

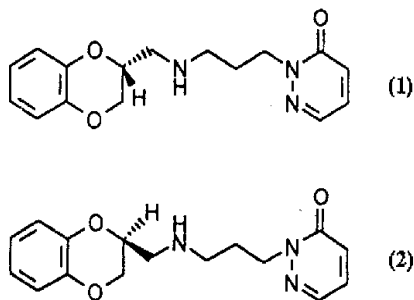


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| <p>(21) International Application Number: PCT/HU96/00030 (22) International Filing Date: 28 May 1996 (28.05.96) (30) Priority Data: P 95 01560 29 May 1995 (29.05.95) HU (71) Applicant (for all designated States except US): GYÓGYSZERKUTATÓ INTÉZET KFT [HU/HU]; Berlíni u. 47-49, H-1045 Budapest (HU). (72) Inventors; and (75) Inventors/Applicants (for US only): MÁTYUS, Péter [HU/HU]; Diósárok u. 23, H-1125 Budapest (HU). HÁRSING, László [HU/HU]; Dembinszky u. 8, H-1071 Budapest (HU). KARIM, Mariann [HU/HU]; Böröndös u. 18, H-1046 Budapest (HU). KOSÁRY, Judit [HU/HU]; Fátra tér 5, H-1112 Budapest (HU). PAPP, Ágnes [HU/HU]; Laborfalvy u. 16, H-1041 Budapest (HU). SIMAY, Antal [HU/HU]; Pagony u. 30, H-1124 Budapest (HU). TILAHUN, Yemane [ET/HU]; Radnóti M. u. 9, H-1137 Budapest (HU). TOMORI, Éva [HU/HU]; Csévi u. 4/a, H-1025 Budapest (HU). HORVÁTH, Edit [HU/HU]; Fejér Lipót u. 48, H-1119 Budapest (HU). HORVÁTH, Katalin [HU/HU]; Nagybányai u. 54/b, H-1025 Budapest (HU). VARGA, Ildikó [HU/HU]; Frangepán u. 69, H-1135</p> | | <p>Budapest (HU). ZÁRA, Erzsébet [HU/HU]; Damjanich u. 32, H-1071 Budapest (HU). BIDLÓ, Margit [HU/HU]; Bartók Béla u. 86, H-1113 Budapest (HU). DRUGA, Alice [HU/HU]; Árnvas u. 1/a, H-1121 Budapest (HU). RABLOCZKY, György [HU/HU]; Batthyány u. 3/b, H-1015 Budapest (HU). VARGA, Márta [HU/HU]; Helsinki u. Hévíalomás, H-1203 Budapest (HU). KÁRPÁTI, Egon [HU/HU]; Tövis u. 7/b, H-1022 Budapest (HU). KASZTREINER, Endre [HU/HU]; Szabolcska M. u. 7, H-1114 Budapest (HU). KIRÁLY, István [HU/HU]; Ösvény u. 6, H-1028 Budapest (HU). MÁTHE, Ildikó [HU/HU]; Eötvös J. u. 15, H-1046 Budapest (HU). MÁTHÉ, György [HU/HU]; Eötvös J. u. 15, H-1046 Budapest (HU). SEBESTYÉN, László [HU/HU]; Kórákás park 44. II. 6, H-1157 Budapest (HU). MAKK, Nándor [HU/HU]; Liget u. 26, H-2623 Kismaros (HU). (74) Agent: DANUBIA; Bajcsy-Zsilinszky u. 16, H-1051 Budapest (HU). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> |
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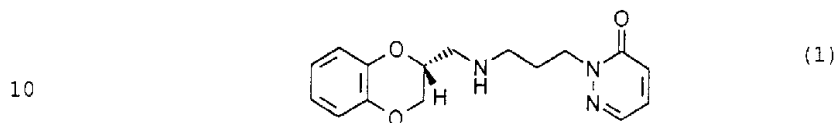
(54) Title: 3(2H)-PYRIDAZINONE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS



(57) Abstract
 The invention relates to R-2-[3-([1,4]benzodioxan-2-ylmethylamino)-1-propyl]-3(2H)-pyridazinone of formula (1), and to S-2-[3-([1,4]benzodioxan-2-ylmethylamino)-1-propyl]-3(2H)-pyridazinone of formula (2), and to acid-addition salts thereof as well as pharmaceutical compositions containing these compounds. Furthermore, the invention relates to a process for the preparation of the above compounds. The new starting compounds of formulae (4) and (5) are also involved in the scope of the invention. The compounds according to the invention possess α_1 - and α_2 -adrenoceptor antagonistic effects and urogenital selectivity. Thus, they are useful for the treatment of the benign prostate hyperplasia.

