NOVEL THERAPEUTIC USE OF P75 RECEPTOR ANTAGONISTS

The subject of the present invention is the use of p75 receptor antagonists for the preparation of medicaments for use in the treatment and/or prevention of overactive bladder and other urinary disorders.

Overactive bladder syndrome (sometimes called an 'irritable' bladder or 'detrusor instability') is a common condition characterized by repeated and uncontrolled bladder contractions. Symptoms include urgency, frequency, nocturia and urge incontinence. Their causes are not fully understood although they are partially due to the defective behaviour of the detrusor. Bladder training is usually the main treatment, and medication (including antimuscarinic agents) does generally not alleviate all symptoms.

Urinary disorders may include, but are not limited to, incontinence (inability to control urine flow), interstitial cystitis (IC), bladder pain syndrome (BPS), benign prostate hyperplasia (PBH), cancers of the urinary tract; some of them can have serious, even life-threatening, complications.

It is therefore highly desirable to provide new medicines for the treatment and/or prevention of the above disorders.

The compounds according to the present invention have an affinity for the p75 neurotrophin receptor.

Neurotrophins belong to a family of proteins of which the biological effect is in particularsurvival, development and function of neurons.

The p75 receptor, which is the receptor for all neurotrophins, is a transmembrane glycoprotein of the tumoral necrosis factor (TNF) receptor family (W.J. Friedman and L.A. Greene, Exp. Cell. Res., (1999), 253, 131-142). The p75 receptor is expressed in several cell types, and several biological functions have been attributed to said receptor: firstly, modulation of the affinity of neurotrophins for receptor tyrosine kinases (trk); secondly, in the absence of trk, induction of a signal for cell death by apoptosis. Moreover, the neurotrophin precursors, proneurotrophins, are capable of binding to p75 with a high affinity, and are considered to be powerful inducers of p75 dependent apoptosis in neurons and certain cell lines.

The p75 receptor is a key component in the process of cell survival/proliferation or death, not only in the central nervous system but also in a number of peripheral tissues like nerves, liver, bladder muscles and prostate. This pleiotropic receptor has multiple and

even opposite functions, which likely depend on the cell and tissue type, as well as on the physio-pathological status of the organism. It has been observed that mice selectively over expressing bladder Nerve Growth Factor exhibited: increased bladder wall innervation, decreased bladder capacity, more frequent micturition, increased non-voiding bladder contractions; all consistent with an overactive bladder (OAB) phenotype (Girard BM and al "Neurotrophin/receptor expression in urinary bladder of mice with overexpression of NGF in urothelium" Am J Physiol Renal Physiol. 300: F345–F355, (2011)).

It has also been observed that in humans with obstructed bladders or those with interstitial cystitis or bladder pain syndrome (IC/BPS), tissue levels of NGF are elevated compared to healthy controls (Steers WD and Tuttle JB, Nat Rev Urol (2006), vol 3(2), 101-110; Liu HZ et al. (2009), BJUI 104, 1476-1481).

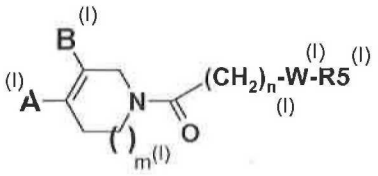
p75 receptors and Trks receptors are expressed throughout the rat urinary bladder and are present in nerve fibers of the detrusor smooth muscle, the suburothelial nerve plexus, urothelial cells, and nerve fibers associated with the suburothelial bladder vasculature (Klinger MB and al"p75NTR Expression in Rat Urinary Bladder Sensory Neurons and Spinal Cord with Cyclophosphamide-Induced Cystitis" J. Comp. Neurol. 507: 1379–1392, (2008)).

p75 receptors overexpression on detrusor smooth muscle cells altogether with overexpression of NGF could play a deleterious role on the functionality of detrusor muscle.

According to a first object, the present invention provides for the use of a p75 receptor antagonist in the preparation of medicaments for use in the treatment and/or prevention of overactive bladder and other urinary disorders.

In the present patent application the terms "use of a p75 receptor antagonist in the preparation of medicaments" have to be understood as synonyms of the terms "a p75 receptor antagonist for the preparation of a medicament for use", or "a p75 receptor antagonist for use", or "a p75 receptor antagonist for use as a medicament"

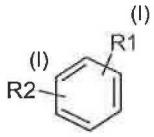
According to another object of the invention, the present invention provides for the use of a p75 receptor antagonist of the following general formula (I):



(I)

in which:

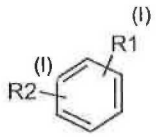
- $m^{(I)}$ represents 0 or 1;
- $A^{(I)}$ represents:



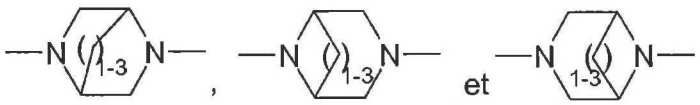
and $B^{(I)}$ represents a hydrogen atom

or

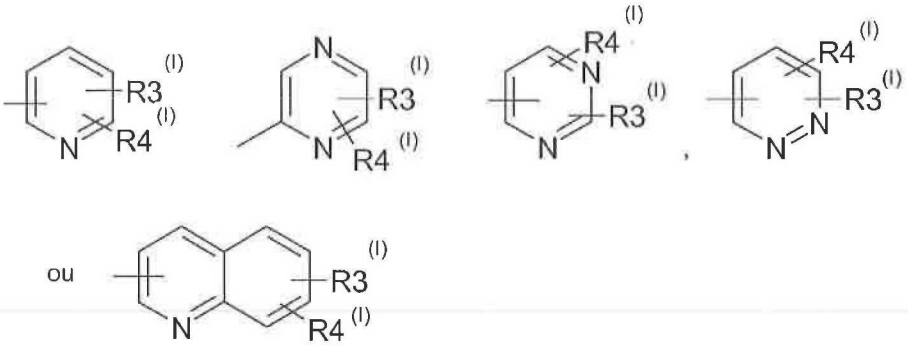
$A^{(I)}$ represents a hydrogen atom and $B^{(I)}$ represents:



- $W^{(I)}$ - is a nitrogenous heterocycle chosen from:



- 1-3 represents 1, 2 or 3;
- $n^{(I)}$ represents 1 or 2;
- $R1^{(I)}$ represents a halogen atom, a (C_1-C_4)alkyl group, a trifluoromethyl radical, a (C_1-C_4)alkoxy group or a trifluoromethoxy radical;
- $R2^{(I)}$ represents a hydrogen atom, a halogen atom, a (C_1-C_4)alkyl group, a trifluoromethyl radical, a (C_1-C_4)alkoxy group, a trifluoromethoxy radical, a $COOR^{(I)}$ group or a $CONH_2$ group;
- $R5^{(I)}$ represents a group of formula:



ou

in which $R3^{(I)}$ and $R4^{(I)}$, located on any one of the available positions, independently represent a hydrogen atom, a halogen atom, a $(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_4)$alkoxy group, a trifluoromethyl or trifluoromethoxy radical, a cyano, or a COOH, $COO(C_1\text{-}C_4)$alkyl, $CONH_2$, $CONR6^{(I)}\ R7^{(I)}$ or $NHCOR^{(I)}$ group;

- $R^{(I)}$, $R6^{(I)}$ and $R7^{(I)}$ represent independently of each other a $(C_1\text{-}C_6)$alkyl group;

in the preparation of medicaments for use in the treatment and/or prevention overactive bladder.

The compounds of Formula (I) may contain one or more asymmetrical carbon atoms. They may therefore exist in the form of enantiomers or of diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures, are part of the invention.

The compounds of Formula (I) may exist in the form of bases or addition salts with acids. Such addition salts are part of the invention.

These salts may be prepared with pharmaceutically acceptable acids, but the salts of other acids that are useful, for example, for purifying or isolating the compounds of Formula (I) are also part of the invention.

In the context of the compounds of general formula (I):

- the term "a halogen atom" is intended to mean: a fluorine, a chlorine, a bromine or an iodine;

- the term "an alkyl group" is intended to mean: a linear or branched, saturated aliphatic group. By way of examples, mention may be made of a $C_1\text{-}C_4$ alkyl group that may represent a methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl;

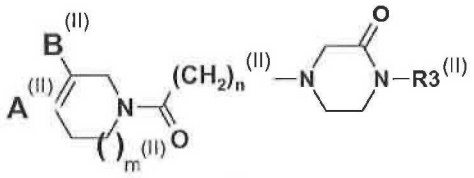
- the term "a fluoroalkyl group" is intended to mean: an alkyl group of which one or more of the hydrogen atoms has (have) been substituted with a fluorine atom;

- the term "a perfluoroalkyl group" is intended to mean: an alkyl group of which all the hydrogen atoms have been substituted with a fluorine atom, for example trifluoroalkyl;

- the term "an alkoxy group" is intended to mean: an –O-alkyl radical where the alkyl group is as defined above.

These compounds and their method of preparation are described in WO2009/150388 (US2011/144116), from which the content is included herein by reference.

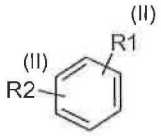
According to another object of the invention, the present invention provides for the use of a p75 receptor antagonist of the following general formula (II):



(II)

in which:

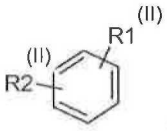
- $m^{(II)}$ is 0 or 1;
- $A^{(II)}$ is:



and $B^{(II)}$ is a hydrogen atom

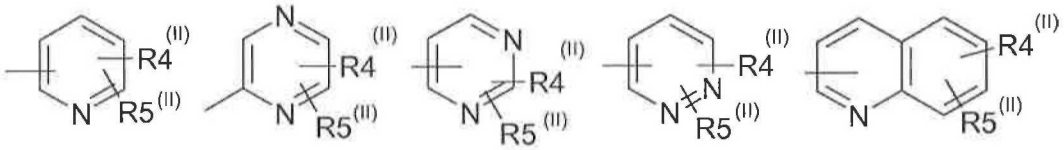
or

$A^{(II)}$ is a hydrogen atom and $B^{(II)}$ is:



;

- $R1^{(II)}$ and $R2^{(II)}$, which may be identical or different, are independently a hydrogen or halogen atom, a $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$fluoroalkyl, $(C_1$-$C_2)$perfluoroalkyl or $(C_1$-$C_4)$alkoxy group or a trifluoromethoxy group;
- $n^{(II)}$ is 1 or 2;
- $R3^{(II)}$ is a group of formula:



where $R4^{(II)}$ and $R5^{(II)}$, which may be identical or different, are located on any available positions and are independently a hydrogen or halogen atom, a hydroxyl, a $(C_1$-$C_4)$alkyl,

(C_1-C_4)fluoroalkyl, (C_1-C_2)perfluoroalkyl or (C_1-C_4)alkoxy group, a trifluoromethoxy group, a cyano group, or a COOH, COO(C_1-C_4)alkyl, $CONH_2$, $CONR6^{(III)}$ $R7^{(III)}$ or $NHCOR^{(III)}$ group;

- $R^{(II)}$, $R6^{(II)}$ and $R7^{(II)}$ are independently of each other a (C_1-C_6)alkyl group;

in the preparation of medicaments for use in the treatment and/or prevention overactive bladder.

The compounds of formula (II) may comprise one or more asymmetrical carbon atoms. They may therefore exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers and also mixtures thereof, including racemic mixtures, form part of the invention.

The compounds of formula (II) may exist in the form of bases or of addition salts with acids. Such addition salts form part of the invention.

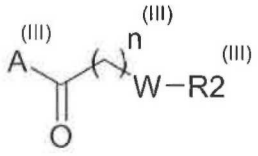
These salts may be prepared with pharmaceutically acceptable acids, but the salts of other acids that are useful, for example, for purifying or isolating the compounds of formula (II) also form part of the invention.

In the context of the compounds of general formula (II):

- the term “a halogen atom” is intended to mean: a fluorine, a chlorine, a bromine or an iodine;
- the term “an alkyl group” is intended to mean: a linear or branched, saturated aliphatic group. By way of examples, mention may be made of a C_1-C_4 alkyl group which may represent a methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl;
- the term “a fluoroalkyl group” is intended to mean: an alkyl group of which one or more hydrogen atoms have been substituted with a fluorine atom;
- the term “a perfluoroalkyl group” is intended to mean: an alkyl group of which all the hydrogen atoms have been substituted with a fluorine atom;
- the term “an alkoxy group” is intended to mean: an –O-alkyl group where the alkyl group is as defined above.

