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SYNTHESIS, *IN VITRO* AND *IN VIVO* 5-HT_{1A}/5-HT_{2A} SEROTONIN RECEPTOR ACTIVITY OF NEW HYBRID 1,2,3,4-TETRAHYDRO-γ-CARBOLINES WITH 1-(2-METHOXYPHENYL)PIPERAZINE MOIETY

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Synthesis, in vitro and in vivo 5-HT_{1A}/5-HT_{2A} serotonin receptor activity of new hybrid 1,2,3,4-tetrahydro-γ-carbolines with 1-(2-methoxyphenyl)piperazine moiety. J. BOKSA, S. CHARAKCHIEVA-MINOL, B. DUSZYŃSKA, R. BUGNO, A. KŁODZIŃSKA, E. TATARCZYŃSKA, E. CHOJNACKA-WÓJCIK, A.J. BOJARSKI. Pol. J. Pharmacol., 2003, 55, 1013–1019.

A series of 15 new 2-H- and 2-substituted 5-{ω-[4-(2-methoxyphenyl)-piperazinyl]-alkyl}-1,2,3,4-tetrahydro-γ-carboline derivatives were prepared, and their affinity for 5-HT_{1A} and 5-HT_{2A} serotonin receptors was determined. Most of those hybrid compounds were found to bind with high affinity to 5-HT_{1A} sites (K_i < 50 nM; **2d**, **3a**, **3b**, **3d**, **3e**, **4b**, **4d**, **4e**) and moreover two of them (**4d**, **4e**) were mixed 5-HT_{1A}/5-HT_{2A} ligands. The results of a lower lip retraction test in rats indicated that the 2-acetyl derivative with a dimethylene spacer (**2d**) had features of a postsynaptic 5-HT_{1A} receptor agonist, whereas its analogues with longer chains (**3d** and **4d**) behaved like antagonists. Both 5-HT_{2A} receptor ligands (**4d**, **4e**) at high doses inhibited the (±)-DOI-induced head twitches in mice and were classified as weak antagonists of those receptors.

Key words*: 1,2,3,4-tetrahydro-γ-carbolines, 2-methoxyphenylpiperazines, 5-HT_{1A} ligands, 5-HT_{2A} ligands*

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INTRODUCTION

Compounds containing a carboline ring system belong to a large family of biologically active indoles which are very important to the function of the central nervous system [19]. Of the four classes of carboline derivatives (α, β, γ, and δ), β-carbolines are the most thoroughly investigated due to their wide occurrence in nature (i.e. in plant alkaloids, endogenous human substances) and diversified pharmacological effects [1].

Among the multiple binding sites recognized by β-carboline derivatives, responses resulting directly from their action on the central serotonin (5-HT) system were also reported [15]. In fact, this phenomenon is not unexpected, because of their structural similarity to 5-HT molecule in an indole nucleus common for all tryptamines.

In our laboratory, a number of tetrahydro-β-carbolines (THBCs) were synthesized and evaluated as 5-HT receptor ligands [6, 7, 16]. Some of them demonstrated significant affinity for 5-HT_{1A} and/or 5-HT_{2A} receptors, and B-193 was extensively studied as an antidepressant agent [20, 21].

We currently decided to extend our investigation to a group of tetrahydro-γ-carbolines (THGCs), since they were definitely less extensively explored than β-analogues, and since relatively little is known about their 5-HT binding profile [14]. Indeed, besides 5-HT_{2A} affinity and some examples of 5-HT_3 antagonistic properties detected for γ-carbolines (Alosetron [9]), other types of serotoninergic activity are difficult to find. Only recently some THGCs have been described as 5-HT_{5A} receptor ligands by Glennon's research group [14]. To the best of our knowledge, the binding of γ-carboline derivatives to 5-HT_{1A} receptors has not been reported so far.

MATERIALS and METHODS

CHEMISTRY

The starting 1,2,3,4-tetrahydro-γ-carbolines **1a**, **1b** and **1c** were obtained according to the methods described by Robinson and Thornley [18], Boekelheide and Ainsworth [4] and Buu-Hoi et al. [8], respectively.

Details of preparation of the final products are shown in Figures 1 (compounds **2a**–**e** and **3a**–**e**) and 2 (**4a**–**e**).

The products were purified by a column chromatography (silica gel, $CHCl_3$-CH_3OH, 99:1 and 9:1 mixtures), and their structures were confirmed by ^1H NMR spectroscopy (free bases – supplementary materials). Free bases were converted into fumarate salts with fumaric acid in a hot methanol-acetone solution, and next, ether was added until the solution became turbid. Molecular formulas were established for the salts by an elemental analysis (supplementary materials). The yields, melting points and molecular formulas are given in Table 1.

PHARMACOLOGY

Radioligand binding studies

The affinity of the investigated compounds for 5-HT_{1A} and 5-HT_{2A} receptors *in vitro* was assessed on the basis of their ability to displace [^3H]-8-OH-DPAT (222 Ci/mmol, Amersham, England) and [^3H]-ketanserin (66.4 Ci/mmol, NEN Chemicals, USA), respectively. Radioligand binding experiments were carried out on rat brain using tissues from the hippocampus for 5-HT_{1A} receptors, and from the cortex for 5-HT_{2A} receptors, according to the previously published procedures [5].

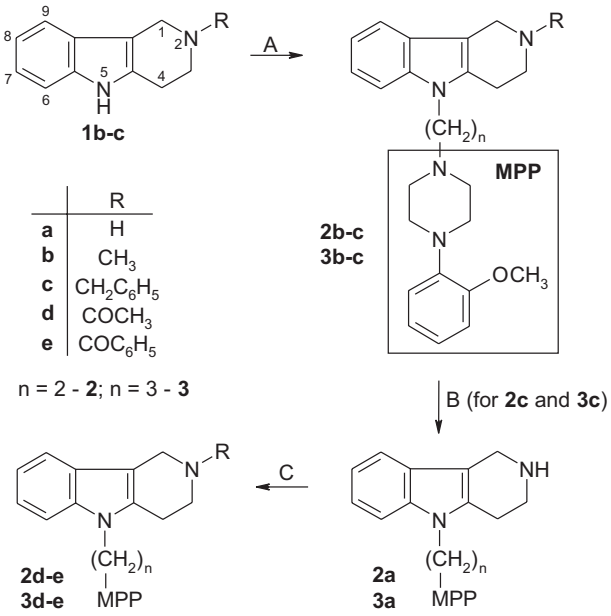

Fig. 1. Synthesis of the investigated of compounds **2a**–**e** and **3a**–**e**. (A)1-[Cl-$(CH_2)_{2\text{-}3}$]-4-(2-methoxyphenyl)piperazine, KF/Al_2O_3, CH_3CN, reflux, 6 h [17]; (B) H_2, 0.3 MPa, 10% Pd/C, MeOH, 50C, 5 h; (C) $(CH_3CO)_2O$ or C_6H_5COCl, 20% Na_2CO_3 aq., $CHCl_3$, stirred, r.t., 3 h

