Structure-Activity Relationship Studies of CNS Agents, Part 23[1]:

N-(3-Phenylpropyl)- and *N*-[(*E*)-Cinnamyl]-1,2,3,4-tetrahydroisoquinoline Mimic 1-Phenylpiperazine at 5-HT$_{1A}$ Receptors

Jerzy L. Mokrosz*, Andrzej J. Bojarski, Sijka Charakchieva-Minol, Beata Duszynska, Maria J. Mokrosz, and Maria H. Paluchowska

Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna St., 31-343 Kraków, Poland

Key Words: *5-HT$_{1A}$ receptor ligands, 1-arylpiperazines, N-substituted 1,2,3,4-tetrahydroisoquinolines, molecular modelling*

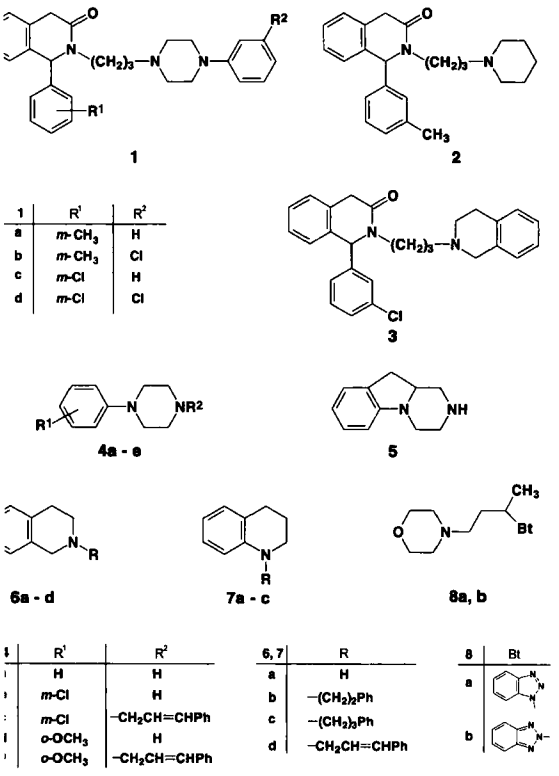
Summary

The 5-HT$_{1A}$ receptor affinities and ionization constants of a set of 1-arylpiperazine (**4**) 1,2,3,4-tetrahydroisoquinoline (**6**), and -quinoline (**7**) containing *N*-(ω-arylalkyl) or *N*-(*E*)-cinnamyl substituents as well as two morpholine derivatives (**8a**, **8b**) were determined. It was shown that some tetrahydroisoquinoline (**6c**, **6d**) and morpholine (**8a**) derivatives were 5-HT$_{1A}$ ligands equipotentto 1-phenylpiperazine (**4a**) and 1,2,3,4,4a,5-hexahydropyrazino[1,2-*a*]indole (**5**). On the basis of molecular modelling studies it was also demonstrated that **6c**, **6d** and **8a** mimicked very well the reference structures of **4a** and its rigid analog **5**. Another, more complex 1,2,3,4-tetrahydroisoquinoline derivative **3**, which served as a model compound to confirm the previously reported 5-HT$_{1A}$ binding mode of derivatives **1a-d** and **2**, had the highest 5-HT$_{1A}$ affinity (K_i = 6.7 ± 0.5 nM) of all the investigated compounds.

Introduction

The N-4 piperazine atom and an aromatic ring of simple 1-arylpiperazines are known to form a pharmacophore which is recognized by the 5-HT$_{1A}$ receptor[2]. However, our previous paper showed that a bioactive complex of some 4-substituted 1-arylpiperazines of type **1** with 5-HT$_{1A}$ receptors may be formed by the piperazine nitrogen atom and the aryl substituent at position 1 of the 3(2*H*)-isoquinolinone moiety, instead of an aromatic substituent of the piperazine ring[3]. In order to verify the proposed interaction mode of derivatives of type **1** with 5-HT$_{1A}$ receptors, we also developed compound **2**[3]. However, its 5-HT$_{1A}$ affinity was fairly low (K_i = 911 nM)[3], probably due to a very high basicity of the piperidine nitrogen atom. In fact, the determined basicity of *N*-propylpiperidine (at 37 °C) was pK_a = 10.24 ± 0.03[4], whereas typical pK_a values of simple 1-arylpiperazines were within the range of 7.94 – 9.14[5].

In search of new model compounds which mimic both the structure and 5-HT$_{1A}$ affinity of 1-phenylpiperazine (**4a**) and its rigid analog (**5**), in the present paper we discuss some structure-activity relationships of compounds **4–8**. In order to explain a fairly low 5-HT$_{1A}$ affinity of **2** and previously proposed binding mode of derivatives **1a–d** and **2** at the 5-HT$_{1A}$ sites[3] we also examined compound **3** which is the tetrahydroisoquinoline analog of **1c** and **1d** (Scheme 1).

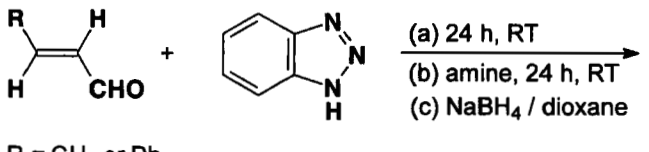


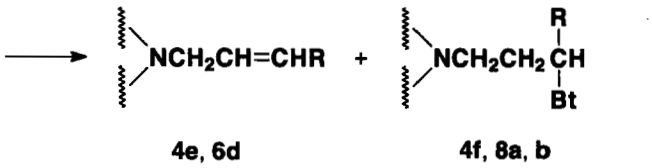
Scheme 1

Results and Discussion

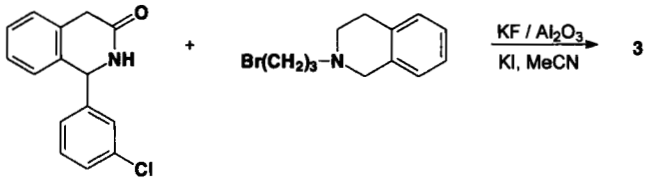
Compounds **4e**, **6d**, **8a**, and **8b** were prepared by a novel synthetic method developed by *Katritzky* and coworkers[6] and already adapted in our laboratory to preparation of derivative **4c**[1]. Reaction of **4d** with cinnamaldehyde and benzotriazole gave both **4e** and **4f**. However, when **6a** was used, only the cinnamyl derivative **6d** was isolated with a low yield of 15%. By contrast, in the reaction between morpholine, crotonaldehyde and benzotriazole only the benzotriazole derivatives **8a,b** were obtained (Scheme 2). *N*-Alkylation of 1-(*m*-chlorophenyl)-1,4-dihydro-3(2*H*)-isoquinolinone with *N*-(3-chloropropyl)-1,2,3,4-tetrahydroisoquinoline was carried out in the presence of KF supported on neutral Al_2O_3 as a catalyst in acetonitrile solution and gave **3** with a yield of 24% (Scheme 3). A simple condensation of the appropriate ω-phenylalkylbromide with **6a** or **7a** under reflux in *n*-butanol, in the presence of K_2CO_3, afforded **6b,c** and **7b,c** in a yield of 38–55% (Scheme 4).

  0365-6233/95/0708-0604 $5.00 + .25/0

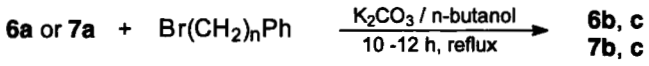




Scheme 2



Scheme 3



Scheme 4

Our previous paper showed that 1-phenylpiperazine (**4a**) had the same, moderate 5-HT$_{1A}$ affinity as its rigid analog **5** (Table 1)[7]. 1-Arylpiperazines **4b** and **4d** were more active than **4a**, and substitution with the *N*-(*E*)-cinnamyl group resulted in further enhancement of the observed 5-HT$_{1A}$ affinity. On the other hand, compounds **6a** and **7a** were completely inactive. Replacement of the hydrogen atom in **6a** with the 2-phenylethyl fragment markedly increased the 5-HT$_{1A}$ affinity of **6b** up to a micromolar level. 3-Phenylpropyl and (*E*)-cinnamyl substituents were even more effective, as derivatives **6c** and **6d** reached almost the same affinity levels which were only 1.5–2 times lower than those of **4a** or **5**. A similar trend was observed in the case of **7a-c**; however, the observed K_i values for **7b** and **7c** were very low. Of the two morpholine derivatives, only **8a** showed a significant yet low micromolar 5-HT$_{1A}$ affinity, whereas **8b** was completely inactive.

Some of the observed substituent effects may be explained by different ionization states of the investigated compounds under experimental conditions (pH = 7.4, temp. 37 °C). It was shown earlier that the apparent binding constants K_i depended on the concentration of the protonated species of a ligand molecule under experimental conditions, and the specific binding constants of the protonated form was defined by eq. (1)[7,9].

$$K_i^{AH+} = K_i/[1 + 10^{(7.4 - pKa)}] \quad (1)$$

Reference compounds **4a** and **5** are almost fully ionized at pH = 7.4 and temp. 37 °C (>92%). By contrast, the inactive 1,2,3,4-tetrahydroquinoline (**7a**) is poorly ionized (0.27%) under the same conditions. Hence a very low concentration of the ionized species of **7b** and **7c** may account for their almost negligible 5-HT$_{1A}$ affinity. The 5-HT$_{1A}$ affinity of **8a** is also low. However, the concentration of the ionized form of the latter compound (ionization percentage = 5.81%) cannot be neglected, and the calculated value K_i^{AH+} = 331 nM is the same as those calculated for **4a** and **5**: K_i^{AH+} = 348 and 329 nM, respectively[7]. The concentration of the ionized form of **8b** is similar (7.52%), hence the lack of activity in this particular case should be of a different nature. Although 1,2,3,4-tetrahydroisoquinoline (**6a**) is fully protonated at pH = 7.4 and temp. 37 °C (98.8%), it does not form a bioactive complex with 5-HT$_{1A}$ receptors, as the crucial distance between the aromatic ring center and the nitrogen atom ($d_{Ar\text{-}N}$ = 3.8 Å) is below the critical value of 4.5 Å[11]. The pK_a values for **6b-6d**, determined in 50% ethanol, are lower by 1.67–2.08 units than that determined for **6a** (Table 1). Hence it may be assumed that **6b–6d** are ionized in water (under the experimental conditions) in about 40–60%. If this is the case, the $K_i^{AH+} \approx$ 230–460 nM values for **6c** and **6d** are within the same range as those calculated for **4a** and **5**. However, the

Table 1. The 5-HT$_{1A}$ binding data (K_i) and ionization constants (pK_a) for 8-OH-DPAT and **3–8**.

No.	K_i [nM] ± SEM[a]	K_i^{AH+} [nM][b]	pK_a[c]
8-OH-DPAT	1.4 ± 0.2		
3	6.7 ± 0.5		[d]
4a[e]	378 ± 54	348	8.46
4b[f]	143 ± 6	131	8.42
4c	76 ± 3		[d]
4d	168 ± 14[g]		8.86[h]
4e	78 ± 5		[d]
5[e]	345 ± 13	329	8.73
6a	> 50 000		9.30[h]; 8.82[i]
6b	2160 ± 35	≈ 860-1300[j]	6.86[i]
6c	582 ± 35	≈ 230–460[j]	7.15[i]
6d	768 ± 40	≈ 230–460[j]	6.74[i]
7a	> 50 000		4.84[h]
7b	26 200 ± 5900		[d]
7c	11 400 ± 350		[d]
morpholine	–		8.17
8a	5700 ± 280	331	6.19
8b	> 50 000		6.31

[a] Hill slopes: for 8-OH-DPAT and **3-6** $0.89 \le n_H \le 1.05$, for **7b**, **7c**, and **8a** n_H = 0.75 and 0.81, respectively.
[b] Calcd. from eq. (1).
[c] Determined by a potentiometric titration[8] in water at 37 °C; standard error ≤ ±0.03.
[d] Solubility of the base in both water and in 50% ethanol was too low to determine the pK_a value.
[e] Data taken from ref.[7].
[f] Data taken from ref.[9].
[g] Ref.[10].
[h] Ref.[5].
[i] Determined in 50% ethanol at 37 °C.
[j] The estimated values for 40–60% ionization in water (*cf.* discussion).

$K_i^{AH+} \approx$ 860–1300 nM value for **6b** remains at least twice as low as those for **6c** and **6d**; again, this phenomenon appears to be of a different nature. In fact, molecular modelling studies have shed some light on the phenomenon in question.

Compounds **6b–6d**, **8a**, and **8b** have a flexible structure, as shown by molecular mechanics calculations. In other words, a random search procedure generated a number of low-energy conformations, which passed the following criterion: $\Delta(\Delta H) \leq 5$ kcal/mol (Table 2). Although the ranges of the two pivotal parameters, *i.e.* the distance between the aromatic system center and the nitrogen atom ($d_{Ar\text{-}N}$) and the deviation of the nitrogen atom from a plane of the aromatic ring system (h), formally match both the $d_{Ar\text{-}N}$ and H values for **4a** and **5**, as well as the values reported by *Hibert et al.*[12,13], the deviation h is usually very strong and indicates some folded conformations (except for **6d**) which do not overlap the reference structure of **5** (Fig. 1a). Therefore only those conformations that met the additional criterion $h \leq 1$ Å were selected from all the generated ones. The data shown in Table 2 indicate that all the selected conformations of **6c**, **6d** and **8a** mimic very well the rigid structure of **5** (Figs. 1b, c).

Table 2. Results of the molecular modelling of compounds **6b–6d**, **8a** and **8b.**

No.	Number of conformations	$d_{Ar\text{-}N}$ [Å] [a]	h [Å] [a]
4a[b]		5.68	0.81
5[b]		5.50	0.06
6b	46[c]	3.62–5.30	0.22–4.67
	8[d]	3.66–5.30	0.22–0.94
6c	35[c]	3.10–6.29	0.65–3.88
	5[d]	5.71–5.79	0.66–0.70
6d	43[c]	5.73–6.13	0.09–2.06
	27[d]	5.73–6.13	0.09–0.83
8a	25[c]	3.24–6.79	0.30–3.97
	4[d]	5.68–5.92	0.30–0.96
8b	20[c]	3.61–6.97	0.66–3.88
	2[d]	6.54–6.68	0.66

[a] Typical ranges reported for different classes of 5-HT_{1A} ligands: $d_{Ar\text{-}N}$ = 5.2-5.6 Å, h = 0.2–1.6 Å[12,13].
[b] Measured for the lowest energy conformer.
[c] All the generated low-energy conformations [$\Delta(\Delta H) \leq 5$ kcal/mol].
[d] The conformations that met the criterion: $h \leq 1$ Å.

Hence it may be concluded that molecular modelling results support the earlier findings that compounds **6c**, **6d** and **8a** are 5-HT_{1A} ligands equipotent to the reference compounds **4a** and **5**, as indicated by their K_i^{AH+} values. Furthermore, the $d_{Ar\text{-}N}$ parameter of the inactive compound **8b** (*i.e.*, 6.54–6.68 Å) exceeds the typical range (*i.e.*, 5.68 Å for **4a** and 5.50 Å for **5**).

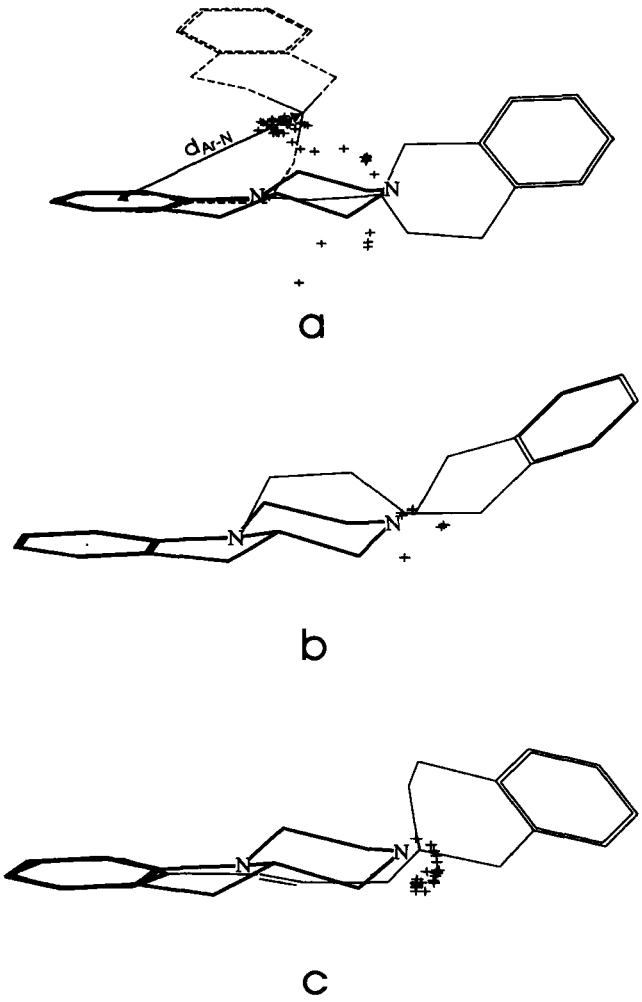


Figure 1. Superimposition of **6b** (a), **6c** (b), and **6d** (c) and the rigid reference structure of **5**. Cross marks indicate the position of the nitrogen atom of **6b-6d** in relation to the fixed position of the phenyl substituent. (a) All the generated conformations [$\Delta(\Delta H) \leq 5$ kcal/mol]; (b) and (c) – the conformations that met the criterion $h \leq 1$ Å.

The presented results clearly indicated that the tetrahydroisoquinoline N-atom may mimic the basic nitrogen atom of 1-arylpiperazine at the 5-HT_{1A} receptors. Therefore we have assumed that the tetrahydroisoquinoline moiety of derivative **3** could be better model than the piperidine fragment of compound **2** to confirm the previously proposed mode of interaction of derivatives **1a–d** with 5-HT_{1A} receptors. Indeed, the 5-HT_{1A} affinity of **3** (K_i = 6.7 ± 0.5 nM) is of the same order as those reported for **1c** and **1d** (K_i = 1.7 ± 0.1 and 9.5 ± 0.6 nM, respectively)[3], whereas the piperidine derivative **2** (K_i = 911 æ 34 nM) was substantially less active at 5-HT_{1A} receptors than **1a** and **1b** (K_i = 2.8 ± 0.6 and 33 ± 1 nM, respectively)[3]. Thus, the present results additionally support our previous conclusion that the 5-HT_{1A} ligands **1-3** may be recognized at the receptor in such a manner that the aryl substituent at position 1 of the 3(2*H*)-isoquinolinone moiety and the basic nitrogen atom of the terminal amine function mimics remarkably well simple 1-arylpiperazines.

Experimental Part

Melting points: Boetius apparatus (uncorrected).– Elemental analyses: Within ± 0.4% of calculated values for C,H, and N. Institute of Organic Chemistry, Warszawa.– ^{1}H NMR spectra ($CDCl_3$): Varian EM-360L (60 MHz) spectrometer, TMS int. standard.– Materials: **6a**, **7a** and other starting materials were commercial products (Aldrich); 1-(3-chlorophenyl)-1,4-dihydro-3(2*H*)-isoquinolinone was obtained according to the published procedure[14].

*1-(3-Chlorophenyl)-2-{3-[2-(1,2,3,4-tetrahydroisoquinolinyl)]propyl}-1,4-dihydro-3(2H)-isoquinolinone hydrochloride (**3**)*

A mixture of 1-(3-chlorophenyl)-1,4-dihydro-3(2*H*)-isoquinolinone (0.26 g, 1 mmol), 2-(3-chloropropyl)-1,2,3,4-tetrahydroisoquinoline (0.21 g, 1.02 mmol), KF/Al_2O_3 catalyst (1.0 g), KI (0.02 g) and MeCN (15 ml) was refluxed for 4 h. The reaction mixture was filtered off and the solvent was evaporated. The oily residues was purified by CC (SiO_2, $CHCl_3$/MeOH - 9/1), then Al_2O_3/$CHCl_3$) to give 24% of **3**. Free base of **3** was transformed into HCl salt in acetone with an excess of Et_2O saturated with gaseous HCl. The resultant crystalline salt was recrystallized from $CHCl_3$/Et_2O (1/1). Mp 121–123 °C.– ^{1}H NMR (base): 1.8-2.2 (m, 2H, CH_2), 2.4-3.1 (m, 8H, 4 CH_2), 3.4 (s, 2H, isoquinoline CH_2N), 3.75 (s, 2H, CH_2CO), 5.8 (s, 1H, CH), 7.0-7.4 (m, 12H, aromatic H).- Anal. $C_{27}H_{27}ClN_2O \cdot HCl$).

*General procedure for preparation of derivatives **4e**, **4f**, **6d**, **8a**, and **8b***

A mixture of benzotriazole (0.95 g, 8 mmol) and cinnamaldehyde (0.53 g, 4 mmol) or crotonaldehyde (0.28 g, 4 mmol) in Et_2O (30 ml, freshly distilled from Na/benzophenone) was stirred at room temp. for 6 h and left overnight. The reaction mixture was cooled in an ice-water bath and a solution of an appropriate amine (4 mmol) was added in one portion upon stirring. Then the mixture was allowed to reach room temp. and the stirring was continued for 20 h. Afterwards the solvent was evaporated, the residue was dissolved in dioxane (40 ml), treated with $NaBH_4$ (0.076 g, 2 mmol), refluxed for 4 h and left overnight at room temp. The reaction mixture was poured into 10% NaOH (40 ml) and extracted with Et_2O (3 × 30 ml). The combined organic layers were washed with water and dried over anhydrous $MgSO_4$. Then the solvent was evaporated, and the crude products were purified by CC (SiO_2, AcOEt/*n*-hexane – 1:2). The products were converted into HCl salts in acetone with an excess of Et_2O/HCl.

*1-(o-Methoxyphenyl)-4-[(E)-cinnamyl]piperazine dihydrochloride (**4e**)*

Yield 40%. Mp 183–185 °C (acetone/ethanol – 9:1).– ^{1}H NMR (base): 2.6–2.9 (m, 4H, 2 CH_2), 3.0–3.3 (m, 6H, 3 CH_2), 3.8 (s, 3H, OCH_3), 6.1–6.6 (m, 2H, CH=CH), 6.8–7.1 m, 4H, aromatic H), 7.2–7.5 (m, 5H, aromatic H).- Anal. ($C_{20}H_{24}N_2O \cdot 2$ HCl).

*1-[3-(Benzotriazol-1-yl)-3-phenylpropyl]-4-(2-methoxyphenyl)piperazine (**4f**)*

Yield 26%. Mp. 95–97 °C (*n*-hexane).– ^{1}H NMR: 2.3–3.3 (cluster, 12H, piperazine H and CH_2CH_2), 3.85 (s, 3H, OCH_3), 6.1 (t, J = 7 Hz, 1H, CH_2CH), 7.1 (s, 2H, aromatic H), 7.2–7.7 (m, 10H, aromatic H), 8.0–8.3 (m, 1H, benzotriazole 4-H).

*N-[(E)-Cinnamyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (**6d**)*

Yield 15%. Mp 220–221 °C (acetone/ethanol – 9:1).- ^{1}H NMR (base): 2.75–3.0 (m, 4H, CH_2CH_2), 3.4 (d, J = 6 Hz, 2H, CH_2CH=CH), 3.7 (s, 2H, CH_2), 6.4–6.7 (m, 2H, CH=CH), 6.9–7.6 (m, 9H, aromatic H).– Anal. ($C_{18}H_{19}N \cdot$ HCl).

*N-[3-(Benzotriazol-1-yl)-3-methylpropyl]morpholine hydrochloride (**8a**)*

Yield 9%. Mp 180–182 °C (acetone), ref.[15] 153–155 °C (picrate salt).– ^{1}H NMR (base): 1.75 (d, J = 7 Hz, 3H, CH_3), 2.1–2.6 (m, 8H, $CHCH_2CH_2N$ and CH_2NCH_2), 3.65 (t, J = 5 Hz, 4H, CH_2OCH_2), 4.9–5.3 (m, 1H, $CHCH_3$), 7.3–7.65 (m, 3H, benzotriazole 4,5,6-H), 8.0–8.25 (m, 1H, benzotriazole 7-H).– Anal. ($C_{14}H_{20}N_4O \cdot$ HCl).

*N-[3-(Benzotriazol-2-yl)-3-methylpropyl]morpholine hydrochloride (**8b**)*

Yield 8%. Mp 193–195 °C (acetone).– ^{1}H NMR (base): 1.8 (d, J = 7 Hz, 3H, CH_3), 2.2–2.5 (m, 8H, $CHCH_2CH_2N$ and CH_2NCH_2), 3.6–3.8 (m, 4H, CH_2OCH_2), 5.1–5.4 (m, 1H, $CHCH_3$), 7.4–7.6 (m, 2H, benzotriazole 5,6-H), 7.9–8.1 (m, 2H, benzotriazole 4,7-H).– Anal. ($C_{14}H_{20}N_4O \cdot$ HCl).

*General procedure for preparation of derivatives **6b**, **6c**, **7b**, and **7c***

A mixture of **6a** or **7a** (3 mmol), the appropriate ω-phenylalkylbromide (3.1 mmol), anhydrous K_2CO_3 (0.5 g, 3.6 mmol), and *n*-butanol (20 ml) was refluxed for 10–12 h. Then the reaction mixture was cooled down, filtered off, and the solvent was evaporated. The residue was purified by CC (SiO_2, AcOEt/*n*-hexane – 1:1 for **6b** and **6c**, and $CHCl_3$/*n*-hexane – 1:1 for **7b** and **8c**). Free bases were converted into salts in acetone solutions using an excess of Et_2O, saturated with HCl or 40% aqueous HBr.

*N-(2-Phenylethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (**6b**)*

Yield 42%. Mp 228–231 °C (acetone, ref.[16] 227–229 °C).– ^{1}H NMR (base): 2.5–3.1 (m, 8H, 4 CH_2), 3.65 (s, 2H, CH_2), 7.1 (s, 4H, aromatic H), 7.3 (m, 5H, aromatic H).– Anal. ($C_{17}H_{19}N \cdot$ HCl).

*N-(3-Phenylpropyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (**6c**)*

Yield 40%. Mp 203–205 °C (acetone, ref.[16] 207–209 °C).– ^{1}H NMR (base): 1.7–2.2 (m, 2H, CH_2), 2.3–3.1 (m, 8H, 4 CH_2), 3.6 (s, 2H, CH_2), 7.0–7.5 (m, 9H, aromatic H).– Anal. ($C_{18}H_{21}N \cdot$ HCl).

*N-(-Phenylethyl)-1,2,3,4-tetrahydroquinoline hydrobromide (**7b**)*

Yield 38%. Mp 137–140 °C (acetone).– ^{1}H NMR (base): 1.8–2.2 (q, J = 6 Hz, 2H, CH_2Ph), 2.6–3.75 (m, 8H, 4 CH_2), 6.6–7.25 (m, 4H, aromatic H), 7.3 (s, 5H, aromatic H).– Anal. ($C_{17}H_{19}N \cdot$ HBr).

*N-(3-Phenylpropyl)-1,2,3,4-tetrahydroquinoline hydrobromide (**7c**)*

Yield 55%. Mp 161–164 °C (acetone).– ^{1}H NMR (base): 1.7–2.2 (m, 2H, CH_2), 2.4–2.9 (m, 4H, 2 CH_2), 3.0–3.6 (m, 6H, 3 CH_2), 6.4–7.2 (m, 4H, aromatic H), 7.25 (s, 5H, aromatic H).– Anal. ($C_{18}H_{21}N \cdot$ HBr).

