8-[4-[2-(1,2,3,4-Tetrahydroisoquinolinyl)]butyl]-8-azaspiro[4.5]decane-7,9-dione: A New 5-HT$_{1A}$ Receptor Ligand with the Same Activity Profile as Buspirone†

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A new analog of buspirone (**1**), *i.e.*, 8-[4-[2-(1,2,3,4-tetrahydroisoquinolinyl)]butyl]-8-azaspiro-[4.5]decane-7,9-dione (**6a**), was synthesized. In was demonstrated that buspirone and its analog **6a** were equipotent 5-HT$_{1A}$ ligands. Several behavioral models showed that **6a** had essentially the same functional profile at 5-HT$_{1A}$ receptors as buspirone. The obtained results permit a conclusion that the basic nitrogen atom and terminal, bulky cycloimide moiety, but not the 2-pyrimidinyl group, of buspirone are directly involved in the formation of the bioactive complex with 5-HT$_{1A}$ receptors.

Introduction

Up to the present, buspirone (**1**) is the only second-generation anxiolytic used in therapy. Its pharmacological[1−9] and receptor binding profiles[9−12] have been well established. Buspirone is classified as a partial agonist of 5-HT$_{1A}$ receptors; moreover, it is believed that such a functional profile is responsible for its anxiolytic activity. Buspirone may be regarded as a classic 5-HT$_{1A}$ ligand with a relatively high affinity (K_i = 9.3−29.5 nM).[9−13] The interaction modes of buspirone and the related compounds with the 5-HT$_{1A}$ receptors, as well as the structure−affinity relationships of long-chain arylpiperazines, have been discussed in a number of papers. Fortunately, the latter issue was extensively reviewed by Glennon *et al.*,[14−16] who formulated some general structure−affinity relationships for the long-chain arylpiperazines of type **1**. The latter authors concluded that a wide range of 1-aryl substituents of piperazine were tolerated at the receptor and that the piperazine ring seemed to be optimal. Other important features of the buspirone-type 5-HT$_{1A}$ ligands are terminal amide or cyclic imide fragments and a spacer that separates these fragments from the N-4 piperazine atom.[16] Moreover, it is generally accepted that the buspirone molecule is recognized by the 5-HT$_{1A}$ receptor due to the presence of 1-(2-pyrimidinyl)piperazine (1-PP).[14,17−19] In other words, the 1-PP fragment of **1** fulfills the minimal structure requirements defined by Hibert *et al.*[18,19] for the interaction with the 5-HT$_{1A}$ binding site, one being the presence of an aromatic ring and the other the presence of a basic nitrogen atom at a distance of 5.2−5.7 Å from the center of the aromatic system. On the other hand, the terminal imide moiety offers an additional site of interaction with the 5-HT$_{1A}$ receptor, which results in a greatly enhanced affinity of buspirone in relation to 1-PP (K_i = 1410 nM),[14,17−19] though the nature of this interaction is so far only speculative.[13,14,18,20,21]

Our previous papers showed that 1,2,3,4-tetrahydroisoquinoline (THIQ, **9**) may be regarded as a model compound in the structure−affinity relationship studies of some 5-HT$_{1A}$ ligands.[22,23] Its ionization constant at 37 °C (pK_a = 9.30)[24] is similar to those reported for simple 1-arylpiperazines (pK_a = 7.94−9.14),[25] but significantly lower than that of piperidine (pK_a = 10.86).[24] The lipophilicity of THIQ is also comparable with that of many 1-arylpiperazines but higher than that of 1-PP.[24,25] The crucial distance between the aromatic ring center and the basic nitrogen atom in THIQ (d_{ArN} = 3.77 Å) is too short to form a bioactive complex of THIQ with 5-HT$_{1A}$ receptors.[22] As a result, THIQ (**9**) shows no affinity for these receptors (K_i > 50 000 nM, Table 1). Hence the THIQ nitrogen atom may mimic the basic N-4 atom of 1-arylpiperazine at the 5-HT$_{1A}$ receptors.[23] In order to have a better insight into the interaction modes of buspirone (**1**; a postsynaptic partial agonist)[1,2] and compounds **2**−**4** (postsynaptic antagonists)[16,26,27] with 5-HT$_{1A}$ receptors, we modified their structures by replacing 1-arylpiperazine fragments with THIQ. If one can assume that the buspirone molecule (or other ligand of this type) is recognized by the 5-HT$_{1A}$ receptor in the manner discussed above,[14,17−19] the applied modification should directly result in a substantial decrease of the receptor affinity.