3(2H)-PYRIDAZINONE DERIVATIVES AND PHARMACEUTICAL
COMPOSITIONS CONTAINING THESE COMPOUNDS

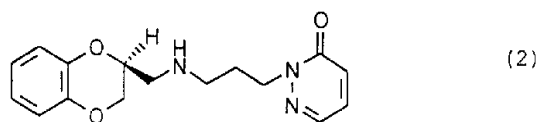
The invention relates to the compounds R-2-[3-([1,4]-
5 -benzodioxan-2-ylmethylamino)-1-propyl]-3(2H)-pyridazi-
none of formula (1)



[Configuration (R)]

and S-2-[3-([1,4]benzodioxan-2-ylmethylamino)-1-propyl]-
15 -3(2H)-pyridazinone of formula (2)

15

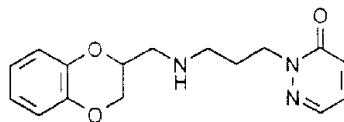


20

[Configuration (S)]

as well as their acid-addition salts. The invention re-
lates also to pharmaceutical compositions containing
these compounds as well as to a process for the prepara-
tion of these compounds.

25 Antihypertensive 2-(aminoalkyl)-3(2H)-pyridazinone
derivatives are published in the Hungarian patent speci-
fication No. 195,645. A typical example of these sub-
stances is 2-[3-([1,4]benzodioxan-2-ylmethylamino)-1-
-propyl]-3(2H)-pyridazinone of formula (3),



(3)

5

[(R,S)]

i.e. racemic form of the compounds of formulae (1) and (2), a very low dose of which significantly decreases the arterial blood pressure in animal experiments under in vivo conditions. According to the description, these pyridazinone derivatives selectively inhibit α_1 -adrenoceptors and possess a calcium antagonistic effect. Thus, they meet the demands of a multicomponent antihypertensive action; no comments are made about any other possible pharmacological effects of these compounds.

Recently, the possibilities of drug treatment of benign prostatic hypertrophy (hereinafter abbreviated: BPH; the benign tissue hyperplasia of the prostate). Till now, a surgical intervention has nearly exclusively been performed to overcome this disorder affecting about 50% of men above 50 years. Due to the higher risk in the elderly and high costs of surgical intervention, drug therapy has called an increased attention.

It has been stated that a major part of symptoms accompanying BPH are related to an increased tone of the smooth muscles of the prostatic zone of urethra and the bladder neck, which leads to an increase in the intraurethral pressure. Furthermore, it has been proven that in these tissues the smooth musculature, having an α -adrenergic innervation containing both α_1 - and α_2 -adrenoceptors, can be relaxed by α -adrenergic blocking agents. Thus, the symptoms of BPH can be favourably influenced by α -adrenergic blocking drugs [see, e.g.: E.

Shapiro et al.: J. Urol. 137, 565 (1987); H. Lepor, J. Androl. 12, 356 (1991); as well as S. Heda et al.: Eur. J. Pharm. 103, 249 (1994). However, for the treatment of BPH, such α -adrenoceptor blocking compounds can only be
5 taken preferably into account, which do not exert any considerable cardiovascular side effects, e.g. a decrease in blood pressure, orthostatic hypotension or syncope.

Due to the inhibition of presynaptic α_2 -receptors by
10 using nonselective α_1 - and α_2 -adrenoceptor blocking agents, other side effects could also appear (e.g. the heart rate is increased). Therefore, exclusively α_1 -adrenoceptor blocking drugs are therapeutically employed at present.

