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The Derivatives of Imidazo[1,2-*a*]Benzimidazole as 5-HT_{2A} Receptor Antagonists

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Abstract—We studied in vitro the 5-HT_{2A} antagonistic activity of 16 imidazo[1,2-*a*]benzimidazole derivatives. Using the radioligand method we showed the binding of 9-(2-diethylaminoethyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]benzimidazol dinitrate to the 2A subtype serotonin receptor.

Keywords: imidazo[1,2-a]benzimidazoles, 5-HT_{2A} receptor, 5-HT_{2A} antagonist
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INTRODUCTION

The serotonin 5-HT_{2A} receptor has been studied as a macromolecular target for drug products rather well. Its ligands are compounds of different chemical classes. Particularly, most of its agonists comprise one of the following basic structures: tryptamine, ergoline, or phentolamine [1]. The structural analysis of antagonists of the 2A subtype serotonin receptor is more interesting. In some publications a typical 5-HT_{2A} antagonist was treated as a chemical structure with two aryl rings and a positively charged nitrogen atom [2, 3], the nitrogen atom and its charge being considered critical for the strategy of ligand-receptor binding [4]. Similarly to other monoaminergic G protein-coupled receptors, the spiral pocket of the 5-HT_{2A} receptor intended for the ligand binding contains an aspartate residue (Asp155), which forms a salt bridge with a ligand amino group [2, 6]. A serine residue (Ser159), which ligands bind to [3], is adjacent to the aspartic acid in the transmembrane domain (TM) III.

Probably, TM III is not the single domain for bonding with antagonists, but it is accepted to be the most important of the seven transmembrane segments [5]. This statement follows from the hypothesis that the serotonin 5-HT_{2A} receptor has two major sites of binding to serotonin-blocking compounds: the A site engages amino acids of TM domains III, IV, V, and VI, whereas site B, amino acids of TM domains I, II, III, and VII [2]. This is TM domain III that is shared by both sites.

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The known antagonists vary in their affinity toward the above mentioned binding sites: the binding to either both sites, for example, for ketanserin, or one site (the A site) for cyproheptadine [2]. Therefore, the A binding site is of special interest. Particularly, the involvement of phenylalanine residues at positions 339 and 340 linked to aryl rings by the π–π type interactions [6, 7], asparagine residue (Asn343) [5], serine 239 and 242 [8–10], and threonine (Thr160) [6] was found in the process of binding. Due to the variety of amino acid residues involved in the ligand binding, the current views on the chemical structure of blockers of subtype 2A serotonin receptor are also manifold. Particularly, the potential 5-HT_{2A} antagonists belong to various chemical classes: quinazolines, indoles, thiazolpyrimidines, imidazolidines, olanzapines, and others (Fig. 1). Also, there are many records implying the potential of benzimidazole derivatives as 2A serotonin blockers [11–14]. With this in mind, it seems rational to search for and develop new compounds with the high 5-HT_{2A} antagonistic activity among benzimidazole derivatives.

RESULTS AND DISCUSSION

In this work we synthesized two new derivatives of N^9,C^2-disubstituted imidazo[1,2-*a*]benzimidazole (**IV**) and (**V**) bearing an acceptor nitrile group. The synthesis of these compounds included the reaction of 1-substituted 2-aminobenzimidazoles (**Ia, b**) with 4-cyanophenacyl bromide followed by the cyclization of intermediate 1-substituted 3-(4-cyano)phenacyl-2-aminobenzimidazolium bromides (**II**), (**III**) to give 9-R-2-(4-cyanophenyl)imidazo[1,2-*a*]benzimidazoles

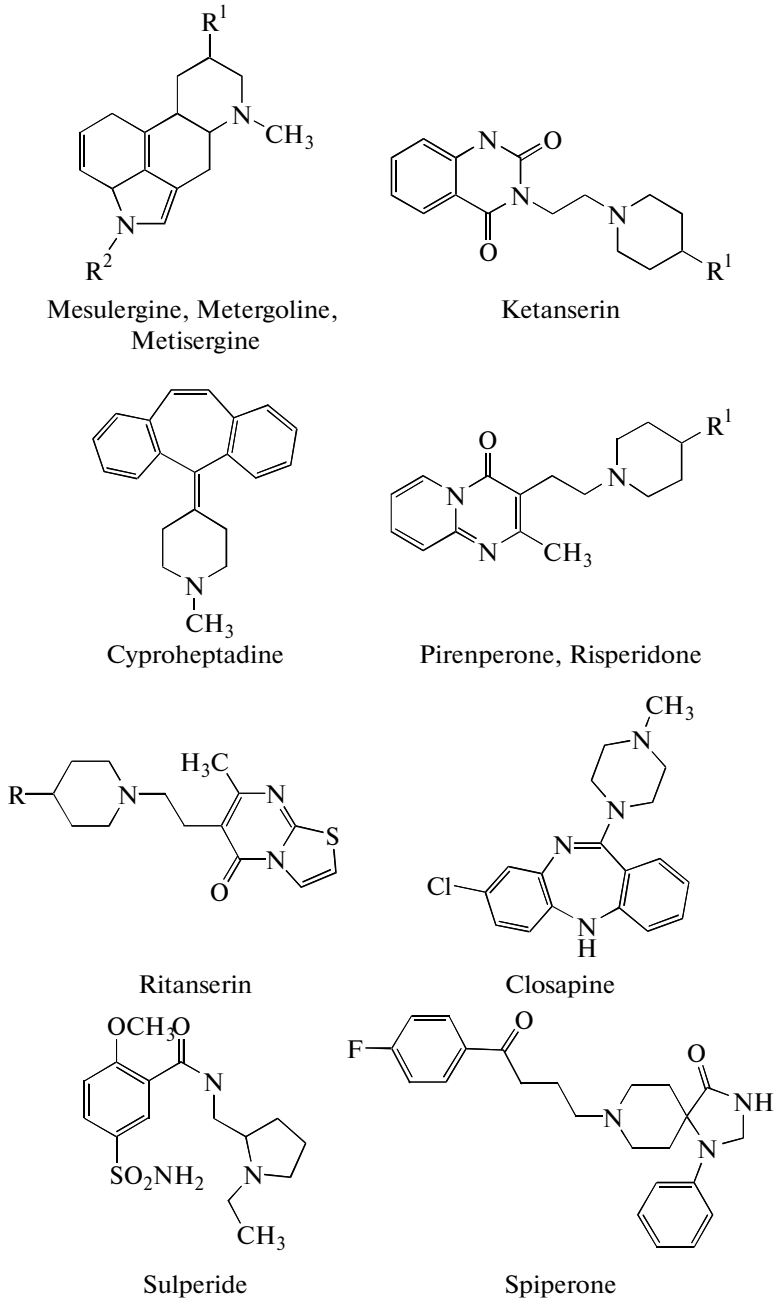


Fig. 1. Chemical structures of 5-HT_{2A} receptor antagonists.

(**IV**), (**V**). The structures of the synthesized compounds were proved by IR and ^{1}H NMR spectra as well as by element analysis.

In the IR spectra of salts (**II**) and (**III**) the absorption bands of the carbonyl group at 1698 cm^{-1} for (**II**) and 1697 cm^{-1} for (**III**) were observed as well as two bands of valent oscillations of the primary amino group in the range of 3158–3208 cm^{-1}, which supported the crystal state of these compounds in the form of 2-aminobenzimidazolium salts. In the ^{1}H NMR spectra of these salts two proton singlets (δ 5.98–5.99 ppm) were observed, which corresponded to the absorption of methylene protons of aroylmethyl radicals. The resonances of amino group protons (2H) were very weak, probably, due to the significant widening of the signals. The resonances of the amino group protons of the previously synthesized compounds were at 8.95–9.54 ppm [15, 16]. These resonances were absent in the spectra of tricyclic compounds (**IV**) and (**V**).

The 5-HT_{2A} antagonistic activity was studied for the new compounds (**IV**) and (**V**) and 14 previously synthesized compounds (**VI**)–(**XIX**) [16, 17, 19–24]. According to the type of the N9 substituent of the tricyclic system, compounds (**IV**)–(**XIX**) were divided

into two groups, namely, diethylaminoethyl- and piperidinoethyl-containing compounds (Table 1).

The imidazo[1,2-*a*]benzimidazole derivatives substituted at N^9 and C2 positions demonstrated different levels of the 5-HT_{2A} antagonistic activity. Five of 16 compounds could block the serotonin response by 40.3–84.9% (**VI**), (**VII**), (**VIII**), (**XII**), (**XVIII**). Two compounds, (9-(2-diethylaminoethyl)- and 9-(2-piperidinoethyl)-2-methylimidazo[1,2-*a*]benzimidazoles) (**IX**, **XV**) did not significantly affect the serotonin activity, unreliably inhibiting it by 4.5 ± 7.33 and 12.8 ± 6.00 Δ% respectively.

Using the serotonin-induced platelet activation we found that the compounds with R = $(CH_2)_2NEt_2$ (**IV**), (**VI**)–(**XII**) were somewhat more active than those with R = $(CH_2)_2C_5H_{10}$ (**V**), (**XIII**)–(**XIX**). In the piperidinoethyl series compound (**XVIII**) demonstrated the highest efficacy by decreasing the serotonin-induced platelet activation (Δ) by 43.5 ± 2.97% while yielding significantly ketanserin. Other derivatives of 9-(2-piperidinoethyl)imidazo[1,2-*a*]benzimidazole showed moderate (26.2 to 37.1 Δ%) to low 5-HT_{2A} antagonistic activity.

Compounds (**VII**), (**VIII**), and (**XII**) containing a diethylaminoethyl group at position 9 displayed a noticeable serotonin-blocking effect decreasing the serotonin-induced activation by 64.0–84.9 Δ%. For the tricyclic compounds bearing an aromatic residue (a phenyl fragment) at position 2 a higher activity was found. The most powerful effect (-84.9 ± 4.44 Δ%) was observed for compound (**VIII**), which contains a 4-methoxyphenyl group at position 2 [17], the obtained values 1.6-fold exceeding the cyproheptadine activity. The introduction of a hydroxyl group in the phenyl radical of compounds (**X**), (**XVI**), (**XVII**), and (**XIX**) did not result in marked antagonistic effects.

For 2-cyanophenyl substituted 9-alkylaminoethylimidazo[1,2-*a*]benzimidazoles (**IV**) and (**V**) the 5-HT_{2A} antagonistic activity was lower than that of the compounds with donor substituents in the phenyl ring (-15.0 ± 6.77 and -9.5 ± 2.03 Δ%).

We studied the antiserotonin effect within a high dose range for the most active compounds (**VII**) and (**VIII**). The IC_{50} value for compound (**VIII**) was 38 nmol/L, which was similar to the ketanserin activity (Table 2).

With the goal of additional confirmation of the capacity of the most active compound (**VIII**) to specific binding to 5-HT_{2A} receptor we also studied its activity toward type 2 serotonin receptors using the radioligand approach (Fig. 2).

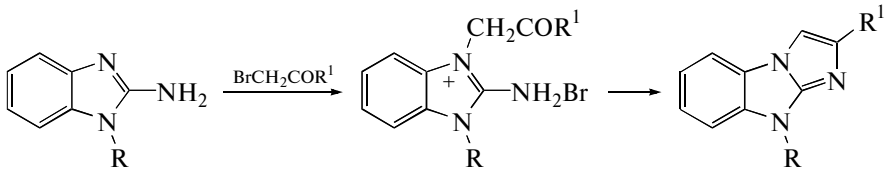
The curve of displacement by compound (**VIII**) of ketanserin, a 5-HT_{2A} receptor antagonist, supported the concurrent with ketanserin interaction with 2A subtype serotonin receptors. The IC_{50} value for compound (**VIII**) in this experiments was close to that of the reference spiperone (IC_{50} 6.98 μM) [18].

On the basis of the results obtained we can claim that blocking properties of N^9-imidazobenzimidazole derivatives toward 5-HT_{2A} receptors are more pronounced for the compounds bearing a diethylaminoethyl group.

To summarize, we studied the 5-HT_{2A} antagonistic activity of two groups of N^9-substituted imidazo[1,2-*a*]benzimidazole derivatives. We found that the compounds bearing a diethylaminoethyl group at position 9 demonstrated the more pronounced serotonin-blocking activity. Compound (**VIII**) was shown to display a high 5-HT_{2A} blocking effect exceeding the activity of reference cyproheptadine and ketanserin.

EXPERIMENTAL

The initial 1-dialkylaminoalkyl-2-aminobenzimidazoles (**Ia, b**) were synthesized from 2-aminobenzimidazole and the corresponding dialkylaminoalkyl chloride hydrochlorides in 42% NaOH–acetone mixture [19]. 2-Aminobenzimidazole was obtained by alkaline hydrolysis of crude methyl *N*-benzimidazolyl-2-carbamate (BMC) used in the synthesis of the fungicide Benomyl [20]. 4-Cyanophenacyl bromide is a commercial reagent of Alfa Aesar company (Great Britain). The synthesis and physicochemical characteristics of the previously synthesized (**VI**)–(**XIX**) were described in [15–17, 19–24].

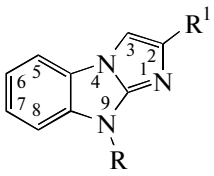


(**Ia, b**) (**II**), (**III**) (**IV**), (**V**)

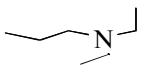
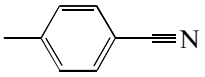
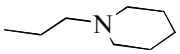
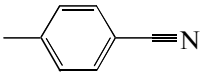
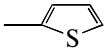
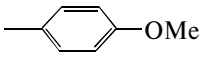
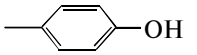
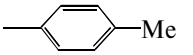
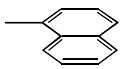
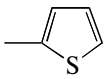
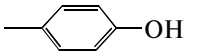
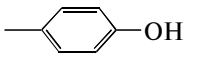
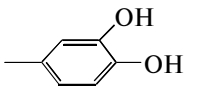
(**Ia**), (**II**), (**IV**): R = $CH_2CH_2N(C_2H_5)_2$: (**Ib**), (**III**), (**V**): R = $CH_2CH_2N(CH_2)_5$;
(**II**)–(**V**) R^1 = 4-CNC_6H_4

Scheme. 1. The scheme of synthesis of 2-phenylimidazo[1,2-*a*]benzimidazole.

Table 1. The structure and 5-HT_{2A}-antagonistic activity of new benzimidazole derivatives (at 1 μM concentration)



*n*HX

Compound	R	R^1	*n*HX	5-HT_{2A}-antagonistic activity, Δ% ($M \pm m$)
(IV)			2HCl	−15.0 ± 6.77 *×
(V)			HCl	−9.5 ± 2.03• *×
(VI)		−C(Me)$_3$	2HCl	−47.4 ± 7.21•*
(VII)			2HCl	−72.7 ± 6.42•×
(VIII)			$2HNO_3$	−84.9 ± 4.44•×
(IX)		−Me	2HCl	−4.5 ± 7.33*×
(X)			2HBr	−26.5 ± 8.27•*×
(XI)			2HCl	−35.6 ± 6.12•*
(XII)			2HI	−64.0 ± 8.1•
(XIII)		−C(Me)$_3$	$2HNO_3$	−26.2 ± 1.83•*×
(XIV)			2HCl	−36.1 ± 6.04•*×
(XV)		−Me	2HCl	−12.8 ± 6.00*×
(XVI)			HI	−37.1 ± 10.38•*
(XVII)			$2HNO_3$	−34.9 ± 5.89•*×
(XVIII)		−Ph	2HCl	−43.5 ± 2.97•*
(XIX)			2HBr + H_2O	−33.8 ± 4.09•*×
Ketanserin				−77.3 ± 4.14•×
Cyproheptadine				−51.3 ± 2.50•*

Δ%—Variation relative to the serotonin-induced activation.

•—Statistically significant relative to the control, the Mann–Whitney test ($p < 0.05$).

*—Statistically significant relative to ketanserin, the Mann–Whitney test ($p < 0.05$).

×—Statistically significant relative to cyproheptadine, the Mann–Whitney test ($p < 0.05$).

Table 2. IC_{50} values of compounds (**VII**) and (**VIII**) and reference ketanserin and cyproheptadine in the serotonin-induced platelet activation assay

Compound	IC_{50} (SD*), M
9-(2-Diethylaminoethyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]benzimidazole dinitrate (**VIII**)	3.8×10^{-8} (8.2×10^{-9}–1.9×10^{-7})
9-(2-Diethylaminoethyl)-2-(thienyl-2) imidazo[1,2-*a*]benzimidazole dihydrochloride (**VII**)	1.5×10^{-7} (2.3×10^{-9}–1.0×10^{-5})
Ketanserin	4.3×10^{-8} (6.7×10^{-9}–4.1×10^{-7})
Cyproheptadine	4.1×10^{-7} (5.0×10^{-8}–8.8×10^{-7})

*SD—standard deviation.

The reaction (see Scheme 1) monitoring and homogeneity of the compounds synthesized were performed by TLC on Al_2O_3 plates eluting with chloroform (detection with iodine vapors in a wet chamber). IR spectra were registered on a Varian Excalibur 3100 FT-IR spectrometer. ^{1}H NMR spectra (δ, ppm) were registered on a Varian Unity-300 spectrometer (300 MHz) for compounds (**II**)–(**V**) in DMSO-d_6; residual protons of deuterated solvents were used as the internal standard. Melting points were measured on a Fisher-Johns Melting Point Apparatus (Fisher Scientific).

2-Amino-1-dialkylaminoethyl-3-[2-(4-cyanophenyl)-2-oxoethyl]benzimidazolium bromides (II, III). 4-Cyanophenacyl bromide (5 mmol) was added to a solution of amine (**Ia, b**) (5 mmol) in acetone (50 mL for (**Ia**) and 85 mL for (**Ib**)). Target bromides (**II**) and (**III**) rapidly precipitated. The reaction mixture was kept at room temperature for 3 h and the precipitate was filtered off, washed with acetone, dried in air, and used in the cyclization without further purification.

2-Amino-1-diethylaminoethyl-3-[2-(4-cyanophenyl)-2-oxoethyl]benzimidazolium bromide (II). The yield 91.2%; mp 162°C. IR, ν_{max}, cm^{-1}: 3208, 3173 (NH_2), 2232 (CN),1698 (C=O), 1664 (C=N), 1602, 1525, 1485 (C=C). Found: C 57.90; H 5.72; Br 17.43; N 15.27%; $C_{22}H_{26}BrN_5O$. Calc.: C 57.94; H 5.70; Br 17.52; N 15.34%. ^{1}H NMR: 8.13–8.25 (m, 4H, H_{Ar}), 7.27–7.63 (m, 4H, H_{Ar}), 5.98 (s, 2H,CH_2), 4.29 (s, 2H, CH_2), 3.34 (br s, 4H, $2CH_2$), 2.74 (s, 2H, CH_2), 0.81 (t, 6H, 2Me).

2-Amino-1-(2-piperidinoethyl)-3-[2-(4-cyanophenyl)-2-oxoethyl]benzimidazolium bromide (III). The yield 94.9%; mp 185°C. IR, ν_{max}, cm^{-1}: 3201, 3158 (NH_2), 2230 (CN), 1697 (C=O), 1667 (C=N), 1604, 1524, 1487 (C=C). Found: C 59.00; H 5.61; Br 16.99; N 14.94. $C_{23}H_{26}Br\,N_5O$. Calc.: C 59.01; H 5.59; Br 17.06, N 14.95%. ^{1}H NMR: 8.13–8.26 (m, 4H, H_{Ar}), 7.28–7.64(m, 4H, H_{Ar}), 5.99 (s, 2H,CH_2), 4.31 (s, 2H, CH_2), 3.37(br s, 4H, $2CH_2$), 2.67(br s, 4H,CH_2NCH_2), 1.43(br s, 6H, $3CH_2$).

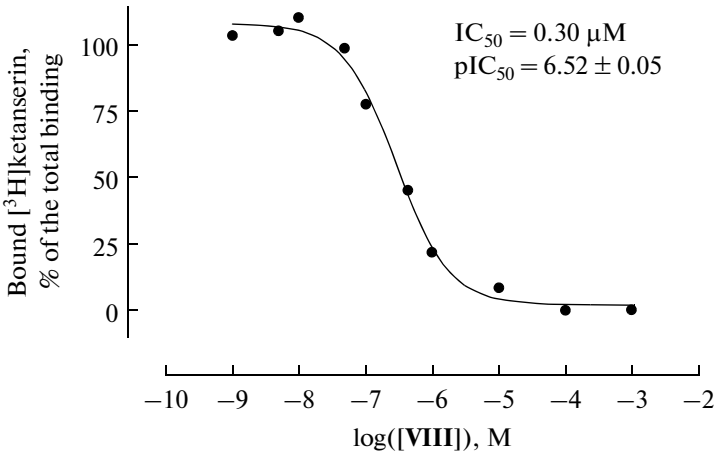


Fig. 2. Binding parameters of 1-(diethylaminoethyl)-2-(4-methoxyphenyl)imidazo[1,2-*a*]benzimidazole dinitrate (**VIII**) with 5-HT_{2A} receptors of rat frontal cerebral hemisphere.

Salts of 9-(2-dialkylaminoethyl)-2-(4-cyanophenyl)imidazo[1,2-*a*]benzimidazoles (IV), (V). Benzimidazolium bromide (3.2 mmol) was refluxed in water (35 mL for (**II**)) or aqueous ethanol (60 mL for (**III**)) until the reaction completion (1.5–3 h). Bromide (**II**) was completely dissolved, whereas compound (**III**) was refluxed as a suspension. The solution was cooled, and the precipitated hydrobromides were filtered off and dried in air to give 93.3 and 97.5% of (**IV**) and (**V**), respectively. The salts were treated with 22% ammonium hydroxide to pH 8.0, and the bases were extracted with chloroform. The extract was concentrated to a minimal volume and purified by column chromatography on Al_2O_3. The solvent was evaporated and the bases (**IV**) and (**V**) were crystallized from acetonitrile. Hydrochlorides of (**IV**) and (**V**) were obtained by the treatment of the tricyclic bases in acetone with HCl-saturated isopropanol.

9-(2-Diethylaminoethyl)-2-(4-cyanophenyl)imidazo[1,2-*a*]benzimidazole dihydrochloride (IV · 2HCl). mp 254–255°C. IR, ν_{max}, cm^{-1}: 2223 (CN), 1664, 1611 (C=N), 1554–1473 (C=C). Found: C 61.36; H 5.91; Cl 16.47; N 16.23%; $C_{22}H_{25}Cl_2N_5$. Calc.: C 61.38; H 5.85; Cl 16.50; N 16.27%. ^{1}H NMR: 11.2 (br s, 2H, 2HCl), 8.65 (s, 1H, H3?), 8.1 (d, 2H, H_{Ar}), 7.89 (t, 4H, H_{Ar}), 7.46–7.35 (dt, 2H, H_{Ar}), 4.82 (s, 2H, N-CH_2), 3.66 (s, 2H, CH_2N), 3.3 (br s, 2H, 4H, $2CH_2$), 1,25 (t, 6H, 2Me).

9-(2-Piperidinoethyl)-2-(4-cyanophenyl)imidazo-[1,2-*a*]benzimidazole hydrochloride (V · HCl). mp 298–299°C. IR, ν_{max}, cm^{-1}: 2219 (CN), 1684, 1610 (C=N), 1580–1473 (C=C). Found: C 68.02; H 6.00; Cl 8.70; N 17.21%. $C_{22}H_{24}ClN_5$. C 68.06; H 5.96; Cl 8.73; N 17.25%. ^{1}H NMR: 10.2 (br s, 1H, HCl), 8.62 (s, 1H, H3), 8.08 (d, 2H, H_{Ar}), 8.05–7.82 (m, 4H, H_{Ar}), 7.45–7.34 (dt, 2H, H_{Ar}), 4.82 (s, 2H, N-CH_2), 3.60 (s, 4H, $\underline{CH_2}(CH_2)_5$), 3.05 (br s, 2H, 4H, CH_2NCH_2), 1.73 (br s, 6H, 3 · CH_2).

The 5-HT_{2A}-blocking activity assay. The antagonistic activity toward 2A subtype serotonin receptors was studied on the in vitro platelet activation model as described in [25]. The platelet-enriched plasma was obtained by centrifugation of blood taken from auricular veins of rabbit males. The platelet number was standardized relative to the optical transmission in the cuvette. The small-angle optical transmission was registered on a Laska-1K device (Lumeks, St. Petersburg). The activation of native 5-HT_{2A} receptors localized on the platelet surface was induced with 1 μM serotonin hydrochloride (Sigma, United States). At the initial stages of the search all the compounds were studied at a concentration of 1 μM. The lead compounds were studied in a wide concentration range followed by calculations of IC_{50} values. 5-HT_{2A}-antagonists, ketanserin tartrate, cyproheptadine (Sigma, United States), and spiperon (Tocris Bioscience), were used as reference compounds.

For the most active compounds the capacity to bind to the 5-HT_{2A}-receptors was confirmed by the radioligand analysis [26] using the tritium-labeled ketanserin with the specific activity of 72 Ci/mmol (Perkin-Elmer).

The study was performed on the membranes isolated from the tissues of cerebral hemisphere frontal area of Wistar rats. The compounds were studied in the range of 1 nM to 1 mM. The radioactivity of the samples was measured on a liquid scintillation TriCarb 2900TR counter (Perkin-Elmer) with the counting efficacy of 42–46%. The results were analyzed using the GraphPad Prism 4 Demo and Statistica 6.0 programs.

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