# *Notes*

## Synthesis and Structure−Activity Relationships of a New Model of Arylpiperazines. 3.[1] 2-[ω-(4-Arylpiperazin-1-yl)alkyl]perhydropyrrolo-[1,2-*c*]imidazoles and -perhydroimidazo[1,5-*a*]pyridines: Study of the Influence of the Terminal Amide Fragment on 5-$HT_{1A}$ Affinity/Selectivity

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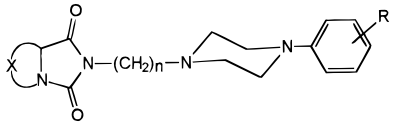
A series of new arylpiperazine derivatives **2**, which are devoid of the terminal amide fragment present in related 5-$HT_{1A}$ ligands, was prepared and evaluated for affinity at 5-$HT_{1A}$ and $\alpha_1$ receptors. All the compounds **2** demonstrated high affinity for the 5-$HT_{1A}$ receptor and moderate affinity for $\alpha_1$ receptor binding sites. Structure−activity relationship (SAR) studies suggest that there is influence of electronic factors on the no-pharmacophoric part of the $\alpha_1$ receptor site. However there is no influence of electronic interactions on the stabilization of the 5-$HT_{1A}$ receptor−ligand complex.

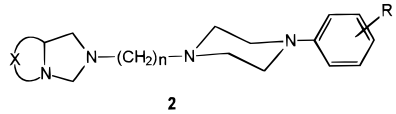
### Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that mediates a wide variety of physiological responses in both the peripheral and central nervous systems.[2−6] The receptors that are activated by 5-HT have been divided into at least seven classes (5-$HT_{1-7}$), and each class has been further subdivided into different subtypes (A, B...).[7−13] Of these receptors, the 5-$HT_{1A}$ receptor subtype is the best studied and it is generally accepted that it is involved in psychiatric disorders such as depression[14−17] and anxiety.[18,19] Long chain arylpiperazines with an amide or imide moiety represent one of the most important classes of the 5-$HT_{1A}$ receptor ligands (*e.g.*, buspirone, gepirone, NAN-190, flesinoxan, WAY 100135, WAY 100635) (Chart 1). The large number of structure−activity relationship (SAR) studies on these compounds have shown that the influence of the nature of the aryl group on *N*1 of the piperazine ring and the length of the alkyl chain on the *N*4 position on 5-$HT_{1A}$ affinity is clear, in contrast to the role of the amide or imide moiety. Some authors have indicated that the presence of the terminal amide fragment plays an important role in the stabilization of the 5-$HT_{1A}$ receptor−ligand complex by $\pi-\pi$ or dipole interactions,[20−22] while another hypothesis[23−27] has suggested that the amide function is not required for binding with the receptor.

In previous papers[28,29] we have reported the synthesis of a new series of bicyclohydantoin−arylpiperazines **1**, which showed moderate to high affinity for 5-$HT_{1A}$ and $\alpha_1$ receptors. As a continuation of our research program to discover compounds with high affinity and selectivity for the 5-$HT_{1A}$ receptor versus the $\alpha_1$ receptor, we have considered a new set of analogs **2**, in which we have carried out a classic isosteric change of a carbonyl group for a methylene group in order to have a better understanding of the influence of the terminal amide fragment on 5-$HT_{1A}$ affinity/selectivity. Herein we report the synthesis of **2** and the affinities for 5-$HT_{1A}$ and $\alpha_1$ receptors obtained by radioligand binding assays. The arylpiperazines (R = *o*-$OCH_3$, *m*-Cl, *m*-$CF_3$) and the length of the alkyl chain (*n* = 3, 4) used for the compounds in the present work are those present in agents **1** with the highest affinity and selectivity for the 5-$HT_{1A}$ receptor.[29]