15 Conclusively, the urogenital selectivity of the active agents, i.e. its selectivity for the prostate-urethra-bladder system is a very important requirement; nevertheless, the selectivity of available drugs (e.g. prazosin, terazosin, alfuzosin) is low or moderate
20 and as a consequence, they show adverse effects. Thus novel urogenitally selective α -adrenoceptor blocking agents are really needed, which are able to favourably influence the symptoms of BPH and are free of untoward side effects.

25 During our investigations it has been surprisingly found that the α -adrenoceptor blocking compounds of formulae (1) and (2) of the invention also have a significant urogenital selectivity; while these compounds diminish the intraurethral pressure at very low doses,
30 they simultaneously exhibit a very weak influence only on other cardiovascular parameters. Thus, they meet the above requirements.

The efficacy and selectivity of the compounds were proven under *in vivo* conditions as well as by *in vitro* experiments on isolated organs and receptor-binding assays.

- 5 In an *in vivo* animal model, in anaesthetized cat, intraurethral hypertension can be induced by α_1 -adrenoceptor agonists [e.g. phenylephrine, which is chemically (-)-1-(3-hydroxyphenyl)-2-(methylamino)ethanol]. This hypertension-inducing effect can be antagonized by α_1 -
 10 -adrenoceptor antagonists. The antihypertensive effect is expressed by reduction of the diastolic pressure. Results of this experiment are summarized in Table 1 (the experiment is described in detail in the Pharmacological part).

15

Table 1

Effects of compounds of formulae (1) and (2) on phenylephrine-induced intraurethral hypertension and diastolic pressure, respectively

| Compound | ED ₅₀ (µg/kg, iv.) | | D/U ^c |
|----------|-------------------------------|---------------------------------|------------------|
| | urethra ^a | diastolic pressure ^b | |
| (1) | 13.9 | >888 | >63.9 |
| (2) | 3.4 | 90 | 26.5 |
| (3) | 28.4 | 130 | 4.6 |
| Prazosin | 18.7 | 25 | 1.3 |

Remarks:

- 20 ^a: Dose decreasing by 50% the hypertension induced by a 15 µg/kg/min intravenous dose of phenylephrine
^b: Dose decreasing by 50 % the diastolic total pressure increased by phenylephrine
^c: ED₅₀ (diastolic pressure)/ED₅₀ (urethra)

It is obvious from the above data that the intraurethral pressure-decreasing effects of compounds of formulae (1) and (2) of the invention appear in a low dose; moreover their urogenital selectivity (expressed as D/U) considerably exceeds the selectivity of the racemic compound of formula (3) and that of prazosin.

In addition, investigations were performed on blood vessel and human hyperplastic prostate tissue preparations. In these experiments, a mesenteric artery was used as a model of resistance vessels which affect the blood pressure. We measured the extent of inhibition of the compounds of the invention and that of the reference drugs, respectively, on the contraction-inducing action of the α_1 -agonist (phenylephrine). The α_1 -adrenoceptor antagonism was then characterized by pA_2 values. The results are shown in Table 2.

Table 2

Evaluation of α_1 -adrenoceptor antagonistic effect in isolated organ experiments

| Compound | pA_2 | | Selectivity ^a (prostate/ artery) |
|-----------|-----------------------|------------------------------------|---|
| | rat mesenteric artery | human hyperplastic prostate tissue | |
| (1) | 6.56 | 7.20 | 4.37 |
| (2) | 7.68 | 8.23 | 3.55 |
| (3) | 7.16 | 7.51 | 2.24 |
| Alfuzosin | 8.60 | 8.01 | 0.26 |
| Terazosin | 8.45 | 8.39 | 0.87 |

Remark:

^a: Antilogarithmic ratio of pA_2 value

The data of Table 2 show that the compounds of formulae (1) and (2) possess a strong α_1 -adrenoceptor antagonistic effect, which is more pronounced on the prostate tissue than on the resistance artery preparation. It is also remarkable that the prostate selectivity of the compounds according to the invention is more favourable than that of any reference drugs including the racemic compound of formula (3).

As mentioned above, an α_2 -adrenoceptor blocking component may also be of importance in treatment of BPH if inhibition of the postsynaptic α_2 -adrenoceptors is more pronounced than that of presynaptic α_2 -receptors.

Moreover, as shown more recently, α_2 -antagonists, besides their capacity of reducing the overactivity of sympathetic control in the prostate, may be able to effectively reduce hormonally induced prostatic stiffness [see, in R. R. Ruffolo et al.: Eur. J. Med. Chem., 30S, 269 (1995)].

The pre- and post-synaptic α_2 -adrenoceptor antagonistic effects of the compounds according to the invention were determined on rat vas deferens and dog vena saphena preparations by using xylazine [chemically 5,6-dihydro-2-(2,6-dimethylphenylamino)-1,3-thiazine] or UK 14304 [chemically 5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline] as agonists. The antagonism was characterized by the pA_2 values. The results are summarized in Table 3.

Table 3

Pre- and postsynaptic α_2 -adrenoceptor antagonistic effects on vas deferens and vena saphena preparations

| Compound | pA ₂ | | Selectivity* postsynaptic/ presynaptic |
|-----------|-----------------|--------------|--|
| | presynaptic | postsynaptic | |
| (1) | 5.81 | 7.87 | 115.0 |
| (2) | 6.81 | 8.14 | 21.4 |
| Yohimbine | 6.93 | 8.05 | 13.2 |

Remark:

- 5 * : Antilogarithmic ratio of pA₂ values

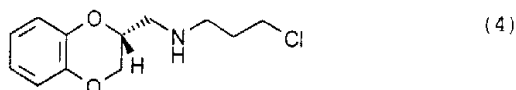
On the basis of the above data it can be stated that both compounds of formulae (1) and (2) do have a strong α_2 -adrenoceptor antagonistic activity and, surprisingly, they exert an excellent selectivity toward the postsynaptic α_2 -receptors. This property represents a favourable additional element in mechanism of action of the compounds according to the invention.

The above-described *in vivo* and isolated organ experiments confirm that, in comparison to the racemic compound of formula (3) and to other reference drugs, the substances of formulae (1) and (2) according to the invention provide considerable advantages from the viewpoint of the treatment of BPH. The low toxicity of both compounds of formulae (1) and (2) also contributes to their high therapeutic value and safety.

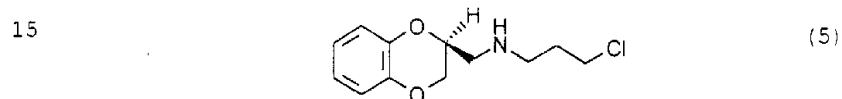
Thus, the invention relates also to pharmaceutical compositions useful for the treatment of benign prostatic hyperplasia, which contain the compound of formula (1) or (2), respectively, as active ingredient.

Furthermore, the invention relates to a process for the preparation of compounds of formulae (1) and (2).

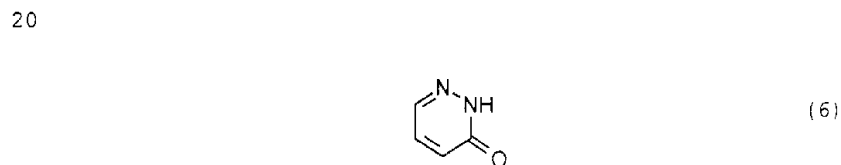
The compounds of formulae (1) and (2) as well as their acid-addition salts are prepared by reacting the corresponding optically active N-(1,4)benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)-amine of R configuration of formula (4)



[Configuration (R)]
or S configuration of formula (5)



[Configuration (S)]
with 3(2H)-pyridazinone of formula (6)



25 and, if desired, converting the free base obtained to an acid-addition salt.

According to a preferred embodiment of the process of invention, a salt of the compound of formula (6), optionally prepared with a base *in situ*, is used and the reaction is carried out in an aprotic or protic solvent at a temperature between 20 °C and 150 °C.

