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(72) Inventeurs/Inventors:
ESPER, FRANZ, DE;
STAEHL, HELMUT, DE;
LUETKE, SVEN, DE;
MURAMATSU, IKUNOBU, JP;
...

(73) Propriétaire/Owner:

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(57) Abrégé/Abstract:
The present invention relates to the use of α1L-agonists for treating urinary incontinence.
(72) Inventeurs(suite)/Inventors(continued): KITAGAWA, HISATO, JP; UCHIDA, SHUJI M.D., JP
(73) Propriétaires(suite)/Owners(continued): BOEHRINGER INGELHEIM KG, DE
(74) Agent: FETHERSTONHAUGH & CO.
Abstract

The present invention relates to the use of $\alpha_{1L}$-agonists for treating urinary incontinence.
Use of $\alpha_{1L}$-agonists for treating urinary incontinence

The present invention relates to the use of $\alpha_{1L}$-agonists for treating urinary incontinence, particularly stress incontinence.

The cause of stress incontinence in women is usually weakness of the pelvic floor, e.g. after numerous difficult births. However, it may also be due to nerve disorders of the pelvic floor, a congenitally short urethra or, occasionally, damage to the sphincter caused by surgery. The reduction in the oestrogen levels post-menopause further encourages stress incontinence.

The term stress incontinence refers to a sudden loss of urine, which is caused by incompetence of the bladder outlet during unobtrusive movement of the bladder as a result of interabdominal increases in pressure due to coughing, pressing, sneezing, heavy lifting, etc.

Surprisingly, it has been found that the $\alpha_{1L}$-subtype of the adrenergic receptor has a significant effect on the continence mechanism of urether tonicisation.

The invention relates to the use of $\alpha_{1L}$-adrenoceptor agonists for treating urinary incontinence, particularly stress incontinence, and for preparing drugs for treating urinary incontinence, particularly stress incontinence. It is particularly interesting to use amino imidazolines of general formula

\[ Y - X - \text{N} \quad \text{or} \quad Y - X = \text{N} \]
and the pharmacologically acceptable acid addition salts thereof.

In general formula I

Y denotes an optionally substituted phenyl or naphthyl group or
Y denotes a 5- or 6-membered, optionally fully unsaturated,
optionally substituted heterocyclic ring which contains
oxygen, sulphur or nitrogen as heteroatoms, and
X denotes -NH-, -CH₂-, -OCH₂-, -O-CHCH₃-, -CH=N-NH-, -N=N- or
-NZ-, wherein Z = -CH₂-CH=CH₂ or cyclopropylmethyl.

Preferred compounds are those wherein X is -NH- and/or Y is an
optionally substituted thienyl, furyl, pyrrole,
tetrahydropyrrole, pyridyl, pyrazinyl, pyranyl, 1,3-thiazolyl,
imidazolyl, imidazolinyl, 1,2,4-triazolyl, 1,2,3-triazolyl,
tetrazolyl, isothiazolyl, pyrimidinyl, thiazolyl, thiadiazinyl
or piperidinyl, bound to the group X via a C atom. It is
preferred to use tiamenidine.
According to one aspect of the present invention, there is provided use of a selective $\alpha_{1b}$-agonist of general formula I

\[
\text{Y} - \text{X} - \text{N} - \text{H}
\]

wherein

$\text{Y}$ denotes an optionally substituted phenyl or naphthyl group and

$\text{X}$ denotes $\text{-NH-}$,

or a pharmaceutically acceptable acid addition salt thereof, in preparing a pharmaceutical composition for treatment of urinary incontinence.

According to another aspect of the present invention, several novel compounds are provided, which also may be used to treat urinary incontinence, particularly stress incontinence. These novel compounds are:

2-(2-methyl-3-phthalimidophenylimino)-imidazolidine, 2-(4,6-dibromo-3-dimethylamino-2-methylphenylimino)-imidazolidine, 2-(4-bromo-3-dimethylamino-2-methylphenylimino)-imidazolidine, 2-(6-bromo-3-dimethylamino-2-methylphenylimino)-imidazolidine, 2-(6-chloro-3-dimethylamino-2-methylphenylimino)-imidazolidine, 2-(6-chloro-3-phthalimidophenylimino)-imidazolidine, 2-(3-dimethylamino-2-methylphenylimino)-imidazolidine and 2-(6-bromo-3-dimethylamino-2-methylphenylimino)-imidazolidine.
Preferred compounds for this purpose are imidazolines of general formula

or imidazolines of general formula
wherein

\[ R^1, R^2, R^3, R^4 \text{ and } R^5 \text{ denote, independently of one another:} \]

hydrogen, \( C_{1-6}-\text{alkyl} \), preferably \( C_{1-4}-\text{alkyl} \), most preferably methyl, \( C_{3-6}-\text{cycloalkyl} \), preferably cyclopropyl, \( C_{1-6}-\text{alkoxy} \), preferably \( C_{1-4}-\text{alkoxy} \), most preferably methoxy, halogen, preferably chlorine or bromine, \(-\text{CF}_3\), \(-\text{OCF}_3\) or \(-\text{NR}^6\text{R}^7\) wherein

\[ R^6 \text{ denotes hydrogen, } C_{3-6}-\text{cycloalkyl, } C_{1-6}-\text{alkyl, preferably } C_{1-4}-\text{alkyl, most preferably methyl, or } C_{2-4}-\text{acyl, most preferably acetyl,} \]

\[ R^7 \text{ denotes hydrogen, } C_{3-6}-\text{cycloalkyl, preferably cyclopropyl, } C_{1-6}-\text{alkyl, preferably } C_{1-4}-\text{alkyl, most preferably methyl, or } C_{2-4}-\text{acyl, most preferably acetyl; or} \]

\[ R^6 \text{ and } R^7 \text{ together with the nitrogen atom form a } 5- \text{ or } 6- \text{membered saturated or unsaturated ring which may contain up to two further heteroatoms selected from oxygen, sulphur or nitrogen, whilst each additional nitrogen atom may be substituted by } C_{1-4}-\text{alkyl, preferably methyl; or} \]

\[ R^6 \text{ and } R^7 \text{ together with the nitrogen atom form phthalimido;} \]

or
- 4 -

R¹ and R² together form a fused pyrazole of formula

![Fused Pyrazole Formula]

wherein R⁸ is C₁₋₃-alkyl, preferably methyl;

or a fused thiadiazole of formula

![Fused Thiadiazole Formula]

wherein R³, R⁴ and R⁵ are as hereinbefore defined, and preferably denote hydrogen,

and the pharmacologically acceptable acid addition salts thereof.

Formulae I and I' and Ib and II are equivalent tautomeric structures. The preparation of one structure (e.g. Ib) includes the other structure (e.g. II) in each case.

Also preferred are imidazolines of general formula Ib

![Imidazoline Formula]

wherein
$R^1$ denotes hydrogen, ethyl, methyl, fluorine, chlorine, bromine or $CF_3$.

$R^2$ denotes methyl, fluorine, chlorine, bromine or $-NR^6R^7$, wherein

$R^6$ denotes hydrogen, $C_{1-4}$-alkyl, preferably methyl, $C_{2-4}$-acyl, preferably acetyl and

$R^7$ denotes hydrogen, $C_{1-4}$-alkyl, preferably methyl, $C_{2-4}$-acyl, preferably acetyl or

$R^6$ and $R^7$ together with the nitrogen atom form phthalimido;

$R^3$ denotes hydrogen, fluorine, chlorine, bromine, $C_{1-4}$-alkyl, preferably methyl, $NH_2$ or cyclopropyl;

$R^4$ denotes hydrogen, $C_{1-4}$-alkyl, preferably methyl, fluorine, chlorine, bromine or $CF_3$;

$R^5$ denotes hydrogen, $C_{1-4}$-alkyl, preferably ethyl or methyl, fluorine, chlorine, bromine or $CF_3$; or

$R^1$ and $R^2$ together form a fused pyrazole of formula

$$\begin{array}{c}
N \\
N \\
\ \ \ R^8
\end{array}$$

wherein $R^8$ is methyl,

or a fused thiadiazole of the formula

$$\begin{array}{c}
N \\
S
\end{array}$$
wherein $R^3$, $R^4$ and $R^5$ are as hereinbefore defined, and preferably represent hydrogen; particularly those wherein

- $R^1$ is hydrogen or methyl;
- $R^2$ is methyl, chlorine, $CF_3$, $NH_2$ or $N(CH_3)_2$;
- $R^3$ is hydrogen, methyl, chlorine or bromine;
- $R^4$ is hydrogen;
- $R^5$ is hydrogen, methyl, methoxy, chlorine or bromine.

