S015119J.63

Use of α_{1L}-agonists for treating urinary incontinence

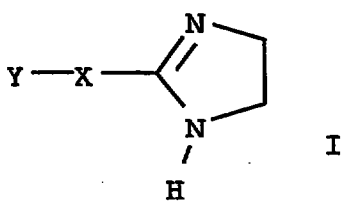
The present invention relates to the use of α_{1L}-agonists for treating urinary incontinence, particularly stress incontinence.

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.

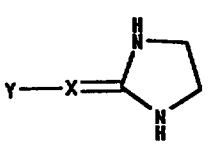
Surprisingly, it has been found that the α_{1L}-subtype of the adrenergic receptor has a significant effect on the continence mechanism of urether tonicisation.

The invention relates to the use of α_{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



I

or



I'

and the pharmacologically acceptable acid addition salts thereof.

In general formula I

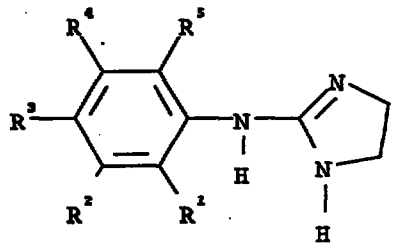
Y denotes an optionally substituted phenyl or napthyl group or

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-, $-CH_2-$, $-OCH_2-$, $-O-CHCH_3-$, -CH=N-NH-, -N=N- or -NZ-, wherein Z = $-CH_2-CH=CH_2$ or cyclopropylmethyl.

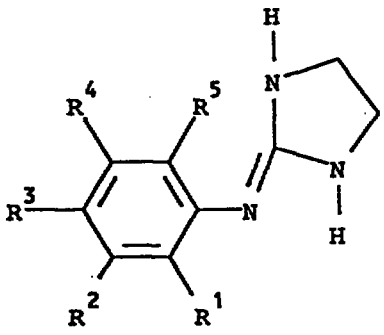
Preferred compounds are those wherein X is -NH- and/or Y is an optionally substituted thienyl, furyl, pyrrole, tetrahydropyrrole, pyridyl, pyrazinyl, pyranyl, 1,3-thiazolyl, imidazolyl, imidazolinyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, isothiazolyl, pyrimidinyl, thiazolyl, thiadiazinyl or piperidinyl, bound to the group X via a C atom. It is preferred to use tiamenidine.

Preferred compounds for this purpose are imidazolines of general formula



Ib

or imidazolines of general formula



II

wherein

R^1, R^2, R^3, R^4 and R^5 denote, independently of one another:

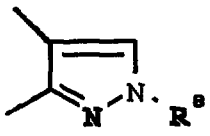
hydrogen, C_{1-6}-alkyl, preferably C_{1-4}-alkyl, most preferably methyl, C_{3-6}-cycloalkyl, preferably cyclopropyl, C_{1-6}-alkoxy, preferably C_{1-4}-alkoxy, most preferably methoxy, halogen, preferably chlorine or bromine, $-CF_3$, $-OCF_3$ or $-NR^6R^7$ wherein

R^6 denotes hydrogen, C_{3-6}-cycloalkyl, C_{1-6}-alkyl, preferably C_{1-4}-alkyl, most preferably methyl, or C_{2-4}-acyl, most preferably acetyl,
R^7 denotes hydrogen, C_{3-6}-cycloalkyl, preferably cyclopropyl, C_{1-6}-alkyl, preferably C_{1-4}-alkyl, most preferably methyl, or C_{2-4}-acyl, most preferably acetyl;
or
R^6 and R^7 together with the nitrogen atom form a 5- or 6-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}-alkyl, preferably methyl;

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

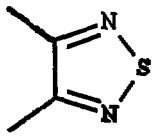
or

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



wherein R^8 is C_{1-3}-alkyl, preferably methyl;

or a fused thiadiazole of formula

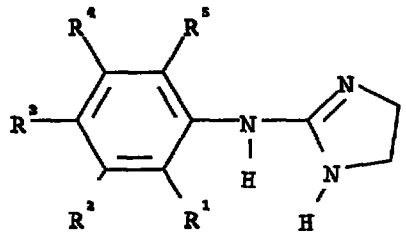


wherein R^3, R^4 and R^5 are as hereinbefore defined, and preferably denote hydrogen,