These compounds and their method of preparation are described in WO2009/150387 (US2011/144122), from which the content is included herein by reference.

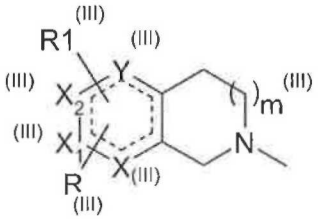
According to another object of the invention, the present invention provides for the use of a p75 receptor antagonist of the following general formula (III):



(III)

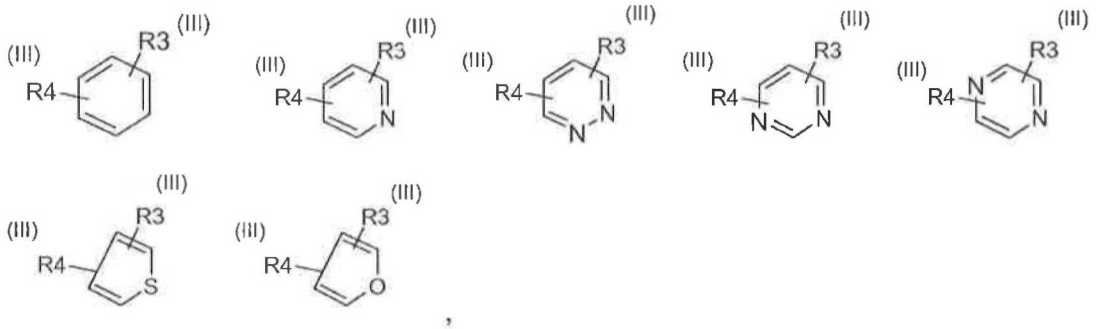
in which:

- $A^{(III)}$ represents a group:



- $n^{(III)}$ represents 1 or 2;
- $m^{(III)}$ represents 0 or 1;
- $Y^{(III)}$ represents a carbon, nitrogen, sulphur or oxygen atom or a single or double bond;
- $X^{(III)}$, $X_1^{(III)}$ and $X_2^{(III)}$ represent a carbon, nitrogen, sulphur or oxygen atom, it being understood that at least one of $X^{(III)}$, $X_1^{(III)}$ and $X_2^{(III)}$ is other than a carbon atom;
- $R^{(III)}$ and $R1^{(III)}$, located on any one of the available positions, independently represent a hydrogen atom, a halogen atom, a $(C_1\text{-}C_4)$alkyl group, a $(C_1\text{-}C_4)$alkoxy group, a perfluoroalkyl radical, a trifluoromethoxy radical, a cyano, or a COOH, $COO(C_1\text{-}C_4)$alkyl, $CONR5^{(III)}\,R6^{(III)}$ or $NHCOR5^{(III)}$ group;

or $R1^{(III)}$ represents a group chosen from:



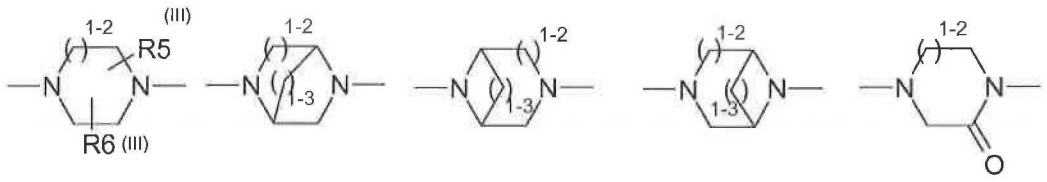
,

the definition of $R^{(III)}$ remaining unchanged;

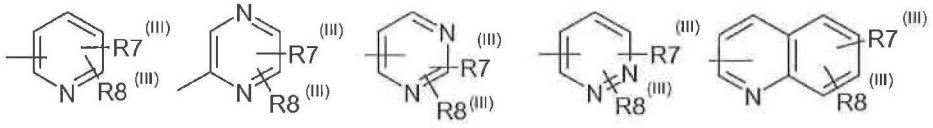
- $R3^{(III)}$ and $R4^{(III)}$, located on any one of the available positions, independently represent a hydrogen atom, a halogen atom, a $(C_1\text{-}C_4)$alkyl group, a $(C(C_1\text{-}C_4)\text{-}C4)$alkoxy group, a

perfluoroalkyl radical, a trifluoromethoxy radical, a cyano, or a COOH, $COO(C_1-C_4)$alkyl, $CONR5^{(III)}$ $R6^{(III)}$ or $NHCOR5^{(III)}$ group;

- $W^{(III)}$ - is a nitrogenous heterocycle chosen from:

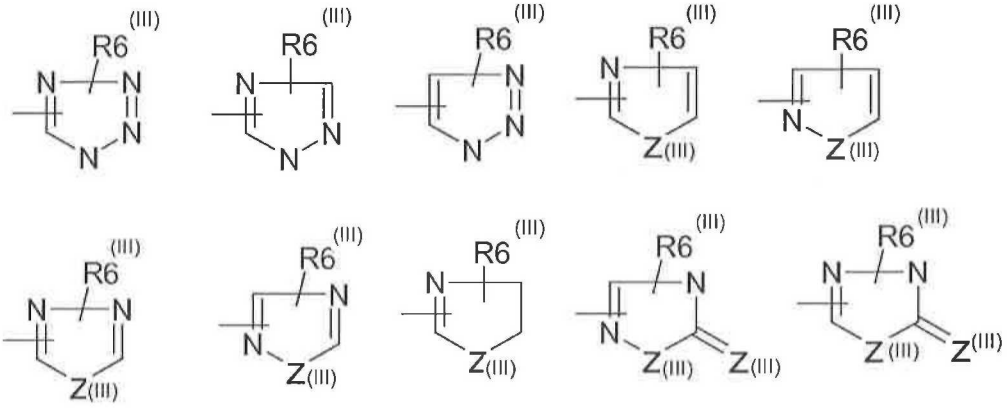


- 1-2 represents 1 or 2;
- 1-3 represents 1, 2 or 3;
- $R2^{(III)}$ represents a group of formula:



- $R7^{(III)}$ and $R8^{(III)}$, located on any one of the available positions, independently represent a hydrogen atom, a halogen atom, a (C_1-C_4))alkyl group, a (C_1-C_4)alkoxy group, a trifluoromethyl radical, a trifluoromethoxy radical, a cyano, or a COOH, $COO(C_1-C_4)$alkyl, $COO(C_1-C_4)$cycloalkyl, $SO(C_1-C_4)$alkyl, $SO2(C_1-C_4)$alkyl, $CONH_2$, $CONR5^{(III)}$ $R6^{(III)}$ or $NHCOR5^{(III)}$ group;

or one of $R7^{(III)}$ and $R8^{(III)}$ represents a heterocycle chosen from:



- $Z^{(III)}$ represents an oxygen or sulphur atom;
- $R5^{(III)}$ and $R6^{(III)}$ represent a hydrogen or a C1-C6 alkyl group;

in the preparation of medicaments for use in the treatment and/or prevention overactive bladder.