Particular mention should be made of the use of

2-(3-dimethylamino-2-methylphenylimino)imidazolidine,
2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,
2-(5-amino-2-chloro-4-methylphenylimino)-imidazolidine,
2-(3-amino-2-methylphenylimino)-imidazolidine
or
2-(2-chloro-5-trifluoromethylphenylimino)-imidazolidine.

Examples of heterocyclic groups $-NR^6R^7$ are as follows:

pyrrole, $\Delta^2$-pyrrole, $\Delta^3$-pyrrole, tetrahydropyrrole,
pyrrolidine, pyrrolidinone, imidazole, imidazoline, 1,3-thiazole,
piperidine, piperazine, 4-4-C$_1$-alkylpiperazine,
C$_1$-alkylpiperazine, 2,5-diketopiperazine, preferably N-
methylpiperazine, morpholine, thiomorpholine, phthalimido or
succinimido.

Examples of alkyl within the above definitions, including those which are components of other groups, are branched or unbranched C$_1$-alkyl groups, e.g. methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, isobutyl, sec.-butyl and tert.-butyl, n-pentyl, isopentyl, neopentyl, hexyl and isoheptyl.
Cycloalkyl generally represents a saturated cyclic hydrocarbon group having 3 to 6 carbon atoms which may optionally be substituted with a halogen atom or several halogen atoms, a hydroxy group, an alkyl group, preferably methyl, which may be the same as or different from one another. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl.

Some of the imidazolines defined in general formula Ib are new. The invention therefore also relates to new substituted 2-phenylimino-imidazolidines, their use in pharmaceutical compositions and to processes for preparing them.

2- (Phenylimino)-imidazolidines, the preparation thereof and their use as pharmaceutical compositions are known, for example from German Patent Application Nos. DE-OS-19 29 950 and DE-OS-23 16 377, in which the hypotensive properties of the compounds described are particularly emphasised.

New substituted 2- (phenylimino)-imidazolidines of general formula II

have surprising pharmacological properties and are particularly suitable for treating urinary incontinence.

The invention thus relates to compounds of general formula II
wherein

$\text{R}^1$ denotes hydrogen, $\text{C}_{1-6}$-alkyl, preferably $\text{C}_{1-4}$-alkyl, most preferably methyl, $\text{C}_{3-6}$-cycloalkyl, preferably cyclopropyl, $\text{C}_{1-6}$-alkoxy, preferably $\text{C}_{1-4}$-alkoxy, most preferably methoxy, halogen, preferably chlorine or bromine, -CF$_3$ or -OCF$_3$;

$\text{R}^2$ denotes -NR$_6^6$R$_7^6$ wherein

$\text{R}^6$ denotes hydrogen, $\text{C}_{3-6}$-cycloalkyl, $\text{C}_{1-6}$-alkyl, preferably $\text{C}_{1-4}$-alkyl, most preferably methyl, $\text{C}_{2-4}$-acyl, most preferably acetyl;

$\text{R}^7$ denotes hydrogen, cyclopropyl, $\text{C}_{3-6}$-cycloalkyl, $\text{C}_{1-6}$-alkyl, preferably $\text{C}_{1-4}$-alkyl, most preferably methyl, $\text{C}_{2-4}$-acyl, most preferably acetyl;

or

$\text{R}^6$ and $\text{R}^7$ together with the nitrogen atom form a 5- or 6-membered saturated or unsaturated ring which may contain up to two additional heteroatoms selected from the group of oxygen, sulphur or nitrogen, whilst each additional nitrogen atom may be substituted by
C_{1-4}-alkyl, preferably methyl; or R^6 and R^7 together with the nitrogen atom from phthalimido;

R^3 denotes hydrogen, halogen, C_{1-6}-alkyl, preferably C_{1-4}-alkyl, most preferably methyl, C_{1-6}-alkoxy, preferably C_{1-4}-alkoxy, most preferably hydrogen, methoxy, -CF_3 or -OCF_3;

R^4 denotes hydrogen, C_{1-6}-alkyl, preferably C_{1-4}-alkyl, most preferably methyl, hydrogen or halogen;

R^5 denotes hydrogen, C_{1-6}-alkyl, preferably C_{1-4}-alkyl, most preferably methyl, C_{1-6}-alkoxy, preferably C_{1-4}-alkoxy, most preferably methoxy, halogen, -CF_3 or -OCF_3, and the pharmacologically acceptable acid addition salts thereof, with the exception of (i) 2-(3-diethylamino-2-methyl)-imidazolidine, and (ii) 2-(3-dimethylamino-2,6-dichlorophenyliminio)-imidazolidine.

Preferred compounds of general formula II are those wherein

R^1 denotes hydrogen, C_{1-4}-alkyl, cyclopropyl, C_{1-4}-alkoxy, halogen, CF_3 or -OCF_3;

R^2 denotes -NR^6R^7 wherein

R^6 is hydrogen, C_{3-6}-cycloalkyl, C_{1-4}-alkyl or acetyl,

R^7 is hydrogen, cyclopropyl C_{1-4}-alkyl or acetyl, or R^6 and R^7 together with the nitrogen atom form phthalimido;

R^3 is hydrogen, halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, CF_3 or -OCF_3;

R^4 is hydrogen, C_{1-4}-alkyl, methyl, halogen;
R^5 is hydrogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, CF_3 or -OCF_3; particularly those wherein

R^1 is hydrogen, C_{1-3}-alkyl, n-butyl, isobutyl, sec.-butyl, preferably methyl, cyclopropyl, C_{1-3}-alkoxy, preferably methoxy, halogen, preferably chlorine or bromine, CF_3;

R^2 denotes -NR_5R_7 wherein

R^6 is hydrogen, cyclopropyl, C_{1-4}-alkyl, preferably methyl,

R^7 denotes hydrogen, C_{1-4}-alkyl, preferably methyl, or R^6 and R^7 together with the nitrogen atom form phthalimido;

R^3 denotes hydrogen, C_{1-3}-alkyl, n-butyl, isobutyl, sec.-butyl, preferably methyl, cyclopropyl, C_{1-3}-alkoxy, preferably methoxy, halogen, preferably chlorine or bromine, CF_3;

R^4 denotes hydrogen, C_{1-3}-alkyl, n-butyl, isobutyl, sec.-butyl, preferably methyl, cyclopropyl, C_{1-3}-alkoxy, preferably methoxy, halogen, preferably chlorine or bromine;

R^5 denotes hydrogen, C_{1-3}-alkyl, n-butyl, isobutyl, sec.-butyl, preferably methyl, cyclopropyl, C_{1-3}-alkoxy, preferably methoxy, halogen, preferably chlorine or bromine, CF_3; particularly those wherein

R^1 is hydrogen or methyl,

R^2 is -NR^6R^7 wherein

R^6 and R^7 independently of each other denote hydrogen, methyl or methoxy or
R⁶ and R⁷ together with the nitrogen atom form phthalimido;

R³ denotes hydrogen, methyl, fluorine, chlorine or bromine;

R⁴ denotes hydrogen,

R⁵ denotes hydrogen, methyl, chlorine or bromine;

and the pharmacologically acceptable acid salts thereof, especially the hydrobromides or hydrochlorides thereof.