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



Ib

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

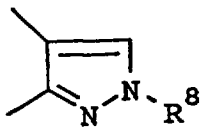
R^7 denotes hydrogen, C_{1-4}-alkyl, preferably methyl, C_{2-4}-acyl, preferably acetyl or

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;

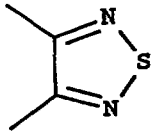
R^4 denotes hydrogen, C_{1-4}-alkyl, preferably methyl, fluorine, chlorine, bromine or CF_3;

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



wherein R^8 is methyl,

or a fused thiadiazole of the formula



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, Δ^2-pyrroline, Δ^3-pyrroline, tetrahydropyrrole, pyrrolidine, pyrrolidinone, imidazole, imidazoline, 1,3-thiazole, piperidine, piperazine, 4-C_{1-4}-alkylpiperazine, C_{1-4}-alkylpiperazine, 2,5-diketopiperazine, preferably N-methylpiperazine, morpholine, thiomorpholine, phthalimido or succinimido.

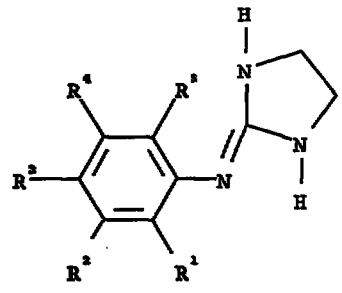
Examples of alkyl within the above definitions, including those which are components of other groups, are branched or unbranched C_{1-6}-alkyl groups, e.g. methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, isobutyl, sec.-butyl and tert.-butyl, n-pentyl, isopentyl, neopentyl, hexyl and isohexyl.

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.

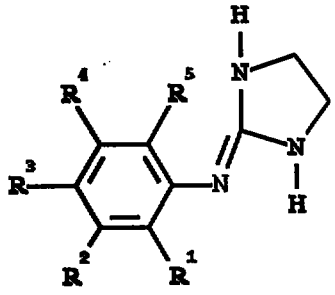
New substituted 2-(phenylimino)-imidazolidines of general formula II



II

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

The invention thus relates to compounds of general formula II



II

wherein

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

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

R^6 denotes hydrogen, C_{3-6}-cycloalkyl, C_{1-6}-alkyl, preferably C_{1-4}-alkyl, most preferably methyl, C_{2-4}-acyl, most preferably acetyl;

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

or

R^6 and 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 2-(3-diethylamino-2-methyl)-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 $-NR_6R_7$ 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

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

R^3 denotes hydrogen, methyl, fluorine, chlorine or bromine;