The compounds of formula (III) may comprise one or more asymmetrical carbon atoms. They may therefore exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures, form part of the invention.

The compounds of formula (III) may exist in the form of bases or of addition salts with acids. Such addition salts form part of the invention.

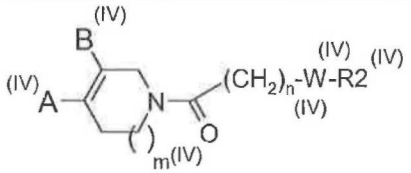
These salts may be prepared with pharmaceutically acceptable acids, but the salts of other acids that are useful, for example, for purifying or isolating the compounds of formula (III) also form part of the invention.

In the context of the compounds of general formula (III):

- the term "a halogen atom" is intended to mean: a fluorine, a chlorine, a bromine or an iodine;
- the term "an alkyl group" is intended to mean: a linear, branched or cyclic, saturated aliphatic group. By way of examples, mention may be made of a C1-C4 alkyl group which may represent a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, cyclopropyl or cyclobutyl;
- the term "a fluoroalkyl group" is intended to mean: an alkyl group of which one or more hydrogen atoms have been substituted with a fluorine atom;
- the term "a perfluoroalkyl group" is intended to mean: an alkyl group of which all the hydrogen atoms have been substituted with a fluorine atom, for example a trifluoroalkyl group such as trifluoromethyl;
- the term "an alkoxy group" is intended to mean: an -O-alkyl radical where the alkyl group is as defined above;
- the term "a perfluoroalkoxy group" is intended to mean: an alkoxy group of which all the hydrogen atoms have been substituted with a fluorine atom, for example a trifluoroalkoxy group such as trifluoromethoxy;
- the term "a cycloalkyl group" is intended to mean: a cyclic alkyl group. By way of examples, mention may be made of cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc., groups.
- the term "a halogen atom" is intended to mean: a fluorine, a chlorine, a bromine.

These compounds and their method of preparation are described in WO2011/080444 (US2012/245149), from which the content is included herein by reference.

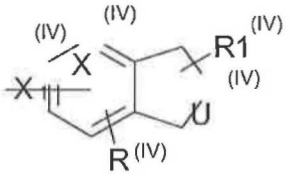
According to another object of the invention, the present invention provides for the use of a p75 receptor antagonist of the following general formula (IV):



(IV)

in which:

- $n^{(IV)}$ represents 1 or 2;
- $m^{(IV)}$ represents 0 or 1;
- $A^{(IV)}$ represents a fused heterocyclic group of formula ($Y^{(IV)}$)



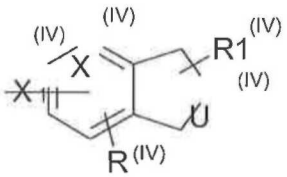
(Y)

and $B^{(IV)}$ represents a hydrogen atom;

or

$A^{(IV)}$ represents a hydrogen atom; and

$B^{(IV)}$ represents a fused heterocyclic group of formula ($Y^{(IV)}$)



(Y)

The fused heterocycle of formula $Y^{(IV)}$ may be attached to the rest of the molecule via any of the available carbon atoms, and in which:

- $U^{(IV)}$ completes:

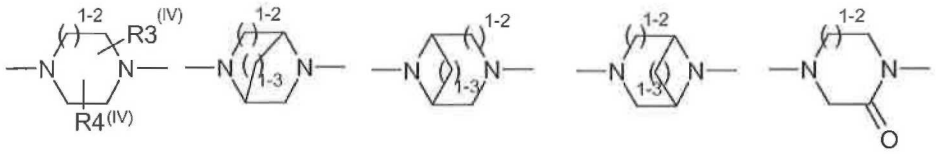
  - either an aromatic or saturated 6-atom nucleus, containing one or two nitrogen atoms, the nucleus possibly being substituted with one or two halogen atoms, one or two (C1-C4)alkyl or (C1-C4)alkoxy groups, or one or two perfluoroalkyl radicals;

  - or an aromatic or saturated 5-atom nucleus, containing a nitrogen, oxygen or sulfur atom, the nucleus possibly being substituted with one or two (C1-C4)alkyl groups;

- $X^{(IV)}$ and $X1^{(IV)}$ represent independently of each other CH or N;

- $R^{(IV)}$ and $R1^{(IV)}$ located on any of the available positions, independently represent a hydrogen atom, a halogen atom, a $(C_1\text{-}C_4)$alkyl group, $(C_1\text{-}C_4)$alkoxy, a perfluoroalkyl or trifluoromethoxy radical, a cyano or a COOH, $COO(C_1\text{-}C_4)$alkyl, $CONR3^{(IV)}R4^{(IV)}$ or $NHCOR3^{(IV)}$ group;

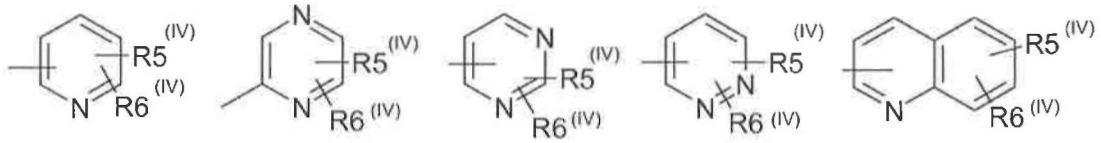
-$W^{(IV)}$- is a nitrogenous heterocycle chosen from:



- 1-2 represents 1 or 2;

- 1-3 represents 1, 2 or 3;

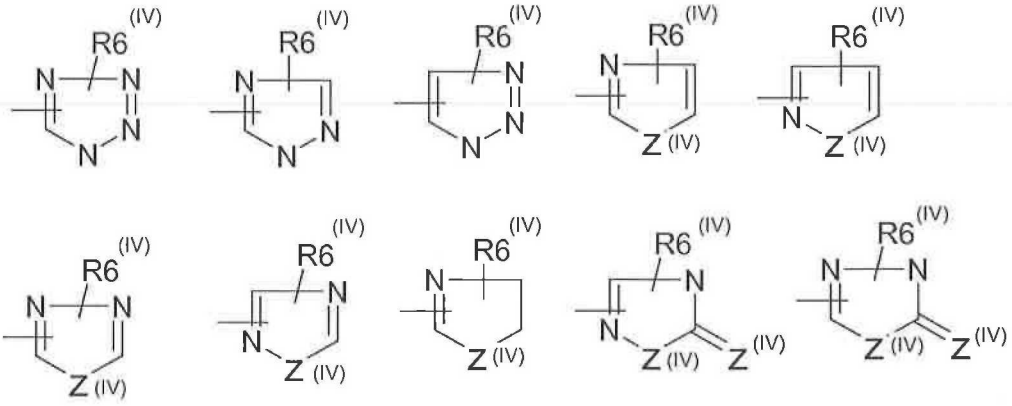
- $R2^{(IV)}$ represents a group of formula:



- in which $R5^{(IV)}$ and $R6^{(IV)}$, located on any of the available positions, independently represent a hydrogen atom, a halogen atom, a $(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_4)$alkoxy group, a trifluoromethyl or trifluoromethoxy radical, a cyano or a group COOH, $COO(C_1\text{-}C_4)$alkyl,

$COO(C_1\text{-}C_4)$cycloalkyl, $SO(C_1\text{-}C_4)$alkyl, $SO2(C_1\text{-}C_4)$alkyl, $CONR3^{(IV)}R4^{(IV)}$, $NR3^{(IV)}R4^{(IV)}$ or $NHCOR3^{(IV)}$;

or one of the groups $R5^{(IV)}$ and $R6^{(IV)}$ may also represent a heterocycle chosen from:



- $Z^{(IV)}$ represents an oxygen or sulfur atom;

- $R3^{(IV)}$ and $R4^{(IV)}$ represent a hydrogen or a $C_1\text{-}C_6$ alkyl group;

in the preparation of medicaments for use in the treatment and/or prevention overactive bladder.

The compounds of formula (IV) may comprise one or more asymmetric carbon atoms. They may thus exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures, form part of the invention.

The compounds of formula (IV) may exist in the form of bases or of acid-addition salts. Such addition salts form part of the invention.

These salts may be prepared with pharmaceutically acceptable acids, but the salts of other acids that are useful, for example, for purifying or isolating the compounds of formula (IV) also form part of the invention.

In the context of of the compounds of general formula (IV), the following definitions apply:

- a halogen atom: a fluorine, a chlorine, a bromine or an iodine;
- an alkyl group: a saturated, linear, branched or cyclic aliphatic group. Examples that may be mentioned include a group (C1-C4)alkyl which may represent a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, cyclopropyl or cyclobutyl;

- a fluoroalkyl group: an alkyl group in which one or more hydrogen atoms have been replaced with a fluorine atom;
- a perfluoroalkyl group: an alkyl group in which all the hydrogen atoms have been replaced with a fluorine atom, for example trifluoroalkyl;
- an alkoxy group: a radical -O-alkyl in which the alkyl group is as defined previously;
- a perfluoroalkoxy group: an alkoxy group in which all the hydrogen atoms have been replaced with a fluorine atom, for example trifluoroalkoxy;
- a cycloalkyl group: a cyclic alkyl group. Examples that may be mentioned include cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc., groups.

These compounds and their method of preparation are described in WO2011/080445 (US2012/245150), from which the content is included herein by reference.

According to another object of the invention, the present invention provides for the use of a p75 receptor antagonist selected from:

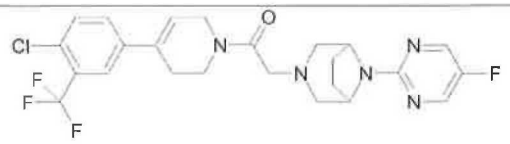
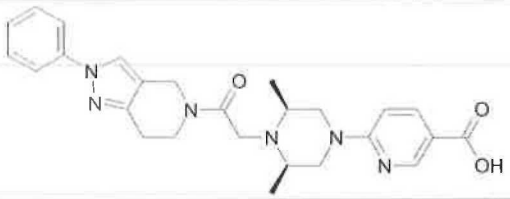
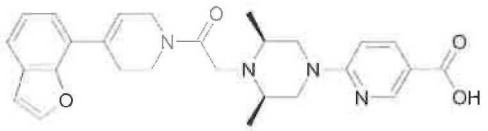
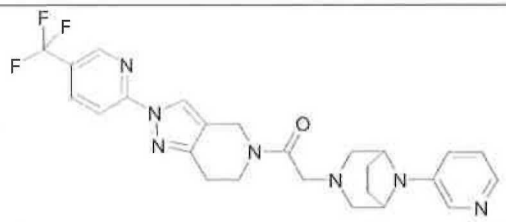
- compound n°1: 1-[4-(4-chloro-3-trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-[8-(5-fluoro-pyrimidin-2-yl)-3,8-diaza-bicyclo[3.2.1]oct-3-yl]-ethanone ;
- compound n°2: 6-{(3S,5R)-3,5-Dimethyl-4-[2-oxo-2-(2-phenyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethyl]piperazin-1-yl}nicotinic acid hydrochloride;
- compound n°3: 6-{(3S,5R)-4-[2-(4-benzofuran-7-yl-3,6-dihydro-2H-pyridin-1-yl)-2-oxoethyl]-3,5-dimethylpiperazin-1-yl}nicotinic acid;
- compound n°4: 1-(2-phenyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)-2-(8-pyridin-3-yl-3,8-diazabicyclo[3.2.1]oct-3-yl)ethanone;

the above compounds can also exist in the form of a base or of an addition salt with an acid;

in the preparation of medicaments for use in the treatment and/or prevention overactive bladder.