Particular mention should be made of the following compounds, for example:

2-(3-dimethylamino-2-methylphenylimino)imidazolidine,
2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,
2-(5-amino-2-chloro-4-methylphenylimino)-imidazolidine
and
2-(3-amino-2-methylphenylimino)-imidazolidine.
The compounds of general formula I and II may be prepared according to analogous processes known \textit{per se} from the prior art. A selection of the preferred processes are shown in the following synthetic schemes with reference to concrete Examples.

Synthetic Scheme I

$$\begin{array}{c}
\text{CH}_3\text{S} & \text{N} \\
\text{N} & \text{H}
\end{array} \quad \text{CH}_3\text{CN} \quad 10\text{h refluxing}$$

or

\begin{array}{c}
\text{Hal} & \text{N} \\
\text{N} & \text{H}
\end{array} \quad \text{CHCl}_3 \quad 2\text{h refluxing}

or

\begin{array}{c}
\text{H} & \text{N} \\
\text{O} & \text{N} \\
\text{O} & \text{CH}_3
\end{array} \quad \text{POCl}_3 \quad 50^\circ \text{C} \quad 25-50\text{h}

1) \quad \text{CH}_3\text{OH} \quad 5\text{h refluxing or 1N NaOH} \quad \text{in Ethanol} \quad 1\text{h 60}^\circ \text{C}

2) \quad \text{CH}_3\text{OH} / 5\text{h refluxing} \quad \text{Ethylendiamine}

$$\begin{array}{c}
\text{S} = \text{C} = \text{N} - \text{C} - \text{O} \\
\text{phenyl}
\end{array} \quad \rightarrow \quad $$

$$\begin{array}{c}
\text{S} \quad \text{N} \\
\text{N} \quad \text{C} - \text{O} \\
\text{phenyl}
\end{array} \quad \text{50\% NaOH} \quad \text{in Ethanol} \quad 1\text{h reflux}$$

\begin{array}{c}
\text{N} \\
\text{H}
\end{array} \quad \text{2h refluxing}

\begin{array}{c}
\text{S} \quad \text{NH}_2 \\
\text{N} \\
\text{H}
\end{array} \quad \text{CH}_3\text{I/CH}_3\text{OH} \quad 2\text{h refluxing}

\begin{array}{c}
\text{NH}_2'
\text{I-}
\end{array} \quad \text{CH}_3\text{OH} / 5\text{h refluxing}

\begin{array}{c}
\text{R}^3 \\
\text{R}^2 \\
\text{R}^1
\end{array} \quad \text{Synthetic Scheme I}
The preferred processes for preparing the compounds according to the invention will be explained with reference to individual Examples.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CH}_3 \\
\text{\textcircled{O}} & \quad \text{\textcircled{O}} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{(CH}_3\text{)}_2\text{N} & \quad \text{(CH}_3\text{)}_2\text{N} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{S} & \quad \text{S} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{CH}_3\text{I} & \quad \text{CH}_3\text{I} \\
\text{(CH}_3\text{)}_2\text{N} & \quad \text{(CH}_3\text{)}_2\text{N} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{SCH}_3 & \quad \text{SCH}_3 \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{H}_2\text{N} & \quad \text{H}_2\text{N} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\end{align*}
\]

Example 1

Synthetic Scheme II

The methylation of the starting material, 2-methyl-3-nitroaniline, may also be carried out analogously to the Leuckart-Wallach reaction using HCOOH/CH\textsubscript{2}O or using dimethylcarbonate instead of dimethylsulphate.
Compound 2 can be prepared by bromination of compound 1 under conventional reaction conditions.

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{N} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H} \\
\text{N} & \quad \text{HN} \\
\text{Br} & \quad \text{H} \\
\text{N} & \quad \text{HN}
\end{align*}
\]

\[
\text{(CH}_3\text{)}_2\text{N} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H} \\
\text{N} & \quad \text{HN} \\
\text{Br} & \quad \text{H} \\
\text{N} & \quad \text{HN}
\]

Example 2

The following synthetic scheme illustrates the preparation of compounds 2, 3 and 4.

\[
\begin{align*}
\text{(CH}_3\text{)}_2\text{N} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H}_2\text{NH} \\
\text{Br}_2 & \quad \downarrow \\
\text{(CH}_2\text{)}_2\text{N} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H}_2\text{NH} \\
\text{Br} & \quad \downarrow \\
\text{(CH}_2\text{)}_2\text{N} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H}_2\text{NH} \\
\text{Br} & \quad \downarrow \\
\text{(CH}_2\text{)}_2\text{N} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H}_2\text{NH} \\
\text{Br} & \quad \downarrow
\end{align*}
\]

Example 2  Example 3  Example 4
Other alternative methods of synthesis are illustrated below.

Compound 5 and compounds of similar structure can be prepared analogously to a method described by N.R. Ayyangar (Synthesis 1987, 64).

Example 5
Example 1

2-(3-Dimethylamino-2-methylphenylimino)imidazolidine

1st Step:
83.6 g of 2-methyl-3-nitroaniline, 190 g of K₂CO₃ and 260 ml of water are together heated to 100°C. 27 ml of dimethylsulphate are added dropwise over 1 hour, then the mixture is heated for a further hour. After cooling to ambient temperature, the top layer is removed and the aqueous phase remaining is extracted four times with ether.

The combined ether extracts are combined with the upper layer, dried with MgSO₄ and evaporated down in vacuo. 73 g of N,N-dimethyl-2-methyl-3-nitroaniline are obtained.

2nd Step:
73 g of N,N-dimethyl-2-methyl-3-nitroaniline are dissolved in 800 ml of methanol and hydrogenated at 20°C under 5 bar of hydrogen using Raney nickel as catalyst. 57 g of 3-dimethylamino-2-methylaniline are obtained.

3rd Step:
57 g of 3-dimethylamino-2-methyl-aniline, 1.15 litres of acetone, 36.6 g of KSCN and 43.8 ml of benzoylchloride are refluxed together for 3 hours. After cooling to ambient temperature the reaction mixture is poured onto 2.4 kg of crushed ice. The precipitate obtained is heated to 60°C for 2 hours together with 85 g of KOH, 85 ml of water and 255 ml of ethanol. After the addition of 850 ml of water the ethanol is distilled off under reduced pressure. After the resulting precipitate has been worked up, 72 g of N-(3-dimethylamino-2-methylphenyl)-thiourea are obtained.
4th Step:
72 g of the thiourea from Step 3 are taken up in 345 ml of methanol and after the addition of 22.6 ml of methyl iodide the mixture is refluxed for 2 hours. The resulting solution is evaporated down under reduced pressure; 120 g of N-(3-dimethylamino-2-methylphenyl)-S-methyl-isothioureia hydroiodide are obtained.

5th Step:
120 g of the thiourea from Step 4 in 350 ml of methanol are combined with 34.4 ml of 1,2-diaminoethane and refluxed for 17 hours. The reaction mixture is then evaporated down in vacuo and the residue is taken up in water. The pH is adjusted to 7 using dilute hydrochloric acid. The aqueous phase is extracted 3 times with ethyl acetate. Then the aqueous phase is made alkaline with 5N NaOH and extracted a further 3 times with ethyl acetate, these extracts are combined, dried with MgSO₄ and evaporated down in vacuo. An oil is obtained which is chromatographed over silica gel (eluant toluene, dioxane, ethanol, ammonia 10:8:3:1 = "Super-T").

17.9 g of 2-(3-dimethylamino-2-methylphenyl-imino)-imidazolididine are obtained.
Melting point 116 - 118°C.