R^4 denotes hydrogen,

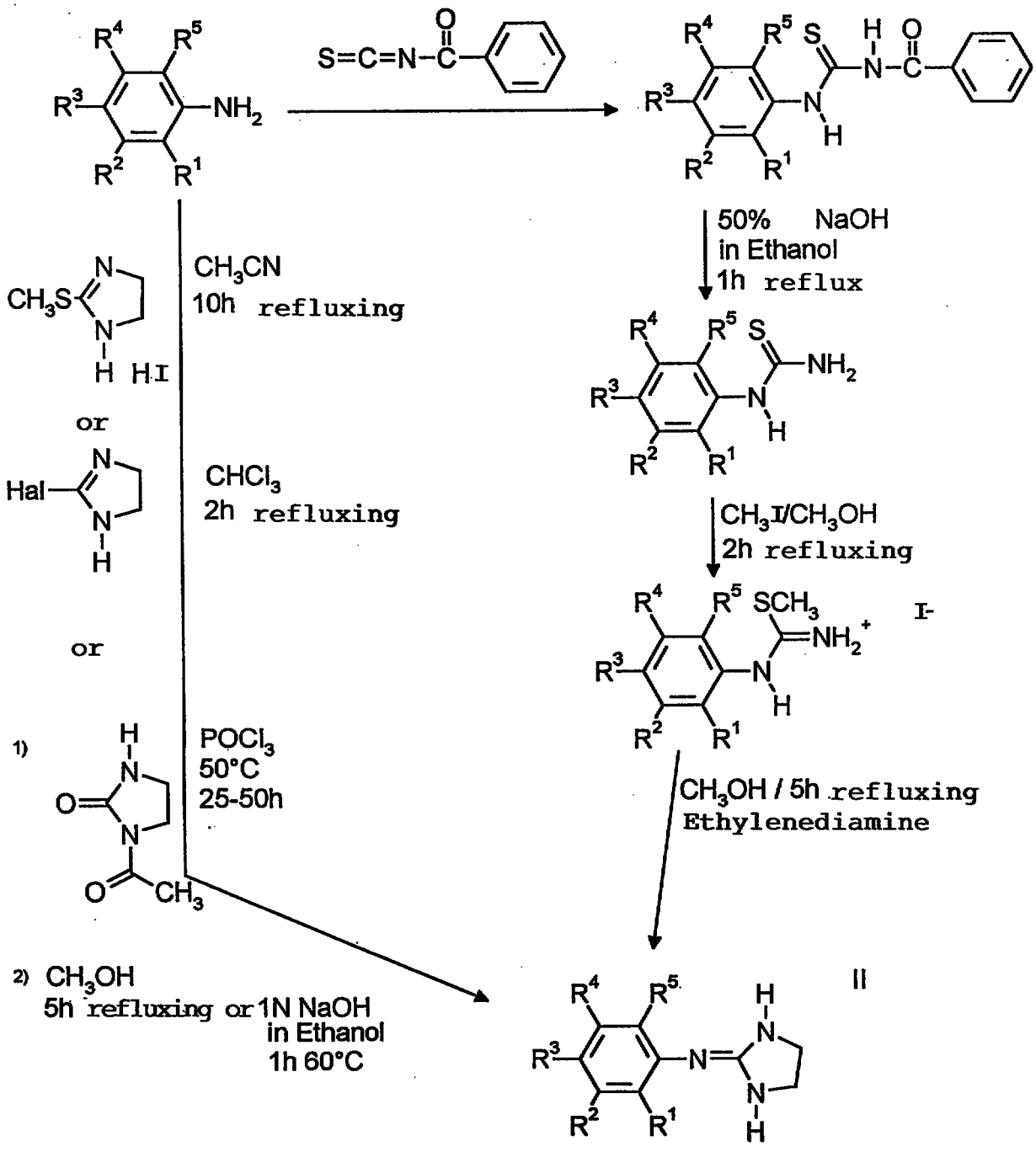
R^5 denotes hydrogen, methyl, chlorine or bromine;

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

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

