Evaluation of 1-Arylpiperazine Derivative of Hydroxybenzamides as 5-HT_{1A} and 5-HT_7 Serotonin Receptor Ligands: An Experimental and Molecular Modeling Approach

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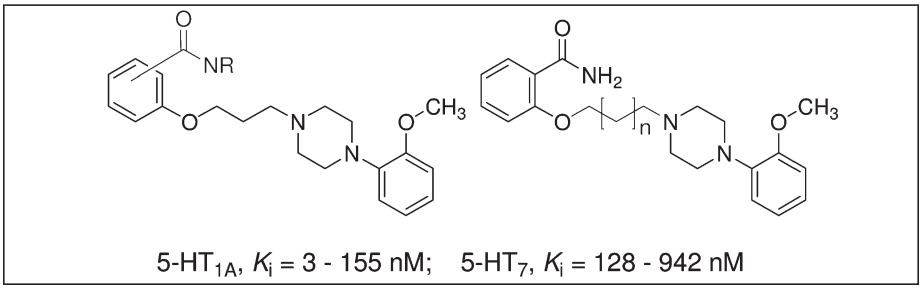

The synthesis and evaluation as 5-HT_{1A} and 5-HT_7 serotonin receptor ligands of the two sets of *O*-substituted hydroxybenzamides, structurally related to 2-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy}benzamide (**1**), (K_i 5-HT_{1A} = 21 nM, 5-HT_7 = 234 nM) are reported. To affect the affinity for 5-HT_{1A} and 5-HT_7 receptors, an amide moiety (**2–6**) and a hydrocarbon chain length (**7–10**) were modified. The serotonergic activity of compounds **2–10** was generally higher in the case of 5-HT_{1A} receptors compared with 5-HT_7 ones; the most active 5-HT_{1A} ligands being *meta*-isomer **2** (K_i = 7 nM) and both analogs of **1** with the longest spacer, i.e., penta- and hexa-methylene derivatives **9** and **10** (K_i = 4 and 3 nM, respectively). The observed biological properties of compounds **1–10** were elucidated using molecular modeling procedures.

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INTRODUCTION

Arylpiperazines are among the most commonly used pharmacophore moieties of serotonergic ligands. Studies of the relationship between structure and affinity within long-chain arylpiperazines, investigated as serotonin 5-HT_{1A} and 5-HT_7 receptor ligands, revealed the important role of terminal fragments and a chain bridge [1–4]. As an aryl group attached to the nitrogen atom of piperazine, a substituted phenyl or a heteroaromatic system is used. The other terminus very often contains an amide or has an imide function, but it may be a phenyl or another aromatic group as well. In many series of arylpiperazine ligands, the alkyl chain consists of two to four methylene units; however, groups other than methylene ones, i.e., heteroatoms, carbonyl, an amide fragment, or multiple bonds have also been introduced to the spacer [5,6]. Therefore, investigations within active compounds consist in structural modifications of all the ligand fragments.

In our recent study on 1-arylpiperazine derivatives of *N*-substituted 1,3-benzoxazine-2,4-dione as well as *O*- and *N*-substituted salicylamides with an *n*-propyl alkyl chain, the effect of cyclic and acyclic salicylamide moieties on their binding affinity for the serotonin receptor has been explored [7]. As a result, 2-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy}benzamide (**1**) was found to be most active 5-HT_{1A} receptor ligand (K_i = 21 nM) with a moderate affinity for 5-HT_7 sites (K_i = 234 nM; Fig. 1).

In this article, we present the synthesis and serotonergic activity of 1-(2-methoxyphenyl)piperazines structurally related to **1** (Fig. 2; Scheme 1). Current modifications are concentrated on terminal amide moiety (**2–6**) and the length of the hydrocarbon chain (**7–10**).