Chemistry

A commercial *N*-(*ω*-bromoalkyl)phthalimide (**7** or **8**) was treated with 1,2,3,4-tetrahydroisoquinoline (**9**) to yield an imide derivative (**5b** or **6b**). Hydrazinolysis of **5b** and **6b** afforded *N*-(*ω*-aminoalkyl)-1,2,3,4-tetrahydroisoquinolines **10** and **11** which, by acylation with **12**, were converted to **5a** and **6a**, respectively (Scheme 1). Compound **6c** was obtained by a simple two-step condensation as shown in Scheme 2.

Pharmacology

The affinity of compounds **1**, **2**, **5**, and **6** for 5-HT$_{1A}$ receptors of the rat brain hippocampus was assessed on the basis of their ability to displace [^{3}H]-8-OH-DPAT (Table 1). In order to show behavioral effects of buspirone (**1**) and its analog **6a**, which are mediated by postsynaptic 5-HT$_{1A}$ receptors, the following *in vivo* models were employed, induction of the lower lip retraction (LLR) in rats,[6,28,29] induction of the behavioral syndrome (flat body posture and forepaw treading), and

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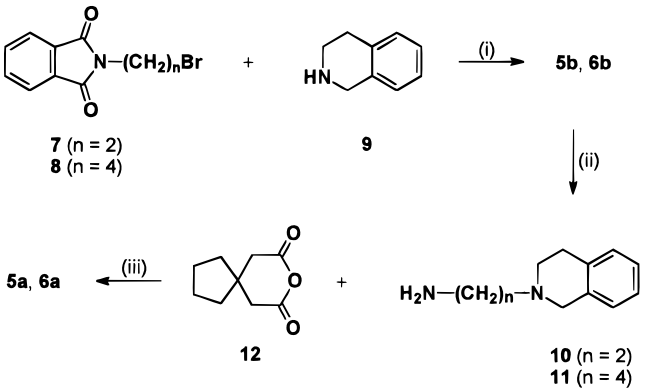
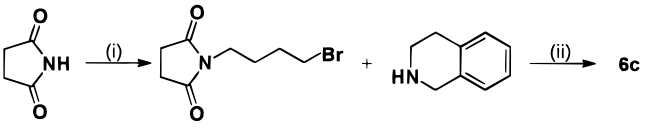
Scheme 1[a]



[a] (i) *n*-BuOH, reflux, 13 h; (ii) $N_2H_4 \cdot H_2O$, EtOH, HCl, reflux, 4 h; (iii) xylene, reflux, 3 h.

Scheme 2[a]



[a] (i) 1,4-Dibromobutane, KF/Al_2O_3, MeCN, reflux 4 h; (ii) *n*-BuOH, K_2CO_3, reflux, 6 h.

Table 1. 5-HT_{1A} Binding Data[a] (K_i) of the Investigated Compounds **1**–**6** and **9**

compd	$K_i \pm$ SEM (nM)	compd	$K_i \pm$ SEM (nM)
1[b]	12.3 ± 0.4	**5b**	41 300 ± 9300
2[b]	8.2 ± 2.4	**6a**	5.0 ± 0.2
3	6.4[c]	**6b**	140 ± 10
4	0.6[c]	**6c**	2920 ± 90
5a	1330 ± 80	**9**	>50 000[c]

[a] Displacement of [^{3}H]-8-OH-DPAT. [b] The literature K_i data: buspirone (**1**), 9.3–29.5 nM;[9–12] BMY-7378, 2.40 nM.[26] [c] The following literature data were used for comparison: **3**,[27] **4** (NAN-190),[17] and **9** (1,2,3,4-tetrahydroisoquinoline).[22]

inhibition of the 8-OH-DPAT-induced behavioral syndrome in reserpinized rats (Table 3).[2,30]