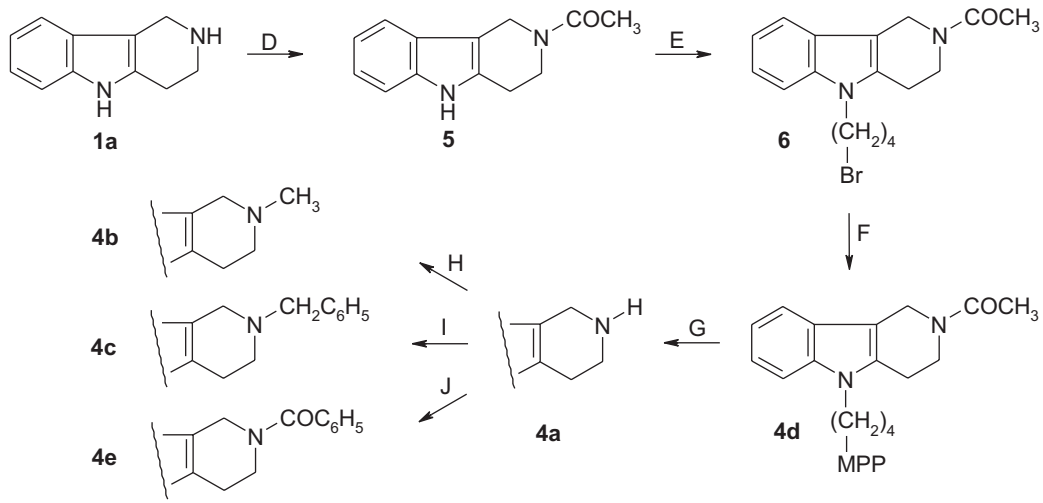

Fig. 2. Synthesis of the investigated of compounds **4a**–**e**. (D) $(CH_3CO)_2$, AcOH, reflux, 1 h [18]; (E) $Br(CH_2)_4Br$, KF/Al_2O_3, CH_3CN, reflux, 5 h; (F) 2-Methoxyphenylpiperazine (H-MPP), K_2CO_3, BuOH, reflux, 8 h; (G) 10% KOH in 80% aq. MeOH, reflux, 2 h; (H) a/ Benzotriazole, $(CH_2O)_n$, C_6H_6, reflux, 1 h; b/ $NaBH_4$, THF, reflux, 1 h [13]; (I) C_6H_5 CH_2Cl, K_2CO_3, EtOH, reflux, 2 h; (J) C_6H_5COCl, 20% Na_2CO_3 aq., $CHCl_3$, stirred, r.t., 3 h

K_i values were determined from at least three competition binding experiments in which 10–14 sample concentrations, run in triplicate, were used. The Cheng and Prusoff [10] equation was used for K_i calculations.

In vivo experiments

The experiments were performed on male Wistar rats (280–310 g) or male Albino Swiss mice (24–28 g). The animals were kept at a room temperature (20 ± 1°C) on a natural day-night cycle (July–September), and were housed under standard laboratory conditions. They had free access to food and tap water before the experiment. Each experimental group consisted of 6–9 animals/dose, and all the animals were used only once. 8-Hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT, Research Biochemical Inc.), *N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl)-cyclohexanecarboxamide trihydrochloride (WAY 100635, synthesized by Dr. J. Boksa, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland) and (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride [(±)-DOI, Research Biochemicals, Inc.] were used as aqueous solutions. Compounds **2d**, **3d**, **3e**, **4d** and **4e** were suspended in a 1% aqueous solution of Tween 80. 8-OH-DPAT and WAY 100635 were injected subcutaneously (*sc*), **2d**, **3d**, **3e**, **4d**, **4e** and (±)-DOI were given intraperitoneally (*ip*) in a volume of 2 ml/kg (rats) or 10 ml/kg (mice). The obtained data were analyzed by a one-way ANOVA, followed by Dunnett's test (when only one drug was given), or by the Newman-Keuls test (when two drugs were administered).

Lower lip retraction (LLR) in rats

The LLR was assessed according to the method described by Berendsen et al. [3]. 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 compounds were administered 45 min before 8-OH-DPAT, and the animals were scored 15, 30 and 45 min after 8-OH-DPAT administration.

Head twitch response in mice

In order to habituate mice to the experimental environment, each animal was randomly transferred to a 12 cm (diameter) × 20 cm (height) glass cage, lined with sawdust, 20 min before treatment. Head twitches of mice were induced by (±)-DOI (2.5 mg/kg). Immediately after the treatment, the number of head twitches was counted during 20 min [11]. The investigated compounds were administered 60 min before (±)-DOI.

Table 1. Physicochemical data, and 5-HT_{1A} and 5-HT_{2A} binding affinities for the tested compounds

Compd	n	R	Yield % (base)	Mp °C (salt)	Molecular formula molecular weight	K_i (nM) ± SEM	
						5-HT_{1A}	5-HT_{2A}
2a	2	a	90.5	182–184	$C_{24}H_{30}N_4OC_4H_4O_4CH_3OH$ 538.6	105 ± 11	4082 ± 90
2b	2	b	42.5	89–91	$C_{25}H_{32}N_4O2C_4H_4O_4CH_3OH$ 668.7	647 ± 20	3857 ± 60
2c	2	c	83.0	106–107	$C_{31}H_{36}N_4O2C_4H_4O_4CH_3OHH_2O$ 762.8	134 ± 21	739 ± 20
2d	2	d	60.0	103–106	$C_{26}H_{32}N_4O_22C_4H_4O_4CH_3OH$ 696.7	33 ± 5	272 ± 30
2e	2	e	95.8	208–210	$C_{31}H_{34}N_4O_22C_4H_4O_4$ 726.8	413 ± 21	1085 ± 60
3a	3	a	44.1	133–135	$C_{25}H_{32}N_4O2C_4H_4O_4CH_3OH0.5H_2O$ 677.7	42 ± 3	1672 ± 45
3b	3	b	93.0	183–185	$C_{26}H_{34}N_4O1.5C_4H_4O_4$ 592.7	36 ± 7	1842 ± 50
3c	3	c	77.5	102–105	$C_{32}H_{40}N_4O2C_4H_4O_4H_2O$ 746.8	64 ± 2	1429 ± 60
3d	3	d	92.5	169–171	$C_{27}H_{34}N_4O_21.75C_4H_4O_4$ 649.7	8.7 ± 0.8	99 ± 10
3e	3	e	94.0	87–89	$C_{32}H_{36}N_4O_22C_4H_4O_4CH_3OHH_2O$ 790.8	8.3 ± 1.1	471 ± 25
4a	4	a	96.0	181–183	$C_{26}H_{34}N_4O1.5C_4H_4O_4$ 592.7	112 ± 11	1378 ± 30
4b	4	b	61.0	103–105	$C_{27}H_{36}N_4O2C_4H_4O_4CH_3OHH_2O$ 714.8	22 ± 4	260 ± 10
4c	4	c	67.5	187–189	$C_{33}H_{40}N_4O2C_4H_4O_4CH_3OHH_2O$ 790.9	75 ± 6	1624 ± 25
4d	4	d	79.5	90–92	$C_{28}H_{36}N_4O_21.25C_4H_4O_4H_2O$ 631.6	40 ± 7	20 ± 3
4e	4	e	94.0	96–98	$C_{33}H_{38}N_4O_22C_4H_4O_4H_2O$ 804.9	34 ± 5	43 ± 8
5	–	d, 5-H	92.0	256–257	$C_{13}H_{14}N_2O$ 214.3		
6	–	d	72.0	oil	raw material was used		