Example 2:

2-(6-Bromo-3-dimethylamino-2-methylphenyl-imino)imidazolididine

6.55 g of 2-(3-Dimethylamino-2-methylphenyl-imino)-imidazolididine are dissolved in 75 ml of chloroform and 1.53 ml of bromine are added, with stirring, at 0°C. After 2 hours at 0°C the solution is evaporated down under reduced pressure and the residue thus obtained is mixed with dilute hydrochloric acid. The aqueous solution is extracted twice with ether,
then the aqueous phase is made alkaline with dilute NaOH and extracted three more times with ether. The combined ether extracts are evaporated down under reduced pressure and the residue remaining is worked up by chromatography (silica gel, eluant "Super-T" (Example 1)).

3.4 g of 2-(6-bromo-3-dimethylamino-2-methyl-phenylimino)-imidazolidine are obtained, Mp. 157 - 158°C, as a white powder.

The following compounds were prepared analogously to the processes described:

2-(4-bromo-3-dimethylamino-2-methylphenylimino)-imidazolidine
2-(4,6-dibromo-3-dimethylamino-2-methylphenylimino)-imidazolidine
2-(6-chloro-3-dimethylamino-2-methylphenylimino)-imidazolidine
2-(3-acetylamino-6-chlorophenylimino)-imidazolidine, Mp. 236 - 238°C
2-(2-methyl-3-phthalimidophenylimino)-imidazolidine, Mp. 189 - 190°C
2-(6-chloro-3-phthalimidophenylimino)-imidazolidine, Mp. 239 - 241°C
2-(5-amino-2-chloro-4-methylphenylimino)-imidazolidine, Mp. 155 - 157°C
2-(3-amino-4-fluorophenylimino)-imidazolidine, (2HCl), Mp. 222°C
2-(3-amino-4-methylphenylimino)-imidazolidine, (HCl),
2-(3-amino-6-methylphenylimino)-imidazolidine, (HCl), Mp. 194 - 196°C
2-(3-amino-6-chlorophenylimino)-imidazolidine, (HCl), Mp. 197 - 198°C
2-(3-amino-4,6-dibromo-2-methylphenylimino)-imidazolidine, Mp. 154 - 155°C
2-(3-amino-2-methylphenylimino)-imidazolidine, (HCl), Mp.
204-206°C

The following compounds are specifically mentioned by name:

2-(2,6-diethylphenyl-imino)-imidazolidine
2-(2-chloro-6-methylphenylimino)-imidazolidine
2-(2,6-dichloro-phenylimino)-imidazolidine
2-(2-chloro-4-methylphenylimino)-imidazolidine
2-(2,4-dichlorophenylimino)-imidazolidine
2-(2-chloro-5-trifluoromethylphenylimino)-imidazolidine
2-(5-fluoro-2-methylphenylimino)-imidazolidine
2-(3-bromo-2-methylphenylimino)-imidazolidine
2-(2-chloro-3-methylphenylimino)-imidazolidine
2-(2-fluoro-6-trifluoromethylphenylimino)-imidazolidine
2-(2-chloro-4-cyclopropylphenylimino)-imidazolidine
2-(4-amino-3,5-dibromophenylimino)-imidazolidine
2-(3-fluoro-4-methylphenylimino)-imidazolidine
2-(6-bromo-2-fluorophenylimino)-imidazolidine
4-(2-imidazolin-2-ylamino)-2-methylindazole
5-chloro-4-(imidazolin-2-yl-amino)-benzothiadiazole
t(Tizanidine)
2-[2-chloro-4-methyl-3-thienyl)amino]-2-imidazoline
(Tiamenidine)
2-(2,5-dichlorophenylimino)-imidazolidine

The compounds of general formulae I and II according to the invention may be converted into their physiologically acceptable acid addition salts in the usual way. Examples of acids suitable for salt formation include, for example, inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, hydrofluoric acid, sulphuric acid, phosphoric acid, nitric acid or organic acids such as acetic acid, propionic acid, butyric acid, caproic acid, capric acid, valeric acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, citric acid,
malic acid, benzoic acid, p-hydroxybenzoic acid, p-aminobenzoic acid, phthalic acid, cinnamic acid, salicylic acid, ascorbic acid, methanesulphonic acid and ethanephosphonic acid.

The corresponding hydrobromides and hydrochlorides are preferred as the acid addition salts.

Pharmaceutical compositions comprising the compounds described may be used in the form of capsules, suppositories, solutions, syrups, emulsions or dispersible powders. Corresponding tablets may be obtained, for example, by mixing the active substance or substances with known excipients such as inert diluents, e.g. calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc, and/or agents for obtaining delayed release, such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also consist of several layers.

Coated tablets may be produced accordingly, by coating cores made analogously to the tablets with agents conventionally used for tablet coating, e.g. colloidone or shellac, gum arabic, talc, titanium dioxide or sugar. In order to achieve delayed release or prevent incompatibilities, the core may also consist of several layers. Similarly, the tablet coating may consist of several layers in order to achieve delayed release, and the excipients mentioned for the tablets may be used.

Syrups of the active substances or combinations of active substances according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerol or sugar.
and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethylcellulose, wetting agents, e.g. condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Injectable solutions are prepared in the usual way, e.g. by adding preservatives such as p-hydroxybenzoates or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid and are then transferred into injection vials or ampoules.

The capsules containing the active substance or combination of active substances may be prepared, for example, by mixing the active ingredients with inert carriers such as lactose or sorbitol and packaging the mixture in gelatine capsules.

Suitable suppositories may be produced, for example, by mixing with carriers provided for this purpose such as neutral fats of polyethyleneglycol or derivatives thereof.

For transdermal application the active substances according to the invention may be incorporated in suitable carriers (plasters), e.g. made of polyacrylates. Suitable adjuvants may be used in order to increase the release rate.

For oral administration a dosage of 1 to 50 mg is proposed as a therapeutically single dose.

Example A: Tablets

2-[(3-Dimethylamino-2-methylphenylimino)-imidazolidine.HBr 10 mg
Lactose 65 mg
Corn starch 125 mg
sec.Calcium phosphate 40 mg
Soluble starch 3 mg  
Magnesium stearate 4 mg  
Colloidal silica 4 mg  
Total 251 mg

Preparation:
The active substance is mixed with some of the excipients, kneaded intensively with an aqueous solution of the soluble starch and granulated with a sieve in the usual way. The granules are combined with the remaining excipients and compressed into tablet cores weighing 250 mg which are then coated in the usual way using sugar, talc and gum arabic.

Example B: Ampoules

2-(3-Dimethylamino-2-methylphenylimino)-imidazolidine.HBr 1.0 mg
Sodium chloride 18.0 mg
Sufficient distilled water to make up to 2.0 ml

Preparation:
The active substance and sodium chloride are dissolved in water and transferred into glass ampoules under nitrogen.

Example C: Drops

2-(3-Dimethylamino-2-methylphenylimino)-imidazolidine.HBr 0.02 g
Methyl p-hydroxybenzoate 0.07 g
Propyl p-hydroxybenzoate 0.03 g
Sufficient demineralised water to make up to 100 ml

Example D: Injectable solution

2-(3-Dimethylamino-2-methylphenylimino)-
imidazolidine.HBr \hspace{1cm} 1.5 parts
Sodium salt of ethylenediamine tetraacetic acid \hspace{1cm} 0.2 parts
Sufficient distilled water to make up to \hspace{1cm} 100.0 parts

Preparation:
The active substance and the sodium salt of ethylenediamine
tetraacetic acid are dissolved in sufficient water and topped
up to the desired volume with water. The solution is filtered
to remove any suspended particles and transferred into 2 ml
ampoules under aseptic conditions. Finally, the ampoules are
sterilised and sealed. Each ampoule contains 20 mg of active
substance.

One advantage of the compounds described is that they act
primarily on the urethra and have little or no effect on the
cardiovascular system.