Results and Discussion

The assessed 5-HT_{1A} affinities of **1**–**3** are similar (K_i = 6.4–12.3 nM, Table 1), though their structures are substantially different. However, the literature data indicated that enlargement of the succinimide moiety of **3**[27] with the benzene ring resulted in an enhanced affinity of NAN-190 (**4**),[17] which is a well-known postsynaptic 5-HT_{1A} antagonist.[16] On the other hand, replacement of the 1-(*o*-methoxyphenyl)piperazine fragment by THIQ caused a dramatic loss of the 5-HT_{1A} affinity as was expected (cf. **2** vs **5a**, **3** vs **6c**, and **4** vs **6b**, Table 1). As mentioned above, THIQ (**9**) did not bind at 5-HT_{1A} receptors (Table 1);[23] hence, it may be concluded that the 1-(*o*-methoxyphenyl)piperazine fragment of the postsynaptic antagonists **2**–**4** plays a major role in the formation of a bioactive complex with 5-HT_{1A} receptors. The latter conclusion is in a good agreement with our previous findings that the methoxy group in the arylpiperazine fragment is a desired feature of the structure for both the affinity and postsynaptic antagonism at 5-HT_{1A} receptors, shown by this class of ligands.[27,31,32] In marked contrast, the THIQ derivative **6a** showed comparable 5-HT_{1A} affinity with buspirone (**1**). Therefore it may be anticipated that the buspirone

Chart 1

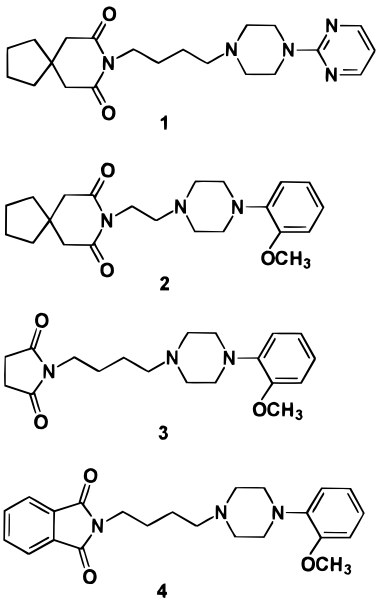


Chart 2

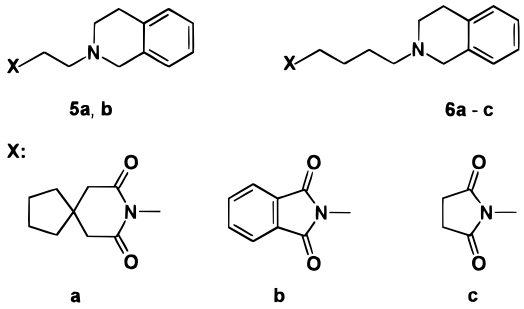


Table 2. Calculated van der Waals Volumes (V)[a] and Hydrophobic Constants (log P_c)[b] for Cyclic Imides **a**–**c** (XH, Chart 2)

cyclic imide	V (Å^3)	log P_c
a	126.8	−0.004
b	104.1	0.025
c	68.1	−2.235

[a] MOLSV (QCPE, Indiana University). [b] PrologP 4.2 expert system (CompuDrug Ltd., Budapest, Hungary).

molecule is recognized by the receptor exclusively due to the presence of a basic nitrogen atom and terminal imide moiety.

The structure of the terminal imide fragment strongly affects the 5-HT_{1A} affinity of the THIQ derivatives **5** and **6**. Therefore the volume (V) and/or lipophilicity (log P_c) of the imide moiety may be regadred as the major parameters that control the observed affinity changes. The calculated V and log P_c values of the respective imides **a**–**c** (XH in Chart 2) are given in Table 2. While the lipophilicity of **a** and **b** is essentially the same, but differs from that of **c**, the volume of **a**–**c** constantly decreases. Thus it may be suggested that the 5-HT_{1A} affinity of **5a**,**b** and **6a**–**c** depends on the volume of the imide fragment rather than on their lipophilicity. Indeed, the larger the volume, the higher the 5-HT_{1A} affinity. The above results are fully consistent with some earlier findings of Glennon *et al.*[14,33] and Orjales *et al.*[34] Having discussed a hypothetical model of 5-HT_{1A} sites, the former authors suggested that there should exist a region of bulk tolerance adjoining the protonation

Table 3. Induction of Lower Lip Retraction[a] (A) and the Behavioral Syndrome[b] (B) by Buspirone (**1**) and Its Analog **6a** and Effect of the Investigated Compounds on the 8-OH-DPAT-Induced Behavior in Reserpine-Pretreated Rats[c] (C)