Binding experiments

In vitro binding studies with 5-HT$_{1A}$ receptors were carried out in the rat brain (hippocampus) using [^{3}H]-8-OH-DPAT (190 Ci/mmol, Amersham) as a radioligand[17]. The K_i values were obtained in at least three independent, competition binding experiments, in which 10–14 drug concentrations run in triplicate were used.

pK_a measurements

Ionization constants were determined by a potentiometric titration at 37 ± 0.1 °C in water or 50% ethanol. The pK_a values were calculated from the experimental data by a standard method[8] using an Enzfitter program (Biosoft, Oxford).

Molecular modelling

All the molecular modelling experiments were performed using a SYBYL v. 6.03 (Tripos Associates, Inc.) integrated package, installed on an ESV 10/33 workstation. The geometry of all the analyzed compounds was optimized using a Tripos force field procedure. Low-energy conformations were generated using a RANDOM SEARCH procedure (only chain bonds were allowed to rotate). The following setup was used to do calculations: minimization details – method: Powell, max iteration: 3000, max displacement: 0.01; energy – force field: Tripos; random search details - max cycles: 1000, energy cutoff: x + 5 kcal/mol, number of hits: 3, RMS threshold: 0.1, convergence threshold: 0.005.

References

[1] Part 22: J. L. Mokrosz, B. Duszynska, M. H. Paluchowska, S. Charakchieva-Minol, M. J. Mokrosz, *Arch. Pharm. (Weinheim)* **1995**, *328*, 623–625.

[2] R. A. Glennon, R. B. Westkaemper, P. Bartyzel in *Serotonin Receptor Subtypes: Basic and Clinical Aspects* (Ed.: S. J. Peroutka), Wiley-Liss, New York, **1991**, chapter 2.

[3] J. L. Mokrosz, A. J. Bojarski, M. Mackowiak, Z. Bielecka, J. Boksa, *Pharmazie* **1994**, *49*, 328–333.

[4] A. J. Bojarski, M. J. Mokrosz, M. H. Paluchowska, *Pharmazie*, in press.

[5] S. Caccia, M. H. Fong, R. Urso, *J. Pharm. Pharmacol.* **1985**, *37*, 567–570.

[6] A. R. Katritzky, S. Rachwal, G. J. Hitchings, *Tetrahedron* **1991**, *47*, 2683–2732.

[7] J. L. Mokrosz, J. Boksa, A. J. Bojarski, S. Charakchieva-Minol, *Med. Chem. Res.* **1993**, *3*, 240–248.

[8] A. Albert, E. P. Serjeant, *Ionization Constants of Acids and Bases*, Methuen, London, **1967**.

[9] J. L. Mokrosz, M. Pietrasiewicz, B. Duszynska, M. T. Cegla, *J. Med. Chem.* **1992**, *35*, 2369–2374.

[10] J. L. Mokrosz, M. J. Mokrosz, S. Charakchieva-Minol, M. H. Paluchowska, A. J. Bojarski, B. Duszynska, *Arch. Pharm. (Weinheim)* **1995**, *328*, 143-148.

[11] J. L. Mokrosz, M. J. Mokrosz, A. J. Bojarski, S. Charakchieva-Minol, *Pharmazie* **1994**, *49*, 781–782.

[12] M. F. Hibert, M. W. Gittos, D. N. Middlemiss, A. K. Mir, J. R. Fozard, *J. Med. Chem.* **1988**, *31*, 1087–1093.

[13] M. F. Hibert, I. McDermott, D. N. Middlemiss, A. K. Mir, J. R. Fozard, *Eur. J. Med. Chem.* **1989**, *24*, 31–37.

[14] J. L. Mokrosz, M. T. Cegla, E. Szneler, *Arch. Pharm. (Weinheim)* **1992**, *325*, 241–245.

[15] A. R. Katritzky, S. Rachwal, C. V. Hughes, Z. Wang, *Polish J. Chem.* **1992** *66*, 1633–1652.

[16] *Beilstein Handbuch der Organischen Chemie*, E III/IV, *20*, 2954.

[17] A. J. Bojarski, M. T. Cegla, S. Charakchieva-Minol, M. J. Mokrosz, M. Mackowiak, S. Misztal, J. L. Mokrosz, *Pharmazie* **1993**, *48*, *289–294*.

Received: April 21, 1995 [FP011]