RESULTS AND DISCUSSION

Chemistry. Starting hydroxybenzamides **11**, **13**, and **16** were commercial products. *m*-Hydroxybenzamide **12**

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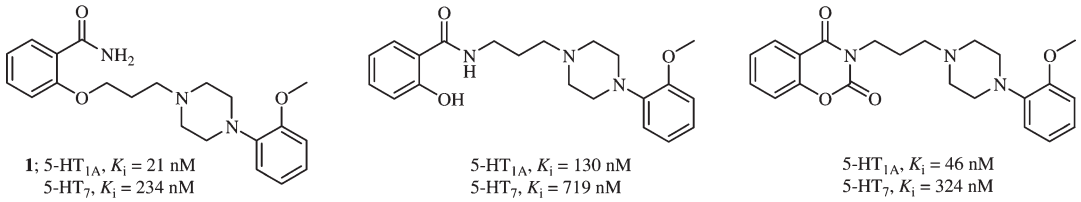


Figure 1. The binding affinities of [4-(2-methoxyphenyl)piperazin-1-yl]propyl derivatives of salicylamides for 5-HT$_{1A}$ and 5-HT$_7$ receptor sites [7].

was obtained from *m*-aminobezoic acid [8], salicylamide **14** was yielded by a hydrolysis of *N*-methyl-1,3-benzoxazine-2,4-dione [9], whereas **15** was prepared from methyl salicylate [10].

ω-Bromoalkyl intermediates **17–26** were obtained by *O*-alkylation of hydroxybenzamides **11–16** with the appropriate 1,ω-dibromoalkanes in the presence of K_2CO_3, using DMF as a solvent and TBAB (tetrabutylammonium bromide) as a catalyst; to prevent formation of disubstituted products, three equivalents of dibromoalkanes were used. The reaction yields and physicochemical properties of **17–26** are given in Table 1.

The designed hydroxybenzamide derivatives **1–10** were synthesized by nucleophilic substitution of bromine atom in **17–26** with 1-(2-methoxyphenyl)piperazine. Compounds **1–10** were isolated as free bases from the reaction mixtures; for biological experiments, they were converted into hydrochloride salts with ethanol saturated with HCl and their molecular formulae and molecular weights were established on the basis of an elemental analysis. The physicochemical properties and binding affinities for 5-HT$_{1A}$ and 5-HT$_7$ receptors of compounds **1–10** are shown in Table 2.

The structure of the obtained compounds was confirmed by ^{1}H-NMR, IR, and MS spectral data, and in some cases by comparing their physical properties to those described in the literature.

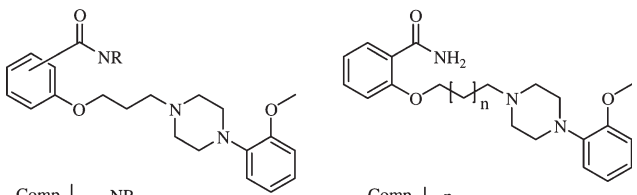
Biology. Experiments on the activity of serotonin receptors indicated (Table 2) that except for the derivative with the shortest spacer (**7**, K_i = 155 nM), the remainder showed high 5-HT$_{1A}$ receptor affinity (K_i = 3–50 nM) comparable to that of parent compound **1**. Of the unsubstituted amide derivatives (**1–3**), the *meta*-isomer **2** (K_i = 7 nM) displayed 5-HT$_{1A}$ affinity threefold and sixfold higher than did its *ortho* (**1**) and *para* (**3**) analogs, respectively. Amide substitution with a methyl or a phenyl group had practically no effect on 5-HT$_{1A}$ binding (**1** vs. **4** and **6**); however, a slight decrease was observed for piperidynyl derivative **5** (K_i = 50 nM). Spacer modifications had a more significant effect on 5-HT$_{1A}$ activity, since its shortening caused a fair decrease (**1**, K_i = 21 nM vs. **7**, K_i = 155 nM), whereas its elongation up to five or six methylene units resulted in a marked increase in affinity (K_i = 4 and 3 nM for **9** and **10**, respectively).

Regarding 5-HT$_7$ receptors, the new compounds demonstrated a moderate affinity (K_i = 128–942 nM), which was always lower than that for 5-HT$_{1A}$ sites; in consequence, the three most active 5-HT$_{1A}$ ligands (**2**, **9**, and **10**) showed a significant selectivity for 5-HT$_7$ receptors: $S_{5\text{-HT7/5-HT1A}}$ = 65–69. The highest 5-HT$_7$ receptor affinity was found for the *N*-phenyl derivative **6** (K_i = 128 nM), whereas compound **7** was again the least active in the series.