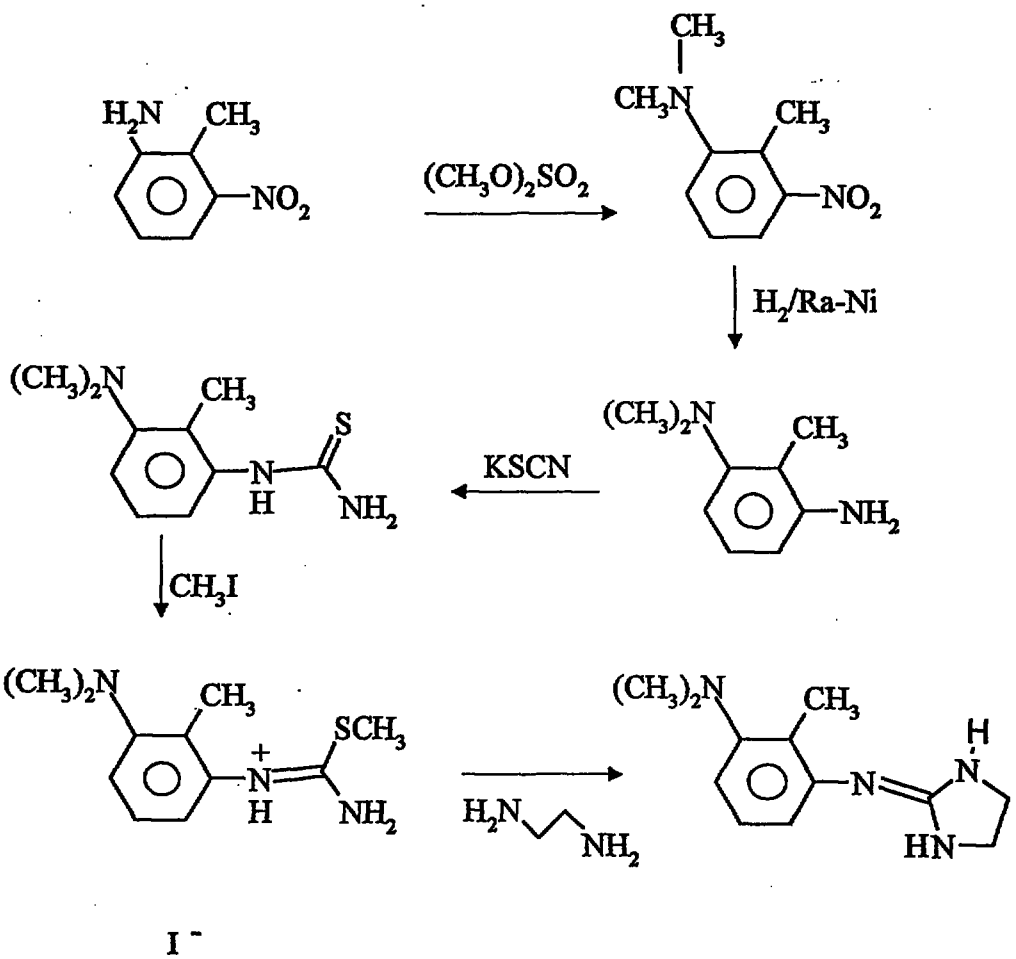
2-(3-dimethylamino-2-methylphenylimino)imidazolidine,
2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,
2-(5-amino-2-chloro-4-methylphenylimino)-imidazolidine
and
2-(3-amino-2-methylphenylimino)-imidazolidine.