treatment	dose, (mg/kg)	A: mean ± SEM, LLR score	B: mean ± SEM behavioral score		C: mean ± SEM behavioral score	
			flat body posture	forepaw treading	flat body posture	forepaw treading
vehicle		0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.2	14.0 ± 0.5	13.2 ± 0.5
buspirone (**1**)	1.25	1.6 ± 0.2[d]	NT	NT	NT	NT
	2.5	2.3 ± 0.2[d]	NT	NT	NT	NT
	5	2.4 ± 0.2[d]	6.8 ± 1.6[d]	0.2 ± 0.2	14.3 ± 0.3	5.0 ± 0.9[e]
	10	NT	6.4 ± 1.4[d]	0.6 ± 0.4	9.5 ± 1.5[e]	3.7 ± 0.6[e]
vehicle		0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.2	14.5 ± 0.2	12.8 ± 0.7
6a	1.25	1.2 ± 0.2[d]	NT	NT	NT	NT
	2.5	1.9 ± 0.1[d]	NT	NT	NT	NT
	5	2.5 ± 0.3[d]	7.8 ± 1.5[d]	2.0 ± 0.7	14.5 ± 0.6	8.9 ± 1.1[e]
	10	NT	11.0 ± 0.7[d]	2.7 ± 1.4	13.7 ± 0.6	7.8 ± 1.2[e]

[a] Buspirone (**1**) and **6a** were administered ip 15 min before the test. [b] Reserpine (1 mg/kg sc) and the investigated compounds were administered 18 h and 3 min, respectively, before the test. [c] Reserpine (1 mg/kg sc) and the investigated compounds (ip) were administered 18 h and 15 min, respectively, before 8-OH-DPAT (5 mg/kg ip). [d] $p < 0.01$ vs vehicle. [e] $p < 0.01$ vs vehicle + 8-OH-DPAT. NT = not tested.

site, which must be capable of accommodating bulky groups such as those found in buspirone-like agents.[14] In fact, other studies permitted a conclusion that large, terminal amide substituents effectively increased the 5-HT$_{1A}$ affinity of some long-chain 1-arylpiperazines.[33,34]

If it is assumed that the proposed interaction mode of buspirone with 5-HT$_{1A}$ receptors is correct, then its analog **6a** should retain not only the 5-HT$_{1A}$ affinity but also the functional profile of buspirone at these receptors. Both buspirone (**1**) and derivative **6a**, injected in doses of 1.25−5.0 mg/kg, induced dose-dependently the LLR in rats, the maximum possible score being 80% and 83%, respectively, after the highest dose used (Table 3). Essentially the same effect, characteristic of activation of the postsynaptic 5-HT$_{1A}$ receptors, was reported by Berendsen *et al.*[6] for 8-OH-DPAT and buspirone. Therefore it may be concluded that the two investigated compounds, **1** and **6a**, are equipotent agonists of postsynaptic 5-HT$_{1A}$ receptors in the behavioral model studied. Smith and Peroutka analyzed the effects of 8-OH-DPAT and buspirone on the behavioral syndrome in normal rats.[2] They showed that buspirone alone evoked flat body posture but did not induce reciprocal forepaw treading. In marked contrast, buspirone blocked effectively the 8-OH-DPAT-induced forepaw treading but not the flat body posture in normal rats.[2] In the present study we evaluated the effects of buspirone (**1**) and compound **6a** on the behavioral syndrome in reserpine-pretreated rats. Our results obtained for buspirone are fully consistent with those discussed above (Table 3). Moreover, compound **6a** showed a similar profile of activity in those models. Buspirone (**1**) and its analog **6a**, administered in doses of 10 mg/kg, induced flat body posture in reserpinized rats, the maximum possible score being 43% and 73%, respectively. However, neither of the compounds produced forepaw treading after the highest doses used (Table 3). Compounds **1** and **6a** antagonized the 8-OH-DPAT-induced forepaw treading by 72% and 39%, respectively. Moreover, buspirone reduced the 8-OH-DPAT-induced flat body posture only by 32%, whereas **6a** failed to inhibit that symptom.

In conclusion, it should be stressed that replacement of the 1-(2-pyrimidinyl)piperazine fragment in buspirone by the 1,2,3,4-tetrahydroisoquinoline ring system, which yielded the model compound **6a**, did not significantly affect either the observed 5-HT$_{1A}$ affinity or the functional profile at those receptors. Both of these compounds (**1** and **6a**) may be classified as partial agonists of postsynaptic 5-HT$_{1A}$ receptors. Furthermore, our results may suggest that a basic nitrogen atom and terminal, bulky cycloimide moiety, but not a 1-(2-pyrimidinyl) substituent, are pivotal features of the buspirone structure, which are directly responsible for both the formation of the bioactive complex and its functional profile at 5-HT$_{1A}$ receptors.

Experimental Section

Chemistry. Melting points were determined on a Boetius apparatus and are uncorrected. ^{1}H NMR spectra were taken with a Varian EM-360L (60 MHz) instrument in $CDCl_3$ solution with Me_4Si as an internal standard. Elemental analyses were performed in the Institute of Organic Chemistry, Polish Academy of Sciences (Warsaw, Poland), and are within ±0.4% of the theoretical values.