These compounds and their mode of preparation are respectively described as compound n°11 in WO2009/150388 for compound n°1, as compounds n°21 and n°28 in WO2011/080444 ((US2012/245149)) for compounds n°2 and n°4 and as compound n°57 in WO2011/080445 (US2012/245150) for compound n°3, from which the content is included herein by reference.

The following table describes the structure of these compounds.

Compound n°	Structure
1	
2	
3	
4	

Said p75 receptor antagonists above, and the pharmaceutically acceptable salts thereof, may be used at daily doses of 0.1 to 200 mg per kilo of body weight of the mammal to be treated, preferably at daily doses of from 0.5 to 100 mg/kg. In humans, the dose may vary preferably from 0.5 mg to 50 mg per day, in particular from 1 to 30 mg, depending on the age of the individual to be treated, the type of treatment, prophylactic or curative, and the seriousness of the disorder. Said p75 receptor antagonists are generally administered as a dosage unit of 0.5 to 50 mg, preferably of 1 to 30 mg, of active principle, one to five times a day. Preferable unit dosage forms comprise 1 or 30 mg of p75 receptor antagonists.

Said dosage units are preferably formulated in pharmaceutical compositions in which the active principle is mixed with a pharmaceutical excipient.

In the pharmaceutical compositions of the present invention, use can me made for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, transdermal or rectal administration.

Said p75 receptor antagonists, and the pharmaceutically acceptable salts thereof, may be administered in unit administration forms, mixed with conventional pharmaceutical

supports, to animals and humans for treating the abovementioned disorders. The unit administration forms which are suitable comprise oral forms such as tablets, gel capsules, powders, granules and oral solutions or suspensions, sublingual and buccal administration forms, subcutaneous, intramuscular or intravenous administration forms, local administration forms and rectal administration forms.

When a solid composition in the form of tablets is prepared, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets may be coated with sucrose or other suitable materials, or they may be treated such that they have sustained or delayed activity and that they release, in a continuous manner, a predetermined amount of active principle. Usual excipients include lactose monohydrate, microcrystalline cellulose, povidone, sodium carboxymethylstarch, magnesium stearate, ethylcellulose, hypromellose, macrogol 400, titane dioxide.

A preparation of gel capsules is obtained by mixing the active ingredient with a diluent and pouring the mixture obtained into soft or hard gel capsules.

A preparation in the form of a syrup or elixir may contain the active ingredient together with a sweetener, preferably a calorie-free sweetener, methylparaben and propylparaben as antiseptics, and also a flavour enhancer and a suitable colorant.

The water-dispersible powders or granules may contain the active ingredient mixed with dispersing agents or wetting agents, or suspending agents, such as polyvinylpyrrolidone, and also with sweeteners or flavour correctors.

For local administration, the active principle is mixed into an excipient for preparing creams or ointments, or it is dissolved in a vehicle for intraocular administration, for example in the form of an eyewash.

For rectal administration, use is made of suppositories prepared with binders which melt at rectal temperature, for example cocoa butter or polyethylene glycols.

For parenteral administration, aqueous suspensions, saline solutions or injectable sterile solutions which contain pharmacologically compatible dispersion agents and/or wetting agents, for example propylene glycol or butylene glycol, are used.

The active principle may also be formulated in the form of microcapsules, optionally with one or more supports or additives.

According to another object, the present invention provides a method of treating and/or preventing overactive bladder or other urinary disorders in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a p75 receptor antagonist. In one aspect, the p75

receptor antagonist is selected from a compound of general formula (I), a compound of general formula (II), a compound of general formula (III), and a compound of the following general formula (IV). In another aspect, the p75 receptor antagonist is selected from the group consisting of compound n°1: 1-[4-(4-chloro-3-trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-[8-(5-fluoro-pyrimidin-2-yl)-3,8-diaza-bicyclo[3.2.1]oct-3-yl]-ethanone; compound n°2: 6-{(3S,5R)-3,5-Dimethyl-4-[2-oxo-2-(2-phenyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)ethyl]piperazin-1-yl}nicotinic acid hydrochloride; compound n°3: 6-{(3S,5R)-4-[2-(4-benzofuran-7-yl-3,6-dihydro-2H-pyridin-1-yl)-2-oxoethyl]-3,5-dimethylpiperazin-1-yl}nicotinic acid; and compound n°4: 1-(2-phenyl-2,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)-2-(8-pyridin-3-yl-3,8-diazabicyclo[3.2.1]oct-3-yl)ethanone; the above compounds can also exist in the form of a base or of an addition salt with an acid.

As used herein, the term "therapeutically effective amount" is meant to describe an amount of a compound, composition, medicament or active ingredient effective in producing the desired therapeutic effect.

The following examples further illustrate the present invention.

EXAMPLES

Brief description of the drawings

Figure 1 is a cystometrogram (CMG) from a rat during the light phase in response to continuously-infused saline, in normal filling-voiding micturition cycle.

Figure 2 shows the effect of the compounds on intercontraction intervals (ICI) in SHR male rats, characterized by overactive bladder (OAB).

Figure 3 represents the positive activity of the compounds according to the invention on bladder capacity of SHR male rats.

Figure 4 shows the dose response activity (3, 10, 30 mg/kg po) of compound 2 on intercontraction intervals in SHR male rats.

Figure 5 represents the dose dependent activity of compound n°2 on bladder capacity in SHR male rats.

Figure 6 shows the effect of a one-week treatment with compound n°2 on intercontraction intervals (ICI) in SHR male rats.

Figure 7 shows the effect of a one-week treatment with compound n°2 on bladder capacity in SHR male rats.

General methods

Animal preparation

Male adult SHR/N Ico rats (250g; Charles River Italy), were housed 7 days prior to the surgery with free access to standard chow and water. Animals were used in accordance with sanofi international ethical code and the international principles governing the care and treatment of laboratory animals, (E.E.E Council Directive 86/609, DJL358, 1 Cec. 12, 1987) in a fully accredited AAALAC facility.
All efforts were made to minimize the potential for animal pain, stress, or distress.