The selective pharmacological activity of the compounds
according to the invention is demonstrated by the compound of
Example 2 - 2-(6-bromo-3-dimethylamino-2-methylphenylimino)-
imidazolidine - and a comparison compound, phenylephrine, by
measuring the intraluminal pressure of the urethra and blood
pressure in the rabbit.

Female Japanese white rabbits (weighing 3.0 to 3.5 kg) are
anaesthetised with urethane (1 g/kg i.p.). A polyethylene
cannula is inserted in the urinary bladder by means of a small
incision. The changes in the intraluminal pressure are
recorded by means of balloon in the urethra which contains
about 1.5 ml of water at 37°C. The intraurethral pressure is
recorded on a polygraph by means of a pressure-voltage
transducer.

The neck is opened up and the carotid artery is cannulated in
order to measure the blood pressure and at the same time the
trachea is intubated in order to maintain breathing. The changes in blood pressure are recorded on a polygraph by means of a pressure-voltage transducer. Heart rate is measured using a tachometer.

Phenylephrine and the compound of Example 2 are introduced into the Vena femoralis i.v. through a polyethylene cannula. Dosages of 30 μg/kg of phenylephrine are compared with 10 μg/kg of the compound of Example 2.

Compared with phenylephrine the compound of Example 2 according to the invention exhibits a potency which is higher by a factor of 2.73 with regard to the contraction of the urethra and with a duration of effect which is longer by a factor of 4.3. By comparison, the increase in blood pressure with the compound according to the invention is only 1.39 times that of the comparison compound phenylephrine. It is notable that the increase in blood pressure is prolonged only to an insignificant degree (by a factor of 1.17) compared with phenylephrine. These experiments show that the compounds according to the invention have a selective effect on the urethra. Being selective α1i-adrenoreceptor agonists, the compounds according to the invention are suitable for treating problems of urinary incontinence, particularly for treating stress incontinence.

The test results are shown in Table 1.
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Contraction of the urethra</th>
<th>Duration of effect</th>
<th>Increase in blood pressure</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Example 2</td>
<td>273</td>
<td>430</td>
<td>139</td>
<td>117</td>
</tr>
</tbody>
</table>

Data given in %
Example 2 = 2-(6-bromo-3-dimethylamino-2-methylphenyl-imino)imidazolidine
CLAIMS:

1. Use of a selective ɑ₁b-agonist of general formula I

\[
\begin{array}{c}
\text{Y--X--N} \\
\text{H}
\end{array}
\]  

I

wherein

Y denotes an optionally substituted phenyl or naphthyl group and

X denotes -NH-,

or a pharmaceutically acceptable acid addition salt thereof,

in preparing a pharmaceutical composition for treatment of

urinary incontinence.

2. Use according to claim 1, wherein the selective ɑ₁b-agonist or the salt thereof corresponds to general

formula Ib

\[
\begin{array}{c}
\text{R₁--R₂--R₃--R₄--N} \\
\text{H--N--H}
\end{array}
\]  

Ib

wherein

R¹, R², R³, R⁴ and R⁵ denote, independently of one another:

hydrogen, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, halogen, CF₃, -OCF₃ or NR⁶R⁷, wherein
R\(^6\) denotes hydrogen, C\(_{3-6}\)-cycloalkyl, C\(_{1-6}\)-alkyl, or C\(_{2-4}\)-acyl,
R\(^7\) denotes hydrogen, C\(_{3-6}\)-cycloalkyl, C\(_{1-6}\)-alkyl, or C\(_{2-4}\)-acyl; or

R\(^6\) and R\(^7\) together with the nitrogen atom to which each is attached form a 5- or 6-membered saturated or unsaturated ring which optionally contains up to two further heteroatoms selected from oxygen, sulphur and nitrogen, wherein each additional nitrogen atom is optionally substituted by C\(_{1-4}\)-alkyl;

or R\(^6\) and R\(^7\) together with the nitrogen atom to which each is attached form phthalimido; or

R\(^1\) and R\(^2\) together form a fused-on pyrazole of formula

\[
\begin{array}{c}
\text{N} \\
\text{R}^8 \\
\text{N} \\
\end{array}
\]

wherein R\(^8\) is C\(_{1-3}\)-alkyl,

or a fused-on thiadiazole of formula

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{N} \\
\end{array}
\]

3. Use according to claim 2,

wherein R\(^1\), R\(^2\), R\(^3\), R\(^4\), R\(^5\) denote independently of one another:
hydrogen, C\textsubscript{1-4}-alkyl, cyclopropyl, C\textsubscript{1-4}-alkoxy, halogen, CF\textsubscript{3}, -OCF\textsubscript{3} or NR\textsuperscript{6}R\textsuperscript{7}, wherein

R\textsuperscript{6} denotes hydrogen, C\textsubscript{3-6}-cycloalkyl, C\textsubscript{1-4}-alkyl, or acetyl, R\textsuperscript{7} denotes hydrogen, cyclopropyl, C\textsubscript{1-4}-alkyl, or acetyl; or

R\textsuperscript{6} and R\textsuperscript{7} together with the nitrogen atom to which each is attached form phthalimido; or

R\textsuperscript{1} and R\textsuperscript{2} together form a fused-on pyrazole of formula

\begin{center}
\begin{tikzpicture}
  \node (N1) at (0,0) {$N$};
  \node (N2) at (0.5,0) {$N$};
  \node (R8) at (1,0) {$R^8$};
  \draw (N1) -- (N2) -- (R8);
\end{tikzpicture}
\end{center}

10 wherein R\textsuperscript{8} is methyl,

or a fused-on thiadiazole of the formula

\begin{center}
\begin{tikzpicture}
  \node (N1) at (0,0) {$N$};
  \node (N2) at (0.5,0) {$N$};
  \node (S) at (1,0) {$S$};
  \draw (N1) -- (N2) -- (S);
\end{tikzpicture}
\end{center}

15 4. Use according to claim 3, wherein, in the definition of R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, R\textsuperscript{4} and R\textsuperscript{5}, the C\textsubscript{1-4}-alkyl is methyl, the C\textsubscript{1-4}-alkoxy is methoxy, the R\textsuperscript{6} is methyl and the R\textsuperscript{7} is methyl.

5. Use according to claim 3 wherein R\textsuperscript{3}, R\textsuperscript{4} and R\textsuperscript{5} each are hydrogen when R\textsuperscript{1} and R\textsuperscript{2} together form the fused-on pyrazole or the fused-on thiadiazole.

6. Use according to claim 2,

wherein R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, R\textsuperscript{4}, R\textsuperscript{5} denote independently of one another:
hydrogen, ethyl, methyl, cyclopropyl, fluorine, chlorine, bromine, CF₃ or NR⁶R⁷ wherein

R⁶ denotes hydrogen, methyl or acetyl,

R⁷ denotes hydrogen, methyl or acetyl; or

R⁶ and R⁷ together with the nitrogen atom to which each is attached form phthalimido; or

R¹ and R² together form a fused-on pyrazole of the formula

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R}^8
\end{array}
\]

wherein R⁸ is methyl,

or a fused-on thia diazole of the formula

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{N}
\end{array}
\]

7. Use according to claim 6 wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thia diazole.

8. Use according to claim 2,

wherein

R¹ is hydrogen, ethyl, methyl, fluorine, chlorine, bromine or CF₃,

R² is methyl, fluorine, chlorine, bromine or -NR⁶R⁷, wherein

R⁶ is hydrogen, C₁₄-alkyl, C₂₄-acyl, and
R\(^7\) is hydrogen, C\(_{1-4}\)-alkyl, C\(_{2-4}\)-acyl, or

R\(^6\) and R\(^7\) together with the nitrogen atom form phthalimido;

R\(^3\) is hydrogen, fluorine, chlorine, bromine, C\(_{1-4}\)-alkyl, NH\(_2\) or cyclopropyl;

R\(^4\) is hydrogen, C\(_{1-4}\)-alkyl, fluorine, chlorine, bromine or CF\(_3\);

R\(^5\) is hydrogen, C\(_{1-4}\)-alkyl, fluorine, chlorine, bromine or CF\(_3\); or

R\(^1\) and R\(^2\) together form a fused-on pyrazole of the formula

\[
\begin{array}{c}
\text{N} \\
\text{R}^8 \\
\text{N}
\end{array}
\]

wherein R\(^8\) is methyl,

or a fused-on thiadiazole of the formula

9. Use according to claim 8, wherein: in the definition of R\(^6\) and R\(^7\) the C\(_{1-4}\)-alkyl is methyl and the definition of the C\(_{2-4}\)-acyl is acetyl; in the definitions of R\(^3\) and R\(^4\), the C\(_{1-4}\)-alkyl is methyl; and in the definition of R\(^5\), the C\(_{1-4}\)-alkyl is methyl or ethyl.