In conclusion, three new 5-HT$_{1A}$ receptor ligands (**2**, **9**, and **10**) with nanomolar affinity and reasonable selectivity for 5-HT$_7$ receptors were identified.

Molecular modeling. The observed differences in serotonin receptor affinity were elucidated by docking the described compounds to homology models of 5-HT$_{1A}$ and 5-HT$_7$ receptors. All docked ligands were placed within the binding sites of the receptors, on the extracellular side of the heptahelical bundle, and were anchored by charge-reinforced hydrogen bonding at the Asp3.32 (Ballesteros–Weinstein nomenclature) [16].

2-Methoxyphenyl moiety, common for all of the compounds, was found between transmembrane helices 3, 5, and 6, interacting with the aromatic cluster of helix 6, especially Phe6.52. *O*-substituted hydroxybenzamides interacted predominantly with the aminoacids localized

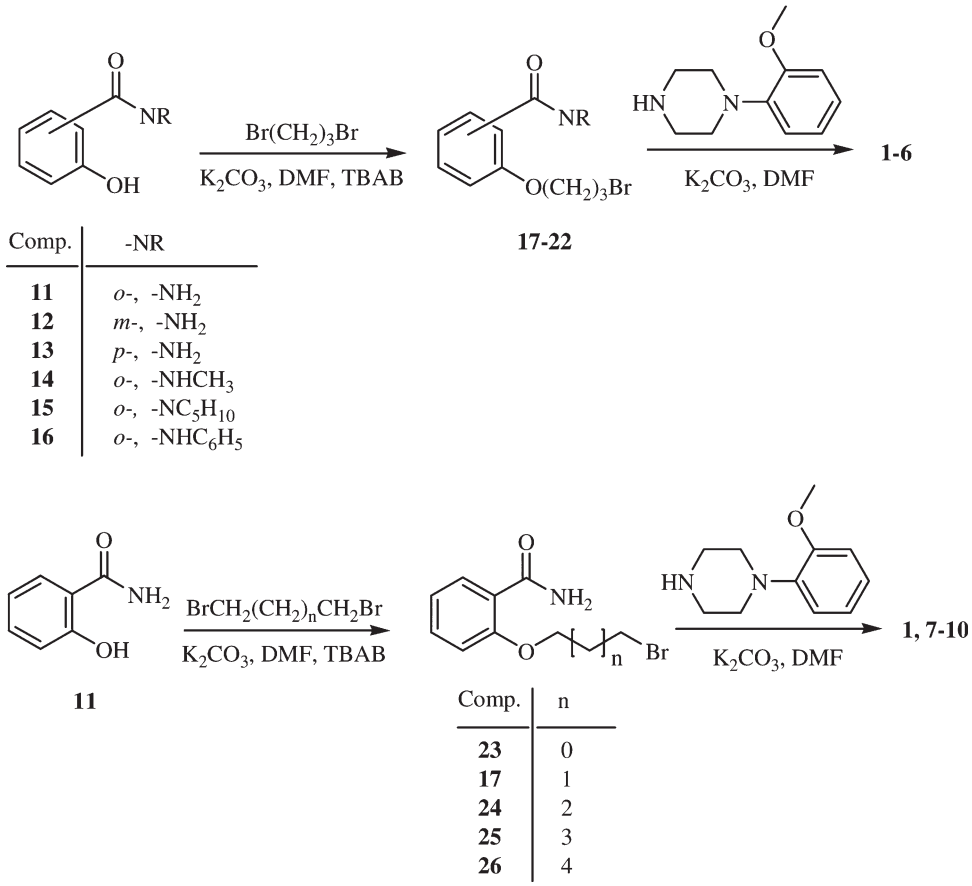


Comp.	-NR
1	*o*-, -NH$_2$
2	*m*-, -NH$_2$
3	*p*-, -NH$_2$
4	*o*-, -NHCH$_3$
5	*o*-, -NC$_5$H$_{10}$
6	*o*-, -NHC$_6$H$_5$

Comp.	n
7	0
1	1
8	2
9	3
10	4

Figure 2. The structure of the investigated compounds.

Scheme 1. The synthesis of the investigated compounds.



on helices 2, 3, and 7, forming both favorable van der Waals (vdW) interactions with hydrophobic residues and hydrogen bonds (H-bonds) with polar sites (Fig. 3).