A lower midline abdominal incision was performed under general anesthesia with 2–3% isoflurane using aseptic techniques. Their body temperature was maintained at 37° C using a homeothermic blanket. Polyethylene tubing was inserted into the dome of the bladder and secured in place with a 6–0 nylon purse-string suture. The distal end of the tubing was sealed, tunneled subcutaneously, and externalized at the back of the neck, out of the animal's reach. At the moment of the surgery animals were 16 weeks old.

Cystometry

After one week from surgery, animals were placed in a Small Animal Cystometry Lab Station (MED Associates, St. Albans, Vermont) for urodynamic measurements. Prior to the start of recording the bladder was emptied and the catheter was connected via a T-tube to a pressure transducer and microinjection pump. Isotonic saline (0.9% NaCl at room temperature) was infused into the bladder at a rate of 10 ml per hour. An analytical balance beneath the wire-bottomed animal cage measured the amount of urine voided during continuous cystometry. A single cystometrogram is defined as the simultaneous recording of intravesical pressure, infused volume and voided volume during a single filling-voiding cycle. At least 4 reproducible micturition cycles are recorded (basal period) after the initial stabilization period of 25 to 30 minutes, using MED-CMG software (Catamount Research &Development Company).
Then, vehicle or compounds were administered orally at 2 ml/kg.

Due to kinetic profile of compounds, urodynamic assessment was performed 1h after treatment and at least 4 reproducible micturition cycles were recorded.

Experiments were performed at similar times of day to avoid the possible impact of circadian rhythm variations (Herrera and al "Diurnal variation in Urodynamics of rat." *PLoS ONE 5(8) (2010)*). At the end of experiments, animals were sacrificed with an overdose of pentobarbital.

Data analysis

The cystometrograms are analyzed using a specific software, SOF-552 cystometry data analysis.

The following endpoints have been considered (Figure 1):

1. Intercontaction intervals (sec) (ICI) - Time between micturition events (micturition interval)
2. Threshold pressure (mmHg) (TP) - Bladder pressure immediately prior to micturition
3. Maximum bladder pressure (mmHg) (Max P) -Highest bladder pressure associated with voiding
4. Minimum bladder pressure (mmHg) (Min P) - Lowest bladder pressure during bladder filling
5. Infused volume (µl) (Inf. Vol) -Volume of saline infused during the micturition cycle
6. Average bladder pressure (mmHg) (Aver P) - Average bladder pressure during bladder filling

Exclusion Criteria

Rats were removed from study, before any treatment when adverse events occurred that included: a reduction in body weight post-surgery, lethargy superior or equal to 20%, pain, or distress not relieved by sanofi's approved regimen of postoperative analgesics or hematuria.

Animals with atypical micturition pattern are excluded from the study.

Expression of data and statistical analysis

In order to limit the impact of inter-group or intra-group variability, all data were expressed as % of control period (100%), as mean ± standard error of mean (SEM) and were averaged per group of treatment. A one way analysis of variance (ANOVA), followed by Newman-Keuls' test or Dunnett's test, were used. A probability value of $p<0.05$ was regarded as significant.

EXAMPLE 1: Effects of an acute treatment with p75 antagonists on urodynamic parameters in SHR rats characterized by spontaneous overactive bladder (OAB).

Drugs

Vehicle: 0.5% Polysorbate 80 (PS80) solution in buffered methylcellulose (MC 0.6%)

Compound n°1 at 10 mg/kg: suspension (0.5% PS80 plus MC 0.6%)

Compound n°2 at 3, 10, 30 mg/kg: suspension (0.5% PS80 plus MC 0.6%)

Compound n°3 at 10 mg/kg: suspension (0.5% PS80 plus MC 0.6%)

Compound n°4 at 10 mg/kg: suspension (0.5% PS80 plus MC 0.6%)

Experimental design:

In order to investigate the role of compounds according to the invention in the micturition pathway, 5 groups of 4-12 rats are used:

Group 1, Vehicle per os (po) (n=10)

Group 2, Compound n°1 at 10 mg/kg po (n=12)

Group 3, Compound n°2 at 10 mg/kg po (n=6)

Group 4, Compound n°3 at 10 mg/kg po (n=4)

Group 5, Compound n°4 at 10 mg/kg po (n=5)

In order to perform a dose response of Compound n°2 (3-10-30 mg/kg), 4 groups of 6-9 rats are used:

Group 1, Vehicle po (n=8)

Group 2, Compound n°2 at 3 mg/kg po (n=7)

Group 3, Compound n°2 at 10 mg/kg po (n=6)

Group 4, Compound n°2 at 30 mg/kg po (n=9)

1. RESULTS

In order to limit the impact of inter-group or intra-group variability that existed; the data have been expressed as percentage of control values.

1. The compounds at 10 mg/kg po increased the ICI (intercontraction intervals) and the bladder capacity (infused volume)

For ICI (Figure 2)

Vehicle 111.7 ± 10.3 %, compound n°1, 195.5± 15.4 %, compound n°2, 10 mg/kg po 199.7 ± 28.5%, compound n°3, 10 mg/kg po 167.2 ± 20.3%, compound n°4, 10 mg/kg po 186.3 ± 26.9%

For Infused volume (Figure 3)

Vehicle 111.7 ± 10.3 %, compound n°1, 194.9± 15.3 %, compound n°2, 10 mg/kg po 198.9 ± 28.3%, compound n°3, 10 mg/kg po 167.14 ± 20%, compound n°4, 10 mg/kg po 186.2 ± 26.9%

2. The compounds at 10 mg/kg po increased the ICI (intercontraction intervals) and the bladder capacity (infused volume) dose dependently

For ICI (Figure 4)

Vehicle 114.3 ± 12.01 %, compound n°2, 3 mg/kg po 160.9 ± 21.8%, compound n°2, 10 mg/kg po 199.7 ± 28.5%, compound n°2, 30 mg/kg po 210.5 ± 24.7%

For Infused volume (Figure 5)

Vehicle 114.3 ± 12 %, compound n°2, 3 mg/kg po 160.8 ± 21.7%, compound n°2, 10 mg/kg po 198.9 ± 28.3%, compound n°2, 30 mg/kg po 209.9 ± 24.5%.

2. CONCLUSION

The compounds increased the ICI and the bladder capacity in this pathophysiological model. The compounds had no effect on micturition pressure parameters suggesting a specific response. These compounds can thus be useful for the treatment and/or prevention of overactive bladder.