**1**




**2**

### Chemistry

The general strategy for the synthesis of compounds **2a**−**j** is summarized in Scheme 1. Treatment of 4-(ω-chloroalkanoyl)-1-arylpiperazines **4** with hydantoins **3**,[30,31] in the presence of NaH and *N*,*N*-dimethylformamide (DMF), gave the corresponding intermediates **5** (in 60−70% yield), which were reduced by $LiAlH_4$ in THF to provide the desired compounds **2a**−**j** (in 40−67% yield). This sequence is particularly useful for preparing compounds **2**, since the direct reduction of **1**[29] (obtained in 20−50% yield) proceeds with low overall yields. Respective hydrochloride salts were prepared as samples for biological assays. All new compounds

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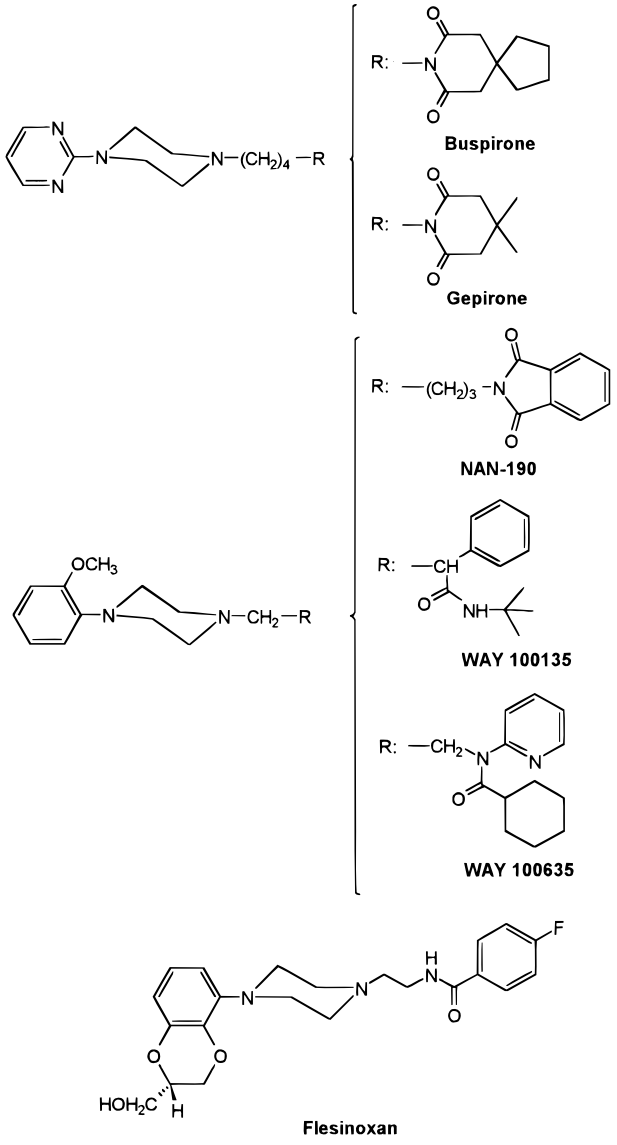
**Chart 1**




were characterized by IR and $^1$H and $^{13}$C NMR spectroscopy and gave satisfactory combustion analyses (C, H, N).

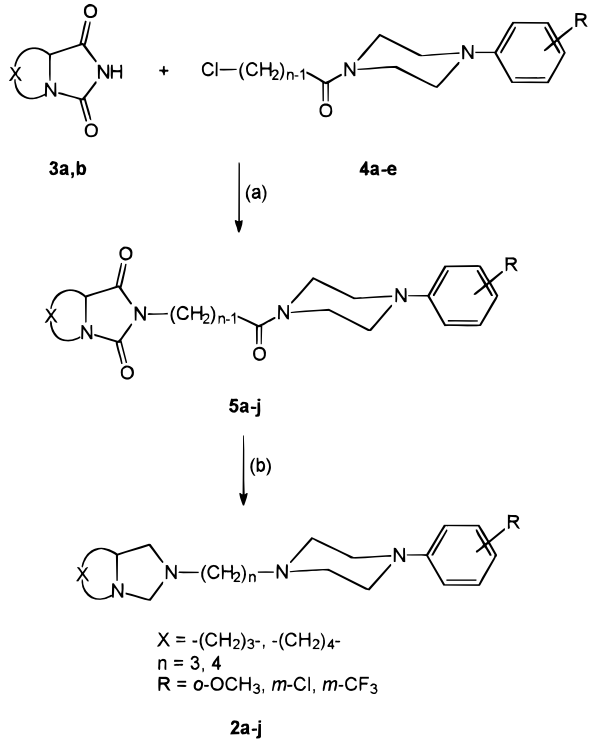
## Biochemistry

The 5-HT$_{1A}$ and $\alpha_1$ receptor binding affinities of synthesized compounds **2a**−**j** were determined by measurement of the displacement of [$^3$H]-8-OH-DPAT and [$^3$H]prazosin binding, respectively, in rat cerebral cortex membranes. All the compounds were used in form of hydrochloride salts and were water-soluble. The inhibition constant $K_i$ was defined from the IC$_{50}$ by the Cheng−Prusoff equation.[32] The results of these assays are illustrated in Table 1.

## Results and Discussion

From the binding data, all the compounds **2** demonstrated high affinity for the 5-HT$_{1A}$ receptor and moderate affinity for $\alpha_1$ receptor binding sites. Considering as a term of comparison the arylpiperazine derivatives **1** (see Table 1), which had been previously studied,[29] it should be noted that (a) Regarding the 5-HT$_{1A}$ receptor, the reduction of the carbonyl groups causes a slight decrease in affinity from 1.5-fold (derivative **2j**) to 8-fold

**Scheme 1**[a]

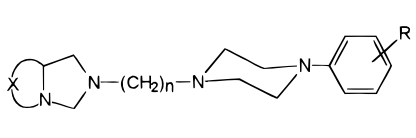



[a] Reagents: (a) NaH/DMF (anhydrous); (b) LiAlH$_4$, THF.

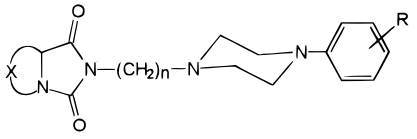
(derivative **2b**) in comparison to their hydantoin analogs. Only the derivative **2h** (R = *o*-OCH$_3$) is equipotent to analog **1h**. (b) Concerning the $\alpha_1$ receptor, the modification of the amide moiety led to a decrease in affinity. This decrease is especially marked for *o*-methoxy analogs with three carbon atoms in the spacer. Therefore derivatives **2a**,**c** displayed 100- and 22-fold lower affinity in comparison with **1a,c**, respectively. (c) With respect to the $\alpha_1$/5-HT$_{1A}$ selectivity, this structural change produces an important and positive effect in compounds with a methoxy group at the *ortho*-position. Thus, the derivative **2a** showed a higher selectivity (37-fold) than the corresponding reference compound. The same effect was found in derivatives **2h** (9-fold), **2c** (6.5-fold), and **2e** (3-fold). In the case of the *m*-trifluoromethyl analogs the reduction of the amide moiety has a slight negative influence on $\alpha_1$/5-HT$_{1A}$ selectivity.

The fact that there is a great steric similarity between compounds **1** and **2** (reduction of the amide moiety led to a van der Waals volume decrease of about 2.5 cm$^3$·mol$^{-1}$), and there is no significant variation in the affinity for the 5-HT$_{1A}$ receptor, suggests that there is no influence of electronic interactions in the stabilization of the 5-HT$_{1A}$ receptor−ligand complex or, if there is an influence, it must be very negligible. Thus, our findings are in agreement with the hypothesis of some authors[23−27] that the presence of the no-pharmacophoric part is not essential for 5-HT$_{1A}$ affinity. On the contrary, the isosteric change of a carbonyl group for a methylene group seems to have a negative influence on the electronic interactions for $\alpha_1$ receptor binding. This fact makes evident a little difference between both receptors in their no-pharmacophoric site. Therefore, it can be stated that this structural modification contributes to an increase in the $\alpha_1$/5-HT$_{1A}$ selectivity, especially for *o*-methoxy derivatives. In fact, compound **2a** (R = *o*-OCH$_3$; *n* = 3) has proven to be the most

**Table 1.** Binding Data[a] for Compounds **2** and **1**[b]



**2**



**1**

| | | | | $K_i$ (nM) ± SEM | | $K_i$ ratio | | $K_i$ (nM) ± SEM | | $K_i$ ratio |
|---|---|---|---|---|---|---|---|---|---|---|
| no. | X | *n* | R | 5-$HT_{1A}$ | $\alpha_1$ | $\alpha_1$/5-$HT_{1A}$ | no. | 5-$HT_{1A}$ | $\alpha_1$ | $\alpha_1$/5-$HT_{1A}$ |
| **2a** | $-(CH_2)_3-$ | 3 | *o*-$OCH_3$ | 12.2 ± 2.3 | 323 ± 37 | 26 | **1a** | 4.4 ± 0.6 | 3.1 ± 0.5 | 0.7 |
| **2b** | $-(CH_2)_3-$ | 3 | *m*-$CF_3$ | 29.1 ± 4.7 | 363 ± 14 | 12.5 | **1b** | 3.8 ± 0.5 | 109 ± 9 | 28.7 |
| **2c** | $-(CH_2)_4-$ | 3 | *o*-$OCH_3$ | 13.9 ± 3.0 | 218 ± 38 | 15.7 | **1c** | 4.1 ± 0.6 | 9.9 ± 10 | 2.4 |
| **2d** | $-(CH_2)_4-$ | 3 | *m*-$CF_3$ | 24.3 ± 0.7 | 278 ± 76 | 11.4 | **1d** | 5.7 ± 0.7 | 90.4 ± 5.1 | 15.9 |
| **2e** | $-(CH_2)_3-$ | 4 | *o*-$OCH_3$ | 17.5 ± 0.1 | 72.6 ± 12.2 | 4.1 | **1e** | 5.5 ± 0.7 | 8.3 ± 0.3 | 1.5 |
| **2f** | $-(CH_2)_3-$ | 4 | *m*-Cl | 28.1 ± 4.5 | 64.9 ± 21.5 | 2.3 | **1f** | 11.3 ± 1.0 | 9.6 ± 0.9 | 0.8 |
| **2g** | $-(CH_2)_3-$ | 4 | *m*-$CF_3$ | 12.3 ± 2.7 | 240 ± 20 | 19.5 | **1g** | 2.4 ± 0.6 | 64.9 ± 2.6 | 27.0 |
| **2h** | $-(CH_2)_4-$ | 4 | *o*-$OCH_3$ | 5.1 ± 0.9 | 45.0 ± 5.0 | 8.8 | **1h** | 8.8 ± 0.9 | 8.6 ± 1.0 | 1.0 |
| **2i** | $-(CH_2)_4-$ | 4 | *m*-Cl | 24.3 ± 2.5 | 64.3 ± 4.6 | 2.6 | **1i** | 7.2 ± 0.6 | 12.1 ± 1.2 | 1.7 |
| **2j** | $-(CH_2)_4-$ | 4 | *m*-$CF_3$ | 15.3 ± 1.1 | 115 ± 23 | 7.5 | **1j** | 9.9 ± 0.9 | 72.4 ± 8.0 | 7.3 |

[a] All values are the mean ± SEM of two to four experiments performed in triplicate. [b] Reference 29.

selective member of the investigated compounds ($\alpha_1$/5-$HT_{1A}$ = 26) and has shown a higher selectivity (37-fold) than the reference compound **1a**.

In summary, this study opens new structural possibilities in the molecular variation of the no-pharmacophoric substructure of this kind of ligand in order to increase the $\alpha_1$/5-$HT_{1A}$ selectivity.

## Experimental Section

**Chemistry.** Melting points (uncorrected) were determinated on a Gallenkamp electrothermal apparatus. Infrared (IR) spectra were obtained on a Perkin-Elmer 781 infrared spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on a Varian VXR-300S or Bruker 250AM instrument. Chemical shifts ($\delta$) are expressed in parts per million relative to internal tetramethylsilane; coupling constants (*J*) are in hertz. Elemental analyses (C, H, N) were determined within 0.4% of the theoretical values. Thin-layer chromatography (TLC) was run on Merck silica gel 60 F-254 plates. For normal pressure and flash chromatography, Merck silica gel type 60 (size 70−230 and 230−400 mesh, respectively) was used. Unless stated otherwise, starting materials used were high-grade commercial products.