Analysis of complexes between the ligands and 5-HT_{1A} receptor model showed that the elongation of the alkyl spacer (compounds **9** and **10**) as well as changing the substitution of the amide group to *meta* [compound **2**, Fig. 3(D)] allowed forming attractive hydrogen bonds with three polar residues Gln2.65, Asn7.39, and Trp7.40. This may explain their higher affinity compared with the parent compound **1** (being an *ortho* derivative with propoxy spacer), which formed hydrogen bonds only with Asn7.39 [Fig. 3(A–C)]. On the other hand, shortening of the spacer hindered the interactions also with Asn7.39, making compound **7** the least active at 5-HT_{1A} receptor sites [Fig. 3(E)].

Complexes of the tested compounds with 5-HT_7 receptor are weaker than with 5-HT_{1A} receptor, most probably due to fewer attractive interactions formed by the hydroxybenzamide moieties [Leu instead of Asn in 7.39 position, Fig. 3(F,G)]. The highest 5-HT_7 receptor affinity of compound **6** may be caused by the presence of additional vdW interactions between the phenyl ring substituted at the amide moiety and the hydrophobic side chain of Leu7.39 [Fig. 3(G)].

Table 1

The physical properties of bromoalkyloxy derivatives **17**–**26**.

Comp.	Yield (%)	Mp (°C)	Recryst. solvent	^{1}H-NMR (δ ppm) O—CH_2	CH_2—Br
17	60	127–129[a]	Methanol	4.33	3.59
18	58	125–128	Methanol	4.12	3.41
19	60	137–138	Chloroform	4.17	3.61
20	54	80–82	Methanol	4.30	3.57
21	64	Oil	–	4.14	3.56
22	58	120–122	Propan-2-ol	4.39	3.62
23	53	113[b]	Chloroform/petr. ether	4.46	3.74
24	57	99–100	Acetone	4.17	3.48
25	65	91–92	Methanol	4.14	3.45
26	60	87–89	Butan-1-ol	4.14	3.43

[a] Ref. [11] Mp 126–128°C.
[b] Ref. [11] Mp 111–112.5°C.

Table 2

The physical properties of compounds **1–10** and their binding affinities for 5-HT_{1A} and 5-HT_7 receptors.

	Base			Hydrochloride		
					K_i (nM)	
Comp.	Yield (%)	Mp (°C)	Recryst. solvent	Mp (°C)	5-HT_{1A}	5-HT_7
1[a]	57	143–145	Acetone	195–198	21	234
2	67	163–164	Propan-2-ol	130–135	7	456
3	80	192–194	Methanol	244–246	44	562
4	85	52–55	DMF/water	233–235	25	458
5	72	Oil	–	156–162	50	252
6	78	Oil	–	186–190	22	128
7	59	114–115	Acetone	232–234	155	942
8	64	92–95	Methanol	200–210	38	558
9	65	109–110	Methanol	158–162	4	259
10	88	Oil	–	260–265	3	208
Buspirone					12[b]	
Methiothepin						2.7[c]

[a] Data taken from ref. [7].
[b] Ref. [12–14] K_i = 9–29 nM.
[c] Ref. [15] K_i = 3.2 nM.

EXPERIMENTAL SECTION

Chemistry.

General. Melting points were determined on a Böetius apparatus and are uncorrected. Ir spectra were measured in KBr pellets on a Bio-Rad FTS-175C spectrophotometer. ^{1}H-NMR spectra were recorded on a Tesla 487C (80 MHz) spectrometer using deuteriochloroform as the solvent. The chemical shifts are expressed as δ values in ppm against TMS as an internal standard. Mass spectra were performed using an Esquire 3000 mass spectrometer (Bruker Daltonik, Bremen, Germany) equipped with an electrospray source. Spectra were registered in a positive-ion mode within the range from 50 to 1000 *m/z*. Elemental analyses (C, H, and N) were performed on a Perkin-Elmer 2400 analyzer, and the results are within ±0.4% of the calculated values. The reactions and the product purification were monitored by TLC on silica-gel plates (Merck 60F_{254}) using chloroform/methanol (9:1) mixture as eluent. For column chromatography, silica gel (Merck) was used. Starting materials, solvents, and reagents were purchased from commercial sources (Aldrich and Merck) and were used without further purification.

Synthesis of 2-(3-bromopropoxy)benzamide (17) (typical procedure). A mixture of 1.37 g (10 mmol) of salicylamide (**11**), 6.06 g (30 mmol) of 1,3-bibromopropane, 4.14 g (30 mmol) of anhydrous potassium carbonate, and 0.32 g (1 mmol) of TBAB in 20 mL of DMF were stirred at ambient temperature for 48 h. Next, to the reaction mixture, 50 mL of water was added and the obtained suspension was extracted with chloroform (3 × 15 mL). The extracts were combined, filtered, dried, and the volatile materials were removed *in vacuo*. The residue was purified by crystallization from methanol to give **17** in 60% yield.

Bromoalkoxybenzamides **18–26** were prepared in a similar manner and the results are shown in Table 1.

Synthesis of 2-{[4-(2-methoxyphenyl)piperazin-1-yl]alkiloxy}benzamides 1–10. Compounds **1–10** were synthesized in the reactions of equimolar amounts of the respective bromoalkoxybenzamides **18–26** and 1-(2-methoxyphenyl)piperazine (Scheme 1), according to the procedure published by us [7,17,18]. Physical and biological properties of their hydrochlorides are collected in Table 2.

*2-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy}benzamide (**1**).* See ref. [7] for the spectral data of the compound 2-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy}benzamide (**1**).

*3-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy}benzamide (**2**).* Base; IR: 749, 1028, 1120, 1243, 1444, 1502, 1662, 2834, 2942, 3163, 3370 cm^{-1}. ^{1}H-NMR: δ 1.93–2.22 (m, 2H, CH_2), 2.51–2.74 (m, 6H, CH_2—N—pip, 2CH_2-pip), 3.06–3.17 (m, 4H, 2CH_2-pip), 3.87 (s, 3H, OCH_3), 4.10 (t, 2H, CH_2—O), 6.00 (s, 2H, NH_2), 6.81–7.41 (m, 8H, ArH). MS: (ESI-MS+) *m/z* 370 $[MH]^+$. Anal. Calcd. for $C_{21}H_{27}N_3O_3 \cdot 2HCl$ (442.38): C, 57.02; H, 6.61; N, 9.50. Found: C, 57.07; H, 6.53; N, 9.23.

*4-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy}benzamide (**3**).* Base; IR: 747, 1183, 1245, 1503, 1607, 1652, 2811, 2955, 3175, 3360 cm^{-1}. ^{1}H-NMR: δ 1.94–2.23 (m, 2H, CH_2), 2.52–2.74 (m, 6H, CH_2—N—pip, 2CH_2-pip), 3.06–3.17 (m, 4H, 2CH_2-pip), 3.87 (s, 3H, OCH_3), 4.10 (t, 2H, CH_2—O), 5.80 (s, 2H, NH_2), 6.89–7.05 (m, 6H, ArH), 7.77 (m, 2H, ArH). MS: (ESI-MS+) *m/z* 370 $[MH]^+$. Anal. Calcd. for $C_{21}H_{27}N_3O_3 \cdot HCl$ (405.92): C, 62.14; H, 6.95; N, 10.35. Found: C, 62.02; H, 6.88; N, 9.99.

*N-Methyl-2-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy}-benzamide (**4**).* Base; IR: 762, 1119, 1141, 1241, 1500, 1643, 2832, 2940, 3413 cm^{-1}; ^{1}H-NMR: δ 2.00–2.27 (m, 2H, CH_2), 2.53–2.75 (m, 6H, CH_2—N—pip, 2CH_2-pip), 3.02 (d, 3H, CH_3—N—amide), 3.09–3.22 (m, 4H, 2CH_2-pip), 3.87 (s, 3H, OCH_3), 4.23 (t, 2H, CH_2—O), 6.91–7.54 (m, 7H, ArH), 7.90 (s, 1H, NH), 8.22 (dd, 1H, ArH). MS: (ESI-MS+) *m/z* 384 $[MH]^+$. Anal. Calcd. for $C_{22}H_{29}N_3O_3 \cdot HCl$ (419.94): C, 62.92; H, 7.20; N, 10.01. Found: C, 63.07; H, 6.96; N, 9.83.

*2-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy}phenyl/(piperidin-1-yl)methanone (**5**).* Base; IR: 750, 1024, 1236, 1446, 1592, 1640, 2925, 2947 cm^{-1}. ^{1}H-NMR: δ 1.58–1.75 (m, 6H, 3CH_2-piperid), 1.90–2.16 (m, 2H, CH_2), 2.59–2.72 (m, 6H,

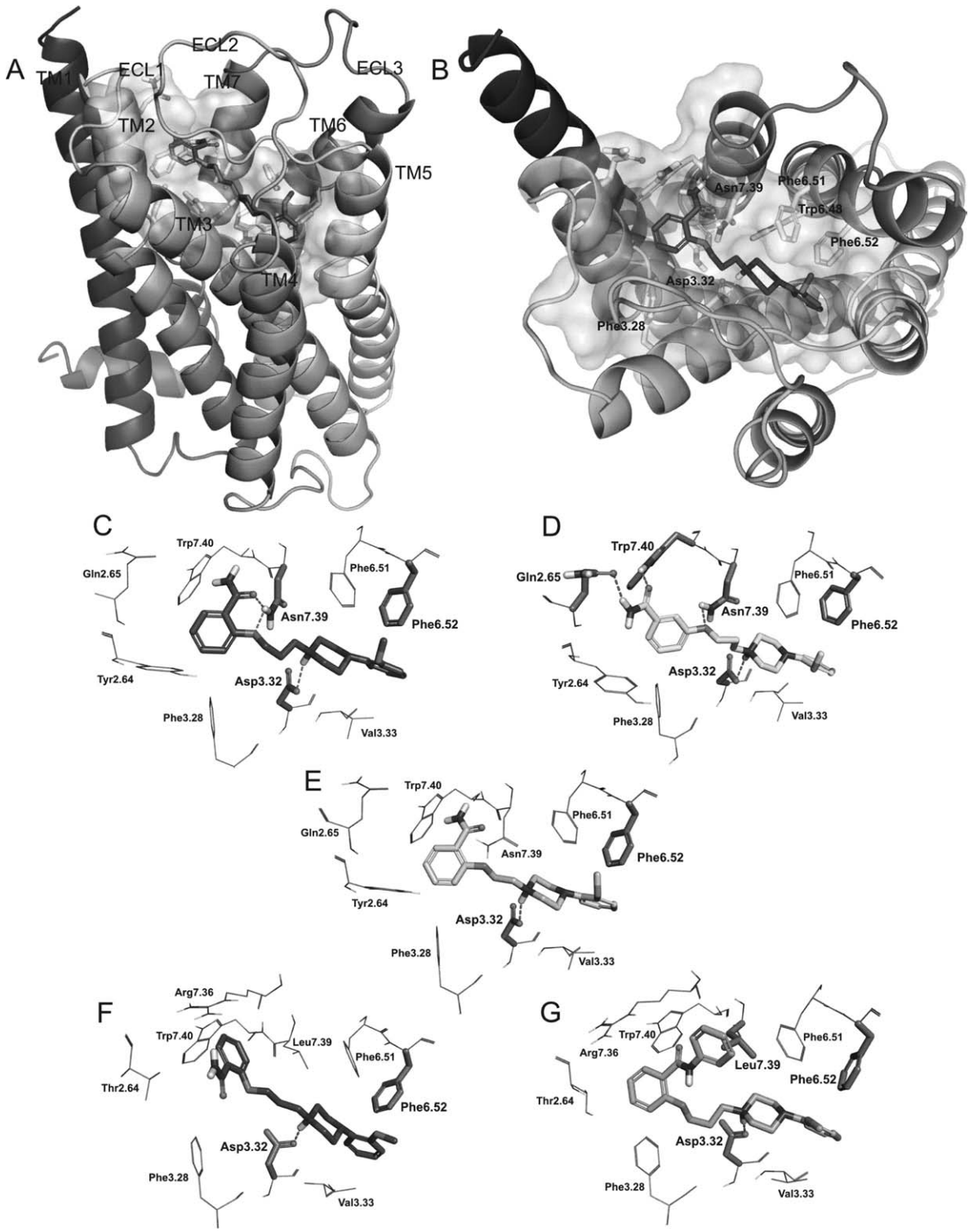


Figure 3. Top-scored ligand—receptor complexes of the selected compounds showing their binding modes (view from the extracellular side). Binding sites of the receptors are shown as transparent surfaces (A, B). Residues forming important interactions with the ligands are presented as thick sticks. Dotted lines represent H-bonds with polar residues. Receptor 5-HT_{1A} (A–E) and receptor 5-HT_7 (F, G). Compounds **1** (A, B, C, F), **2** (D), **6** (G), and **7** (E). TM, transmembrane helix; ECL, extracellular loop.

CH_2—N—pip, 2CH_2-pip), 3.00–3.25 (m, 8H, 2CH_2-pip, 2CH_2-piperid), 3.85 (s, 3H, OCH_3), 4.06 (t, 2H, CH_2—O), 6.86–7.31 (m, 8H, ArH). MS: (ESI-MS+) *m/z* 438 $[MH]^+$. Anal. Calcd. for $C_{26}H_{35}N_3O_3 \cdot HCl$ (474.03): C, 65.88; H, 7.65; N, 8.86. Found: C, 65.65; H, 7.61; N, 8.83.

*N-Phenyl-2-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy}-benzamide (**6**).* Base; IR: 724, 1080, 1349, 1394, 1711, 2934, 3046, 3460 cm^{-1}. ^{1}H-NMR: δ 2.22–2.46 (m, 2H, CH_2), 2.71–2.93 (m, 6H, CH_2—N—pip, 2CH_2-pip), 3.13–3.28 (m, 4H, 2CH_2-pip), 3.83 (s, 3H, OCH_3), 4.27 (t, 2H, CH_2—O), 5.80 (s, 1H, NH), 6.79–7.79 (m, 12H, ArH), 8.16 (dd, 1H, ArH). MS: (ESI-MS+) *m/z* 446 $[MH]^+$. Anal. Calcd. for $C_{27}H_{31}N_3O_3 \cdot HCl \cdot H_2O$ (500.03): C, 64.85; H, 6.85; N, 8.40. Found: C, 64.97; H, 7.02; N, 8.14.

*2-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethoxy}benzamide (**7**).* Base; IR: 751, 1148, 1239, 1455, 1597, 1670, 2820, 2946, 3168, 3361 cm^{-1}. ^{1}H-NMR: δ 2.60–2.82 (m, 4H, 2CH_2-pip), 2.89 (t, 2H, CH_2—N—pip), 2.94–3.15 (m, 4H, 2CH_2-pip), 3.86 (s, 3H, OCH_3), 4.26 (t, 2H, CH_2—O), 5.85 (s, 1H, NH_2), 6.83–7.48 (m, 7H, ArH), 8.20 (dd, 1H, ArH), 8.66 (s, 1H, NH_2). MS: (ESI-MS+) *m/z* 356 $[MH]^+$. Anal. Calcd. for $C_{20}H_{25}N_3O_3 \cdot 2HCl$ (428.35): C, 56.08; H, 6.35; N, 9.81. Found: C, 56.34; H, 6.44; N, 9.65.

*2-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butoxy}benzamide (**8**).* Base; IR: 755, 1015, 1233, 1456, 1597, 1677, 2342, 2938, 3171, 3451 cm^{-1}. ^{1}H-NMR: δ 1.76–1.97 (m, 4H, CH_2), 2.51 (t, 2H, CH_2—N—pip), 2.61–2.74 (m, 4H, 2CH_2-pip), 3.04–3.18 (m, 4H, 2CH_2-pip), 3.86 (s, 3H, OCH_3), 4.18 (t, 2H, CH_2—O), 6.10 (s, 1H, NH_2), 6.87–7.48 (m, 7H, ArH), 7.80 (s, 1H, NH_2), 8.20 (dd, 1H, ArH). MS: (ESI-MS+) *m/z* 384 $[MH]^+$. Anal. Calcd. for $C_{22}H_{29}N_3O_3 \cdot HCl$ (419.94): C, 62.92; H, 7.20; N, 10.01. Found: C, 62.88; H, 7.40; N, 9.93.

