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Structure–Activity Relationship Studies of CNS Agents—XVII. Spiro[Piperidine-4',1-(1,2,3,4-Tetrahydro-β-Carboline)] as a Probe Defining the Extended Topographic Model of 5-HT_{1A} Receptors

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Abstract–Spiro[piperidine-4',1-(1,2,3,4-tetrahydro-β-carboline)] (**10**), its derivatives **11**–**15** and its analogs **16** and **17** were examined as ligands of serotonin 5-HT_{1A} receptors. It was shown that compounds **12** and **14** had essentially the same 5-HT_{1A} affinity as 1-phenylpiperazine and its rigid analog **7**, whereas there were substantial differences in the steric arrangement of their crucial pharmacophores, i.e. aromatic and protonation centers. On the basis of the existing models and using the (+)-LSD structure as a template, a new, extended three-point topographic model of 5-HT_{1A} receptors has been proposed.

Introduction

The hitherto most convincing, three-dimensional models of the 5-HT_{1A} receptors have been proposed by Hibert *et al.*[1,2] and Mellin *et al.*[3] Both models assume two pharmacophoric elements of a ligand, which are responsible for formation and stabilization of the receptor–ligand complex, namely a protonation center at the basic nitrogen atom and an aromatic nucleus. Hibert *et al.*[1,2] deduced the model of 5-HT_{1A} receptors on the basis of topographic similarities between several classes of ligands, such as 2-aminotetralins, 1-arylpiperazines or tryptamines, and the rigid ergot skeleton of lisuride. According to this model, the center of the aromatic nucleus is located at a distance of 5.2–5.4 Å from the basic nitrogen atom, which deviates from the aromatic ring plane by 0.9–1.6 Å; besides the electron lone pair is perpendicular to this plane (Fig. 1).

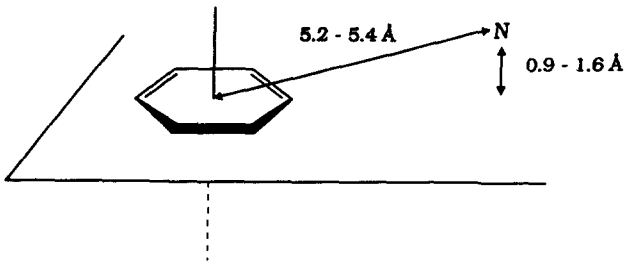


Figure 1. A topographic model of the 5-HT_{1A} recognition site (after Hibert *et al.*).[1,2]

Hacksell and co-workers carried out the mapping of 5-HT_{1A} receptors on the basis of stereoselective and conformationally restricted analogs of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT).[3] Their model was defined by an aromatic site and a dummy atom–nitrogen vector. The dummy atom, which was assumed to mimic the carboxylate ion within the active site of the receptor, deviates from the aromatic ring plane by 2.1–2.6 Å and lies 5.2–5.7 Å away from the normal of the aromatic center (Fig. 2). The latter authors also defined two crucial angles: α (–28° to 28°) and β (–4° to 0.4°), which can distinguish between enantiomers of the model compounds.

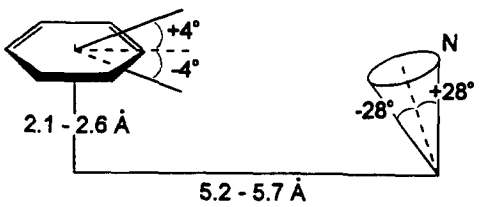
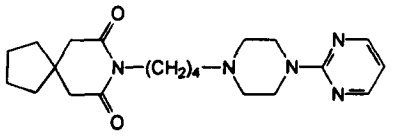


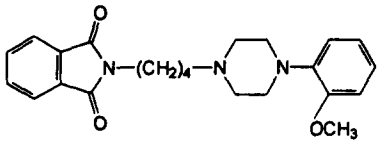
Figure 2. A topographic model of the 5-HT_{1A} recognition site, derived by Mellin *et al.*[3]

