The Synthesis of Cyclic and Acyclic Long-chain Arylpiperazine Derivatives of Salicylamide as Serotonin Receptor Ligands

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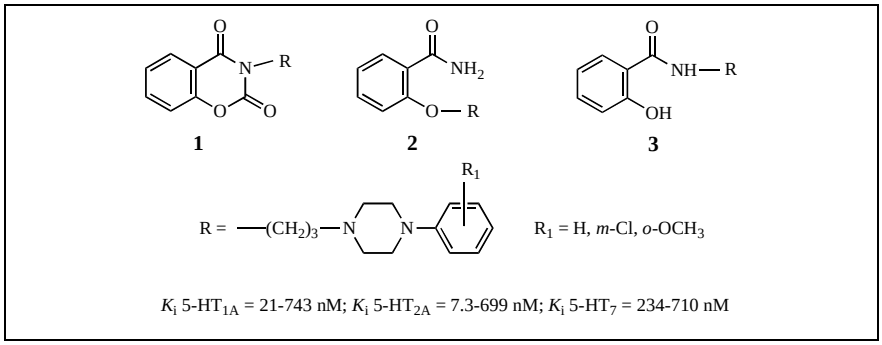

The 1-arylpiperazine series of *N*-substituted 1,3-benzoxazine-2,4-diones as well as *O*- and *N*-substituted salicylamides with an *n*-propyl chain were synthesized in order to explore the effect of cyclic and acyclic salicylamide moieties on their binding affinity for 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptor sites. Target compounds **1** and **2** were prepared by a two-step procedure, *i.e.* by alkylation of 1,3-benzoxazine-2,4-dione or salicylamide with 1,3-dibromopropane and next by condensation of 3-bromopropyl intermediates with arylpiperazines; syntheses of 3-bromopropyl intermediates were performed in solvent-free conditions. Compounds **3** were prepared by hydrolysis of **1**. In respect of salicylamide moieties, binding affinities for 5-HT_{1A} and 5-HT_7 receptors increase according to the rank of derivatives **3** < **1** < **2**, for the same arylpiperazines. Regarding 5-HT_{2A} receptors, increased activity of ligands was changed in reverse order to the affinity for 5-HT_{1A}, *i.e.* **2** < **1** < **3**. 5-HT_{1A} and 5-HT_7 receptor binding constants were the highest for the 2-methoxyphenyl ligand **2c**, while the 3-chlorophenyl ligand **3b** was most active for 5-HT_{2A} receptors.

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INTRODUCTION

Long-chain arylpiperazines with a general structure presented in Figure 1 are the largest class of 5-HT_{1A} serotonin receptor ligands [1-4]. An *Ar* group attached to N1 of a piperazine moiety is usually a substituted phenyl or heteroaromatic (one or two rings) system. With regard to the alkyl chain, two to four methylene groups (n = 0–2) are optimal for 5-HT_{1A} activity. The terminus usually contains an amide or an imide function, but neither is required for high activity, *i.e.* it may also be a phenyl or another aromatic group (see Figure 2.).

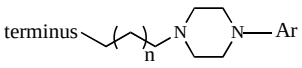


Figure 1. The general chemical structure of long-chain arylpiperazines.

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that mediates a wide variety of sensory, motor, and cortical functions through multiple 5-HT receptor subtypes [5]. It is generally accepted that 5-HT_{1A} receptors are involved in psychiatric disorders, such as anxiety and depression [9,10].

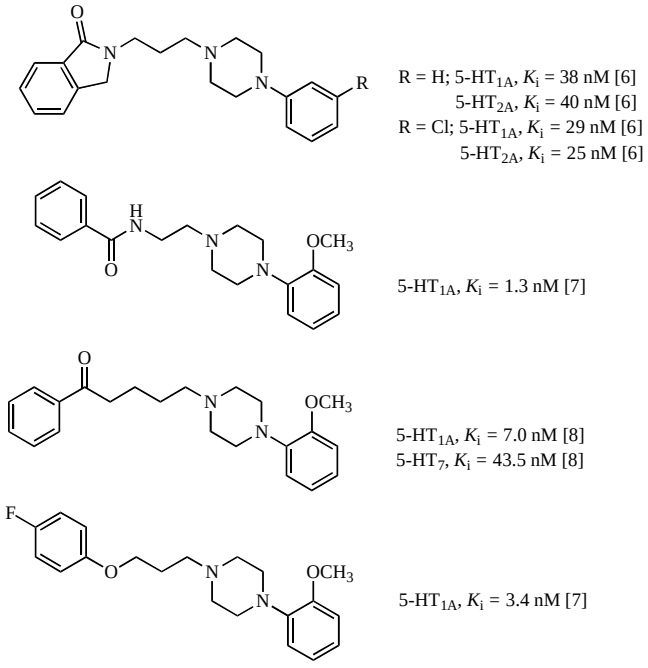


Figure 2. Selected long-chain arylpiperazine derivatives and their binding data for 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 serotonin receptors [6-8].