*2-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentoxy}benzamide (**9**).* Base; IR: 755, 1150, 1241, 1596, 1669, 2818, 2945, 3166, 3440 cm^{-1}. ^{1}H-NMR: δ 1.59–2.06 (m, 6H, CH_2), 2.81 (t, 2H, CH_2—N—pip), 2.92–3.12 (m, 4H, 2CH_2-pip), 3.28–3.42 (m, 4H, 2CH_2-pip), 3.86 (s, 3H, OCH_3), 4.17 (t, 2H, CH_2—O), 6.05 (s, 1H, NH_2), 6.83–7.59 (m, 7H, ArH), 7.72 (s, 1H, NH_2), 8.18 (dd, 1H, ArH). MS: (ESI-MS+) *m/z* 398 $[MH]^+$. Anal. Calcd. for $C_{23}H_{31}N_3O_3 \cdot HCl \cdot H_2O$ (451.99): C, 61.12; H, 7.58; N, 9.30. Found: C, 61.00; H, 7.45; N, 9.46.

*2-{6-[4-(2-Methoxyphenyl)piperazin-1-yl]hexoxy}benzamide (**10**).* Base; IR: 751, 1148, 1239, 1455, 1597, 1670, 2820, 2946, 3157, 3361 cm^{-1}. ^{1}H-NMR: δ 1.40–1.65 (m, 6H, CH_2), 1.78–1.96 (m, 2H, CH_2), 2.44 (t, 2H, CH_2—N—pip), 2.62–2.75 (m, 4H, 2CH_2-pip), 3.01–3.19 (m, 4H, 2CH_2-pip), 3.86 (s, 3H, OCH_3), 4.13 (t, 2H, CH_2—O), 5.95 (s, 1H, NH_2), 6.90–7.47 (m, 7H, ArH), 7.80 (s, 1H, NH_2), 8.21 (dd, 1H, ArH). MS: (ESI-MS+) *m/z* 412 $[MH]^+$. Anal. Calcd. for $C_{24}H_{33}N_3O_3 \cdot HCl$ (448.00): C, 64.34; H, 7.65; N, 9.38. Found: C, 64.57; H, 7.48; N, 9.30.

Biology. The activity of the compounds was tested in competition binding experiments on rat hippocampal membranes for 5-HT_{1A}, and with membranes from HEK 293 cells, stably expressing human 5-HT_7 receptors according to the previously described procedures [7]. The results of those assays and the previously published data on compound **1** from our laboratory are displayed in Table 2.

Molecular modeling. Homology models of human 5-HT_{1A} and 5-HT_7 serotonin receptors were generated according to the method presented below. The crystal structure of the heptahelical bundle of β_2-adrenergic receptor (PDB code 2rh1) was used as a template [19]. The latest studies show the usefulness of this structure for homology modeling of GPCRs [20,21]. Aminoacid sequences of the receptors (P08908 for 5-HT_{1A} and P34969 for 5-HT_7) were downloaded from the Uniprot database (http://www.uniprot.org) and sequence alignment was prepared using the GeneSilico Metaserver (https://genesilico.pl/meta2). The starting homology models of each receptor were generated using the SwissModel server (accessible from the program DeepView/SwissPdb-Viewer). Further modifications of the models were performed using components of Schrödinger Suite 2008. The models were initially optimized in Protein Preparation Wizard and the extracellular loops were refined using Prime. In the next step, induced fit docking (IFD) was involved for ligand-based optimization of the receptors [22,23]. For this purpose, a group of possibly the most rigid compounds with high affinity for given receptors was chosen. Receptor models found in the top-scored complexes (12 structures for 5-HT_{1A} and six structures for 5-HT_7 receptor) were selected to serve as molecular targets in further docking studies.

The docking of novel compounds (**1**–**10**) was carried out using Glide with XP precision mode. An interaction constraint on a hydrogen bond between Asp3.32 and the protonated nitrogens of the ligands was applied, since that interaction was considered crucial for the monoaminergic GPCRs [24].

Glide, IFD, Prime and Protein Preparation Wizard are implemented in Schrödinger Suite 2008, licensed for Jagiellonian University Collegium Medicum.

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