The following compounds were commercial products: **7**−**9** and **13** (Aldrich) and **12** (Lancaster Syntheses). Compound **2** was obtained according to the described procedure.[35]

General Procedure. Preparation of Compounds 5b and 6b. A mixture of *N*-(2-chloroethyl)- or *N*-(4-bromobutyl)-phthalimide (3 mmol), 1,2,3,4-tetrahydroisoquinoline (0.4 g, 3 mmol), and *n*-butanol (30 mL) was refluxed for 13 h. Then the reaction mixture was filtered off, and the solvent was evaporated to give a crude product, which was purified by crystallization.

2-(2-*N*-Phthalimidoethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (5b): yield 63%; mp 203−206 °C (EtOH); ^{1}H NMR (base) δ 2.7−2.95 (m, 6 H, 3 CH_2), 3.7 (s, 2 H, CH_2), 3.9 (t, 2 H, CH_2, $J = 7$ Hz), 7.1 (s, 4 H arom), 7.5−7.9 (m, 4 H arom). Anal. ($C_{19}H_{18}N_2O_2$·HCl) C, H, N.

2-(4-*N*-Phthalimidobutyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide (6b): yield 55%; mp 233−235 °C (MeOH); ^{1}H NMR (base) δ 1.5−1.9 (m, 4 H, 2 CH_2), 2.4−3.0 (m, 6 H, 3 CH_2), 3.55 (s, 2 H, CH_2), 3.7 (t, 2 H, CH_2, $J = 7$ Hz), 6.9−7.2 (m, 4 H arom), 7.6−8.0 (m, 4 H arom). Anal. ($C_{21}H_{22}N_2O_2$·HBr) C, H, N.

General Procedure. Preparation of Compounds 5a and 6a. A solution of **5b** or **6b** (free bases, 1.2 mmol) and hydrazine (0.5 mL, 15 mmol) in 99.8% ethanol (15 mL) was refluxed for 1 h. The reaction mixture was cooled down and treated with an additional amount of 99.8% ethanol (15 mL) and concentrated HCl (1.3 mL). Then the reaction mixture was refluxed for 4 h and left overnight in a refrigerator. The precipitate was filtered off, and the solvent was evaporated. The residue was treated with *n*-hexane (20 mL) and NH_3 (aqueous, 15 mL). The solution was extracted with $CHCl_3$ (3 × 15 mL), the organic layer was dried over anhydrous K_2CO_3, and the solvents were evaporated to give a product which was used without further purification.

2-(2-Aminoethyl)-1,2,3,4-tetrahydroisoquinoline (10): yield 76%; ^{1}H NMR δ 1.85 (t, 2 H, NH_2, $J = 10$ Hz), 2.55−3.2 (m, 8 H, 4 CH_2), 3.6 (s, 2 H, CH_2), 6.9−7.2 (m, 4 H arom).

2-(4-Aminobutyl)-1,2,3,4-tetrahydroisoquinoline (11): yield 83%; ^{1}H NMR δ 1.2−1.75 (m, 6 H, NH_2, 2 CH_2), 2.3−3.0 (m, 8 H, 4 CH_2), 3.6 (s, 2 H, CH_2), 6.9−7.2 (m, 4 H arom).

A solution of **10** or **11** (1 mmol) and anhydride **12** (0.17 g, 1 mmol) in dry xylene (15 mL) was refluxed for 3 h. Then the solvent was evaporated, and the residue was purified using column chromatography (SiO_2, $CHCl_3$−MeOH, 95:5). Free bases were dissolved in acetone (5−7 mL), treated with an excess of diethyl ether saturated with dry, gaseous HCl, and kept in a refrigerator to yield colorless, crystalline products.

8-[2-[2-(1,2,3,4-Tetrahydroisoquinolinyl)]ethyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride (5a): yield 37%; mp 183−185 °C; ^{1}H NMR (base) δ 1.4−1.7 (m, 8 H, 4 CH_2), 2.6 (s, 4 H, 2 CH_2CO), 2.65−2.8 (m, 6 H, 3 CH_2), 3.65 (s, 2 H, CH_2), 4.0 (t, 2 H, CH_2, J = 7 Hz). Anal. ($C_{20}H_{26}N_2O_2\cdot HCl\cdot H_2O$) C, H, N.