The compounds of general formula I and II may be prepared according to analogous processes known 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

The preferred processes for preparing the compounds according to the invention will be explained with reference to individual Examples.

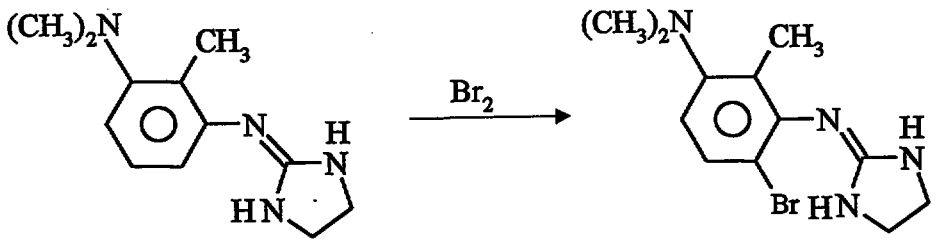


Example 1

Synthetic Scheme II

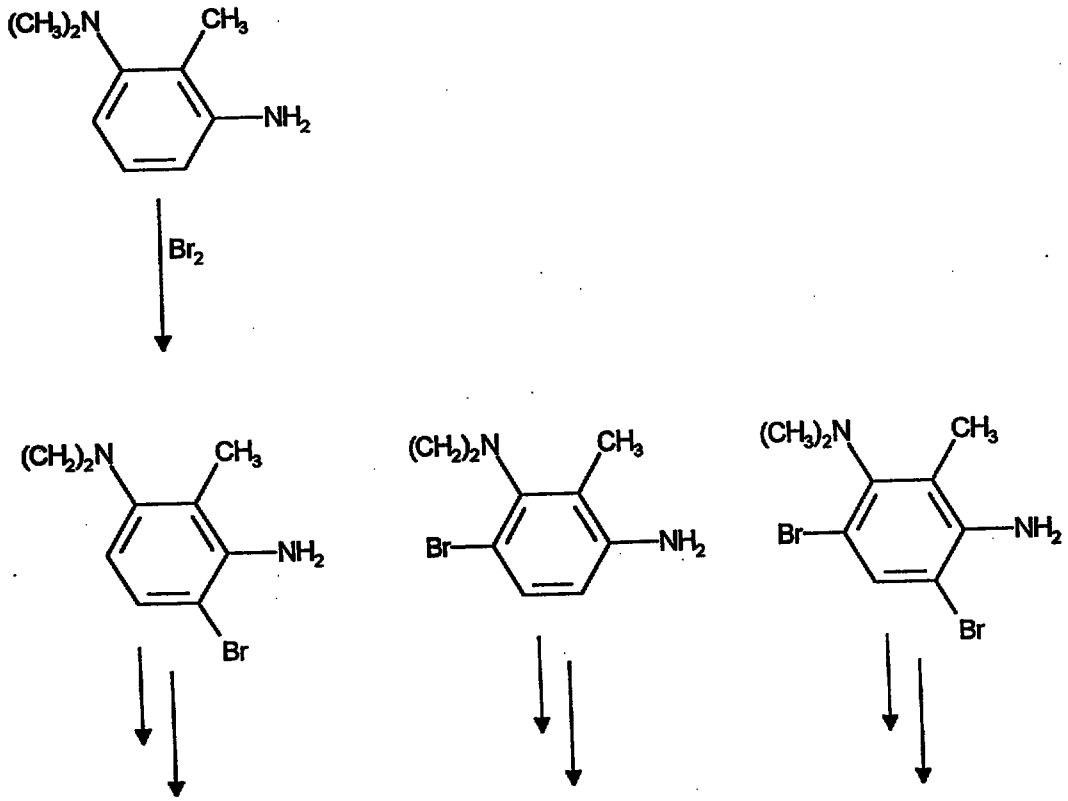
The methylation of the starting material, 2-methyl-3-nitro-aniline, may also be carried out analogously to the Leuckart-Wallach reaction using $HCOOH/CH_2O$ or using dimethylcarbonate instead of dimethylsulphate.