10. Use according to claim 8 wherein R\(^3\), R\(^4\) and R\(^5\) each are hydrogen when R\(^1\) and R\(^2\) together form the fused-on pyrazole or the fused-on thiadiazole.

11. Use according to claim 2, wherein,
R¹ is hydrogen or methyl;

R² is methyl, chlorine, CF₃, NH₂ or N(CH₃)₂;

R³ is hydrogen, methyl, chlorine or bromine;

R⁴ is hydrogen;

R⁵ is hydrogen, methyl, methoxy, chlorine or bromine.

12. Use according to claim 2, wherein the selective α₁L-agonist of formula Ib is

2-(3-dimethylamino-2-methylphenylimino)imidazolidine.

13. Use according to claim 2, wherein the selective α₁L-agonist of formula Ib is

2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine.

14. Use according to claim 2, wherein the selective α₁L-agonist of formula Ib is

2-(5-amino-2-chloro-4-methylphenylimino)-imidazolidine.

15. Use according to claim 2, wherein the selective α₁L-agonist of formula Ib is

2-(3-amino-2-methylphenylimino)-imidazolidine.

16. Use according to claim 2, wherein the selective α₁L-agonist of formula Ib is

2-(2-chloro-5-trifluoromethylphenylimino)-imidazolidine.

17. Use according to any one of claims 1 to 16 wherein the urinary incontinence is stress incontinence.

18. Use of a selective α₁L-agonist of general formula I
wherein

5 Y denotes an optionally substituted phenyl or naphthyl group and

X denotes -NH-,

or a pharmaceutically acceptable acid addition salt thereof,

for treatment of urinary incontinence.

10 19. Use according to claim 18, wherein the selective

$\alpha_{1b}$-agonist or the salt thereof corresponds to general

formula Ib

\[
\begin{array}{c}
\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 \text{ and } \text{R}^5 \text{ denote, independently of one another:}

\text{hydrogen, C}_1-6\text{-alkyl, C}_3-6\text{-cycloalkyl, C}_1-6\text{-alkoxy, halogen, CF}_3, -\text{OCF}_3 \text{ or NR}^6\text{R}^7, \text{ wherein}

\text{R}^6 \text{ denotes hydrogen, C}_3-6\text{-cycloalkyl, C}_1-6\text{-alkyl, or C}_2-4\text{-acyl,}

\text{R}^7 \text{ denotes hydrogen, C}_3-6\text{-cycloalkyl, C}_1-6\text{-alkyl, or C}_2-4\text{-acyl; or}
\end{array}
\]
R<sup>6</sup> and R<sup>7</sup> together with the nitrogen atom to which each is attached form a 5- or 6-membered saturated or unsaturated ring which optionally contains up to two further heteroatoms selected from oxygen, sulphur and nitrogen, wherein each additional nitrogen atom is optionally substituted by C<sub>1-4</sub>-alkyl;

or R<sup>6</sup> and R<sup>7</sup> together with the nitrogen atom to which each is attached form phthalimido; or

R<sup>1</sup> and R<sup>2</sup> together form a fused-on pyrazole of formula

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R}^8
\end{array}
\]

wherein R<sup>8</sup> is C<sub>1-3</sub>-alkyl,

or a fused-on thiadiazole of formula

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{S}
\end{array}
\]

Use according to claim 19,

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> denote independently of one another:

hydrogen, C<sub>1-4</sub>-alkyl, cyclopropyl, C<sub>1-4</sub>-alkoxy, halogen, CF<sub>3</sub>, -OCF<sub>3</sub> or NR<sup>6</sup>R<sup>7</sup>, wherein

R<sup>6</sup> denotes hydrogen, C<sub>3-6</sub>-cycloalkyl, C<sub>1-4</sub>-alkyl, or acetyl,
R⁷ denotes hydrogen, cyclopropyl, C₁₄-alkyl, or acetyl; or R⁶ and R⁷ together with the nitrogen atom to which each is attached form phthalimido; or R¹ and R² together form a fused-on pyrazole of formula

\[
\text{N} \quad \text{N} \quad \text{R⁸}
\]

wherein R⁸ is methyl,

or a fused-on thiadiazole of the formula

\[
\text{N} \quad \text{S} \quad \text{N}
\]

21. Use according to claim 20, wherein, in the definition of R¹, R², R³, R⁴ and R⁵, the C₁₄-alkyl is methyl, the C₁₄-alkoxy is methoxy, the R⁶ is methyl and the R⁷ is methyl.

22. Use according to claim 20 wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thiadiazole.

23. Use according to claim 19,

20 wherein R¹, R², R³, R⁴, R⁵ denote independently of one another:

hydrogen, ethyl, methyl, cyclopropyl, fluorine, chlorine, bromine, CF₃ or NR⁶R⁷ wherein

R⁶ denotes hydrogen, methyl or acetyl,
R' denotes hydrogen, methyl or acetyl; or
R^6 and R' together with the nitrogen atom to which each is
attached form phthalimido; or
R^1 and R^2 together form a fused-on pyrazole of the formula

\[
\begin{array}{c}
\text{N} \\
\text{R}^8 \\
\text{N}
\end{array}
\]

wherein R^3 is methyl,
or a fused-on thiadiazole of the formula

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{N}
\end{array}
\]

24. Use according to claim 23 wherein R^3, R^4 and R^5
each are hydrogen when R^1 and R^2 together form the fused-on
pyrazole or the fused-on thiadiazole.

25. Use according to claim 19,
wherein

R^1 is hydrogen, ethyl, methyl, fluorine, chlorine, bromine or
CF_3,
R^2 is methyl, fluorine, chlorine, bromine or -NR^6R^7, wherein
R^6 is hydrogen, C_1-4-alkyl, C_2-4-acyl, and
R^7 is hydrogen, C_1-4-alkyl, C_2-4-acyl, or
R^6 and R^7 together with the nitrogen atom form phthalimido;
R³ is hydrogen, fluorine, chlorine, bromine, C₁₋₄-alkyl, NH₂ or cyclopropyl;

R⁴ is hydrogen, C₁₋₄-alkyl, fluorine, chlorine, bromine or CF₃;

R⁵ is hydrogen, C₁₋₄-alkyl, fluorine, chlorine, bromine or CF₃; or

R¹ and R² together form a fused-on pyrazole of the formula

wherein R⁸ is methyl,

or a fused-on thiaadiazole of the formula

26. Use according to claim 25, wherein: in the definition of R⁶ and R⁷ the C₁₋₄-alkyl is methyl and the definition of the C₂₋₄-acyl is acetyl; in the definitions of R³ and R⁴, the C₁₋₄-alkyl is methyl; and in the definition of R⁵, the C₁₋₄-alkyl is methyl or ethyl.