8-[4-[2-(1,2,3,4-Tetrahydroisoquinolinyl)]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride (6a): yield 32%; mp 160−162 °C; ^{1}H NMR (base) δ 1.3−1.9 (m, 12 H, 6 CH_2), 2.55 (s, 4 H, 2 CH_2CO), 2.3−3.0 (m, 6 H, 3 CH_2), 3.65 (s, 2 H, CH_2), 3.95 (t, 2 H, CH_2, J = 7 Hz), 7.0−7.3 (m, 4 H arom). Anal. ($C_{22}H_{30}N_2O_2\cdot HCl\cdot 0.5H_2O$) C, H, N.

2-(4-*N*-Succinimidobutyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6c). A mixture of succinimide (0.2 g, 2 mmol), 1,4-dibromobutane (0.43 g, 2 mmol), KF/Al_2O_3 catalyst (2 g), and acetonitrile (15 mL) was refluxed for 4 h and left overnight at room temperature. Then the inorganic precipitate was filtered off, and the solvent was evaporated to give *N*-(4-bromobutyl)succinimide **(14):** yield 69%, oil; ^{1}H NMR δ 1.7−2.2 (m, 4 H, 2 CH_2), 2.75 (s, 4 H, 2 CH_2), 3.35−3.7 (m, 4 H, 2 CH_2).

A mixture of **14** (0.29 g, 1 mmol), 1,2,3,4-tetrahydroisoquinoline (0.17 g, 1.3 mmol), K_2CO_3 (0.5 g), and *n*-butanol (10 mL) was refluxed for 6 h and left overnight at room temperature. Then the inorganic precipitate was filtered off, the solvent was evaporated, and the residue was purified using silica gel chromatography (Chromatotron) and $CHCl_3$ as an eluent. The product was converted into HCl salt as described above: yield 55%; mp 187−190 °C (acetone); ^{1}H NMR (base) δ 1.5−1.9 (m, 4 H, 2 CH_2), 2.65 (s, 4 H, 2 CH_2), 2.4−3.1 (m, 6 H, 3 CH_2), 3.4−3.75 (m, 4 H, 2 CH_2), 7.0−7.25 (m, 4 H arom). Anal. ($C_{17}H_{22}N_2O_2\cdot HCl$) C, H, N.

Radioligand Binding Experiments. Radioligand binding studies with 5-HT_{1A} receptors were conducted in the rat brain (hippocampus) according to the published procedure.[36] The radioligand used in the binding assays was [^{3}H]-8-OH-DPAT (190 Ci/mmol, Amersham). The K_i values were determined from at least three competition binding experiments in which 10−14 drug concentrations, run in triplicate, were used.

***In Vivo* Experiments.** The experiments were performed on male Wistar rats (220−260 g). The animals were kept at room temperature (20 ± 1 °C) on a natural day−night cycle (May−June) and housed under standard laboratory conditions. They had free access to food (Bacutil pellets) and tap water before the experiment. Each experimental group consisted of 6−8 animals/dose, and all the animals were used only once.

Buspirone hydrochloride (Bristol Myers), 8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT; Research Biochemicals Inc.), reserpine (Ciba), and compound **6a** were used in the form of freshly prepared aqueous solutions.

Lower Lip Retraction (LLR) in Rats. The LLR was assessed according to the method described by Berendsen *et al.*[6] The rats were individually placed in cages, having been scored three times (at 15, 30, and 45 min after ip administration of **6a** or buspirone) as follows: 0 = lower incisors not visible, 0.5 = partly visible, 1 = completely visible. The total maximum score amounted to 3/rat.

Behavioral Syndrome in Reserpinized Rats. Reserpine (1 mg/kg sc) was administered 18 h before the test. The rats were individually placed in the experimental cages 5 min before injection of **6a** or buspirone. Observation sessions, lasting 45 s each, began 3 min after the injection and were repeated every 3 min. Reciprocal forepaw treading and flat body posture were scored using a ranked intensity scale, where 0 = absent, 1 = equivocal, 2 = present, and 3 = intense. The total maximum score, of five observation periods, amounted to 15/animal/symptom.[30] The effect of **6a** and buspirone on the behavioral syndrome induced by 8-OH-DPAT (5 mg/kg ip) in reserpinized rats was estimated in an independent experiment. Compound **6a** and buspirone were administered ip 15 min before 8-OH-DPAT. Observations began 3 min after 8-OH-DPAT administration and were repeated every 3 min for a period of 15 min.

Statistics. The obtained data were analyzed by Dunnett's test.

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