Compound 2 can be prepared by bromination of compound 1 under conventional reaction conditions



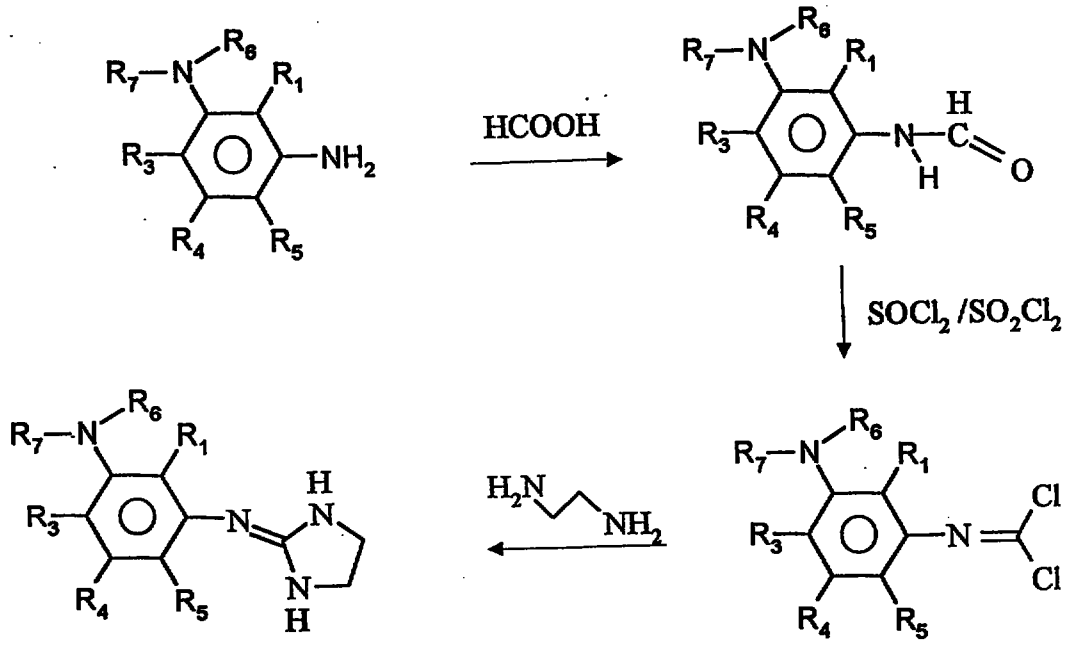
Example 2

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

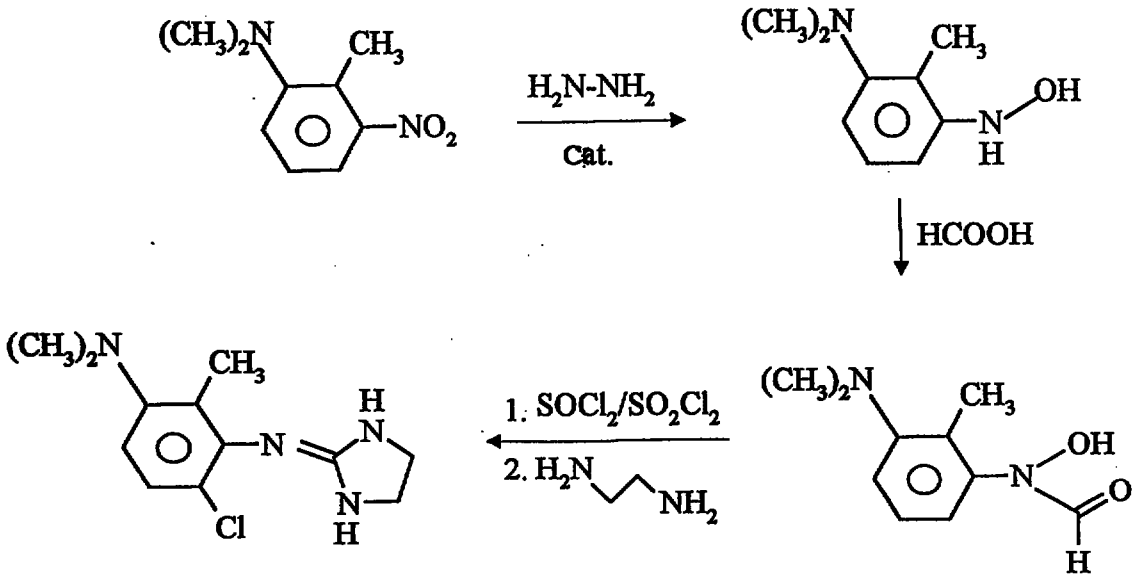


Example 2 **Example 3** **Example 4**

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 K_2CO_3 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 $MgSO_4$ 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 methyliodide 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-isothiourea 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 $MgSO_4$ 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)-imidazolidine are obtained.
Melting point 116 - 118°C.

Example 2:

2-(6-Bromo-3-dimethylamino-2-methylphenylimino)imidazolidine

6.55 g of 2-(3-Dimethylamino-2-methylphenyl-imino)-imidazolidine 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
(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, hydiodic 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. collidone 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	1.5 parts
Sodium salt of ethylenediamine tetraacetic acid	0.2 parts
Sufficient distilled water to make up to	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 α_{1L}-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

	Contraction of the urethra	Duration of effect	Increase in blood pressure	Duration of effect
Phenylephrine	100	100	100	100
Example 2	273	430	139	117

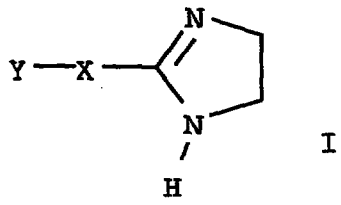
Data given in %

Example 2 = 2-(6-bromo-3-dimethylamino-2-methylphenyl-imino)imidazolidine

Claims

1. Use of α_{1L}-agonists for the preparation of pharmaceutical compositions for treating urinary incontinence, particularly stress incontinence.

2. Use according to claim 1, in which the α_{1L}-agonists have the general formula I



I

wherein

Y denotes an optionally substituted phenyl or napthyl 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-, $-CH_2-$, $-OCH_2-$, $-O-CHCH_3-$, -CH=N-NH-, -N=N- or -NZ-, wherein Z = $-CH_2-CH=CH_2$ or cyclopropylmethyl,

and the pharmacologically acceptable acid addition salts thereof.

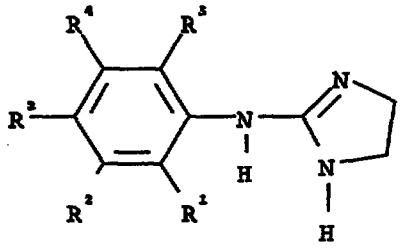
3. Use according to claim 2, wherein X in the compound of formula I denotes -NH-.

4. Use according to claim 2 or 3, wherein in the compound of formula I Y is an optionally substituted thienyl, furyl, pyrrole, tetrahydropyrrolyl, pyridyl, pyrazinyl, pyranyl, 1,3-

thiazolyl, imidazolyl, imidazolinyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, isothiazolyl, pyrimidinyl, thiazolyl, thiadiazinyl or piperidinyl, which is bound to the group X via a carbon atom.