Some currently widely used drugs (buspirone [11], ziprasidone [12], aripiprazol [13]) are effective 5-HT_{1A} ligands, belonging to the arylpiperazine class. The high sequence homology of 5-HT_{1A} receptor binding sites with other serotonin receptor subtypes [14-16] causes that long-chain arylpiperazines are investigated also as 5-HT_{2A} and 5-HT_7 receptor ligands (Figure 2).

In consequence of an our sustained interest in 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 serotonin receptor ligands, we found a number of active long-chain arylpiperazine derivatives of benzoxazinone, benzoxazolinone, quinazolinone, phthalazinedione, pyridazinedione, benzoxazolindione and others [6,17-23]. Their affinity, selectivity, and function towards the particular type of the receptor were affected by relatively small structure modifications in either terminal fragments or a chain bridge.

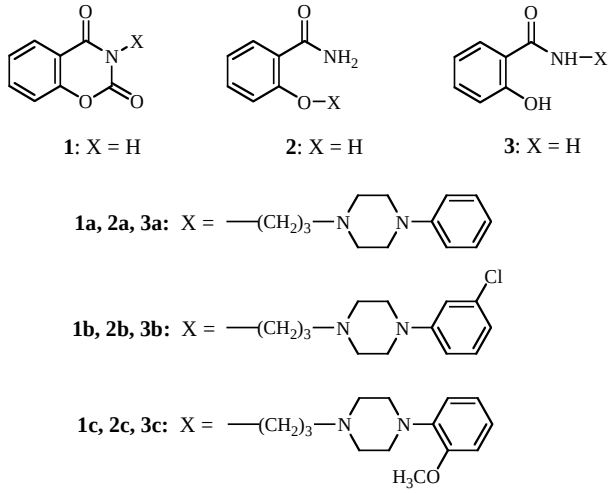


Figure 3. Structures of the investigated compounds **1a,b,c**–**3a,b,c**.

In the present paper we explored the effect of salicylamide moieties in serotonin receptor ligands of the long-chain arylpiperazine family on their binding affinity for 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptor sites. Both cyclic and acyclic derivatives of the salicylamide were chosen, i.e. the *N*-substituted derivatives of 1,3-benzoxazine-2,4-dione (**1**) and *O*- (**2**), as well as *N*-substituted (**3**) salicylamides (Figure 3). The influence of the above terminus on receptor affinities was studied for three classic arylpiperazines with a propylene linker **a**–**c**.

RESULTS AND DISCUSSION

Synthesis. Compounds **1a–c** and **2a–c** were prepared by a two-step procedure by alkylation of 1,3-benzoxazine-2,4-dione (**1**) or salicylamide (**2**) with 1,3-dibromopropane (**4**), and next, condensation of 3-bromopropyl intermediates **5** or **6** with 1-phenylpiperazine (**7**), 1-(3-chlorophenyl)piperazine (**8**), and 1-(2-methoxyphenyl)-piperazine (**9**) (Scheme 1).

In comparison with the previously described method [6,19,21], the alkylation of **1** was performed in the absence of a solvent at an ambient temperature using 3 equivalents of **4**, K_2CO_3 and tetrabutylammonium bromide (TBAB) as a catalyst. In the above conditions, the reaction was completed in *ca.* 30 min. and the yield of **5** was 92%. The usefulness of the solvent-free protocol to synthesize *N*-alkyl derivatives of 1,3-benzoxazine-2,4-dione was confirmed by experimental results on their *N*-benzylation, *N*-ethylation, and *N*-(ω-halogenation) (Table 1). In all the cases, the reaction occurred in a few minutes, with the high yield.

A solvent-free alkylation procedure was also applied to synthesize *O*-(3-bromopropyl)salicylamide (**6**) (Scheme 1). In that case, however, progress of the reaction of 1,3-dibromopropane (**4**) with salicylamide (**2**) was observed only after heating on a water bath.