27. Use according to claim 25 wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thiaadiazole.

28. Use according to claim 19, wherein,

R¹ is hydrogen or methyl;

25 R² is methyl, chlorine, CF₃, NH₂ or N(CH₃)₂;
R³ is hydrogen, methyl, chlorine or bromine;
R⁴ is hydrogen;
R⁵ is hydrogen, methyl, methoxy, chlorine or bromine.

29. Use according to claim 19, wherein the selective α₁L-agonist of formula Ib is
2-(3-dimethylamino-2-methylphenylimino)imidazolidine.

30. Use according to claim 19, wherein the selective α₁L-agonist of formula Ib is
2-(6-bromo-3-dimethylamino-2-
10 methylphenylimino)imidazolidine.

31. Use according to claim 19, wherein the selective α₁L-agonist of formula Ib is
2-(5-amino-2-chloro-4-methylphenylimino)-imidazolidine.

32. Use according to claim 19, wherein the selective α₁L-agonist of formula Ib is
2-(3-amino-2-methylphenylimino)-imidazolidine.

33. Use according to claim 19, wherein the selective α₁L-agonist of formula Ib is
2-(2-chloro-5-trifluoromethylphenylimino)-imidazolidine.

34. Use according to any one of claims 18 to 33 wherein the urinary incontinence is stress incontinence.

35. A selective α₁L-agonist of general formula I
wherein

5 \( Y \) denotes an optionally substituted phenyl or naphthyl group and

\( X \) denotes \(-NH-\),

or a pharmaceutically acceptable acid addition salt thereof, for treatment of urinary incontinence.

10 36. An agonist according to claim 35, wherein the selective \( \alpha_{1A} \)-agonist or the salt thereof corresponds to general formula Ib

\[
\begin{align*}
\text{Ib} & \\
R^1, R^2, R^3, R^4, R^5 & \\
\text{hydrogen, } C_{1-6}\text{-alkyl, } C_{3-6}\text{-cycloalkyl, } C_{1-6}\text{-alkoxy, halogen, } \\
\text{CF}_3, \text{ } -\text{OCF}_3 \text{ or } NR^6R^7, \text{ wherein} \\
R^6 & \text{ denotes hydrogen, } C_{3-6}\text{-cycloalkyl, } C_{1-6}\text{-alkyl, or } C_{2-4}\text{-acyl,} \\
R^7 & \text{ denotes hydrogen, } C_{3-6}\text{-cycloalkyl, } C_{1-6}\text{-alkyl, or } C_{2-4}\text{-acyl; or}
\end{align*}
\]
R⁶ and R⁷ together with the nitrogen atom to which each is attached form a 5- or 6-membered saturated or unsaturated ring which optionally contains up to two further heteroatoms selected from oxygen, sulphur and nitrogen, wherein each additional nitrogen atom is optionally substituted by C₁₋₄-alkyl;

or R⁶ and R⁷ together with the nitrogen atom to which each is attached form phthalimido; or

R¹ and R² together form a fused-on pyrazole of formula

wherein R⁸ is C₁₋₃-alkyl,

or a fused-on thiadiazole of formula

37. An agonist according to claim 36,

wherein R¹, R², R³, R⁴, R⁵ denote independently of one another:

hydrogen, C₁₋₄-alkyl, cyclopropyl, C₁₋₄-alkoxy, halogen, CF₃, -OCF₃ or NR⁶R⁷, wherein

R⁶ denotes hydrogen, C₃₋₆-cycloalkyl, C₁₋₄-alkyl, or acetyl,

R⁷ denotes hydrogen, cyclopropyl, C₁₋₄-alkyl, or acetyl; or
R⁶ and R⁷ together with the nitrogen atom to which each is attached form phthalimido; or

R¹ and R² together form a fused-on pyrazole of formula

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R}^8
\end{array}
\]

wherein R⁸ is methyl,

or a fused-on thiaadiazole of the formula

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{N}
\end{array}
\]

38. An agonist according to claim 37, wherein, in the definition of R¹, R², R³, R⁴ and R⁵, the C₁₄-alkyl is methyl, the C₁₄-alkoxy is methoxy, the R⁶ is methyl and the R⁷ is methyl.

39. An agonist according to claim 37 wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thiaadiazole.

40. An agonist according to claim 36,

wherein R¹, R², R³, R⁴, R⁵ denote independently of one another:

hydrogen, ethyl, methyl, cyclopropyl, fluorine, chlorine, bromine, CF₃ or NR⁶R⁷ wherein

R⁶ denotes hydrogen, methyl or acetyl,

R⁷ denotes hydrogen, methyl or acetyl; or
R⁶ and R⁷ together with the nitrogen atom to which each is attached form phthalimido; or

R¹ and R² together form a fused-on pyrazole of the formula

wherein R⁸ is methyl,

or a fused-on thiadiazole of the formula

41. An agonist according to claim 40 wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thiadiazole.

42. An agonist according to claim 36,

wherein

R¹ is hydrogen, ethyl, methyl, fluorine, chlorine, bromine or CF₃,

R² is methyl, fluorine, chlorine, bromine or -NR⁶R⁷, wherein

R⁶ is hydrogen, C₁₋₄-alkyl, C₂₋₄-acyl, and

R⁷ is hydrogen, C₁₋₄-alkyl, C₂₋₄-acyl, or

R⁶ and R⁷ together with the nitrogen atom form phthalimido;

R³ is hydrogen, fluorine, chlorine, bromine, C₁₋₄-alkyl, NH₂ or cyclopropyl;
R¹ is hydrogen, C₁₋₄-alkyl, fluorine, chlorine, bromine or CF₃;

R² is hydrogen, C₁₋₄-alkyl, fluorine, chlorine, bromine or CF₃; or

R¹ and R² together form a fused-on pyrazole of the formula

wherein R⁸ is methyl,

or a fused-on thiadiazole of the formula

An agonist according to claim 42, wherein: in the definition of R⁶ and R⁷ the C₁₋₄-alkyl is methyl and the definition of the C₂₋₄-acyl is acetyl; in the definitions of R³ and R⁴, the C₁₋₄-alkyl is methyl; and in the definition of R⁵, the C₁₋₄-alkyl is methyl or ethyl.

An agonist according to claim 42 wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thiadiazole.

An agonist according to claim 36, wherein,

R¹ is hydrogen or methyl;

R² is methyl, chlorine, CF₃, NH₂ or N(CH₃)₂;

R³ is hydrogen, methyl, chlorine or bromine;
R^4 is hydrogen;

R^5 is hydrogen, methyl, methoxy, chlorine or bromine.

46. An agonist according to claim 36, wherein the selective α_{1L}-agonist of formula Ib is

5 2-(3-dimethylamino-2-methylphenylimino)imidazolididine.

47. An agonist according to claim 36, wherein the selective α_{1L}-agonist of formula Ib is

2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolididine.

48. An agonist according to claim 36, wherein the selective α_{1L}-agonist of formula Ib is

2-(5-amino-2-chloro-4-methylphenylimino)-imidazolididine.

49. An agonist according to claim 36, wherein the selective α_{1L}-agonist of formula Ib is

2-(3-amino-2-methylphenylimino)-imidazolididine.

50. An agonist according to claim 36, wherein the selective α_{1L}-agonist of formula Ib is

2-(2-chloro-5-trifluoromethylphenylimino)-imidazolididine.

51. An agonist according to any one of claims 35 to 50 wherein the urinary incontinence is stress incontinence.

52. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a selective α_{1L}-agonist of general formula I
wherein

5 Y denotes an optionally substituted phenyl or naphthyl group and
X denotes -NH-, or a pharmaceutically acceptable acid addition salt thereof, for treatment of urinary incontinence.

