_6)-alkyl, acyl, aryloxy, hydroxy, nitro, trifluoromethyl, or cyano group, or a group of the formula (C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, CO_2R^9, CONR^{10}R^{11} or NR^{10}R^{11} wherein each of R^9, R^{10} and R^{11} independently represents a hydrogen atom or a (C_1-C_6)-alkyl group;

each of R^4, R^5 and R^6 independently represents a hydrogen atom or a (C_1-C_6)-alkyl group;

A denotes (CR^{13}R^{14})_q or (CR^{13}R^{14})_r-D where q is 2, 3 or 4, r is 0, 1 or 2, each of R^{13} and R^{14} independently represents a hydrogen atom or a (C_1-C_6)-alkyl group,
and D denotes O, S or (CR\(^{13}\)=CR\(^{14}\));
B denotes O, S(O)\(_b\), CR\(^{15}\)R\(^{16}\) or NR\(^{17}\) wherein b is 0, 1 or 2 and each of R\(^{15}\), R\(^{16}\)
and R\(^{17}\) independently represents a hydrogen atom or a (C\(_1\)-C\(_6\))-alkyl group;
m is 1, 2 or 3; and
n is 1, 2 or 3.

5. Use according to claim 1 in which the compound having 5-HT\(_{1B}\) antagonist activity is
- N-[3-(2-dimethylamino-ethoxy)-4-methoxyphenyl-2’ ρ-methyl-4’ ρ-(5-
methyl-1,2,4-oxadiazol-3-yl)]-1,1 ρ-biphenyl-4-carboxamide
- 1 ρ-methyl-5’-[2’ ρ-methyl-4’ ρ-(5-methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-
yl]carbonyl]-2,3,6,7-tetrahydrospiro[furo[2,3-f]indole-3,4’ ρ-piperidine, or
- 3-(3-dimethylamino-propyl)-4-hydroxy-N-[4-(4-pyridinyl)-phenyl benzamide dihydrochloride.

6. Use of a compound having both 5-HT\(_{1A}\) and 5-HT\(_{1B}\) antagonist activity (or of a
pharmaceutically acceptable salt, enantiomer, diastereomer, N-oxide, crystalline
form, hydrate, solvate, active metabolite or prodrug of such a compound) for the
preparation of a medicament for the treatment of neuromuscular dysfunction of
the lower urinary tract.

7. Use according to claim 6 in which the compound having both 5-HT\(_{1A}\) and 5-
HT\(_{1B}\) antagonist activity is a compound of one of the following formulae T to W:

![Diagram of formula T]

wherein
R\(^1\) represents a group of the formula G\(^1\), G\(^2\), G\(^3\), G\(^4\), G\(^5\), G\(^6\) or G\(^7\) depicted below
in which a is zero or an integer from one to eight;
each \( R^{13} \) independently represents a \((C_1-C_6)\)-alkyl group or a \((C_1-C_4)\)-methylene bridge extending from one of the ring carbon atoms of the piperazine or piperidine ring of \( G^1 \) or \( G^2 \) to an available bonding site which is the same or another ring carbon atom or a ring nitrogen atom of the piperazine or piperidine ring of \( G^1 \) or \( G^2 \) or is a ring carbon atom of \( R^6 \);
\( E \) denotes \( O, S, SO_2, \) or \( SO_3 \);
\( R^6 \) represents (a) a hydrogen atom, (b) a \((C_1-C_6)\)-alkyl group optionally substituted with a \((C_1-C_6)\)-alkoxy group or with from one to three fluorine atoms, or (c) a \((C_1-C_4)\)-phenyl group, a \((C_1-C_4)\)-alkyl-naphthyl group or a group of the formula \( \text{Het}-(\text{CH}_2)_q \) wherein \( \text{Het} \) represents a pyridyl, pyrimidyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl or benzisothiazolyl group and \( q \) is zero or an integer of from 1 to 4, and in which the phenyl, naphthyl and Het groups may optionally be substituted with one or more substituents independently selected from chlorine, fluorine, bromine and iodine atoms and/or from \((C_1-C_6)\)-alkyl, \((C_1-C_6)\)-alkoxy, trifluoromethyl, cyano, \((C_1-C_6)\)-alkylthio, \((C_1-C_6)\)-alkylsulphinyl and \((C_1-C_6)\)-alkylsulphonyl groups;
\( R^7 \) represents (a) a hydrogen atom, (b) a \((C_1-C_6)\)-alkyl group or (c) a \((C_1-C_6)\)-phenyl group, a \((C_1-C_4)\)-alkyl-naphthyl group or a group of the formula \( \text{Het}-(\text{CH}_2)_q \) wherein \( \text{Het} \) and \( q \) are as defined for \( R^6 \) and in which the phenyl, naphthyl and Het groups may optionally be substituted with one or more substituents independently selected from chlorine, fluorine, bromine and iodine.
atoms and/or from (C\textsubscript{1}-C\textsubscript{6})-alkyl, (C\textsubscript{1}-C\textsubscript{6})-alkoxy, trifluoromethyl, (C\textsubscript{1}-C\textsubscript{6})-alkylcarbonyl, cyano, (C\textsubscript{1}-C\textsubscript{6})-alkythio, (C\textsubscript{1}-C\textsubscript{6})-alkylsulphinyl and (C\textsubscript{1}-C\textsubscript{6})-alkylsulphonyl groups;
or R\textsuperscript{6} and R\textsuperscript{7} taken together form a 2 to 4 carbon atom chain;
R\textsuperscript{8} represents a hydrogen atom or a (C\textsubscript{1}-C\textsubscript{3})-alkyl group;
R\textsuperscript{9} represents a hydrogen atom or a (C\textsubscript{1}-C\textsubscript{6})-alkyl group;
or R\textsuperscript{6} and R\textsuperscript{9}, together with the nitrogen atom to which they are attached form a 5- to 7-membered heteroalkyl ring that may contain from 0 to 4 further heteroatoms selected from nitrogen, sulphur and oxygen;
p is 1, 2 or 3;
R\textsuperscript{2} represents a hydrogen atom, a (C\textsubscript{1}-C\textsubscript{4})-alkyl group, or a phenyl or naphthyl group, which phenyl or naphthyl group is unsubstituted or is substituted with one or more substituents independently selected from chlorine, fluorine, bromine and iodine atoms and/or from (C\textsubscript{1}-C\textsubscript{6})-alkyl, (C\textsubscript{1}-C\textsubscript{6})-alkoxy, trifluoromethyl, cyano, (C\textsubscript{1}-C\textsubscript{6})-alkythio, (C\textsubscript{1}-C\textsubscript{6})-alkylsulphinyl and (C\textsubscript{1}-C\textsubscript{6})-alkylsulphonyl groups;
X represents a hydrogen, chlorine, fluorine, bromine or iodine atom or a cyano, (C\textsubscript{1}-C\textsubscript{6})-alkyl, hydroxy, trifluoromethyl, (C\textsubscript{1}-C\textsubscript{6})-alkoxy, (C\textsubscript{1}-C\textsubscript{6})-alkythio, (C\textsubscript{1}-C\textsubscript{6})-alkylsulphinyl, (C\textsubscript{1}-C\textsubscript{6})-alkylsulphonyl group or a group of the formula CO\textsubscript{2}R\textsuperscript{10} or -CONR\textsuperscript{11}R\textsuperscript{12} in which each of R\textsuperscript{10}, R\textsuperscript{11} and R\textsuperscript{12} independently represents a moiety as defined in R\textsuperscript{2}, or R\textsuperscript{11} and R\textsuperscript{12} together with the nitrogen atom to which they are attached form a 5- to 7-membered heteroalkyl ring which may contain from 0 to 4 further heteroatoms selected from nitrogen, sulphur and oxygen;
Y denotes an optionally substituted 1- to 4-membered heteroalkyl bridge which, together with the -C-C(O)-N- moiety to which it is attached, forms a 1,3-oxazolidin-4-one, 1,3-oxazolidin-2,4-dione, 4,5-dihydro-1,2-oxazolidin-3-one, 1,3-thiazolidin-4-one, 1,3-thiazolidin-2,4-dione, 1,3-pyrazolidin-4-one, 1,3-imidazolidin-2,4-dione, 2-pyrazolidin-3-one, 1,2-thiazolidin-1,1,3-trione, 1,2-thiazolidin-3-one, tetrahydro-1,2-oxazin-3-one, tetrahydro-1,3-oxazin-4-one, tetrahydro-1,3-oxazin-2,4-dione, morpholin-3-one, morpholin-3,5-dione, 2,3-dihydro-1,4-oxazin-3-one, tetrahydro-1,3-thiazin-4-one, tetrahydro-1,3-thiazin-2,4-dione, tetrahydro-1,2-thiazin-3-one, thiomorpholin-3-one, thiomorpholin-3,5-dione, 2,3-dihydro-1,4-thiazin-3-one, hexahydro-1,2-diazin-3-one, 4,5-
dihydro-2H-pyridazin-3-one, hexahydro-1,3-diazin-4-one, hexahydro-1,3-
diazin-2,4-dione, piperazin-2-one, piperazin-2,6-dione, tetrahydro-1,3,4-
thiadiazin-5-one, 5,6-dihydro-1,3,4-thiadiazin-5-one, 1,3,4-oxadiazin-5-one,
5,6-dihydro-1,2,4-oxadiazin-5-one, tetrahydro-1,2,4-oxadiazin-5-one, 1,2,4-
triazin-5-one, tetrahydro-1,2,4-oxadiazin-5-one, 5,6-dihydro-1,2,4-oxadiazin-5-
one, 1,2,4-oxadiazin-3,5-dione, 1,2,4-triazin-6-one, hexahydro-1,2-oxazepin-3-
one, hexahydro-1,3-oxazepin-4-one, hexahydro-1,4-oxazepin-3-one, hexahydro-
1,4-oxazepin-3,5-dione, hexahydro-1,4-oxazepin-3,5-dione, 2,3,5,6-tetrahydro-
1,4-oxazepin-5,7-dione, hexahydro-1,4-oxazepin-5-one, hexahydro-1,3-
oxazepin-2,4-dione, hexahydro-1,2-thiazepin-3-one, hexahydro-1,4-thiazepin-3-
one, 2,3,4,5-tetrahydro-1,4-thiazepin-3-one, hexahydro-1,4-thiazepin-3,5-dione,
hexahydro-1,4-thiazepin-3,5-dione, 2,3,6,7-tetrahydro-1,4-thiazepin-5-one, 6,7-
dihydro-1,4-thiazepin-5-one, hexahydro-1,3-thiazepin-2,4-dione, hexahydro-
1,2-diazepin-3-one, hexahydro-1,3-diazepin-2,4-dione, hexahydro-1,4-diazepin-
2-one, hexahydro-1,4-diazepin-5-one, hexahydro-1,4-diazepin-5,7-dione,
hexahydro-1,3,5-thiadiazepin-3-one, 4,5,6,7-tetrahydro-1,3,5-thiadiazepin-6-
one, and 2,3,5,6-tetrahydro-1,2,4-triazepin-3,5-dione ring, the optional
substituents on any of the carbon atoms of the 1- to 4-membered heteroalkyl
bridge capable of supporting an additional bond being selected from chlorine
and fluorine atoms and (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, trifluoromethyl and cyano
groups, and the optional substituents on any of the nitrogen atoms of the 1- to 4-
membered heteroalkyl bridge capable of supporting an additional bond being
selected from (C₁-C₆)-alkyl and trifluoromethyl groups;
B represents a hydrogen atom or a phenyl, naphthyl or 5- or 6-membered
heteroaryl group containing from 1 to 4 ring heteroatoms, each of the foregoing
groups being unsubstituted or being substituted with one or more substituents
independently selected from chlorine, fluorine, bromine and iodine atoms and/or
from (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxy-(C₁-C₆)-alkyl,
trifluoromethyl, trifluoromethoxy, cyano, hydroxy, carboxy, (C₁-C₆)-alkylthio,
(C₁-C₆)-alkylsulphenyl and (C₁-C₆)-alkylsulphonyl groups;
the broken lines indicate optional double bonds, with the proviso that when the
broken line in G² is a double bond then R⁸ is absent; and
m is 0, 1, 2 or 3
wherein

$R^1$ represents (a) a hydrogen atom, (b) a $(C_1$-$C_4$)-alkyl, acetyl or benzoyl group, (c) a phenyl-$(C_1$-$C_4$)-alkyl group in which the phenyl ring is unsubstituted or is substituted by one or more halogen atoms and/or $(C_1$-$C_4$)-alkyl, trifluoromethyl, hydroxy, $(C_1$-$C_4$)-alkoxy, amino, cyano or nitro groups, (d) a naphthyl-$(C_1$-$C_4$)-alkyl group, or (e) a phenyl-$(C_1$-$C_3$)-alkanone or phenylcarbamoyl ethyl group in which the phenyl ring is unsubstituted or is substituted by a halogen atom,

$R^2$ represents (a) a phenyl, pyridyl, pyrimidyl or pyrazinyl group, each of which is unsubstituted or is substituted by (i) one to three of the following: halogen, $(C_1$-$C_4$)-alkyl, trifluoromethyl, trifluoromethoxy, hydroxy, $(C_1$-$C_4$)-alkoxy, amino, monomethylamino, dimethylamino, cyano and nitro groups and (ii) one benzyl, phenethyl, benzyloxy or phenylethoxy group, in each of which the phenyl ring is unsubstituted or is substituted by a halogen atom or a methyl, trifluoromethyl or methoxy group, or (b) a group as described in (a) in which two adjacent ring carbon atoms are bridged to form a benzo-fused or a pyridino-fused bicyclic wherein the bridging moiety is unsubstituted or is substituted by one or two substituents selected from halogen atoms and/or $(C_1$-$C_4$)-alkyl, hydroxy, trifluoromethyl, $(C_1$-$C_4$)-alkoxy, amino, cyano and nitro groups, or (c) a group as described in (a) in which two adjacent ring carbon atoms are bridged to form a 5- or 6-membered ring consisting of carbon ring members or carbon ring members and one or two oxygen atoms as ring members,

A denotes NH or O,

B represents a hydrogen atom or a methyl group,

C represents a hydrogen atom or a methyl or hydroxy group,

Y denotes CH$_2$, CH$_2$-CH$_2$, CH$_3$-CH$_2$-CH$_2$ or CH$_2$-CH,

Z denotes N, C or CH, wherein the linkage between Y and Z is a single or a double bond, and

$n$ is 2, 3 or 4
wherein

$R^1$ represents a hydrogen atom, a (C$_1$-C$_4$)-alkyl group, an acetyl group, a (C$_1$-C$_3$)-alkyl carboxylate radical, or is a phenyl-(C$_1$-C$_4$)-alkyl radical where the aromatic ring is unsubstituted or substituted by halogen, (C$_1$-C$_4$)-alkyl, trifluoromethyl, hydroxy, (C$_1$-C$_4$)-alkoxy, amino, cyano or nitro groups,

$R^2$ represents a phenyl, pyridyl, pyrimidinyl or pyrazinyl group which is unsubstituted or is mono- or disubstituted by halogen atoms, (C$_1$-C$_4$)-alkyl, trifluoromethyl, trifluoromethoxy, hydroxy, (C$_1$-C$_4$)-alkoxy, amino, monomethylamino, dimethylamino, cyano or nitro groups, and may be fused to a benzene nucleus which may be mono- or disubstituted by halogen atoms, (C$_1$-C$_4$)-alkyl, hydroxy, trifluoromethyl, (C$_1$-C$_4$)-alkoxy, amino, cyano or nitro groups and may contain 1 nitrogen atom, or to a 5- or 6-membered ring which may contain 1-2 oxygen atoms,