The synthesis of amides **3** was based on literature reports describing that under alkali conditions 1,3-benzoxazin-2,4-dione and its *N*-methyl derivative underwent hydrolysis to the corresponding salicylamides [27,28]. In our experiment, the parent substances in synthesis of the compounds **3** were the *N*-substituted derivatives **1**. The optimization of hydrolysis conditions showed that the highest yield of **3** was obtained using a 5% water solution of sodium hydroxide (Scheme 2).

Scheme 1

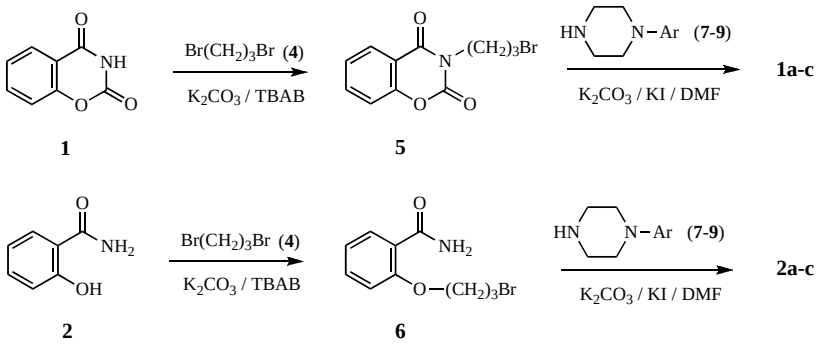
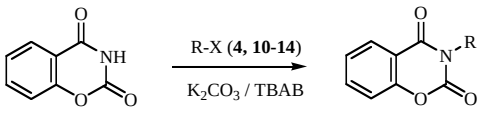


Table 1

Synthesis of *N*-alkyl derivatives of 1,3-benzoxazine-2,4-dione (**5**, **15**–**19**) in solvent-free conditions.

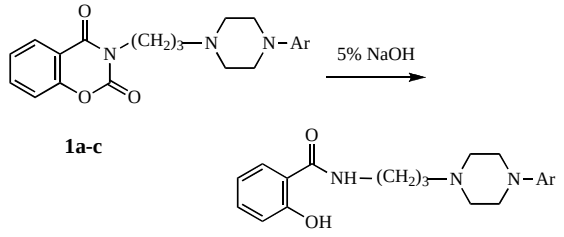


1 **5**, **15-19**

Compound	R-X	Molar ratio imide : R-X	Yield, %	Mp, °C	Recryst. solvent
5	$Br(CH_2)_3$-Br, **4**	1 : 3	92	102-103	methanol
15	$C_6H_5CH_2$-Cl, **10**	1 : 1.2	93	133-135 [a]	methanol
16	CH_3CH_2-Br, **11**	1 : 1.2	70	109-111 [b]	methanol
17	$Br(CH_2)_2$-Br, **12**	1 : 3	91	113-115 [c]	methanol
18	$Br(CH_2)_4$-Br, **13**	1 : 3	84	64-66	propan-1-ol
19	$Br(CH_2)_5$-Br, **14**	1 : 3	85	81-83	acetone-water

[a] ref. 24, mp 133–134 °C. [b] ref. 25, mp 110–112 °C. [c] ref. 26, mp 111–112 °C.

Scheme 2



1a-c **3a-c**

The structure of the obtained compounds was confirmed by infrared and ^{1}H nmr spectra, and in some cases by comparison of their physical properties to those described in the literature. For biological experiments, bases **1a–c**, **2a–c** and **3a–c** were converted into hydrochloride salts. Their physicochemical properties and binding affinities for 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors are collected in Table 2.

Receptor Binding Assays. Radioligand studies with native 5-HT_{1A} and 5-HT_{2A} receptors were conducted according to the methods previously described by us [29]. Briefly, in 5-HT_{1A} assays, rat hippocampal membranes, [^{3}H]-8-OH-DPAT (106 Ci/mmol, NEN Chemicals) and 10 μM of 5-HT (for non–specific binding) were used, whereas in 5-HT_{2A} assays, rat cortical membranes, [^{3}H]-ketanserin (67.0 Ci/mmol, PerkinElmer) and methylsergide (1 μM) were employed. 5-HT_7 binding assays were performed on membranes from HEK 293 cells, stably expressing the human 5-$HT_{7(b)}$ receptor according to the procedure described by Thomas *et al.* [30]. [^{3}H]-5-CT (93.0 Ci/mmol, Amersham) was used as a radioligand, while the non-specific binding was defined in the presence of 10 μM of 5-HT.