The compounds **3a,b** were synthesized by published procedures. The physical data are in agreement with those given in refs 30 and 31.

**2-[*ω*-Oxo-*ω*-(4-arylpiperazin-1-yl)alkyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazoles and -1,3-dioxoperhydroimidazo[1,5-*a*]pyridines 5a−j. General Procedure.** To a suspension of the corresponding hydantoins **3a,b** (10.0 mmol) in anhydrous *N*,*N*-dimethylformamide (11 mL) was added 60% NaH (0.40 g, 10.0 mmol), and the mixture was stirred for 1 h at 60 °C under argon. After the solvent was evaporated under reduced pressure, a solution of the appropriate 4-(*ω*-chloroalkanoyl)-1-arylpiperazines **4** (20.0 mmol) in anhydrous *N*,*N*-dimethylformamide (11 mL) was added dropwise. The mixture was refluxed for 90 min under argon; then, the solvent was evaporated *in vacuo*, and the residue was resuspended in water and extracted with methylene chloride. The organic layers were washed with water and dried over $MgSO_4$. After evaporation of the solvent the crude oil was purified by column chromatography (ethyl acetate/hexane, 9:1, as eluent).

**2-[3-Oxo-3-[4-(*o*-methoxyphenyl)piperazin-1-yl]propyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole (5a)**: yield 2.70 g (70%) (oil); IR ($CHCl_3$, $cm^{-1}$) 1770 (CON), 1710 (NCON), 1640 (CO), 1600, 1500, 1450 (Ar); $^1$H NMR ($CDCl_3$) $\delta$ 1.72−1.81 (m, 1H, $H_7$), 2.04−2.13 (m, 2H, $2H_6$), 2.19−2.28 (m, 1H, $H_7$), 2.72 (t, *J* = 7.4 Hz, 2H, $CH_2CO$), 3.14−3.27 (m, 5H, $2CH_2$-pip, $H_5$), 3.58 (t, *J* = 4.8 Hz, 2H, $CH_2$-pip), 3.61−3.72 (m, 3H, $CH_2$-pip, $H_5$), 3.82 (t, *J* = 6.9 Hz, 2H, $NCH_2$), 3.84 (s, 3H, $OCH_3$), 4.09 (dd, *J* = 9.0, 7.9 Hz, 1H, $H_{7a}$), 6.88−6.93 (m, 3H, $H_3$, $H_4$, $H_6$-phenyl), 7.01−7.06 (m, 1H, $H_5$-phenyl); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.5 ($C_6$), 27.4 ($C_7$), 30.6 ($CH_2CO$), 35.1 ($NCH_2$), 41.5 ($CH_2$-pip), 45.3 ($CH_2$-pip or $C_5$), 45.6 ($CH_2$-pip or $C_5$), 50.2 ($CH_2$-pip), 50.4 ($CH_2$-pip), 55.2 ($OCH_3$), 63.6 ($C_{7a}$), 111.4 ($C_6$-phenyl), 117.9 ($C_3$-phenyl), 120.5 ($C_4$-phenyl), 123.1 ($C_5$-phenyl), 140.3 ($C_1$-phenyl), 152.0 ($C_2$-phenyl), 160.4 ($C_3$), 169.9 (CO), 175.0 ($C_1$). Anal. ($C_{20}H_{26}N_4O_4$) C, H, N.

**2-[*ω*-(4-Arylpiperazin-1-yl)alkyl]perhydropyrrolo[1,2-*c*]imidazoles and -perhydroimidazo[1,5-*a*]pyridines 2a−j. General Procedure.** A solution of **5a−j** (2.6 mmol) in dry THF (12 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.39 g, 10.4 mmol) in dry THF (12 mL) under an argon atmosphere and in an ice bath. After 15 h at room temperature, the reaction was quenched by the sequential dropwise addition of $H_2O$ (1 mL), 15% NaOH (1 mL), and $H_2O$ (2 mL). The coarse precipitate formed was filtered off, and the filtrate was washed with 5% methanol/ethyl acetate, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by column chromatography (methylene chloride/methanol, 2:8 → 1:9, as eluent). Spectral data of title compounds refer to the free bases, and then hydrochloride salts were prepared.