RESULTS and DISCUSSION

New γ-carboline derivatives were designed as hybrid compounds consisting of two biologically active systems. The same strategy had already been successfully applied in our previous investigations, where the fusion of β-carboline and arylpiperazine moieties resulted in several potent 5-HT_{1A} and/or 5-HT_{2A} ligands [7, 16]. Now we combined THGCs with a 2-methoxyphenylpiperazine (MPP) fragment,

Table 2. Induction of lower lip retraction (LLR) by the investigated compounds (A), and their effect on the 8-OH-DPAT-induced LLR (B) in rats

Treatment	Dose mg/kg	Mean ± SEM LLR score	
		A	B
Vehicle	–	0.1 ± 0.1	2.8 ± 0.2
2d	10	1.6 ± 0.1[b]	3.0 ± 0.0
	20	1.7 ± 0.2[b]	NT
3d	10	0 ± 0	1.8 ± 0.2[b]
	20	0.4 ± 0.2	1.4 ± 0.3[b]
Vehicle	–	0.1 ± 0.1	2.8 ± 0.1
3e	10	0 ± 0	2.3 ± 0.3
	20	0 ± 0	2.1 ± 0.2[a]
4d	10	0.2 ± 0.1	1.9 ± 0.2[b]
	20	0.3 ± 0.1	1.3 ± 0.2[b]
Vehicle	–	0.1 ± 0.1	2.9 ± 0.2
4e	10	0 ± 0	2.4 ± 0.2
	20	0 ± 0	2.3 ± 0.2
WAY 100635	0.1	0.1 ± 0.1	0.3 ± 0.2[b]

The investigated compounds (*ip*) and WAY 100635 (*sc*) were administered 15 min before the test (A), or 45 min before 8-OH-DPAT (1 mg/kg, *sc*) (B); n = 6 rats per group; [a] $p < 0.05$, [b] $p < 0.01$ vs. vehicle (A) or vs. vehicle + 8-OH-DPAT (B); NT – not tested

since it is known that this system prefers 5-HT$_{1A}$ binding sites. Both those pharmacophoric groups were linked *via* an alkyl spacer of different length (2–4 units), thus, generally the new compounds can be regarded as long chain arylpiperazines, where a γ-carboline core plays a role of a complex terminal fragment. Additional structural modification was restricted to R substituents at N2 of the THGC moiety (Tab. 1).

All the new compounds were examined *in vitro* for their affinity for 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors. The results presented in Table 1 indicate that most of them are potent 5-HT$_{1A}$ receptors ligands. In fact, 8 derivatives are characterized by the K_i values lower than 50 nM, and only two compounds (**2b**, **2e**) can be regarded as moderate agents (K_i > 400 nM).

Generally, the lowest affinity for 5-HT$_{1A}$ receptors was detected for compounds with a dimethylene spacer (series **2**), with the exception of acetyl derivative **2d** (K_i = 33 nM).