A denotes NH or O,

B represents a hydrogen atom or a methyl group,

Z denotes N, C or CH, wherein the linkage between Y and Z is a single or a double bond, and

n is 2, 3 or 4

wherein

one of $X$ and $Y$ represents a methylene group and the other of $X$ and $Y$ represents a group of the formula NR$_1^1$ in which $R^1$ is hydrogen, (C$_1$-C$_8$)-alkyl, CO-(C$_1$-C$_4$)-alkyl, t.butoxycarbonyl, aroyl or phenyl-(C$_1$-C$_4$)-alkyl which in turn
may be substituted on the aromatic system by F, Cl, Br, I, (C\textsubscript{1}-C\textsubscript{4})-alkyl, (C\textsubscript{1}-C\textsubscript{4})-alkoxy, trifluoromethyl, hydroxyl, amino, cyano or nitro,
A represents a (C\textsubscript{1}-C\textsubscript{10})-alkylene group or a (C\textsubscript{2}-C\textsubscript{10})-alkylene group which comprises at least one group Z which is selected from O, S, NR\textsuperscript{2}, cyclopropyl, CO\textsubscript{2}, CHOH, or a double or triple bond,
R\textsuperscript{2} represents a hydrogen atom or a (C\textsubscript{1}-C\textsubscript{4})-alkyl group,
B represents a 1,4-piperidinylene, 1,2,3,6-tetrahydro-1,4-pyridinium or 1,4-piperazinylene group or the corresponding cyclic compounds enlarged by one methylene group, with the linkage to A being via an N atom of B, and
Ar represents (a) a phenyl group which is unsubstituted or is substituted by (C\textsubscript{1}-C\textsubscript{6})-alkyl, (C\textsubscript{1}-C\textsubscript{8})-alkoxy, F, Cl, Br, I, trifluoromethyl, NR\textsuperscript{2}, CO\textsubscript{2}R\textsuperscript{2}, cyano or phenyl, or (b) a tetraaryl, indanyl or fused aromatic systems (e.g., naphthalene) which is unsubstituted or substituted by (C\textsubscript{1}-C\textsubscript{4})-alkyl or (C\textsubscript{1}-C\textsubscript{4})-alkoxy, anthracene or 5- or 6-membered aromatic heterocycles having 1 or 2 heteroatoms which are selected, independently of one another, from O and N, which may be fused to other aromatic radicals.

8. Use according to claim 6 in which the compound having both 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} antagonist activity is
- (Z)-4-(3,4-dichlorophenyl)-2-[2-(4-methylpiperazin-1-yl)-benzyldiene]thiomorpholin-3-one.

9. Use according to any one of claims 1 to 8 in which the medicament is prepared for oral, parenteral, intranasal, sublingual, rectal or transdermal administration, for administration by insufflation or inhalation, lyophilized composition.

10. Use according to any one of claims 1 to 9 in which the medicament is prepared in a dosage form suitable for administration in an amount of from 0.01 to 25mg/kg/day.
Fig. 3

- GR 55562 3 mg/kg i.v.
- Rec 0.0311 0.01 mg/kg i.v.
- GR 55562 + Rec 0.0311

Disappearance time (min)

Fig. 4

- GR 55562 3 mg/kg i.v.
- Rec 27/0206 0.1 mg/kg i.v.
- GR 55562 + Rec 27/0206

Disappearance time (min)

\[ p < 0.01 \]

\[ p < 0.05 \]
Fig. 5

- SB 224289 1 mg/kg i.v.
- Rec 0.0311 0.01 mg/kg i.v.
- SB 224289 + Rec 0.0311

Disappearance time (min)

Fig. 6

- SB 224289 1 mg/kg i.v.
- Rec 270206 0.1 mg/kg i.v.
- SB 224289 + Rec 270206

Disappearance time (min)

p < 0.01

p < 0.05
Fig. 9

5AUC (practical-theoretical) at 5 hrs

-40
-20
0
20
40
60

controls
WAY
100635
0.01 mg/kg

GR
55562
3 mg/kg

WAY +
GR

p<0.05