The binding affinity for 5-HT_{1A} receptors of the compounds studied clearly depends on the structure of a terminus amide, as well as on nature of a phenyl attached to the piperazine ring (Table 2). In respect of salicylamide moieties, the binding affinity for 5-HT_{1A} receptors increased in the following order: **3** < **1** < **2** for the same arylpiperazines. In the case of compounds with the same salicylamide motif, the affinity was changed in order: phenyl (**a**) < 3-chlorophenyl (**b**) < 2-methoxyphenyl (**c**) piperazine derivatives. Thus compound **2c** turned out to be the most active 5-HT_{1A} receptor ligand.

The influence of the salicylamide fragment on 5-HT_7 receptor activity was similar to that found for 5-HT_{1A} sites; however, it was investigated for *O*-(2-methoxyphenyl)piperazine derivatives only, and the observed K_i values were within a moderate range.

Regarding 5-HT_{2A} receptors, the increase of ligands activity in respect of salicylamide moieties was in reverse order, *i.e.* **2** < **1** < **3**, obviously, for the same arylpiperazine (Table 2). Compounds with the 3-chlorophenyl group attached to the piperazine ring (**b**) were the most active, whereas the 2-methoxyphenyl fragment was detrimental for 5-HT_{2A} receptors activity. The highest binding constant (K_i = 7.3 nM), detected for the *N*-(3-chlorophenyl)piperazine derivative of acyclic salicylamide (**3b**), distinguished it as a selective 5-HT_{2A}/5-HT_{1A} agent.

The present results confirm the importance of both the salicylamide motif and N1-aryl fragment for the modulation of serotonin 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 activity. The most striking effect was observed for *O*-substituted derivatives **2**, whose 5-HT_{1A} affinities were reinforced compared to *N*-substituted analogues **3**, with simultaneous decrease in the 5-HT_{2A} binding constants

Table 2

Physical properties of compounds **1a**-**c**, **2a**-**c**, and **3a**-**c** and their binding affinities to 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors.

Compound	Base			Hydrochloride,	K_i (nM)		
	Yield, %	Mp, °C	Recryst. solvent	mp, °C	5-HT_{1A}	5-HT_{2A}	5-HT_7
1a	70 [a]	124-127	acetonitrile	233-236 [b]	402 [c]	49 [c]	–
1b	68 [d]	97-99	acetone	211-214 [e]	126 [c]	18 [c]	–
1c	56	104-105	methanol	212-215	46	417	324
2a	74	144-146	methanol	207-110	143	641	–
2b	65	176-178	methanol	228-229	77	402	–
2c	57	143-145	acetone	195-198	21	699	234
3a	68	114-116	acetonitrile/water	192-194	743	32	–
3b	61	96-98 [f]	methanol	193-194 [g]	191	7.3	–
3c	55	125-6 [h]	propan-2-ol	176-179 [i]	130	322	719
buspirone					12 [j]	–	–
ritanserin					–	1.1 [k]	–
methiothepin					–	–	2.7 [l]

[a] ref. 17, Yield 67 %. [b] ref. 17, mp 234-236 °C. [c] data taken from ref. 17. [d] ref. 17, Yield 53 %. [e] ref. 17, mp 215-217 °C. [f] ref. 31, mp 105 °C. [g] ref. 31, mp 193 °C. [h] ref. 31, mp 77 °C. [i] ref. 31, mp 176 °C. [j] ref. 24,32-35, K_i = 9–29 nM. [k] ref. 36, 37 K_i = 0.56 nM, [l] ref. 30, K_i = 3.2 nM.

EXPERIMENTAL

Melting points were determined on a Böetius melting point apparatus and are uncorrected. Elemental analyses were performed on Perkin Elmer 2400 analyzer and the results are within ±0.4% of the calculated values. Infrared spectra were recorded as pressed KBr discs on a Bio-Rad FTS 175B spectrometer. ^{1}H NMR spectra were taken on Tesla 587A (80MHz) spectrometer in $CDCl_3$ solution, using TMS as an internal standard; the chemical shifts are given in ppm (δ). The reactions and purifications were monitored by tlc (uv detection) on aluminum sheets coated with silica gel 60 F254 (Merck) using chloroform/methanol (90:10) mixture as eluent. All starting materials were purchased from commercial sources (Sigma-Aldrich and Merck) and were used without further purification.

General procedure for the synthesis of *N*-alkyl derivatives of 1,3-benzoxazine-2,4-dione (**5, 15–19**). A powdered mixture of 1.63 g (0.01 mol) of 1,3-benzoxazine-2,4-dione (**1**), 4.14 g (0.03 mol) of anhydrous potassium carbonate and 0.32 g (0.001 mol) of TBAB was placed in a vessel. Then, 3 equivalents of dibromoalkanes **4**, **12–14**, or 1.2 equivalents of alkyl halides **10**, **11** were added, respectively; the mixture was stirred with a spatula for *ca*. 1 minute. The reaction mixture was left at an ambient temperature. During 10–15 minutes, the mixture was warmed up spontaneously up to a temp. of 40–60 °C, and after another 15–20 minutes the temperature fell, which signified that the reaction was completed. The reaction mixture was poured into 100 mL of water. In the case of compound **5** and **17–19**, the precipitate was extracted with chloroform, and after evaporation of the solvent, crude products were purified by crystallization (Table 1). Compounds **15** and **16** were collected by filtration and were recrystallized from methanol (Table 1).

3-(3-bromopropyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (**5**). ^{1}H nmr: δ 2.14-2.48 (m, 2H, CH_2), 3.47 (t, 2H, CH_2-Br), 4.20 (t, 2H, CH_2-N-imide), 7.26-8.15 (m, 4H, ArH). *Anal*. Calcd. for $C_{11}H_{10}BrNO_3$ (284.11): C, 46.50; H, 3.55; N, 4.93. Found: C, 46.68; H, 3.51; N, 4.74.

3-(4-bromobutyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (**18**). ^{1}H nmr: δ 2.10-2.46 (m, 4H, CH_2-CH_2), 3.46 (t, 2H, CH_2-Br), 4.09 (t, 2H, CH_2-N-imide), 7.23-8.15 (m, 4H, ArH). *Anal*. Calcd. for $C_{12}H_{12}BrNO_3$ (298.13): C, 48.34; H, 4.06; N, 4.70. Found: C, 48.46; H, 4.11; N, 4.94.

3-(5-bromopentyl)-2*H*-1,3-benzoxazine-2,4(3*H*)-dione (**19**). ^{1}H nmr: δ 1.52-2.02 (m, 6H, CH_2-CH_2-CH_2), 3.42 (t, 2H, CH_2-Br), 4.06 (t, 2H, CH_2-N-imide), 7.23-8.15 (m, 4H, ArH). *Anal*. Calcd. for $C_{13}H_{14}BrNO_3$ (312.16): C, 50.02; H, 4.52; N, 4.49. Found: C, 49.86; H, 4.50; N, 4.33.

Synthesis of 2-(3-bromopropoxy)benzamide (**6**). A powdered mixture of 1.37 g (0.01 mol) of salicylamide (**2**) 4.14 g (0.03 mol) of anhydrous potassium carbonate, 0.32 g (0.001 mol) of TBAB were placed in vessel. Next, 3 equivalents of 6.06 g of 1,3-dibromopropane (**4**) was added, and the mixture was stirred by spatula for *ca*. 1 minute. The reaction mixture was heated during 60 minutes on boiling water bath, and after cooling was poured into 100 mL of water. The precipitate was extracted with chloroform. After evaporation of the solvent, the crude product was purified by crystallization from methanol to give **6** in 58% yield, mp 126–129 °C (mp. 126–128 °C [38]).

General procedure for the synthesis of 1a–c and 2a–c. A mixture of 0.01 mol of **5** or **6**, 0.01 mol of the respective amines **7–9**, 0.02 mol of anhydrous potassium carbonate (when a hydrochloride salt of an amine was used, an equivalent of potassium carbonate was also added), and a few crystals (~0.01 g) of potassium iodide in 20 mL of dimethylformamide were stirred with a magnetic stirrer at room temperature for 40 hours. Them, the reaction mixture was poured into 100–150 mL of water, and the precipitate was either colleted by filtration or extracted with chloroform. The crude products were purified by crystallization. The yields and physical properties of **1a–c** and **2a–c** are shown in Table 2. Compounds **1a** and **1b** have been described previously [17].