**2-[3-[4-(*o*-Methoxyphenyl)piperazin-1-yl]propyl]perhydropyrrolo[1,2-*c*]imidazole (2a)**: yield 0.58 g (42%); mp 89−90 °C (methanol/ethyl ether); IR ($CHCl_3$, $cm^{-1}$) 1600, 1500, 1455 (Ar); $^1$H NMR ($CDCl_3$) $\delta$ 1.41−1.48 (m, 1H, $H_7$), 1.62−1.79 (m, 4H, $CH_2$, $2H_6$), 1.89−1.95 (m, 1H, $H_7$), 2.27−2.42 (m, 5H, $H_1$, $CH_2N$, $NCH_2$), 2.51−2.63 (m, 6H, $H_1$, $H_5$, $2CH_2$-pip), 2.95−3.10 (m, 5H, $H_5$, $2CH_2$-pip), 3.15 (d, *J* = 6.9 Hz, 1H, $H_3$), 3.46 (d, *J* = 7.2 Hz, 1H, $H_3$), 3.52 (qd, *J* = 6.9, 3.0 Hz, 1H, $H_{7a}$), 3.79 (s, 3H, $OCH_3$), 6.77−6.95 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.4 ($CH_2$ or $C_6$), 26.5 ($CH_2$ or $C_6$), 32.9 ($C_7$), 50.7 ($2CH_2$-pip), 51.7 ($NCH_2$), 53.6 ($2CH_2$-pip), 55.4 ($OCH_3$), 56.0 ($C_5$), 56.9 ($CH_2N$), 59.5 ($C_1$), 63.1 ($C_{7a}$), 78.1 ($C_3$), 111.1 ($C_6$-phenyl), 118.3 ($C_3$-phenyl), 121.0 ($C_4$-phenyl), 123.0 ($C_5$-phenyl), 141.4 ($C_1$-phenyl), 152.3 ($C_2$-phenyl). Anal. ($C_{20}H_{32}N_4O\cdot 4HCl\cdot {}^5/_2H_2O$) C, H, N.

**Radioligand Binding Assays.** For all receptor binding assays, male Sprague−Dawley rats (*Rattus norvegicus albinus*), weighing 180−200 g, were killed by decapitation and the brains rapidly removed and dissected.

**5-$HT_{1A}$ Receptor.** The receptor binding studies were performed by a modification of a previously described procedure.[33] The cerebral cortex was homogenized in 10 volumes of ice-cold Tris buffer (50 mM Tris-HCl, pH 7.7 at 25 °C) and centrifuged at 28000*g* for 15 min. The membrane pellet was washed twice by resuspension and centrifugation. After the second wash the resuspended pellet was incubated at 37 °C for 10 min. Membranes were then collected by centrifugation, and the final pellet was resuspended in 50 mM Tris-HCl, 5 mM $MgSO_4$, and 0.5 mM EDTA buffer (pH 7.4 at 37 °C). Fractions of the final membrane suspension (about 1 mg of

protein) were incubated at 37 °C for 15 min with 0.6 nM [$^3$H]-8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin) (133 Ci/mmol), in the presence or absence of several concentrations of the competing drug, in a final volume of 1.1 mL of assay buffer (50 mM Tris-HCl, 10 nM clonidine, 30 nM prazosin, pH 7.4 at 37 °C). Nonspecific binding was determined with 10 $\mu$M 5-HT.

**$\alpha_1$ Adrenoceptor.** The radioligand receptor binding studies were performed according to a previously described procedure.[34]

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**Supporting Information Available:** Full experimental details and spectral data for compounds **4a**−**e**, **5b**−**j**, and **2b**−**j** (11 pages). Ordering information is given on any current masthead page.

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