10 53. A pharmaceutical composition according to claim 52, wherein the selective α₁₂-agonist or the salt thereof corresponds to general formula Ib

wherein

R¹, R², R³, R⁴ and R⁵ denote, independently of one another:
hydrogen, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, halogen, CF₃, -OCF₃ or NR⁶R⁷, wherein

R⁶ denotes hydrogen, C₃₋₆-cycloalkyl, C₁₋₆-alkyl, or C₂₋₄-acyl,
R⁷ denotes hydrogen, C₃₋₆-cycloalkyl, C₁₋₆-alkyl, or C₂₋₄-acyl; or
R⁶ and R⁷ together with the nitrogen atom to which each is attached form a 5- or 6-membered saturated or unsaturated ring which optionally contains up to two further heteroatoms selected from oxygen, sulphur and nitrogen, wherein each additional nitrogen atom is optionally substituted by C₁₋₄-alkyl;

or R⁶ and R⁷ together with the nitrogen atom to which each is attached form phthalimido; or

R¹ and R² together form a fused-on pyrazole of formula

\[
\begin{array}{c}
\text{N} \\
\text{R}^8
\end{array}
\]

wherein R⁸ is C₁₋₃-alkyl,

or a fused-on thiadiazole of formula

\[
\begin{array}{c}
\text{N} \\
\text{S}
\end{array}
\]

54. A pharmaceutical composition according to claim 53,

wherein R¹, R², R³, R⁴, R⁵ denote independently of one another:

hydrogen, C₁₋₄-alkyl, cyclopropyl, C₁₋₄-alkoxy, halogen, CF₃, -OCF₃ or NR⁶R⁷, wherein

R⁶ denotes hydrogen, C₃₋₆-cycloalkyl, C₁₋₄-alkyl, or acetyl,

R⁷ denotes hydrogen, cyclopropyl, C₁₋₄-alkyl, or acetyl; or
R⁶ and R⁷ together with the nitrogen atom to which each is attached form phthalimido; or

R¹ and R² together form a fused-on pyrazole of formula

wherein R⁸ is methyl,

or a fused-on thiadiazole of the formula

A pharmaceutical composition according to claim 54, wherein, in the definition of R¹, R², R³, R⁴ and R⁵, the C₁₄-alkyl is methyl, the C₁₄-alkoxy is methoxy, the R⁶ is methyl and the R⁷ is methyl.

A pharmaceutical composition according to claim 54 wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thiadiazole.

A pharmaceutical composition according to claim 53,

wherein R¹, R², R³, R⁴, R⁵ denote independently of one another:

hydrogen, ethyl, methyl, cyclopropyl, fluorine, chlorine, bromine, CF₃ or NR⁶R⁷ wherein

R⁶ denotes hydrogen, methyl or acetyl,
R⁷ denotes hydrogen, methyl or acetyl; or
R⁶ and R⁷ together with the nitrogen atom to which each is attached form phthalimido; or
R¹ and R² together form a fused-on pyrazole of the formula

![Pyrazole](attachment:image.png)

wherein R⁸ is methyl,
or a fused-on thiadiazole of the formula

![Thiadiazole](attachment:image.png)

58. A pharmaceutical composition according to claim 57 wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thiadiazole.

59. A pharmaceutical composition according to claim 53,

wherein

R¹ is hydrogen, ethyl, methyl, fluorine, chlorine, bromine or CF₃,

R² is methyl, fluorine, chlorine, bromine or -NR⁶R⁷, wherein

R⁶ is hydrogen, C₁₋₄-alkyl, C₂₋₄-acyl, and

R⁷ is hydrogen, C₁₋₄-alkyl, C₂₋₄-acyl, or

R⁶ and R⁷ together with the nitrogen atom form phthalimido;
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R³ is hydrogen, fluorine, chlorine, bromine, C₅₋₄-alkyl, NH₂ or cyclopropyl;

R⁴ is hydrogen, C₅₋₄-alkyl, fluorine, chlorine, bromine or CF₃;

R⁵ is hydrogen, C₅₋₄-alkyl, fluorine, chlorine, bromine or CF₃; or

R¹ and R² together form a fused-on pyrazole of the formula

\[ \text{N} \quad \text{R}^8 \]

wherein R⁸ is methyl,

or a fused-on thiadiazole of the formula

\[ \text{N} \quad \text{S} \]

15 60. A pharmaceutical composition according to claim 59, wherein: in the definition of R⁶ and R⁷ the C₅₋₄-alkyl is methyl and the definition of the C₂₋₄-acyl is acetyl; in the definitions of R³ and R⁴, the C₅₋₄-alkyl is methyl; and in the definition of R⁵, the C₅₋₄-alkyl is methyl or ethyl.

61. A pharmaceutical composition according to claim 59, wherein R³, R⁴ and R⁵ each are hydrogen when R¹ and R² together form the fused-on pyrazole or the fused-on thiadiazole.

25 62. A pharmaceutical composition according to claim 53, wherein,
R¹ is hydrogen or methyl;
R² is methyl, chlorine, CF₃, NH₂ or N(CH₃)₂;
R³ is hydrogen, methyl, chlorine or bromine;
R⁴ is hydrogen;
R⁵ is hydrogen, methyl, methoxy, chlorine or bromine.

63. A pharmaceutical composition according to claim 53, wherein the selective α₁L-agonist of formula Ib is 2-(3-dimethylamino-2-methylphenyllimino)imidazolidine.

64. A pharmaceutical composition according to claim 53, wherein the selective α₁L-agonist of formula Ib is 2-(6-bromo-3-dimethylamino-2-methylphenyllimino)imidazolidine.

65. A pharmaceutical composition according to claim 53, wherein the selective α₁L-agonist of formula Ib is 2-(5-amino-2-chloro-4-methylphenyllimino)-imidazolidine.

66. A pharmaceutical composition according to claim 53, wherein the selective α₁L-agonist of formula Ib is 2-(3-amino-2-methylphenyllimino)-imidazolidine.

67. A pharmaceutical composition according to claim 53, wherein the selective α₁L-agonist of formula Ib is 2-(2-chloro-5-trifluoromethylphenyllimino)-imidazolidine.

68. A pharmaceutical composition according to any one of claims 53 to 67 wherein the urinary incontinence is stress incontinence.
69. 2-(2-methyl-3-phthalimidophenylimino)-imidazolidine.

70. 2-(4,6-dibromo-3-dimethylamino-2-methylphenylimino)-imidazolidine.

71. 2-(4-bromo-3-dimethylamino-2-methylphenylimino)-imidazolidine.

72. 2-(6-bromo-3-dimethylamino-2-methylphenylimino)-imidazolidine.

73. 2-(6-chloro-3-dimethylamino-2-methylphenylimino)-imidazolidine.

74. 2-(6-chloro-3-phthalimidophenylimino)-imidazolidine.

75. 2-(3-dimethylamino-2-methylphenylimino)-imidazolidine.

76. 2-(6-bromo-3-dimethylamino-2-methylphenylimino)-imidazolidine.

77. A pharmaceutical composition comprising a compound according to any one of claims 69 to 76 and a pharmaceutically acceptable carrier or excipient.

78. A pharmaceutical composition according to claim 77 for treatment of urinary incontinence.

79. A pharmaceutical composition according to claim 78, wherein the urinary incontinence is stress incontinence.

80. Use of a compound according to any one of claims 69 to 76 in preparation of a pharmaceutical composition for treatment of urinary incontinence.
81. Use according to claim 80, wherein the urinary incontinence is stress incontinence.

82. Use of a compound according to any one of claims 69 to 76 for treatment of urinary incontinence.

83. Use according to claim 82, wherein the urinary incontinence is stress incontinence.

84. A compound according to any one of claims 69 to 76 for treatment of urinary incontinence.

85. A compound according to claim 84, wherein the urinary incontinence is stress incontinence.

86. A process for preparing a pharmaceutical composition wherein a compound as defined in any one of claims 69 to 76 is admixed with a pharmaceutically acceptable carrier or excipient.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS