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Preliminary communication

Novel tricyclic spiropiperidines. Synthesis and adrenergic activity of spiro[1,3-benzodioxolopiperidines] and spiro[1,3-benzodioxanepiperidines]

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Summary — The synthesis of new series of spiropiperidines is reported. Some of these compounds showed interesting adrenergic activity. The biological activities of the new compounds were evaluated on-guinea pig atria (β1), guinea-pig trachea (β2) and rat vas deferens (α). Compounds **6a**, **6c** and **6f** showed activity comparable to propranolol, in spite of being tertiary amines.

spiropiperidine / adrenergic antagonist / tertiary amine

Introduction

The synthesis and pharmacological activity of a series of spiropiperidines exemplified by benzofuran derivatives **1** and isobenzofuran **2** (fig 1) has been described previously [1, 2].

The heterocyclic system has served as a source for a variety of pharmacodynamic agents. Noteworthy antidepressant [2], neuroleptic [3], hypotensive [4] and diuretic [5] activities have been demonstrated in animal models by various compounds with the spiropiperidine subunit in their structure but are unknown as adrenergic blockers. It is known that aryloxypropanolamines are the most important structural class of β-adrenergic antagonists [6]. Nevertheless, structure–activity relationships have not been completely established and systematic studies indicated that the tertiary amine in this structure reduces the potency markedly [7].

We decided to synthesize a series of new tricyclic 2,4'-spiro-1,3-benzodioxolo and 2,4'-spiro-1,3-benzodioxanepiperidines combined with several types of *N*-substituents (compounds **6a–o**), in order to ascertain their activity as a class of adrenergic compounds (fig 2).

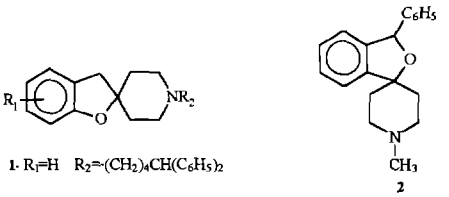

Fig 1. Structures of compounds **1** and **2**.

Chemistry

The synthetic route used to prepare compounds **6a–o** is illustrated in scheme 1. 1,3-Benzodioxole derivatives have considerable importance in biological chemistry and their syntheses have been investigated on several occasions [8]. It was shown that the reaction of acetalization of catechol with ketones was efficiently catalysed by a trace of *p*-toluensulfonic acid (pTSA) [9], and the water thus formed could readily be removed by azeotropic distillation with benzene or toluene. However, the procedure was not satisfactory in our work. Under these conditions the starting material was recovered, even after being refluxed for a long period of time. Our modified procedure was the transacetalization of ketone dimethyl acetal, obtained from the *N*-acetyl-4-piperidone and methyl orthoformate [10], with 1,2-di-

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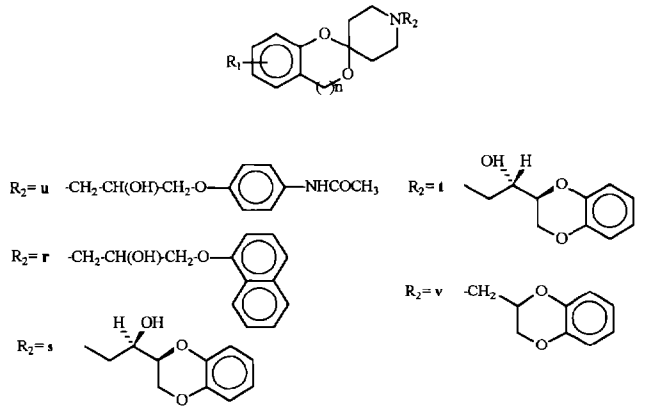
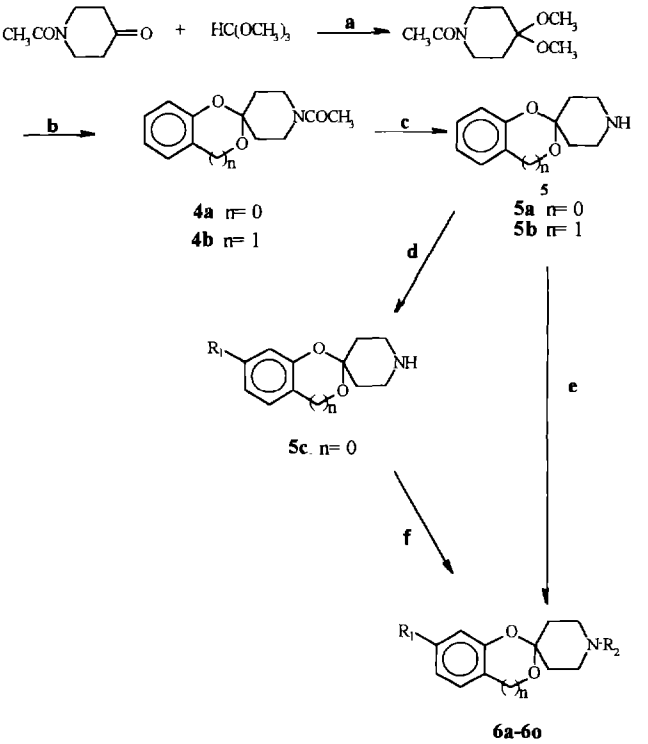


Series	*Compound*	*n*	R_1	R_2
I	**6a**	0	H	u
	6b	0	H	r
	6c	0	H	s
	6d	0	H	t
	6e	0	H	v
II	**6f**	1	H	u
	6g	1	H	r
	6h	1	H	s
	6i	1	H	t
	6j	1	H	v
III	**6k**	0	Br	u
	6l	0	Br	r
	6m	0	Br	s
	6n	0	Br	t
	6o	0	Br	v

Fig 2. Structures of compounds **6a–o**.

hydroxybenzene. The same method was employed to obtain the 1,3-benzodioxane derivatives from 2-hydroxybenzyl alcohol (scheme 1). Compound **5c** was directly obtained by treatment of hydrochloride **5a** with *N*-bromosuccinimide (NBS) in the methanol at room temperature.

Acetals derived from *N*-acetyl-4-piperidone were, upon hydrolysis, converted to **6a–o** by reaction with alkyl iodide (**7e**) or from the cleavage of the respective epoxides (**7a–d**). The intermediate compounds **7a,b** were prepared in good yields by reaction of epichlorohydrin with the appropriate phenol in basic media [11] (scheme 2). The *erythro* and *threo* **7c,d** were obtained from the reactions between catechol and the *trans-* or *cis*-2,3-bis(chloromethyl)oxirane respectively [12] (scheme 3). The reduction of ester with $LiAlH_4$ afforded compound **7e** [13]. The hydroxy group was then displaced by the iodine atom via the Mitsunobu reaction [14, 15] (scheme 4).



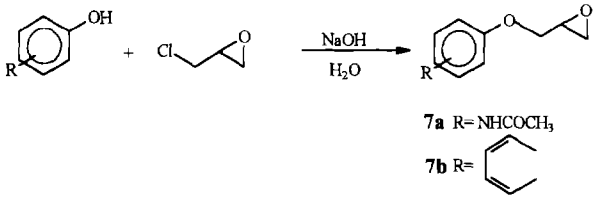
Scheme 1. Reagents and conditions: a) MeOH/pTSA; b) 1,2-dihydroxybenzene or 2-hydroxybenzyl alcohol; c) KOH/H_2O; d) (i) HCl/ether, (ii) NBS/MeOH; e or f) **7a–7e**, DMF, K_2CO_3, stirring, rt.

Pharmacology

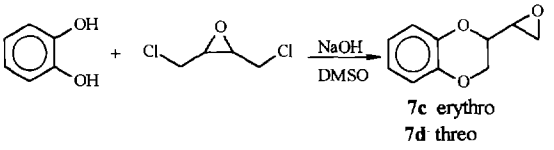
The biological profiles of the compounds listed in table I at α, β_1 and β_2 adrenoceptors were assessed on rat vas deferens, electrically stimulated guinea-pig left atria and guinea-pig tracheal chains, respectively. Isoproterenol was used as the agonist; detailed test procedures have been reported previously [16]. The potency of drugs is expressed as pA_2 calculated according to Van Rossum [17].

Results and discussion

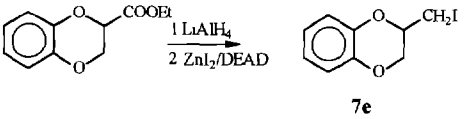
These compounds **6a–o** were evaluated in vitro for their α-blocking activity against noradrenaline in rat vas deferens. The in vitro β-blocking potency of **6a–o** was measured against isoprenaline, in tracheal smooth muscle (β_2) and electrically stimulated left atrium (β_1) of guinea pigs. Compounds **8** and **9** are aryloxypropanolamine analogues of propranolol and have a tertiary amine as the *N*-substituent (piperidine or 4-piperidone); these were prepared by classical methods [11,



Scheme 2.



Scheme 3.



Scheme 4.

18] and were tested under the same conditions and compared with compounds **6a–o**. The resulting potencies are collected in table I.

In the present study, the potency of each series (I, II and III) was generally a function of the *N*-substituents.

Compounds **6e**, **6j** and **6o**, with a substituent without hydroxyl group on the *N*-substituent, showed β-adrenergic inactivity and little α-blocking activity. This result is compatible with those obtained for Piperoxan and WB-4101, which are known as α-blocking compounds [19].

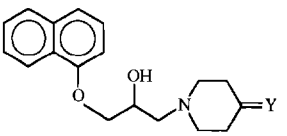
The higher mean pA_2 on atrium found for compounds **6a** and **6f** indicated that the aryloxypropanolamine subunit and the aromatic ring with the acetamido substituent in position 4 are the best groups in these spiro series for adrenergic activity.

Table I. Activity values for compounds **6a–o**.

Compound	*β-Adrenergic antagonism*[a]		β_1/β_2	*α-Adrenergic antagonism*[b]
	pA_2 ($\beta 1$)[c]	pA_2 (β_2)[d]		pD'_2[e]
6a	8.42 ± 0.31	7.59 ± 0.25	6.8	Inactive
6b	7.21 ± 0.12	7.14 ± 0.28	1.2	Inactive
6c	8.15 ± 0.15	6.96 ± 0.21	15.5	Inactive
6d	< 5	< 5		Inactive
6e	Inactive	Inactive		5.57 ± 0.22
6f	8.35 ± 0.24	7.23 ± 0.35	13.2	Inactive
6g	7.75 ± 0.19	7.70 ± 0.17	1.1	Inactive
6h	8.07 ± 0.23	7.04 ± 0.15	10.7	Inactive
6i	5.60 ± 0.27	4.90 ± 0.35	5.0	Inactive
6j	Inactive	Inactive		4.27 ± 0.21
6k	7.57 ± 0.28	7.12 ± 0.36	2.9	Inactive
6l	6.23 ± 0.15	6.75 ± 0.22	0.3	Inactive
6m	7.80 ± 0.12	7.32 ± 0.37	3.0	Inactive
6n	< 5	< 5		Inactive
6o	Inactive	Inactive		5.01 ± 0.21
Propranolol	8.60 ± 0.32	8.47 ± 0.25	1.4	Inactive
8	7.69 ± 0.33	7.52 ± 0.18	–	Inactive
9	7.04 ± 0.35	6.84 ± 0.13	–	Inactive

[a]pA_2 values ± SD were calculated in the same way as described by Van Rossum [17]. A minimum of three different concentrations were tested in each preparation. Where pA_2 values are given, the slope of Schild plot was equal to 1 ± 0.1. [b]Non-competitive antagonism in vas deferens is expressed as the pD'_2 value. [c]Antagonism of the isoprenaline-induced positive inotropic effect in guinea-pig left atrium. [d]Antagonism of the isoprenaline-induced relaxation effect in tracheal preparation. [e]Antagonism of the noradrenaline-induced contraction of rat vas deferens.

In previous studies on adrenergic compounds, the conversion of secondary amine into tertiary amine decreased the activity, as in the case of compounds **8** and **9** (fig 3) in comparison with the propranolol [20]. Tertiary amines were not markedly active as α- or β-adrenergic blocking agents, but had some anticonvulsive activity on the central nervous system [21], whereas these series of compounds **6a–o** with the *N*-cyclic group are less affected by structural modifications than classic aryloxypropanolamines.



8 Y=H,H
9 Y=O

Fig 3. Structures of compounds **8** and **9**.

The *erythro* isomers with 1-(1,4-benzodioxan-2-yl)ethanol as the *N*-substituent were consistently more active than their *threo* counterparts, a result which agrees with literature data for α-branched β-blockers [16] or β-agonists [22–24]. The *erythro* compound **6c** is the most active β_1-blocker; with this stereochemistry its selectivity β_1/β_2 is ten times more than the propranolol and its very potent competitive β_1-adrenergic antagonism is potentially the best in the series.

In summary, this study shows that when some analogues were substituted on the basic nitrogen by specific aralkyl groups, they showed α-blocking activity (**6e,j,o**) or β-blocking activity (**6a–c,f–i,k–m**). It is interesting to note that in the cases **6a**, **6c**, **6f** and **6h** high β_1-activity is observed, which is similar the propranolol activity. But there are no compounds known with a combination of effects. Substitution in the aromatic ring (**6k**, **6l** and **6m**) for the bromine atom was generally disadvantageous in this series for their activity in vitro. Whereas in the other series, the positive effect in lowering blood pressure in hypertensive animals was observed [25].

Experimental protocols

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Perkin Elmer FTIR-1600. The ^{1}H-NMR spectra were recorded on Varian Gemini 200 or 300 or Bruker-300 spectrometer with tetramethylsilane as internal standard and using $CDCl_3$ as the solvent; chemical shifts are in δ (ppm) and coupling constants (*J*) are measured in Hz. All compounds were analyzed for C, H and N. Analytical results obtained for these elements were within ±0.4% of the calculated values for the formula shown. All compounds were purified by chromatography column on silica gel (Merck 70-200 mesh) and used for the subsequent reaction. Thin layer chromatography was performed on silica-gel pre-coated plates (Merck, Kieselgel 60 F-254). All reagents were of commercial quality or were purified before use. Organic solvents were purified by standard procedures.

N-Acetylspiro[1,3-benzodioxolo-2,4'-piperidine] and N-acetylspiro[1,3-benzodioxane-2,4'-piperidine] ***4a,b****. General procedure*

A mixture of *N*-acetyl-4-piperidone (7.05 g, 50 mmol), methyl orthoformate (6.36 g, 60 mmol), methanol (30 mL), and *p*-toluenesulfonic acid (50 mg) was gently heated, while the methyl formate formed (bp 34 °C) in the reaction was distilled off through a short vigreux column. The cooled reaction mixture was made basic by addition of few drops of 2 N sodium methoxide, and partitioned between ether (100 mL) and water (100 mL). The organic phase was washed with brine (50 mL) and dried with potassium carbonate. Evaporation of the solvent affords a good yield of dimethyl acetal. Purification was performed by flash chromatography. The crude product thus obtained may be used in the following step without further purification.

A mixture of ketone dimethyl acetal (9.35 g, 50 mmol), 1,2-dihydroxybenzene (6.6 g, 60 mmol), or 2-hydroxybenzyl alcohol (8.9 g, 72 mmol) and benzene (100 mL) was brought reflux and part of the solvent (10 mL) was distilled through a short vigreux column. Heating was discontinued, the temperature was lowered to 60 °C and *p*-toluenesulfonic acid (50 mg) was added. The distillation of the solvent was slowly continued until pure benzene was being collected. During this operation, addition of benzene was sometimes necessary to prevent the reaction mixture from becoming dry. Triethylamine (1 mL) was added to the cooled reaction mixture, which was then partioned between ether (100 mL) and water (100 mL). The organic phase was washed with water (2 x 50 mL), 10% sodium hydroxide (50 mL), brine (50 mL), dried with potassium carbonate and the solvent evaporated. Purification was performed by flash chromatography (petroleum ether/ethyl acetate 70:30).

Hydrolysis of the acetamide to ***5a,b****. General procedure*

A solution of **4** (1.28 mmol) in ethanol (15 mL) and KOH/water (1.15 g in 5 mL) was heated at reflux for 12 h. Solvents were removed in vacuo, the residue was dissolved in water and extracted with dichloromethane to afford an oil, which was chromatographed on a silica-gel column (ether/dichloromethane 80:20) to give the amine.

General bromination to ***5c***

To a solution of **5a** chlorhydrate (230 mg, 1.07 mmol) in 6 mL methanol cooled in an ice/salt bath, was added dropwise the NBS (180 mg, 1.01 mmol). The mixture was stirred for 2 h. The solvent was removed in vacuo, the residue was dissolved in water and extracted with dichloromethane afford an oil, which was chromatographed on a silica gel (hexane/ethyl acetate/ethanol 70:29:1) to give 254 mg of amine **5c**, yield 88%.

Alkylation to ***6a–o****. General procedure*

To 20 mL dry DMF was added the amine (1 mmol), 1.93 g (14 mmol) of anhydrous potassium carbonate, 10 mg KI and then the epoxide (1.5 mmol) or alkylating agent (5 mmol). After stirring at room temperature for 72 h under argon, the

mixture was cooled, filtered and the solvent evaporated to an oil. The oil was dissolved in 15 mL water and 30 mL 3 N hydrochloric acid and was extracted with ether. The water layer was basified with 5 N sodium hydroxide. The alkaline mixture was extracted with dichloromethane and the organic extracts were successively dried and evaporated to dryness, leaving an oil. The oil was chromatographed on a silica-gel column eluting with (ether/dichloromethane 80:20).

Analytical data

N-Acetylspiro[1,3-benzodioxolo-2,4'-piperidine] ***4a***
$C_{13}H_{15}NO_3$, n = 0. Yield 65%. Mp 162–163 °C (ethanol). IR (ν cm^{-1}), 1640, 1590, 1210, 1160; ^{1}H-NMR δ (ppm) (250 MHz, $CDCl_3$), 2.01 (m, 4H, CH_2), 2.18 (s, 3H, CH_3), 3.62 (t, 2H, J = 5, CH_2N), 3.81 (t, 2H, J = 5, CH_2N), 6.81 (m, 4H, Ar).

N-Acetylspiro[1,3-benzodioxane-2,4'-piperidine] ***4b***
$C_{14}H_{17}NO_3$, n = 1. Yield 84%. Oil. IR (ν cm^{-1}), 1645, 1590, 1240, 1100; ^{1}H-NMR δ (ppm) (250 MHz, $CDCl_3$), 1.90 (m, 4H, CH_2), 2.16 (s, 3H, CH_3), 3.60 (m, 2H, CH_2N), 3.81 (m, 2H, CH_2N), 4.81 (s, 2H, CH_2O), 7.02 (m, 4H, Ar).

Spiro[1,3-benzodioxolo-2,4'-piperidine] ***5a***
$C_{11}H_{13}NO_2$, n = 0. Yield 97%. Mp 244–246 °C (ethanol). IR (ν cm^{-1}), 3300, 1480, 1230, 850; ^{1}H-NMR, δ (ppm) (250 MHz, $CDCl_3$), 1.51 (s, 1H, NH), 1.97 (t, J = 6, 4H, CH_2C), 3.01 (t, J = 6, 4H, CH_2N), 6.75 (s, 4H, Ar).

Spiro[1,3-benzodioxane-2,4'-piperidine] ***5b***
$C_{12}H_{15}NO_2$, n = 1. Yield 98%. Oil. Mp 240–242 °C (ether). IR (ν cm^{-1}), 3340, 1480, 1225, 850; ^{1}H-NMR, δ (ppm) (250 MHz, $CDCl_3$), 1.83 (m, 4H, CH_2C), 2.46 (s, 1H, NH), 2.98 (t, J = 5, 4H, CH_2N), 4.81 (s, 2H, CH_2O), 6.82 (m, 3H, Ar), 7.25 (m, 1H, Ar).

5-Bromo spiro[1,3-benzodioxolo-2,4'piperidine] ***5c***
$C_{11}H_{12}BrNO_3$, R_1 = Br, n = 0. Yield 88%. Mp 258–259 °C (ether). IR (ν cm^{-1}), 3340, 1490, 1235, 660; ^{1}H-NMR, δ (ppm) (250 MHz, $CDCl_3$), 1.93 (t, J = 5, 4H, CH_2C), 2.52 (s, 1H, NH), 3.08 (t, J = 5, 1H, CH_2N), 6.61 (d, J = 8, 1H, H_7-Ar), 6.88 (s, 1H, H_4-Ar), 6.92 (d, J = 8, 1H, H_6-Ar).

N-3-(4-Acetylaminophenoxy)-2-hydroxypropyl spiro[1,3-benzodioxolo-2,4'-piperidine] ***6a***
$C_{22}H_{26}N_2O_5$, R_1 = H, n = 0, R_2 = u (see fig 2). Yield 65%. Oil. IR (ν, cm^{-1}), 3580, 1680, 1590, 1280; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$) 2.21 (m, 4H, CH_2C), 2.25 (s, 3H, CH_3), 2.63 (d, J = 8, 2H, CH_2N), 2.67 (t, J = 12, 2H, CH_2N), 2.98 (t, J = 12, 2H, CH_2N), 3.99 (d, J = 12, 2H, CH_2O), 4.18 (m, 1H, CHO), 6.96 (m, 4H, Ar), 7.38 (m, 4H, Ar).

N-3-(1-Naphthoxy)-2-hydroxypropyl spiro[1,3-benzodioxolo-2,4'-piperidine] ***6b***
$C_{24}H_{25}NO_4$, R_1 = H, n = 0, R_2 = r (see fig 2). Yield 62%. Oil. IR (ν, cm^{-1}), 3590, 1590, 1280, 1100; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.51 (m, 4H, CH_2C), 2.83 (m, 2H, CH_2N), 2.98 (m, 2H, CH_2N), 3.5 (m, 2H, CH_2N), 3.98 (m, 2H, CH_2O), 4,32 (m, 1H, CHO), 6.83 (t, J = 8, 2H, Ar), 7.48 (m, 5H, Ar), 7.89 (m, 2H, Ar), 8.23 (m, 1H, Ar), 8.34 (m, 1H, Ar).

erythro-N-[2-Hydroxy-2(1,4-benzodioxan-2-yl)]ethyl spiro[1,3-benzodioxolo-2,4'-piperidine] ***6c***
$C_{21}H_{23}NO_5$, R_1 = H, n = 0, R_2 = s (see fig 2). Yield 43%. Oil. IR (ν, cm^{-1}), 3500, 1410, 1270, 1100; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.22 (m, 4H, CH_2C), 2.60 (d, J = 8, 2H, CH_2N), 2.69 (m, 2H, CH_2N), 3.00 (m, 2H, CH_2N), 3.91–4.20 (m, 4H, CHO), 6.96 (m, 4H, Ar), 7.12 (m, 4H, Ar).

threo-N-[2-Hydroxy-2(1,4-benzodioxan-yl)]ethyl spiro[1,3-benzodioxolo-2,4'-piperidine] ***6d***
$C_{21}H_{23}NO_5$, R_1 = H, n = 0, R_2 = t (see fig 2). Yield 80%. Oil. IR (ν, cm^{-1}), 3530, 1480, 1280, 1190; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.12 (m, 4H, CH_2C), 2.54 (dd, J = 5, J = 12, 2H, CH_2N), 2.65 (m, 2H, CH_2N), 2.95 (m, 2H, CH_2N), 3.95 (t, J = 5, 1H, CHO), 4.18 (dt, J = 5, 1H, CHO), 4.35 (m, 2H, CHO), 6.98 (m, 8H, Ar).

N-(1,4-Benzodioxan-2-ylmethyl) spiro[1,3-benzodioxolo-2,4'-piperidine] ***6e***
$C_{20}H_{21}NO_4$, R_1 = H, n = 0, R_2 = v (see fig 2). Yield 72%. Oil. IR (ν, cm^{-1}), 1480, 1230, 1080, 790; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.12 (t, J = 4, 4H, CH_2C), 2.85 (m, 6H, CH_2N), 4.01 (dd, J = 7, J = 9, 2H, CH_2O),4.45 (m, 1H, CHO), 6.85 (m, 8H, Ar).

N-3-(4-Acetylaminophenoxy)-2-hydroxypropyl spiro[1,3-benzodioxane-2,4'-piperidine] ***6f***
$C_{23}H_{28}N_2O_5$, R_1 = H, n = 1, R_2 = u (see fig 2). Yield 84%. Oil. IR (ν, cm^{-1}), 3570, 1670, 1580, 1400; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.05 (m, 4H, CH_2C), 2.15 (s, 3H, CH_3), 2.62 (m, 4H, CH_2N), 2.85 (m, 2H, CH_2N), 3.99 (d, J = 5, 2H, CH_2O), 4.05 (m, 1H, CHO), 4.80 (s, 2H, CH_2O), 7.06 (m, 8H, Ar).

N-3-(1-Naphthoxy)-2-hydroxypropyl spiro[1,3-benzodioxane-2,4'-piperidine] ***6g***
$C_{25}H_{27}NO_4$, R_1 = H, n = 1, R_2 = r (see fig 2). Yield 58%. Oil. IR (ν, cm^{-1}), 3590, 1590, 1450, 1260; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.02 (m, 4H, CH_2C), 2.62 (m, 2H, CH_2N), 2.73 (d, J = 5, 2H, CH_2N), 2.83 (m, 2H, CH_2N), 4.32 (m, 3H, CHO), 4.73 (s, 2H, CH_2O), 6.98 (m, 4H, Ar), 7.21 (m, 1H, Ar), 7.52 (m, 4H, Ar), 7.83 (m, 1H, Ar), 8.43 (m, 1H, Ar).

erythro-N-[2-Hydroxy-2-(1,4-benzodioxan-2-yl)]ethyl spiro [1,3-benzodioxane-2,4'-piperidine] ***6h***
$C_{22}H_{25}NO_5$, R_1 = H, n = 1, R_2 = s (see fig 2). Yield 45%. Oil. IR (ν, cm^{-1}), 3560, 1590, 1210, 1190; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.01 (m, 4H, CH_2C), 2.58 (dd, J = 5, J = 11, 2H, CH_2N), 2.65 (m, 2H, CH_2N), 2.97 (m, 2H, CH_2N), 3.98 (t, J = 3, 1H, CHO), 4.23 (t, J = 3, 1H, CHO), 4.37 (m, 2H, CH_2O), 4.79 (s, 2H, CH_2O), 6.99 (m, 8H, Ar).

threo-N-[2-Hydroxy-2-(1,4-benzodioxan-2-yl)]ethyl spiro [1,3-benzodioxane-2,4'-piperidine] ***6i***
$C_{22}H_{25}NO_5$,1 = H, n = 1, R_2 = t (see fig 2). Yield 33%.Oil. IR (ν, cm^{-1}), 3530, 1490, 1260, 1105; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 1.98 (m, 4H, CH_2C), 2.51 (m, 2H, CH_2N), 2.88 (m, 2H, CH_2N), 2.89 (dd, J = 5, J = 11, 2H, CH_2N), 3.92 (m, 1H, CHO), 4.21 (m, 1H, CHO), 4.42 (m, 2H, CHO), 4.87 (s, 2H, CH_2O), 6.95 (m, 7H, Ar), 7.21 (m, 1H, Ar).

N-(1,4-Benzodioxan-2-yl methyl)spiro[1,3-benzodioxane-2,4'-piperidine] ***6j***
$C_{21}H_{23}NO_4$, R_1 = H, n = 1, R_2 = v (see fig 2). Yield 58%. Oil. IR (ν, cm^{-1}), 1480, 1235, 1075, 790; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 1.95 (m, 4H, CH_2C), 2.63 (m, 6H, CH_2N), 4.01 (m, 2H, CH_2O), 4.38 (m, 1H, CHO), 4.87 (s, 2H, CH_2O), 6.94 (m, 7H, Ar), 7.06 (m, 1H, Ar).

5-Bromo-N-3-(4-acetylaminophenoxy)-2-hydroxypropyl spiro[1,3-benzodioxolo-2,4'-piperidine] ***6k***
$C_{22}H_{25}BrN_2O_5$, R_1 = Br, n = 0, R_2 = u (see fig 2). Yield 90%. Oil. IR (ν, cm^{-1}), 3510, 1490, 1250, 790; ^{1}H-NMR, δ (ppm)

(300 MHz, $CDCl_3$), 2.01 (m, 4H, CH_2C), 2.21 (s, 3H, CH_3), 2.61 (m, 2H, CH_2N), 2.73 (m, 2H, CH_2N), 2.83 (m, 2H, CH_2N), 3.98 (d, J = 6, 2H, CH_2O), 4.12 (m, 1H, CHO), 7.06 (m, 7H, Ar).

5-Bromo-N-3(1-naphthoxy)-2-hydroxypropyl spiro[1,3-benzodioxolo-2,4'-piperidine] ***6l***

$C_{24}H_{24}BrN_2O_4$, R_1 = Br, n = 0, R_2 = r (see fig 2). Yield 43%. Oil. IR (ν, cm^{-1}), 3490, 1480, 1100, 1080; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.03 (m, 4H, CH_2C), 2.64 (m, 4H, CH_2N), 2.78 (m, 2H, CH_2N), 4.35 (m, 3H, CHO), 6.56 (d, J = 6, 1H, Ar), 6.83 (m, 2H, Ar), 7.47 (m, 5H, Ar), 7.78 (m, 1H, Ar), 8.42 (m, 1H, Ar).

erythro-5-Bromo-N-[2-hydroxy-2-(1,4-benzodioxan-2-yl)]ethyl spiro [1,3-benzodioxolo-2,4'-piperidine] ***6m***

$C_{21}H_{22}BrNO_5$, R_1 = Br, n = 0, R_2 = s (see fig 2). Yield 62%. Oil. IR (ν, cm^{-1}), 3490, 1485, 1232, 1070; ^{1}H-NMR, δ (ppm) (200 MHz, $CDCl_3$), 2.00 (m, 4H, CH_2C), 2.51 (m, 2H, CH_2N), 2.88 (m, 2H, CH_2N), 2.89 (m, 2H, CH_2N), 3.89 (m, 1H, CHO), 4.12 (dt, J = 3, 1H, CHO), 4.23 (m, 2H, CH_2O), 6.66 (d, J = 6, 1H, Ar), 6.97 (m, 6H, Ar).

threo-5-Bromo-N-[2-hydroxy-2-(1,4-benzodioxan-2-yl)]ethyl spiro [1,3-benzodioxolo-2,4'-piperidine] ***6n***

$C_{21}H_{22}BrNO_5$, R_1 = Br, n = 0, R_2 = t (see fig 2). Yield 71%. Oil. IR (ν, cm^{-1}), 3500, 1490, 1200, 1100; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.02 (m, 4H, CH_2C), 2.52 (m, 2H, CH_2N), 2.63 (m, 2H, CH_2N), 2.84 (m, 2H, CH_2N), 3.98 (m, 1H, CHO), 4.12 (m, 1H, CHO), 4.45 (m, 2H, CHO), 6.62 (d, J = 7, 1H, Ar), 6.98 (m, 6H, Ar).

5-Bromo-N-(1,4-benzodioxan-2-ylmethyl) spiro[1,3-benzodioxolo-2,4'-piperidine] ***6o***

$C_{20}H_{20}BrNO_4$, R_1 = Br, n = 0, R_2 = v (see fig 2). Yield 70%. Oil. IR (ν, cm^{-1}), 1475, 1220, 1080, 790; ^{1}H-NMR, δ (ppm) (300 MHz, $CDCl_3$), 2.10 (t, J = 5, 4H, CH_2C), 2.63 (dd, J_1 = 5, J_2 = 11, 2H, CH_2N), 2.75 (m, 4H, CH_2N), 4.01 (dd, J_1 = 5, J_2 =11, 1H, CHO), 4.26 (m, 1H, CHO), 4.46 (m, 1H, CHO), 6.63 (d, J = 6, 1H, Ar), 6.87 (m, 6H, Ar).

2-Iodomethyl-1,4-benzodioxan 7

Diethyl azodicarboxylate (DEAD, 2 mmol) was added dropwise at 0 °C to a stirred dry toluene suspension containing the alcohol (1 mmol), triphenylphosphine (2 mmol) and ZnI_2 (0.75 mmol). After the reaction was complete, purification was effected by direct silica-gel column chromatography (hexane/ethyl acetate 90:10). Yield 85%. ^{1}H-NMR was identical that the spectral data described in reference [14].

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