EXAMPLE 2: Effects of one-week chronic treatment with a p75 antagonist on urodynamic parameters in SHR rats characterized by spontaneous overactive bladder (OAB).

Drug:

Compound n°2 at 10 mg/kg: suspension (0.5% PS80 plus MC 0.6%)

The treatment started at least 5 days after surgery, and lasted 7 days. The cystometry test was performed 24 h after the end of the last treatment.

Experimental design:

2 groups of 14-15 rats were constituted:

- Control rats vehicle treated vehicle 7 days
- Treated rats 7 days with compound n°2 at 10 mg/kg/2ml po

For avoiding numerosity problems linked to loss of intrabladder-catheter, 30% animals more were used in this experiment.

1. RESULTS

In order to limit the impact of inter-group or intra-group variability that existed; the data have been expressed as percentage of control values.

For ICI (Figure 6) Vehicle 122.5 ±10.15 %, compound n°2, 173.8 ± 21.1%,

For Infused volume (Figure 7) Vehicle 339.90 ± 28.07 %, compound n°2 173.7 ± 21.1 %

2. CONCLUSION

The chronic treatment (one week) with a p75 antagonist, affects the micturition reflex in SHR rats, characterized by DO-OAB. The compound n°2 increased the ICI and the bladder capacity in this pathophysiological model. The compound had no effect on micturition pressure parameters suggesting a specific response. This compound can thus be useful for the treatment and/or prevention of overactive bladder.

Pharmaceutical composition according to the invention

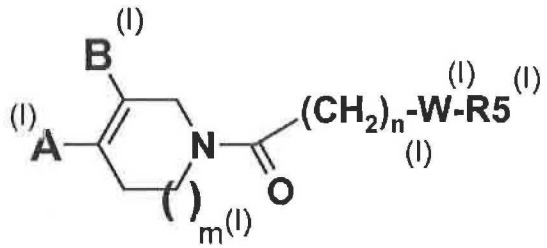
As a representative example, a unitary dosage form of a compound of the invention in the form of a tablet may comprise the following constituents:

p75 receptor antagonist	5,0 mg
Lactose	122,0 mg
Microcristalline cellulose	36,0 mg
Sodium carboxymethylstarch	7,0 mg
Polyvidone	9 mg
Magnesium stearate	1,0 mg

CLAIMS

1. Use of a p75 receptor antagonist in the preparation of medicament for use in the treatment and/or prevention of overactive bladder,

wherein said p75 receptor antagonist is a compound of general formula (I):

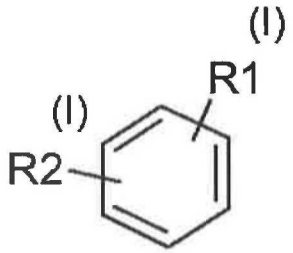


(I)

in which:

- $m^{(I)}$ represents 0 or 1;

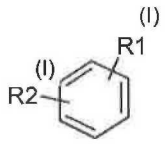
- $A^{(I)}$ represents:



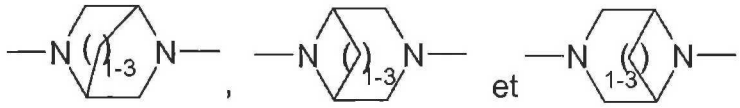
and $B^{(I)}$ represents a hydrogen atom

Or

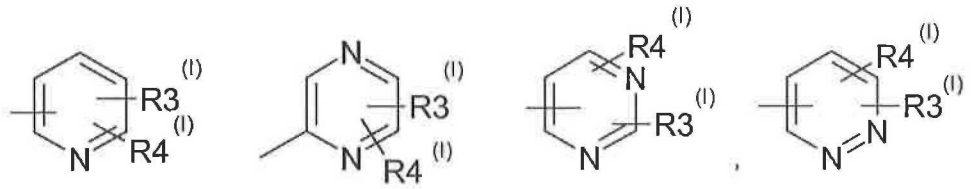
$A^{(I)}$ represents a hydrogen atom and $B^{(I)}$ represents:



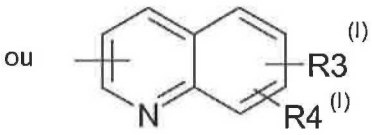
- $W^{(I)}$ - is a nitrogenous heterocycle chosen from:



- 1-3 represents 1, 2 or 3;
- $n^{(I)}$ represents 1 or 2;
- $R1^{(I)}$ represents a halogen atom, a $(C_1$-$C_4)$alkyl group, a trifluoromethyl radical, a $(C_1$-$C_4)$alkoxy group or a trifluoromethoxy radical;
- $R2^{(I)}$ represents a hydrogen atom, a halogen atom, a $(C_1$-$C_4)$alkyl group, a trifluoromethyl radical, a $(C_1$-$C_4)$alkoxy group, a trifluoromethoxy radical, a $COOR^{(I)}$ group or a $CONH_2$ group;
- $R5^{(I)}$ represents a group of formula:



ou



in which $R3^{(I)}$ and $R4^{(I)}$, located on any one of the available positions, independently represent a hydrogen atom, a halogen atom, a $(C_1$-$C_4)$alkyl or $(C_1$-$C_4)$alkoxy group, a trifluoromethyl or trifluoromethoxy radical, a cyano, or a COOH, $COO(C_1$-$C_4)$alkyl, $CONH_2$, $CONR6^{(I)}$ $R7^{(I)}$ or $NHCOR^{(I)}$ group;

- $R^{(I)}$, $R6^{(I)}$ and $R7^{(I)}$ represent independently of each other a $(C_1$-$C_6)$alkyl group;
- in the form of bases or addition salts with acids.

2. Use according to claim 1, wherein said p75 receptor antagonist is:

- compound n°1: 1-[4-(4-chloro-3-trifluoromethyl-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-[8-(5-fluoro-pyrimidin-2-yl)-3,8-diaza-bicyclo[3.2.1]oct-3-yl]-ethanone ;

in the form of a base or of an addition salt with an acid.

NOVEL THERAPEUTIC USE OF P75 RECEPTOR ANTAGONISTS

Abstract

The present invention provides for the use of a p75 receptor antagonist or its pharmaceutically acceptable salts for the preparation of a medicament for use in the treatment and/or prevention of overactive bladder.

No suitable figure