5. Use according to one of claims 2 to 4, wherein the compound of formula I is tiamenidine.

6. Use of phenylaminoimidazolines of general formula Ib



Ib

wherein R^1, R^2, R^3, R^4 and R^5 denote, independently of one another:

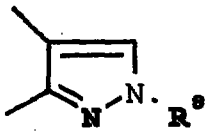
hydrogen, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-alkoxy, halogen, $-CF_3$, $-OCF_3$ or $-NR^6R^7$ wherein

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

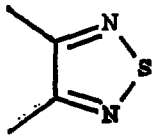
R^6 and R^7 together with the nitrogen atom form a 5- or 6-membered saturated or unsaturated ring which may contain up to two additional heteroatoms from the group comprising oxygen, sulphur or nitrogen, whilst each additional nitrogen atom may be substituted by C_{1-4}-alkyl;
or

R^6 and R^7 together with the nitrogen atom form phthalimido;
or
R^1 and R^2 together form a fused pyrazole of the formula



wherein R^8 is C_{1-3}-alkyl,

or a fused thiadiazole of the formula



wherein R^3, R^4 and R^5 are as hereinbefore defined, and the pharmacologically acceptable acid addition salts thereof, for preparing pharmaceutical composition for treating urinary incontinence, particularly stress incontinence.

7. Use of phenyliminoimidazolines of general formula Ib according to claim 6,
wherein R^1, R^2, R^3, R^4 and R^5 independently of one another denote:

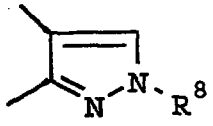
hydrogen, C_{1-4}-alkyl, preferably methyl, cyclopropyl, C_{1-4}-alkoxy, preferably methoxy, halogen, CF_3, $-OCF_3$ or NR^6R^7 wherein

R^6 is hydrogen, C_{3-6}-cycloalkyl, C_{1-4}-alkyl, preferably methyl,

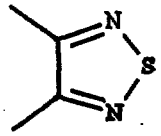
* C L M S *

or acetyl,

R^7 denotes hydrogen, cyclopropyl, C_{1-4}-alkyl, preferably methyl, or acetyl;
or
R^6 and R^7 together with the nitrogen atom form phthalimido;
or
R^1 and R^2 together form a fused pyrazole of the formula



wherein R^8 is methyl,
or a fused thiadiazole of the formula



wherein R^3, R^4 and R^5 are as hereinbefore defined, and preferably represent hydrogen.

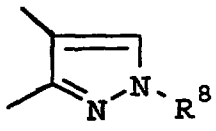
8. Use of phenylaminoimidazolines of general formula Ib according to claim 6,

wherein R^1, R^2, R^3, R^4, R^5 independently of one another denote:

hydrogen, ethyl, methyl, cyclopropyl, fluorine, chlorine, bromine, $-CF_3$ or $-NR^6R^7$ wherein

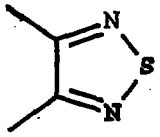
R^6 denotes hydrogen, methyl or acetyl,

R^7 denotes hydrogen, methyl or acetyl;
or
R^6 and R^7 together with the nitrogen atom form phthalimido;
or
R^1 and R^2 together form a fused pyrazole of the formula



wherein R^8 is methyl,

or a fused thiadiazole of the formula



wherein R^3, R^4 and R^5 are as hereinbefore defined, and preferably represent hydrogen.

9. Use of phenylaminoimidazolines of general formula Ib according to claim 6,

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;

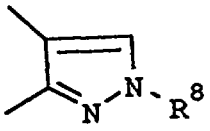
R^3 denotes hydrogen, fluorine, chlorine, bromine, C_{1-4}-alkyl, preferably methyl, $-NH_2$ or cyclopropyl;

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 $-CF_3$;

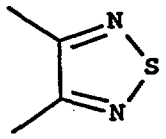
or

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



wherein R^8 is methyl,

or a fused thiadiazole of the formula



wherein R^3, R^4 and R^5 are as hereinbefore defined, and preferably represent hydrogen.

10. Use of phenylaminoimidazolines of formula Ib according to claim 6, wherein

R^1 is hydrogen or methyl;

R^2 is methyl, chlorine, $-CF_3$, $-NH_2$ or $-N(CH_3)_2$;

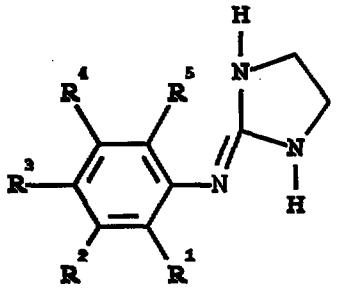
R^3 is hydrogen, methyl, chlorine or bromine;

R^4 is hydrogen;

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

11. Use of phenylaminoimidazolines of formula Ib according to claim 6, wherein the compound is
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.

12. New phenyliminoimidazolidines of general formula II



II

wherein

R^1 denotes hydrogen, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-alkoxy, halogen, $-CF_3$ or $-OCF_3$;

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

R^6 is hydrogen, C_{3-6}-cycloalkyl, C_{1-6}-alkyl, C_{2-4}-acyl,

R^7 is hydrogen, C_{3-6}-cycloalkyl, C_{1-6}-alkyl, C_{2-4}-acyl,

or

R^6 and R^7 together with the nitrogen atom form a 5- or 6-membered saturated or unsaturated ring which may contain up to two further heteroatoms from the group comprising 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 form phthalimido;

R^3 denotes hydrogen, halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, $-CF_3$ or $-OCF_3$;

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

R^5 denotes hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen, $-CF_3$ or $-OCF_3$,

and the pharmacologically acceptable acid addition salts thereof, with the exception of 2-(3-diethylamino-2-methyl)-imidazolidine.

13. Phenyliminoimidazolidines according to claim 12, 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 $-OCF_3$.

14. Phenyliminoimidazolidines according to claim 12, 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 $-NR_6R_7$ 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, $-CF_3$.

15. Phenyliminoimidazolines according to claim 12, 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

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

R^3 denotes hydrogen, methyl, fluorine, chlorine or bromine;

R^4 denotes hydrogen,

R^5 denotes hydrogen, methyl, chlorine or bromine.

16. A phenyliminoimidazolidine according to claim 12, which is
2-(3-dimethylamino-2-methylphenylimino)imidazolidine,
2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,
2-(5-amino-2-chloro-4-methylphenylimino)-imidazolidine
or
2-(3-amino-2-methylphenylimino)-imidazolidine.

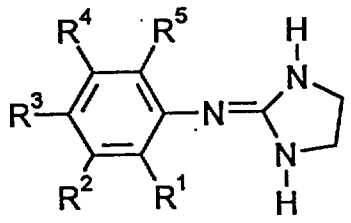
17. Pharmaceutical preparation comprising a compound of general formula II according to one of claims 12 to 16 as well as conventional diluents, excipients and/or carriers.

18. Process for preparing pharmaceutical preparations according to claim 17, characterised in that compounds of general formula II are mixed with conventional galenic diluents, excipients and/or carriers.

* C L M S *

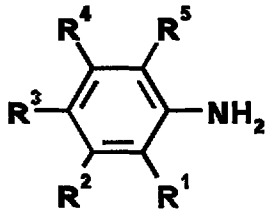
19. Use of compounds of general formula II as defined in any one of claims 12 to 16 for preparing pharmaceutical compositions for the treatment of urinary incontinence, particularly stress incontinence.

20. Analogy processes for preparing compounds of general formula



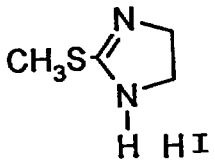
II

according to any one of claims 12 to 16 characterised in that an aniline of general formula



wherein R^1 to R^5 are as hereinbefore defined is reacted with one of the following compounds

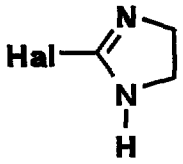
a)



HI

or

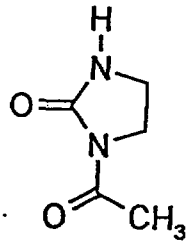
b)



or

c)

1)



2) CH_3OH
5h refluxing or 1N NaOH
in ethanol
1h 60°C

and
the compounds obtained according to one of processes a-c are optionally converted into the pharmacologically acceptable acid addition salts thereof.