30 Preferably an alkaline metal salt, e.g. potassium or sodium salt, of the compound of formula (6) is reacted

with the compound of formula (4) or formula (5) in a polar or apolar aprotic solvent at a temperature between 20 °C and the boiling point of the solvent employed. Dimethyl sulfoxide, dimethyl formamide or toluene are preferable solvents for this reaction. Optionally, a catalyst, e.g. potassium or sodium iodide and/or a quaternary ammonium salt, e.g. tetrabutylammonium bromide, can be used in the reaction.

According to a particularly preferred embodiment of the process of the invention, the anhydrous potassium salt of the compound of formula (6) is reacted with the chloropropyl alkylating agent of formula (4) in order to obtain the compound of formula (1); whereas the chloropropyl alkylating agent of formula (5) is used for preparing the compound of formula (2). The reaction is carried out in dimethyl sulfoxide at room temperature for about 20 hours under stirring.

According to another advantageous embodiment of the process the above reactants are brought to interaction in toluene, in the presence of tetrabutylammonium bromide at the boiling point of the reaction mixture.

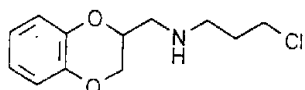
The reaction mixture may be processed in a manner known per se, e.g. in such a way that, after treatment with water and optionally, after alkalization of the mixture, the product is extracted into a water-immiscible solvent. The crude product may be purified in its base form, e.g. by using chromatographical methods; or can be transformed to one of its acid-addition salts which may be recrystallized or, if desired, from the acid-addition salt obtained another acid-addition salt can be prepared.

3(2H)-pyridazinone of formula (6) used as starting substance in the above reaction is a known compound

[see, e.g. Staehelin et al.: Helv. Chim. Acta 39, 1741 (1956)].

The optically active compounds of formulae (4) and (5) are new and also involved in the scope of the invention. These compounds can be prepared e.g. by the resolution of the racemic compound of formula (7).

10



(7)

[R, S]

The compound of formula (7) can be obtained e.g. according to the German patent specification No. 1,118,218.

The resolution can be performed e.g. by preparation of the diastereomeric salts from the racemic base with an optically active acid by separating, e.g. by fractional crystallization, the diastereomeric salt pair and then, after liberating the bases from the separated diastereomeric salts, the enantiomers of formulae (4) and (5) are individually obtained. The diastereomeric salts are preferably prepared by using L(-)-dibenzoyltartaric acid. An example of resolution will be described in connection with the preparative Examples.

As mentioned above, the compounds of formulae (1) and (2) possess a valuable pharmacological action; they favourably influence the symptoms of BPH.

For therapeutic purposes, the doses of active compounds of the invention are:

in general from 0.05 mg/kg of body weight up to 2.0 mg/kg of body weight;

preferably from 0.1 mg/kg of body weight up to 0.5 mg/kg of body weight; which are optionally divided to subdoses, by considering also the conditions of absorption. Nevertheless, doses
5 different from the above doses may also be employed depending upon the severity of the treated clinical symptoms and with consideration of the general state of the treated patient.

For therapeutical purposes the administration can be
10 performed e.g. in the form of tablets, pills, capsules, granules, fine powders, suppositories, ointments, aqueous or non-aqueous injections, or injectable emulsions or suspensions and the like, as well as in the form of a solid injectable composition which should be dissolved,
15 emulsified or suspended before use. The use of pharmaceutical compositions of the invention can be effective both in oral and parenteral routes (e.g. by administration of an injectable solution in intravenous, intramuscular or subcutaneous route); or by rectal use and the
20 like. The oral administration is usually preferred.

The pharmaceutical compositions according to the invention may contain commonly used carriers and vehicles such as sterile water, vegetable oils and the like; and may include biologically acceptable solvents, e.g. ethanol, glycerol, propylene glycol and the like; as well as
25 fillers, adhesives, lubricating, dyeing, flavouring, emulsifying and suspending agents (e.g. Tween 80, acacia gum and the like); as well as other additives.

The invention is illustrated in detail by the following non-limiting Examples.
30

The chemical and optical purity of the compounds were established by using high pressure liquid chromatography (HPLC).

Examination of the chemical purity: Nucleosil C₁₈ column; mobile phase: KH₂PO₄ phosphate buffer/Na lauryl sulfate/acetonitrile.

Examination of the optical purity: Chiral-AGP column; phosphate buffer/acetonitrile.

Melting points were taken on a Boëtius type melting point apparatus.

Example 1

**R-2-[3-([1,4]Benzodioxan-2-ylmethylamino)-1-propyl]-
-3(2H)-pyridazinone hydrochloride**

After portionwise adding 1.40 g (29.2 mmol) of 50 % sodium hydride to 57 ml of anhydrous dimethyl sulfoxide under nitrogen while stirring, the suspension is stirred at room temperature for 10 minutes. Then, after adding 2.80 g (9.2 mmol) of 3(2H)-pyridazinone, a solution containing 7.00 g (29.0 mmol) of R-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine in 11 ml of dimethyl sulfoxide is dropped to within 10 minutes. The reaction mixture is stirred at room temperature for about 4 hours and let to stand overnight. Subsequently, it is poured into 50 ml of ice-water and extracted four times with 10 ml of toluene each. After clarifying the organic phases with activated carbon and then extracting them twice with 50 ml of 1 N hydrochloric acid each, the combined aqueous-acidic phase is washed with toluene. After making the aqueous phase alkaline by adding 35 % sodium hydroxide solution up to pH 9 under cooling by ice, it is extracted 5 times with 20 ml of methylene chloride each, then the combined organic phase is dried over anhydrous potassium carbonate. The residue obtained after filtration and evaporation of the solvent is purified by chromatography on a silica gel column. The elution is performed with a mixture of acetone and toluene.

After dissolving the crude base obtained in a mixture of 6 ml of ethanol and 14 ml of ethyl ether, the solution is acidified until pH 5 by adding 20 % ethanolic hydrogen chloride solution at -5 °C. The reaction mixture is stirred for one hour at -5 °C, then the precipitate is filtered, washed with ether and dried to give the title hydrochloride in a yield of 3.0 g (31 %), m.p.: 151-152 °C.

Optical activity: $[\alpha]_D^{25} = +50.3^\circ$ (c = 1, ethanol)

Chemical and optical purity as determined by HPLC method: $\geq 99.5\%$.

Example 2

S-2-[3-([1,4]Benzodioxan-2-ylmethylamino)-1-propyl]-3(2H)-pyridazinone hydrochloride

The process described in Example 1 is followed, except that S-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine is used instead of R-N([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine to obtain the title hydrochloride in a yield of 3.2 g (33 %), m.p.: 152-153 °C.

Optical activity: $[\alpha]_D^{25} = -50.8^\circ$ (c = 1, ethanol)

Chemical and optical purity as determined by HPLC method: $\geq 99.5\%$.

R- and S-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine used as starting materials in Example 1 and 2, respectively, can be prepared e.g. as follows.

To a solution containing 12.0 g (50.0 mmol) of racemic N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine base (liberated from its hydrochloride salt by adding 35% sodium hydroxide solution) in 97 ml of acetone, 18.85 g (50.0 mmol) of L(-)-dibenzoyltartaric acid monohydrate are added under stirring. The solution is

stirred at room temperature for 4 hours, then let to stand overnight. The precipitate is collected by filtration and recrystallized several times from acetone.

Thus, the L(-)-dibenzoyltartarate salt of R-N-
5 -([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine is obtained with 1:1 stoichiometric composition in a yield of 4.5 g (30 %), m.p.: 149-150. °C.

After evaporating the above filtrate under reduced pressure, the base [containing S-N-([1,4]benzodioxan-2-
10 -ylmethyl)-N-(3-chloro-1-propyl)amine as main component] is separated from the evaporation residue [which is a mixture rich in S-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine salt] by adding 35% sodium hydroxide solution. The pure amine salt of (S) configura-
15 tion is obtained from the base prepared as follows:

To the solution of 7.1 g (30.0 mmol) of crude base in 15 ml of ethanol, 5.65 g (15.0 mmol) of L(-)-dibenzoyltartaric acid monohydrate are added. After stirring the reaction mixture at room temperature for 2
20 hours, the precipitate is filtered, recrystallized from ethanol several times and dried. Thus, the L(-)-dibenzoyltartarate salt of S-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine is obtained with 2:1 stoichiometric composition in a yield of 4.2 g (33
25 %), m.p.: 100-101 °C.

The chemical and optical purity of both diastereomeric salts are ≥99% based on HPLC analysis.

The amine bases of R and S configuration are liberated by adding 35% sodium hydroxide solution to the
30 diastereomeric salts in water, and used directly for the preparation of the compounds of Examples 1 and 2, respectively.

Pharmacological studies

Effect on the intraurethral and diastolic blood pressure on anaesthetized cats

This investigation was performed according to the
5 method of Lefèvre et al. [Br. J. Pharmacol. 109, 1282
(1993)]. The essence of the method can be summarized as follows.

Cannules were introduced into the femoral artery and vein of pentobarbitone-anaesthetized, artificially ven-
10 tilated cats of both sexes weighing 2.5 to 3.5 kg for administration of the compounds and measurement of blood pressure. The bladder was exposed by lower median lapo-
rotomy and a catheter was introduced into the urethra through the trigonum. The arterial and intraurethral
15 pressures were registered on a Hellige polygraph by using a pressure transducer.

For excluding autonomic effects mediated not through α -adrenoceptors, mecamlamine, atropine and propranolol were administered intravenously in doses of 0.5, 0.75
20 and 0.5 mg/kg, respectively.

An increase in intraurethral and blood pressure was induced by phenylephrine infusion of 15 μ g/kg/min; the change over the baseline pressure was considered to be 100%. The test substances were administered intrave-
25 nously in 1 - 1000 μ g/kg cumulative bolus doses. An interval of at least 5 minutes was allowed after each dose. The dose of α -antagonist inhibiting by 50% the phenylephrine-induced increase in urethral pressure (ED_{50} : urethra) as well as the dose decreasing by 50% the
30 phenylephrine-induced diastolic total pressure elevation (ED_{50} diastolic value) were determined.

α_1 -Adrenoceptor antagonistic effect in isolated organ experiments

A) Investigation of postsynaptic α_1 -adrenoceptors on the rat mesenteric artery

5 This test was performed according to the method of Angus et al. [J. Physiol. 403, 495 (1988)]. The upper mesenteric artery preparation was suspended in Krebs solution bubbled with carbogen at 37 °C. A pre-tension of 1 g and an equilibration period of 1.5 hour were used. A
10 cumulative dose/effect curve was established for phenylephrine. Then, after two washings and a 30-minute incubation with the antagonist, the dose/effect curve was repeatedly determined. For characterizing the antagonistic effects, pA_2 values were calculated.

15 B) Investigation of postsynaptic α_1 -adrenoceptors on human prostate preparation

This test was performed according to the method of Scheu-Eei Yu et al. [Eur. J. Pharmacol. 252, 29 (1994)].

20 Strips prepared from human hyperplastic prostate tissue were suspended in a Krebs solution bubbled with carbogen at 37 °C. A pre-tension of 1 g and an equilibration period of 1 hour were used. A dose/effect curve was established for phenylephrine. Then, after washing out and incubation with the antagonist for 30 minutes, the
25 dose/effect curve was again determined. For characterizing the antagonistic effects, pA_2 values were calculated.

Pre- and postsynaptic α_2 -adrenoceptor antagonistic effects

30 A) Presynaptic α_2 -adrenoceptor antagonism on the rat vas deferens preparation

Briefly, the experiment was performed as follows.

Vasa deferents were isolated from SPRD rats according to Vizi et al. [N. S. Arch. Pharmacol. 280, 79 (1973)]. The preparation was suspended in a Krebs solution at 35 °C and stimulated electrically.

5 A dose/effect curve was determined for xylazine. Then, after washing out, the organ was incubated with the antagonist. The dose/effect curve was taken again with xylazine in the presence of the antagonist. The antagonism was characterized by the pA_2 value determined
10 according to the method of Arunlakshana and Schild [Br. J. Pharmacol. 14, 48 (1959)].

B) Postsynaptic α_2 -adrenoceptor antagonism in dog vena saphena preparation

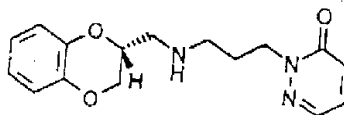
This investigation was carried out by the method of
15 Fowler et al. [J. Pharmacol. Exp. Ther. 229, 712 (1984)] with slight modification.

β -Adrenoceptors were inactivated with propranolol. A cumulative dose/effect curve was established for the selective α_2 -adrenoceptor agonistic compound UK 14304. After
20 30 minutes, the organs were incubated with the agonist for 30 minutes. Also here, the antagonism was characterized by the pA_2 values.

Claims

1. R-2-[3-([1,4]Benzodioxan-2-ylmethylamino)-1-
-propyl]-3(2H)-pyridazinone of formula (1)

5

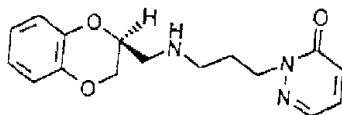


(1)

10 and acid-addition salts thereof.

2. S-2-[3-([1,4]Benzodioxan-2-ylmethylamino)-1-
-propyl]-3(2H)-pyridazinone of formula (2)

15

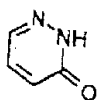


(2)

and acid-addition salts thereof.

3. Process for the preparation of the compounds
20 claimed in claim 1 or claim 2 and acid-addition salts
thereof, which comprises reacting 3(2H)-pyridazinone
of formula (6)

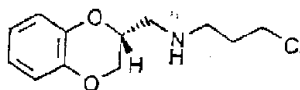
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(6)

or a salt thereof formed with a base
with R-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-
30 -propyl)amine of formula (4)

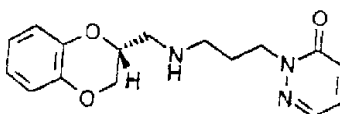




(4)

5

to obtain R-2-[3-([1,4]benzodioxan-2-ylmethylamino)-1-propyl]-3(2H)-pyridazinone of formula (1)

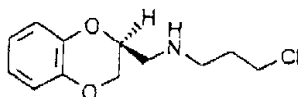


(1)

10

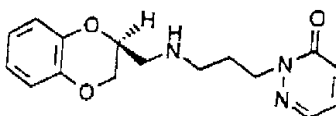
or with S-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine of formula (5)

15



(5)

20 to obtain S-2-[3-([1,4]benzodioxan-2-ylmethylamino)-1-propyl]-3(2H)-pyridazinone of formula (2)



(2)

25

and, if desired, converting the base obtained to an acid-addition salt thereof and, if desired, converting an acid-addition salt thereof to an other acid-addition salt thereof.

30

4. A pharmaceutical composition for the treatment of benign prostate hyperplasia, which comprises a compound claimed in claim 1 or claim 2 or a pharmaceuti-



cally acceptable acid-addition salt thereof and optionally additives commonly used in the manufacture of medicaments.

5. Use of R-2[3-([1,4]benzodioxan-2-ylmethylamino)-1-propyl]-3(2H)-pyridazinone for the manufacture of a medicament for treating benign prostate hyperplasia.

6. Use of S-2[3-([1,4]benzodioxan-2-ylmethylamino)-1-propyl]-3(2H)-pyridazinone for the manufacture of a medicament for treating benign prostate hyperplasia.

10 7. R-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine.

8. S-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine.

15 9. Use of R-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine for the preparation of the compound of claim 1.

10. Use of S-N-([1,4]benzodioxan-2-ylmethyl)-N-(3-chloro-1-propyl)amine for the preparation of the compound of claim 2.

20 11. Method of treating benign prostate hyperplasia in mammals which comprises administering to a mammal in need of such treatment an effective dosage of a compound of claim 1.

25 12. Method of treating benign prostate hyperplasia in mammals which comprises administering to a mammal in need of such treatment an effective dosage of a compound of claim 2.