The spacer elongation by one methylene unit resulted in a significant increase in the observed *in vitro* activity. The derivatives of series **3** were indeed very potent 5-HT$_{1A}$ receptor ligands, the most active ones being **3d** and **3e** (K_i = 8.7 and 8.3 nM, respectively). It is worth to note that in the case of the previously studied β-carboline analogues, the most *in vitro* active 5-HT$_{1A}$ ligands were found among butylene chain analogues [7].

It seems that apart from derivative **2e**, the introduction of acyl groups which reduced the basicity of the N2 nitrogen atom had a positive effect on the compound binding ability to 5-HT$_{1A}$ receptors. On the other hand, the investigated THGCs were significantly less active at 5-HT$_{2A}$ sites, except for **4d** and **4e** (K_i = 20 and 43 nM, respectively). Moreover, those two compounds were at the same time potent 5-HT$_{1A}$ agents, and interestingly, such dual ligands were previously found also in the group of n-butyl-β-carboline derivatives of MPP only.

Some compounds with high 5-HT$_{1A}$ (**2d**, **3d**, **4d** – with an acetyl; **3e**, **4e** with a benzoyl substituent) and 5-HT$_{2A}$ (**4d**, **4e**) receptor affinity were further examined in functional *in vivo* assays. In order to determine a 5-HT$_{1A}$ receptor agonistic effect, compound's ability to induce LLR in rats was tested. The LLR in rats, induced by 8-OH-DPAT, a well known 5-HT$_{1A}$ receptor agonist, depended on stimulation of 5-HT$_{1A}$ receptors located postsynaptically [2].

The ability of the studied compounds to inhibit that symptom produced by 8-OH-DPAT was regarded as postsynaptic 5-HT$_{1A}$ receptor antagonistic activity. The capacity of the tested compounds to reduce head twitches in mice, observed after administration of (±)-DOI, a 5-HT$_{2A}$ receptor agonist [11], was used to evaluate 5-HT$_{2A}$ receptor antagonistic properties.

In the animal model used, the investigated compounds presented a diversified 5-HT$_{1A}$ functional activity (Tab. 2). Of all the tested ligands, only derivative **2d** with a dimethylene spacer behaved like a postsynaptic 5-HT$_{1A}$ receptor agonist. Indeed, when given at high doses (10–20 mg/kg), it induced LLR in rats, however, the intensity of that effect did not reach maximum possible scores. On the contrary, the analogs of **2d** with tri- (**3d**) or tetramethylene (**4d**) spacer used at doses of 10–20 mg/kg, presented features of postsynaptic 5-HT$_{1A}$ receptor an-

tagonists. Those compounds at doses of 10–20 mg/kg inhibited the LLR induced by 8-OH-DPAT in rats. On the other hand, both the benzoyl derivatives (**3e** and **4e**) were practically inactive in the LLR test; only at a dose of 20 mg/kg, they very slightly attenuated the 8-OH-DPAT-induced LLR in rats. At the same time, WAY 100635 (0.1 mg/kg), used as a standard 5-HT_{1A} receptor antagonist [12], completely blocked that effect of 8-OH-DPAT.

At high doses, compounds **4d** and **4e** inhibited the (±)-DOI-induced head twitches in mice (ED_{50} = 11 (7.9–15.4) and 15 (11.1–20.3) mg/kg, respectively), whereas the reference 5-HT_{2A} receptor antagonist ketanserin blocked that effect at significantly lower doses (ED_{50} = 0.12 (0.07–0.20) mg/kg). Therefore, compounds **4d** and **4e** may by regarded as weak 5-HT_{2A} receptor antagonists.

In summary, we present the synthesis of 15 new THGC-MPP hybrids and *in vitro*/*in vivo* evaluation of their activity at 5-HT_{1A} and 5-HT_{2A} receptors. Most of them displayed a high 5-HT_{1A} receptor affinity, and two (**4d** and **4e**) were mixed 5-HT_{1A}/5-HT_{2A} ligands. It is worth to note that such a profile of the serotonin activity of γ-carboline derivatives is reported for the first time. The results of *in vivo* experiments indicate that in the case of 2-acetyl-THGC derivatives (series **d**) the length of the spacer influences functional profile; compound **2d** shows features of a postsynaptic 5-HT_{1A} receptor agonist, whereas its analogues with longer linkers (**3d** and **4d**) behave like antagonists. Despite the high 5-HT_{1A} affinity of the investigated ligands, their *in vivo* potency was relatively weak, thus, further structural optimization is necessary to obtain more active agents.

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