Either of the above models satisfactorily explains the 5-HT_{1A} activity of relatively small ligands. However, none of them elucidates the observed effects of the terminal π-electron system in 4-(ω-substituted)alkyl-1-arylpiperazines on their 5-HT_{1A} affinity. Although the majority of simple 1-arylpiperazines show moderate 5-HT_{1A} affinity (K_i = 10^{-6}–10^{-7} M), their more complex long-chain derivatives, such as buspirone (**1**) or NAN-190 (**2**), are classified as highly active 5-HT_{1A} ligands (K_i = 10^{-10}–10^{-8} M).[4,5] While discussing a hypothetical model of 5-HT_{1A} sites, Glennon *et al.*[4] suggested that there should exist a region of bulk tolerance adjoining the protonation site, which must be capable of accommodating large, bulky groups, such as those found in the buspirone-type agents. Moreover, our previous study indicated that the specific electron

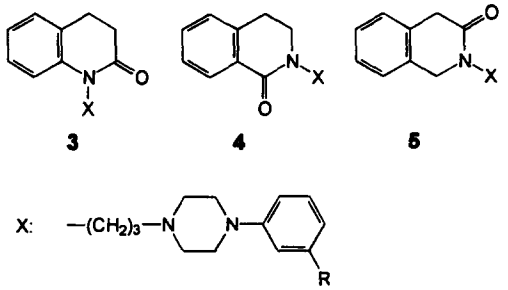
density distribution within the amide bond and the arrangement of that bond significantly modified the 5-HT_{1A} affinity of derivatives **3–5**.[6] Therefore we assumed that the terminal amide fragment in buspirone-like ligands stabilizes the 5-HT_{1A} receptor–ligand complex by either π-electron or local dipole–dipole interactions.[6]



Buspirone (1)



NAN - 190 (2)

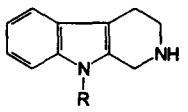


3 **4** **5**

X: $-(CH_2)_3-$

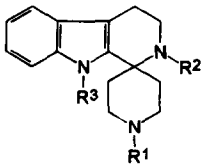
Figure 3.

6 **7**



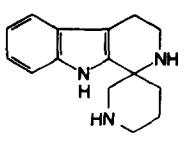
	R
8	H
9	CH_3

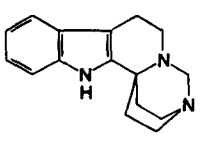
8, 9



	R1	R2	R3
10	H	H	H
11	$CH_2C_6H_5$	H	H
12	$CH_2C_6H_5$	H	CH_3
13	H	$COCH_3$	H
14	$CH_2C_6H_5$	$COCH_3$	H
15	$COCH_3$	H	H

10 - 15





16 **17**

Figure 4.

According to topographic models of 5-HT_{1A} sites, 1-arylpiperazines should adopt a conformation at the receptor in which the electron lone pair at the basic nitrogen atom is oriented perpendicularly to the aromatic ring plane. It was shown that such a conformation was frozen in the rigid structures of **6** and **7**, and that the 5-HT_{1A} affinity of those model compounds was the same as that of parent 1-arylpiperazines.[7,8] In spite of all these findings, our previous results of the quantitative structure–5-HT_{1A} affinity relationships and conformational analysis indicated that some *ortho*-substituted 1-arylpiperazines should adopt a bioactive conformation in which the electron lone pair is oriented in the aromatic ring plane.[8,9]

In order to verify the existing topographic models of 5-HT_{1A} sites, the present paper deals with the 5-HT_{1A} affinity–structure analysis of the set of model compounds **7–17**.

Results and Discussion

The 5-HT_{1A} binding data of the analyzed compounds are shown in Table 1. The affinity of the unsubstituted spiro compound **10** was very low. Derivatives **11** and **13** were more active—by an order of magnitude—than the parent compound **10**. However, compounds **12** and **14** showed the highest 5-HT_{1A} affinity of all the investigated derivatives. Although the observed 5-HT_{1A} affinities of **12** and **14** were fairly moderate, their K_i values were fully comparable with those reported for 1-phenylpiperazine (K_i = 378 nM)[8] and its rigid analog **7** (Table 1). On the other hand, compounds **15–17** were completely inactive at 5-HT_{1A} receptors.

It seems that the R^1, R^2 and R^3 substituents may contribute to the affinity of the basic structure of **10**. However, it is assumed that two crucial pharmacophores, i.e. the basic nitrogen atom and the aromatic nucleus, as well as their steric arrangement, are responsible for the recognition and stabilization processes of the investigated compounds at 5-HT_{1A} receptors. Compared to the simple tetrahydro-β-carbolines **8** and **9**, the indole fragment of compounds **10–17** may be regarded as a π-electron system which stabilizes the bioactive complex, whereas protonation of a molecule followed by a formation of an ionic bond at the receptor is possible either at the N-3 or N-7 atoms. We reported previously that the determined pK_a values of **10** at 20 °C were equal to 9.69 ± 0.09 and 5.94 ± 0.02 for the N-3 and N-7 atoms, respectively. The pK_a values of **10**, determined in water and in a 50% ethanol solution at 37 °C, were similar to those mentioned above. Moreover, the N-3 or N-2 atom in compounds **10–12** and **16** was more basic than the N-7 one, as indicated by their pK_a values (Table 1). Therefore, the N-3 or N-2 atom was almost completely protonated under experimental conditions (pH = 7.4, 37 °C), whereas the ionization percentage of the N-7 atom was negligible (2.2% or < 1% for **10** or **11**, **12** and **16**,

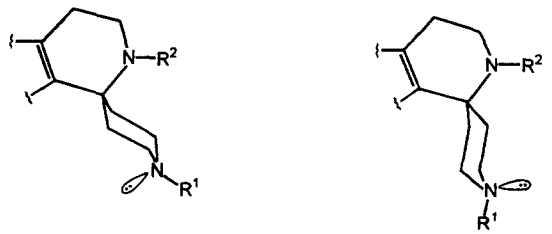
Table 1. 5-HT_{1A} receptor affinity (K_i) and ionization constants (pK_a) of compounds 7–17

No.	K_i (nM)[a]	pK_{a1} (N-7)[b]	pK_{a2} (N-3 or 2)[b]
7[c]	345 ± 13		
8[d]	2510 ± 80		
9[d]	1410 ± 110		
10	10100 ± 350	5.76 ± 0.03[e]	9.80 ± 0.03[e]
11	1016 ± 21	5.33 ± 0.03[e]	[e,f]
12	471 ± 18	[e,f]	[e,f]
13	984 ± 35		[f]
14	213 ± 13		[f]
15	>50000		7.08 ± 0.03
16	>50000	4.42 ± 0.02	9.05 ± 0.03
17	>50000	[f]	[f]

[a]Mean value from at least three independent experiments.
[b]Determined at 37 °C.
[c]Data taken from Ref. 8.
[d]Data taken from Ref. 10.
[e]pK_{a1} and pK_{a2} values, determined in a 50% ethanol (v/v) at 37 ± 0.1 °C, are: **10** 5.33 ± 0.03 and 9.42 ± 0.01, **11** 4.86 ± 0.02 and 7.93 ± 0.02, **12** 4.49 ± 0.03 and 7.76 ± 0.02, respectively.
[f]The solubility of the free base in water was too low to allow determination of the pK_a value.

respectively). The observed 5-HT_{1A} affinity of **13–15** was in accordance with the above conclusion. The affinity of the N_7-acetyl derivatives **13** and **14** was of the same order as that found for **11** and **12** (R^2 = H). In contrast, blockade of the N-3 amino function by the acetyl group yielded the completely inactive derivative **15** (Table 1).

The investigated compounds have a well-defined geometry. Our previous results of a conformational analysis in the solution using high-resolution NMR techniques indicated that the spiropiperidine ring in derivatives **10**, **11** and **16** existed predominantly in a chair conformation, whereas a boat conformation was found only in a rigid, bicyclic structure of **17**.[11,12] The semiempirical MNDO calculations agreed with the above results. In fact, the applied optimization procedure does produce a realistic geometry of the ring system, as the obtained conformations closely match the reported crystal structure of (+)-LSD[13] or the solution conformations of **10**[12] or **17**.[10] It has been found that there exist two extreme low-energy conformations, shown in Figure 5. The spiropiperidine ring in derivatives **10–12** adopts a chair form in both the **a** and



a **b**

Figure 5. Two low-energy conformations of **10–12**.

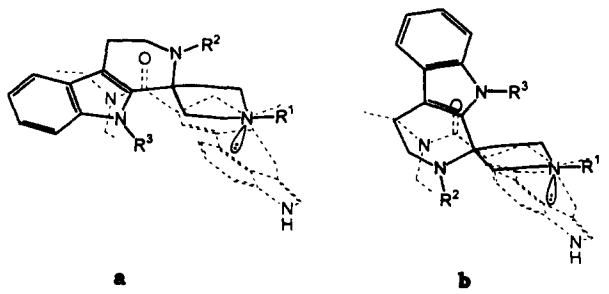
b conformations. On the other hand, in the case of N_7-acetyl derivatives **13** and **14**, the chair conformations **a** and **b** are deformed and may be classified as twist-chair ones. The calculated heats of formation (ΔH°) indicate that conformer **a** of compounds **10–12** has lower energy—by at least 1.5 kcal mol^{-1}—than its counterpart **b**. The energy difference between the two extreme conformations **a** and **b** reached a value of 0.97 kcal mol^{-1} for compound **16**; in the case of the N_7-acetyl derivatives **13** and **14** those values were even lower, i.e. 0.15 and 0.46 kcal mol^{-1}, respectively (Table 2).

Table 2. Heats of formation of the two extreme conformations (**a** and **b**) of spiro derivatives **10–14** and **16**

No.	ΔH° (kcal/mol)	
	conformer **a**	conformer **b**
10	45.17	46.99
11	79.08	80.64
12	86.93	88.45
13	21.60	21.75
14	55.03	55.49
16	43.96	44.93

Compounds **10–14** possess one common feature of the structure which distinguishes them from typical 5-HT_{1A} ligands. The electron lone pair at the N-3 protonation center of compounds **10–14** is oriented in a plane of the indole ring system, due to the spiro junction at position 1 of the tetrahydro-β-carboline skeleton, whereas the known topographic models of 5-HT_{1A} sites assume a perpendicular orientation to the aromatic ring plane of the electron lone pair at the basic nitrogen.[1–3] It has been shown that the steric arrangement of the electron lone pair at the protonation center and aromatic system plane controls the stereoselectivity of 3-substituted 1,2,3,4-tetrahydro-β-carbolines[10] and 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indoles[14] at 5-HT_{1A} receptors. It has also been reported that the (+)-LSD amide function contributes to stabilization of its bioactive complex with 5-HT_{1A} receptors.[15] Moreover, 1-(*o*-isopropylphenyl)piperazine, which is a fairly active 5-HT_{1A} ligand (K_i = 74 nM),[8] has an electron lone pair at the N-4 atom, oriented in the plane of the benzene ring in the predominating conformation.[8] Therefore, on the basis of

the above findings, we previously assumed that 1-(*o*-isopropylphenyl)piperazine may mimic the (+)-LSD structure in such a manner that the benzene ring occupies the same space at the receptor as the substituted amide group of the (+)-LSD molecule.[8] The same may be anticipated for the investigated compounds **10–14**. Fitting experiments indicated that of the two possible conformations **a** and **b** of **10–12**, only the former ones mimic very well the (+)-LSD structure (Fig. 6). This means that only in the case of conformations **a** may the indole nucleus of compounds **10–12** occupy the same space as the amide substituent of the (+)-LSD. Therefore, the assumption that the energetically more favorable conformations **a** of compounds **10–12** may be regarded as bioactive ones at the receptor seems to be justified.



a **b**

Figure 6. Superimposition of compounds **10–12** in conformation **a** or **b** on the (+)-LSD molecule.

In order to describe precisely the mutual position of the protonation center and the aromatic nucleus in compounds **10–14**, we have defined the following parameters (Fig. 7): (i) d — a distance between the centroid of the indole nucleus (c_{ar}) and the protonation center at the basic nitrogen atom; (ii) h — a deviation of the nitrogen atom from the aromatic ring (indole) plane (Π_{ar}); (iii) γ — an angle between vector d and the vector $N_{l.p.}$, which determines the direction of the electron lone pair; (iv) δ — an angle between the aromatic ring plane (Π_{ar}) and the vector d; (v) ϕ — a dihedral angle between the aromatic ring plane (Π_{ar}) and the plane ($\Pi_{l.p.}$), described by three elements: the centroid (c_{ar}), nitrogen atom (N) and its electron lone pair (l.p.).

Specific values of the defined distances and angles were measured from optimized geometry (by an MNDO method) and are shown in Table 3.

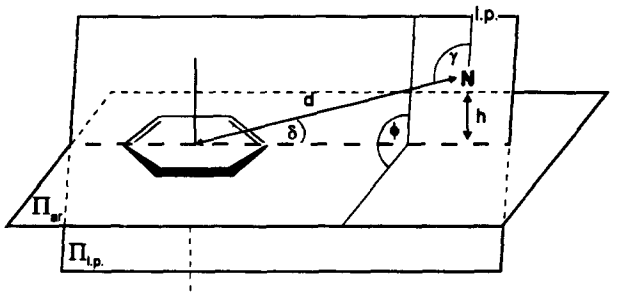


Figure 7. Parameters describing steric relations between the aromatic ring system and protonation center of a molecule. Π_{ar}, a plane of the aromatic ring system, $\Pi_{l.p.}$, a plane defined by the center of the aromatic nucleus (c_{ar}), nitrogen atom (N) and the position of an electron lone pair (l.p.).

Specific steric parameters of conformers **10a–14a** do not differ basically, except for the ϕ value of **14a**, and may define a range of topographic relations at the receptor (Table 3). On the other hand, it is not obvious which of the two extreme conformations **a** and **b** of derivatives **13** and **14** would be preferred at the receptor. However, a comparison of steric parameters for (+)-LSD and compounds **10–14** with their 5-HT_{1A} binding data may suggest that the distance (d) and the deviation of the nitrogen atom (h) from the π-electron system plane (Π_{ar}) are the major factors that control the observed 5-HT_{1A} affinity of the investigated compounds. Angles γ and δ are only derivatives of these two crucial elements. This view seems to be justified, since a qualitative relationship between the 5-HT_{1A} affinity and the value of d or h is observed for **10–14**: the shorter the distance d or the stronger the deviation h, the higher the observed 5-HT_{1A} affinity. Moreover, a value of ~6.6 Å may be regarded as the upper limit of the distance d in relation to d = 4.30 Å, which is characteristic of the (+)-LSD molecule (Table 3). On the other hand, an entirely different arrangement of basic pharmacophores results in completely inactive compounds **16** and **17** (Fig. 4, Table 1).

The above results, analyzed together with the known models of 5-HT_{1A} sites and using the (+)-LSD molecule as a template, permit us to propose an extended three-point topographical model of the 5-HT_{1A} receptor, as shown in Figure 8. In this model, two π-electron systems A and B (e.g. the indole nucleus and the amide group of the (+)-LSD molecule, respectively) are

Table 3. Steric relations[a] between the indole nucleus and protonation center of compounds **10a–14a**, **13b**, **14b** and (+)-LSD

No.	d (Å)	h (Å)	γ (°)	δ (°)	ϕ (°)
10a	6.83	0.11	76.2	0.9	4.4
11a	6.62	0.14	67.0	1.2	4.7
12a	6.65	0.78	66.2	4.4	6.7
13a	6.20	0.27	57.9	2.5	4.3
13b	5.94	0.69	131.2	6.7	12.9
14a	5.55	0.46	39.8	4.8	36.0
14b	5.96	0.73	121.8	7.0	13.4
(+)-LSD[b]	4.30	1.12	92.7	15.1	15.1

[a]The d, h, γ, δ and ϕ parameters are defined in the text and shown in Figure 7.
[b]Steric relations between the amide group and protonation center.

almost perpendicular and are located at distances d_1 and d_2 from the protonation center of the molecule. The nitrogen atom deviates from the aromatic plane A by 0.9–1.6 Å, as was originally proposed by Hibert *et al.*,[1,2] and from the π-electron system plane B by 0.1–1.1 Å (*c.f.* h values for compounds **10–14** and (+)-LSD, Table 3). The lower limits of the crucial distances were taken from the (+)-LSD molecule, whereas the upper ones come from Hibert's model (d_1) and from the data obtained for compounds **10–14** (d_2). The angle α = 98.6°, measured from (+)-LSD molecule, was set to calculate the distance d_3.

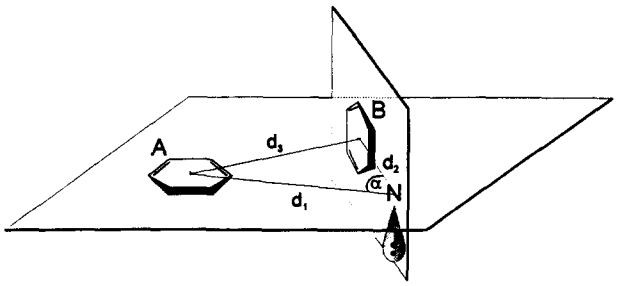


Figure 8. A three-point topographic model of 5-HT_{1A} receptors. d_1 = 5.0–5.4 Å, d_2 = 4.3–6.6 Å, d_3 = 7.1–9.1 Å, α = 98.6°. Deviations of the nitrogen atom from planes A and B (not shown for clarity) are: h_1 = 0.9–1.6 Å and h_2 = 0.1–1.1 Å, respectively. Benzene rings represent two π-electron system.

The proposed model not only offers an explanation of the 5-HT_{1A} affinity of the investigated compounds **10–14**, but also sheds some light on the role of the terminal amide fragment of 5-HT_{1A} ligands of types **1** and **2**. This implies that the more complex 5-HT_{1A} ligands are flexible enough to adopt a bioactive conformation in which the 1-arylpiperazine portion overlaps the aromatic system A at the distance d_1 from the nitrogen atom, whereas the terminal amide fragment may reach a position which corresponds to the aromatic system B at the distance d_2 from the protonation center.

Experimental

Melting points are uncorrected and were determined on a Boetius apparatus. Proton NMR spectra were recorded on a Varian EM-360L (60 MHz) spectrometer; chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane. Elemental analyses indicated by the symbols were within ±0.4% of theoretical values and were carried out in the Institute of Organic Chemistry, PAN, Warszawa, Poland. pH Measurements were taken on a pH-meter N517 (Mera Elwro) with a combined OSH-10-00 electrode. Radioligand binding studies were performed using the following equipment: a K-70 ultracentrifuge (Janetzky), a 1B-18 cell harvester (Brandel) and an LS 6000PA scintillation counter (Beckman).

The following compounds were synthesized by published procedures: **10**, **11**, **16**,[12] **12**[16] and **17**.[11] N-Acetylation of **10** and **11** was carried out according to the previously published procedure.[11] Commercially available reagent grade solvents and reagents were used without further purification.

Spiro[1'-benzylpiperidine-4',1-(2-acetyl-1,2,3,4-tetrahydro-β-carboline)] (14)

Spiran **11** (2.0 g, 5 mmol) was dissolved in chloroform (32 mL) and a 20% aqueous K_2CO_3 (32 mL). Then acetyl chloride (0.45 mL, 6.3 mmol) was added on stirring at room temperature and the reaction mixture was left overnight. The organic layer was separated, washed with water (2 × 10 mL), and dried over anhydrous $MgSO_4$. The inorganic precipitate was filtered off, the solvent was evaporated and the crude product was purified by silica gel chromatography ($CHCl_3$:MeOH, 95:5) to give **14** (1.5 g, 81%). An oil; ^1H NMR ($CDCl_3$) 1.60–2.20 (2H, *m*), 2.33 (3H, *s*), 2.40–3.30 (8H, *m*), 3.40–3.80 (4H, *m*), 7.0–7.6 (9H, *m*), 10.45 (1H, *s*). Free base of **14** was converted into HCl salt; mp 216–218 °C; Anal. $C_{24}H_{27}N_3O \cdot HCl \cdot H_2O$ (C, H, N).

Spiro[piperidine-4',1-(2-acetyl-1,2,3,4-tetrahydro-β-carboline)] (13)

A mixture of **14** (0.45 g, 1.2 mmol), palladium supported on charcoal (0.07 g), acetic acid (2.4 mL) and methanol (24 mL) was reduced with hydrogen (5 atm) in an autoclave at room temperature for 24 h. Then the catalyst was filtered off and the solvents were evaporated to dryness. The crude product was recrystallized from benzene to give **13** (0.32 g, 85%); mp 224–226 °C; ^1H NMR ($CDCl_3$) 2.30 (3H, *s*), 2.40–2.60 (1H, *m*), 2.67–3.2 (2H, *m*), 3.20–3.40 (2H, *m*), 3.40–3.90 (6H, *m*), 4.20 (2H, *s*), 7.03–7.70 (4H, *m*), 10.45 (1H, *s*). The hydrochloride salt was prepared in acetone using an excess of Et_2O, saturated with HCl and recrystallized from benzene:acetone (4:1); mp 213–215 °C; Anal. $C_{17}H_{21}N_3O \cdot HCl$ (C, H, N).

Spiro[1'-acetylpiperidine-4',1-(1,2,3,4-tetrahydro-β-carboline)] (15)

Spiran **10** (0.39 g, 1.6 mmol) was suspended in a 20% aqueous K_2CO_3 (8 mL). Then chloroform (8 mL) and acetyl chloride (0.15 mL, 2.1 mmol) were added at room temperature, and the reaction mixture was stirred for 4 h. The solid product was filtered off. The organic layer of the filtrate was washed with water (2 × 5 mL) and dried over anhydrous $MgSO_4$. Then the inorganic precipitate was filtered off and the solvent was evaporated to dryness to give an additional amount of the crude product. The combined organic precipitates were recrystallized from ethanol:acetone (1:1) to give **15** (0.18 g, 40%); mp 292–293 °C; ^1H NMR ($CDCl_3$:MeOH-d_4) 1.80–2.10 (2H, *m*), 2.20 (3H, *m*), 2.60–2.90 (2H, *m*), 2.90–3.40 (3H, *m*), 3.50–3.90 (2H, *m*), 3.90–4.20 (2H, *m*), 4.30–4.70 (1H, *m*), 7.0–7.6 (4H, *m*). Free base of **15** was converted into HCl salt; mp 268–270 °C (decomp.); Anal. $C_{17}H_{21}N_3O \cdot HCl$ (C, H, N).

Potentiometric titration

Ionization constants were determined by a potentiometric titration at 37 ± 0.1 °C in water or a 50% ethanol (v/v) solution. The pK_a values were calculated from the experimental data by a standard method.[17]

Radioligand binding experiments

Radioligand binding studies with 5-HT_{1A} receptors were conducted in the rat brain (hippocampus), according to the previously published procedure.[10] The radioligand used in the binding assays was [^{3}H]-8-OH-DPAT (190 Ci mmol^{-1}, Amersham). IC_{50} Values were determined from a nonlinear single fit to data, obtained from competition binding experiments in which 10–14 drug concentrations, run in triplicate, were used. K_i Values were calculated using an ACCUFIT (Lundon Software) program.

Molecular modeling

The preferred conformations of compounds **10–14**, **16** and (+)-LSD were calculated by an MNDO method. The MNDO calculations (full geometry optimization, gradient norm < 0.1 kcal mol^{-1} Å^{-1}) were conducted using a MOPAC-5 program implanted into a SYBYL 5.51 integrated package (Tripos), installed on an ESV 10/33 workstation.

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