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SUBSTITUTION MODE OF THE AMIDE FRAGMENT IN SOME NEW N-{ω-[4-(2-METHOXYPHENYL)PIPERAZIN--1-YL]ALKYL}PYRID-2(1H)-ONES AND THEIR 5-HT_{1A}/5-HT_{2A} ACTIVITY

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Substitution mode of the amide fragment in some new N-{ω-[4-(2-methoxyphenyl)piperazin-1-yl]alkyl}pyrid-2(1H)-ones and their 5-HT_{1A}/5-HT_{2A} activity. M.H. PALUCHOWSKA, R. BUGNO, S. CHARAKCHIEVA--MINOL, A.J. BOJARSKI, A. WESOŁOWSKA. Pol. J. Pharmacol., 2001, 53, 369–376.

A series of ω-[4-(2-methoxyphenyl)piperazin-1-yl]alkyl derivatives with terminal pyrid-2(1H)-one fragments was synthesized and evaluated for their 5-HT_{1A} and 5-HT_{2A} activity. Enlargement of the aromatic amide system by its substitution with phenyl and/or *p*-methoxyphenyl in positions 4, 5 and/or 6, as well as modification of an aliphatic spacer allowed us to better understand structure-activity relationships in that group of compounds. The results of *in vitro* and *in vivo* experiments showed that only unsubstituted (**1b**) and monosubstituted (**2b**–**4b**) derivatives with the tetramethylene spacer demonstrated high 5-HT_{1A} receptor affinity (K_i = 15–40 nM) and 5-HT_{1A}/5-HT_{2A} selectivity; they exhibited features of 5-HT_{1A} antagonists. Those results suggested that the mode of substitution of the terminal amide moiety in the tested tetramethylene arylpiperazines was not significant for their 5-HT_{1A} receptor activity. Conformational analysis calculations indicated that despite its great capacity for adaptation at 5-HT_{1A} receptor site, an aryl substituent in position 4 in the pyrid-2(1H)-one ring destabilized the ligand-5-HT_{1A} receptor complex formation in the case of trimethylene derivatives. Diarylsubstituted derivatives (**5a**–**8a** and **5b**–**8b**) were characterized by a low 5-HT_{2A} affinity (K_i > 446 nM) regardless of the spacer length, while those with the tetramethylene aliphatic chain had a higher 5-HT_{2A} affinity than the remaining investigated compounds.

Key words: *5-HT_{1A} receptor antagonists, 5-HT_{2A}/5-HT_{1A} selectivity, pyrid-2(1H)-one derivatives*

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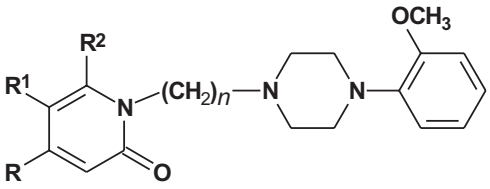
INTRODUCTION

Arylpiperazines with a mixed 5-HT_{1A}/5-HT_{2A} activity still attract researchers' attention as potential atypical antipsychotics, anxiolytics and/or antidepressants [1, 9, 19]. Thus a search for such ligands and determination of their structural features that change their 5-HT_{1A} and/or 5-HT_{2A} activity seems to be justified. We previously described a series of arylpiperazines containing a terminal six--member cyclic amide fragment, i.e. pyrid-2(1H)--one [13], quinolin-2(1H)-one, isoquinolin-1(2H)--one [11, 16] and 1,4-benzoxazin-3(4H)-one [15] systems with a distinct 5-HT_{1A}/5-HT_{2A} affinity and a functional activity. Additionally, some of them exhibited 5-HT_{1A}, 5-HT_{2A} and D_2 receptor affinities and in a behavioral study they showed features of atypical neuroleptics [11].On the other hand, investigations into enlargement of the aromatic fragment of some 2-(4-methyl-piperazin-1-yl)pyrimidine derivatives yielded compounds with a high 5-HT_{2A} receptor affinity and 5-HT_{2A}/5-HT_{1A} selectivity, which exhibited significant antagonistic properties towards 5-HT_{2A} receptors [18]. In our earlier studies [13], the unsubstituted pyrid-2(1H)-one derivative with the *m*-chloropiperazine fragment and the trimethylene spacer was characterized as a non-selective 5-HT_{1A}/5-HT_{2A} receptor ligand with a very good affinity for both types of the receptors.

In line with those findings, we designed and synthesized a new series of N-{ω-[4-(2-methoxyphenyl)piperazin-1-yl]alkyl}pyrid-2(1H)-ones (**1**–**8**, Tab. 1) with the tri- (series **a**) and tetramethylene

Table 1. Structure of the investigated compounds and their affinities for the 5-HT_{1A} and 5-HT_{2A} receptors



Compound	R	R^1	R^2	n	K_i (nM)		5-HT_{2A}/5-HT_{1A}
					5-HT_{1A}	5-HT_{2A}	Selectivity
1a	H	H	H	3	109 ± 10	1841 ± 17	16.9
1b	H	H	H	4	18 ± 3	717 ± 19	39.8
2a	Ph	H	H	3	487 ± 17	953 ± 11	1.9
2b	Ph	H	H	4	40 ± 2	522 ± 14	13.0
3a	H	Ph	H	3	71 ± 2	1076 ± 84	15.1
3b	H	Ph	H	4	15 ± 2	296 ± 11	19.7
4a	H	H	Ph	3	86 ± 8	802 ± 14	9.3
4b	H	H	Ph	4	31 ± 1	399 ± 10	12.9
5a	Ph	H	Ph	3	446 ± 25	1154 ± 16	2.6
5b	Ph	H	Ph	4	1495 ± 54	584 ± 41	0.4
6a	Ph	H	*p*-OCH_3Ph	3	289 ± 13	1637 ± 31	5.7
6b	Ph	H	*p*-OCH_3Ph	4	2799 ± 39	168 ± 44	0.06
7a	*p*-OCH_3Ph	H	Ph	3	3106 ± 40	1914 ± 10	0.6
7b	*p*-OCH_3Ph	H	Ph	4	795 ± 55	365 ± 10	0.5
8a	*p*-OCH_3Ph	H	*p*-OCH_3Ph	3	2123 ± 16	1284 ± 20	0.6
8b	*p*-OCH_3Ph	H	*p*-OCH_3Ph	4	2644 ± 19	509 ± 14	0.2

spacer (series **b**). The terminal fragment of aromatic amide was modified by introduction of phenyl and *p*-methoxyphenyl substituent in positions 4, 5 and/or 6 of the pyridone ring. We tried to determine whether such structural modifications would affect *in vitro* and *in vivo* 5-HT_{1A}/5-HT_{2A} receptor activities of compounds of that group.

MATERIALS and METHODS

CHEMISTRY

The structure of compounds described in this study is shown in Table 1, and the methods of their preparation are outlined in Figure 1. Compounds **1a**–**8a** were synthesized by alkylation of the appropriate substituted pyrid-2(1H)-one with 4-(3-chloropropyl)-1-(2-methoxyphenyl)piperazine in the presence of the KF/Al_2O_3 catalyst [14]. In the synthesis of compounds **1b**–**8b**, 8-(2-methoxyphenyl)-8--aza-5-azoniospiro[4,5]decane bromide was used as an alkylating agent. The reaction was carried out in the presence of anhydrous K_2CO_3 and a catalytic amount of 18-crown-6 [12]. The starting 4- and 6-phenylpyrid-2(1H)-ones were obtained according to Thesing and Müller [20]. The synthesis of 5-phenylpyrid-2(1H)-one was conducted by a method described by Church et al. [5], whereas for the synthesis of 4,6-diarylpyrid-2(1H)-ones Katritzky's method was applied [8]. All the products were purified by a column chromatography on silica gel; the eluents are shown in Table 2. The purity and homogeneity of all the final products were checked by TLC on silica gel, and the spots were visualized in UV light. The structure of new derivatives was confirmed by ^{1}H NMR spectra (see: supplementary materials). The physicochemical data of new compounds are presented in Table 2. For pharmacological experiments free bases were converted into hydrochloride salts, and their molecular weights were determined on the basis of an elemental analysis (see: supplementary materials). Rotation barriers between the phenyl and piryd-2(1H)-one rings were studied by a semiempirical AM1 method implemented in the Sybyl package, ver. 6.6. (Tripos Associates, Inc. St. Louis, MO, USA). The rotamers were minimized over all the bonds and angles, except for the respective torsion angle which was constrained at values between 0° and 360° with a 10° increment.

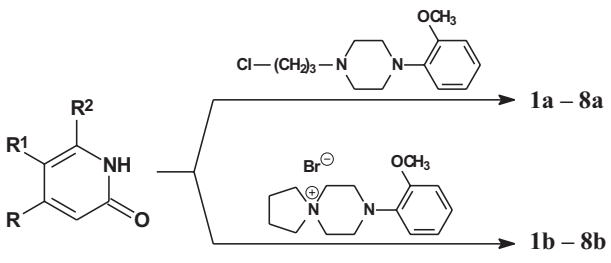


Fig. 1. Methods of preparation of new compounds

PHARMACOLOGY

In vitro experiments

Radioligand binding studies were performed on rat brain using the following structures: the hippocampus for 5-HT_{1A} receptors and the cortex for 5-HT_{2A} receptors, according to the previously used method [3]. The binding affinity of the investigated compounds for 5-HT_{1A} and 5-HT_{2A} receptors was evaluated on the basis of their ability to displace [^{3}H]-8-OH-DPAT (222 Ci/mmol, Amersham) and [^{3}H]-ketanserin (66.4 Ci/mmol, NEN Chemicals), respectively. The Cheng and Prusoff equation [4] was used for K_i calculations. K_i values were determined on the basis of at least three competition binding experiments in which 10–14 drug concentrations, run in triplicate, were used.

In vivo experiments

Experiments were performed on male Wistar rats (250–300 g) or male Albino Swiss mice (24–28 g) of our own breading (Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland). The animals were kept at a room temperature of 20 ± 1°C on a natural day–night cycle (December–March), and were housed under standard laboratory conditions. They had free access to food (Bacutil pellets) and tap water before the experiment. Each experimental group consisted of 6–10 animals/dose, and all the animals were used only once. 8-Hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT, Research Biochemical Inc.), reserpine (Ciba, ampoules) and N-{2-[4-(2--methoxyphenyl)-1-piperazinyl]ethyl-N-(2-pyridynyl)cyclohexanecarboxamide trihydrochloride (WAY 100635, synthesized by Dr. J. Boksa, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland) were used as aqueous solutions. All the investigated compounds were suspended in

Table 2. Physicochemical data of new compounds

Compound	M.p. (°C) Cryst. solvent	Yield (%)	Eluents for column chromatography[a]	Molecular formula (mol. weight)[b]
1a	127–129 ethanol-chloroform	89	A	$C_{19}H_{25}N_3O_2 \cdot 2HCl \cdot 3.5H_2O$ (463.4)
1b	157–159 ethanol-chloroform	61	A	$C_{20}H_{27}N_3O_2 \cdot 2HCl \cdot 2H_2O$ (450.4)
2a	184–186 ethanol-diethyl ether	97	A	$C_{25}H_{29}N_3O_2 \cdot 2HCl \cdot 2H_2O$ (512.5)
2b	204–206 ethanol-diethyl ether	60	A	$C_{26}H_{31}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$ (499.5)
3a	136–138 ethanol-diethyl ether	84	A	$C_{25}H_{29}N_3O_2 \cdot 2HCl \cdot 2.6H_2O$ (523.3)
3b	148–150 ethanol	60	A	$C_{26}H_{31}N_3O_2 \cdot 2HCl \cdot 2.5H_2O$ (535.5)
4a	209–210 ethanol-diethyl ether	97	A	$C_{25}H_{29}N_3O_2 \cdot 2HCl \cdot 2.1H_2O$ (514.2)
4b	178–180 ethanol-diethyl ether	61	B	$C_{26}H_{31}N_3O_2 \cdot 2HCl \cdot 0.3H_2O$ (495.9)
5a	203–205 ethanol-acetone	69	C	$C_{31}H_{33}N_3O_2 \cdot 2HCl$ (552.5)
5b	160–162 methanol-acetone	96	C	$C_{32}H_{35}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$ (575.6)
6a	139–141 acetone	47	B	$C_{32}H_{35}N_3O_3 \cdot 2HCl \cdot 2.5H_2O$ (627.6)
6b	161–163 ethanol-hexane	96	B	$C_{33}H_{37}N_3O_3 \cdot 2HCl \cdot 3.2H_2O$ (654.2)
7a	134–136 ethanol-diethyl ether	59	D	$C_{32}H_{35}N_3O_3 \cdot 2HCl \cdot 3.5H_2O$ (645.6)
7b	104–106 methanol-acetone	92	C	$C_{33}H_{37}N_3O_3 \cdot 2HCl \cdot 3H_2O$ (650.6)
8a	157–158 ethanol-hexane	65	B	$C_{33}H_{37}N_3O_4 \cdot 2HCl \cdot 4H_2O$ (684.7)
8b	134–136 acetone	95	C	$C_{34}H_{39}N_3O_4 \cdot 2HCl \cdot 6.5H_2O$ (743.7)

[a] A – chloroform : methanol (19:1), B – chloroform : methanol (49:1), C – chloroform, D – ethyl acetate : *n*-hexane (1:1); [b] calculated from elemental analysis

a 1% aqueous solution of Tween 80. 8-OH-DPAT, reserpine and WAY 100635 were injected subcutaneously (*sc*); the tested compounds were given intraperitoneally (*ip*) in a volume of 2 ml/kg (rats) and 10 ml/kg (mice). The obtained data were analyzed by a one-way analysis of variance, followed by Dunnett's test.

Lower lip retraction (LLR) in rats

LLR was assessed according to a method described by Berendsen et al. [2]. The rats were individually placed in cages (30 × 25 × 25 cm) and were scored three times: at 15, 30 and 45 min after administration of the tested compounds as follows: 0 = lower incisors not visible, 0.5 = partly visible, 1= completely visible. The total maximum score amounted to 3/rat. In a separate experiment, the effect of the studied compounds on the LLR induced by 8-OH-DPAT (1 mg/kg) was tested. The investigated compounds and WAY 100635 were administered 45 and 15 min, respectively, before 8-OH-DPAT, and the animals were scored at 15, 30 and 45 min after 8-OH-DPAT administration.

Behavioral syndrome in reserpinized rats

Reserpine (1 mg/kg) was administered 18 h before the test. The rats were individually placed in experimental cages (30 × 25 × 25 cm) 5 min before the injection of the tested compounds. Observation sessions, lasting 45 s each, began 3 min after the injection and were repeated every 3 min. Flat body posture (FBP) and reciprocal forepaw treading (FT) 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 for each symptom/animal [21]. The effect of the tested compounds on the behavioral syndrome induced by 8-OH-DPAT (5 mg/kg) in reserpinized rats was estimated in an independent experiment. The investigated compounds and WAY 100635 were administered 60 and 30 min, respectively, 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.

Body temperature in mice

The effects of the studied compounds given alone on the rectal body temperature in mice (measured with an Ellab thermometer) were recorded 30, 60, 90 and 120 min after their administration. In an independent experiment, the effect of WAY 100635 (0.1 mg/kg) on the hypothermia induced by the investigated compounds was tested. WAY 100635 was administered 15 min before the tested compounds, and the rectal body temperature was recorded 30 and 60 min after the injection of the investigated compounds. The results were expressed as a change in body temperature (Δt) with respect to the basal body temperature measured at the beginning of the experiment.

RESULTS and DISCUSSION

The investigated compounds with the tri- (**1a**–**8a**) or the tetramethylene (**1b**–**8b**) spacer showed a diversified affinity for both 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors (Tab. 1). In series **a**, compound **1a** with an unsubstituted pyridone ring, as well as compounds **3a** and **4a** with 5- and 6-phenyl substituent, showed a fairly good affinity for 5-HT$_{1A}$ receptors (K_i ranged between 71 and 109 nM), whereas substitution in position 4 of the pyridone ring (compound **2a**) decreased the affinity for those receptors (K_i = 487 nM). Replacement of the trimethylene chain between the amide fragment and the piperazine moiety in those compounds with the tetramethylene spacer (compounds **1b**–**4b**) resulted in a substantial improvement in 5-HT$_{1A}$ receptor affinity (K_i = 15–40 nM). Compounds **1a**–**4a**, as well as **1b**–**4b** demonstrated a weak 5-HT$_{2A}$ receptor affinity (K_i = 296–1841 nM).

Further extension of the terminal aromatic amide fragment by introducing the second aryl substituent yielded 4,6-diarylpyrid-2(1H)-ones (**5a**–**8a** and **5b**–**8b**) whose structures are shown in Table 1. Introduction of the phenyl substituent into position 6 of 4-phenylpyrid-2(1H)-ones **2a** and **2b** practically did not change 5-HT$_{1A}$ and 5-HT$_{2A}$ affinities for the trimethylene derivative (**2a** vs **5a**), while in the case of tetramethylene analog **2b** the same modification led to compound **5b** which revealed a very low 5-HT$_{1A}$ receptor affinity (K_i = 1495 nM). Interestingly, substitution of *p*-methoxyphenyl in position 6 of the amide ring slightly improved 5-HT$_{1A}$ receptor affinity for trimethylene derivative **6a** vs **2a** and **5a**. Contrariwise, in the case of compound **6b** with the tetramethylene aliphatic chain, an increase in 5-HT$_{2A}$ receptor affinity was observed (**6b** vs **2b** and **5b**). Further modification of the structure of aromatic amide by introducing *p*-methoxyphenyl in position 4 resulted in 4,6-di-

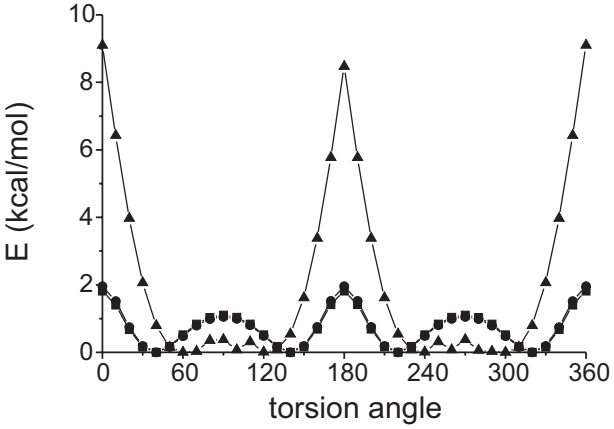


Fig. 2. Rotation energy profiles of phenyl substituents in positions 4 (■), 5 (●) and 6 (▲) of piryd-2(1H)-one ring

arylpyrid-2(1H)-ones **7a**, **7b**, **8a** and **8b** with low 5-HT_{1A} and 5-HT_{2A} receptor affinities. The above described results of *in vitro* studies showed that disubstituted derivatives (**5a**–**8a** and **5b**–**8b**) were characterized by insignificant affinities for both 5-HT_{1A} and 5-HT_{2A} receptors, whereas monosubstituted compounds (**3a**, **4a** and **2b**–**4b**) demonstrated a high 5-HT_{1A} and a low 5-HT_{2A} receptor affinity. Thus, a conformational analysis was carried out for monosubstituted pyrid-2(1H)-one fragments. Figure 2 shows rotation barriers for the phenyl substituent in position 4, 5 or 6 of the pyridone ring. As can be perceived, rotation of the substituent in position 6 is limited, and the angle between the planes of aromatic rings ranges from 50 to 130°. In the case of both 4- and 5-phenylpyrid-2(1H)-one systems, the rotation barriers are low and their values are about 2 kcal/mol. These observations and the binding results cited above suggest that despite conformational freedom and a great capacity for adaptation at the 5-HT_{1A} receptor, the aryl substituent in position 4 destabilizes the ligand-5-HT_{1A} receptor complex, yet only in case its distance from the basic N-4 atom in piperazine is adequate (**2a** vs **2b**).

In the following phase of our investigation we concentrated on *in vivo* effects of four selected compounds (**1b**, **2b**, **3b** and **4b**) with the highest affinity for 5-HT_{1A} receptors (K_i up to 40 nM). To determine postsynaptic 5-HT_{1A} agonistic effects of the investigated compounds, their ability to induce LLR in rats and the behavioral syndrome, i.e. FBP and FT, in reserpinized rats was tested [2, 21]. The ability of the studied compounds to inhibit those symptoms produced by 8-OH-DPAT, a well-known 5-HT_{1A} receptor agonist, was regarded as a postsynaptic antagonistic activity. Derivatives **1b** (5–10 mg/kg), **2b** (10–20 mg/kg), **3b** (5–10 mg/kg) and **4b** (10–20 mg/kg) given alone evoked no changes in the behavior of either normal or reserpine-pretreated rats (data not shown). All the tested compounds administered at the same doses inhibited the LLR induced by 8-OH-DPAT in rats; the most effective compound was **1b** which – at the highest dose used – inhibited that effect of 8-OH-DPAT by 81.5% (Tab. 3A). The 8-OH-DPAT-induced FBP and FT in reserpinized rats were dose-dependently attenuated by **1b** (5–10 mg/kg), **2b** (10–20 mg/kg) and **3b** (5–10 mg/kg); the most effective compound, **1b**, at the highest dose used reduced the effects of 8-OH-DPAT by 48% (FBP) and 76% (FT). Derivative **4b** (10–20 mg/kg) attenuated the FT (but not FBP) produced by 8-OH-DPAT (Tab. 3B). The obtained results of behavioral studies indicate that compounds **1b**, **2b**, **3b** and **4b** behave like postsynaptic 5-HT_{1A} receptor antagonists. In those tests, the most effective was compound **1b** with an unsubstituted pyridone ring and tetramethylene spacer, at the same time, the functional activity of its 5-phenyl analog **3b** was only slightly lower. However, their antagonistic activity was less potent than that of WAY 100635, a well-known full 5-HT_{1A} antagonist (Tab. 3A and B). Moreover, none of the tested derivatives, like WAY 100635, produce the effects which would be characteristic of postsynaptic 5-HT_{1A} receptor agonists in the behavioral models used. On the other hand, like 8-OH-DPAT, the investigated compounds **1b** (0.625–5 mg/kg), **2b** (0.625–5 mg/kg), **3b** (1.25–5 mg/kg) and **4b** (2.5–10 mg/kg), induced a dose-dependent decrease in the rectal body temperature in mice. The maximum hypothermic effect induced by those compounds, administered at the highest dose, was –3.3°C (**1b**), –3.1°C (**2b**), –2°C (**3b**) and –2.2°C (**4b**), and was observed 30 min after their injection (data not shown). It had been demonstrated previously that the hypothermia induced by 8-OH-DPAT in mice was mediated by presynaptic 5-HT_{1A} receptors and abolished by 5-HT_{1A} antagonists such as, e.g. WAY 100635 or MP3022 [6, 7, 10, 17]. In contrast to the 8-OH-DPAT-induced hypothermia in mice, the decrease in the body temperature evoked by **1b** (0.625 mg/kg), **2b** (0.625 mg/kg), **3b** (1.25 mg/kg) or **4b** (2.5 mg/kg) was not changed by WAY 100635 (0.1 mg/kg) (data not shown), hence

Table 3. Effect of the tested compounds on the 8-OH-DPAT-induced lower lip retraction (LLR) in rats (A) and on the 8-OH-DPAT--induced behavioral syndrome in reserpinized rats (B)

Compound	Dose mg/kg	Behavioral score, mean ± SEM		
		A: LLR	B: Flat body posture	Forepaw treading
1b	–	2.7 ± 0.2	13.4 ± 0.4	11.8 ± 0.8
	5	1.8 ± 0.2[a]	8.3 ± 1.3[a]	4.3 ± 1.0[b]
	10	0.5 ± 0.1[b]	7.0 ± 1.4[b]	2.8 ± 0.4[b]
2b	–	2.8 ± 0.2	13.6 ± 0.4	13.4 ± 0.8
	10	1.7 ± 0.2[a]	9.0 ± 0.9[a]	11.4 ± 1.0
	20	1.7 ± 0.1[a]	7.2 ± 1.2[b]	8.0 ± 0.5[b]
3b	–	2.7 ± 0.2	13.8 ± 0.7	12.4 ± 0.9
	5	1.3 ± 0.1[b]	10.0 ± 0.3[a]	6.6 ± 0.5[b]
	10	0.7 ± 0.2[b]	6.8 ± 0.8[b]	3.5 ± 0.6[b]
4b	–	2.7 ± 0.2	13.6 ± 0.4	13.4 ± 0.8
	10	2.3 ± 0.2	14.0 ± 0.4	8.7 ± 0.8[b]
	20	1.6 ± 0.2[a]	11.6 ± 1.3	9.2 ± 1.1[a]
WAY 100635	–	2.7 ± 0.2	13.7 ± 0.4	12.0 ± 0.7
	0.1	0.3 ± 0.2[b]	0.8 ± 0.4[b]	1.2 ± 0.7[b]

(A) The tested compounds (*ip*) and WAY 100635 (*sc*) were administered 45 min and 15 min, respectively, before 8-OH-DPAT (1 mg/kg, *sc*); (B) reserpine (1 mg/kg, *sc*) and the tested compounds (*ip*) and WAY 100635 (*sc*) were administered 18 h, 60 and 30 min, respectively, before 8-OH-DPAT (5 mg/kg, *sc*); n = 6 rats per group, [a] $p < 0.05$, [b] $p < 0.01$ vs vehicle

it is probably not connected with the stimulation of presynaptic 5-HT$_{1A}$ receptors. The results of our *in vivo* experiments indicate that the mode of substitution of pyridone (in position 4, 5 or 6) with the phenyl group in the tested tetramethylene arylpiperazines is not significant for their 5-HT$_{1A}$ receptor intrinsic activity, since **2b**–**4b** as well as an unsubstituted **1b** can be regarded as postsynaptic 5-HT$_{1A}$ antagonists.

In conclusion, for compounds with the tetramethylene spacer and one phenyl substituent, the mode of substitution of pyrid-2(1H)-one moiety is not important, since they all are potent 5-HT$_{1A}$ receptor ligands with an antagonistic activity and a high 5-HT$_{2A}$/5-HT$_{1A}$ selectivity. Additionally, it seems that such pyridone modification is not indispensable for the binding at the 5-HT$_{1A}$ receptor site; the unsubstituted derivative **1b** is the most potent and selective 5-HT$_{1A}$ agent. The obtained results also indicate that substitution of the pyridone ring with two aryl substituents is not beneficial for the formation of the ligand-5-HT$_{1A}$ receptor complex, however, in the case of tetramethylene analogs slight improvement of the 5-HT$_{2A}$ receptor affinity is observed. Hence, the present study is an attempt to better explain structure-activity relationships for arylpiperazines with terminal amide fragments.

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