3-{3-[4-(2-Methoxyphenyl)piperazin-1-yl)propyl]-2*H*-1,3-benzoksazyno-2,4(3*H*)-dion (**1c**). Base; ir (KBr): ν 750, 1244, 1351, 1469, 1504, 1702, 1760, 2820, 2958 cm^{-1}; ^{1}H nmr: δ 1.78-2.12 (m, 2H, CH_2), 2.48-2.70 (m, 6H, CH_2-N-pip, $2CH_2$-pip),

2.88-2.98 (m, 4H, $2CH_2$-pip), 3.83 (s, 3H, OCH_3), 4.17 (t, 2H, CH_2-N-imide), 6.81-8.14 (m, 8H, ArH). *Anal.* Calcd. for $C_{22}H_{25}N_3O_4 \cdot 2HCl \cdot 0.5H_2O$ (477.38): C, 55.35; H, 5.91; N, 8.80. Found: C, 55.72; H, 5.99; N, 8.59.

2-[3-(4-Phenylpiperazin-1-yl)propoxy]benzamide (**2a**). Base; ir (KBr): ν 753, 1151, 1236, 1597, 1666, 2816, 2934, 3173, 3379 cm^{-1}; ^1H nmr: δ 1.93-2.24 (m, 2H, CH_2), 2.51-2.68 (m, 6H, CH_2-N-pip, $2CH_2$-pip), 3.14-3.29 (m, 4H, $2CH_2$-pip), 4.22 (t, 2H, CH_2-O), 6.32 (s, 1H, NH_2), 6.76-7.57 (m, 8H, ArH), 7.87(s, 1H, NH_2), 8.21 (d, 1H, ArH). *Anal.* Calcd. for $C_{20}H_{25}N_3O_2 \cdot HCl$ (375.89): C, 63.91; H, 6.97; N, 11.18. Found: C, 63.77; H, 6.91; N, 11.37.

2-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propoxy}benzamide (**2b**). Base; ir (KBr): ν 760, 1150, 1240, 1592, 1664, 2823, 2930, 3168, 3377 cm^{-1}; ^1H nmr: δ 2.04-2.28 (m, 2H, CH_2), 2.64-2.86 (m, 6H, CH_2-N-pip, $2CH_2$-pip), 3.17-3.30 (m, 4H, $2CH_2$-pip), 4.24 (t, 2H, CH_2-O), 5.86 (s, 1H, NH_2), 6.87-7.58 (m, 7H, ArH), 7.86 (s, 1H, NH_2), 8.21(d, 1H, ArH). *Anal.* Calcd. for $C_{20}H_{24}ClN_3O_2 \cdot 2HCl \cdot 0.5H_2O$ (455.81): C, 52.70; H, 5.97; N, 9.22. Found: C, 53.06; H, 5.82; N, 8.87.

2-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy}benzamide (**2c**). Base; ir (KBr): ν 771, 1150, 1236, 1594, 1663, 2830, 2940, 3173, 3454 cm^{-1}; ^1H nmr: δ 2.05-2.28 (m, 2H, CH_2), 2.57-2.77 (m, 6H, CH_2-N-pip, $2CH_2$-pip), 3.07-3.19 (m, 4H, $2CH_2$-pip), 3.87 (s, 3H, OCH_3), 4.24 (t, 2H, CH_2-O), 5.92 (s, 1H, NH_2), 6.91-7.58 (m, 7H, ArH), 7.86 (s, 1H, NH_2), 8.22 (m, 1H, ArH). *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, 56.91; H, 6.63; N, 9.41.

General procedure for the hydrolysis of 1a–c to 3a–c. Compound **1a–c** (0.5 g) was heated 10-15 minutes in 10 mL middle boiling 5% water solution of sodium hydroxide until the reaction mixture becomes clear. After cooling the reaction mixture was neutralized with 10% hydrogen chloride to neutral pH. Precipitate was collected by filtration and recrystallized from appropriate solvent. The yields and physical properties of **3a–c** are collected in the Table 2.

***N*-{3-[4-(Phenyl)piperazin-1-yl]propyl}-2-hydroxybenzamide** (**3a**). Base; ir (KBr): ν 755, 1240, 1494, 1597, 1643, 2830, 2957, 3188, 3437 cm^{-1}; ^1H nmr: δ 1.67-1.97 (m, 2H, CH_2), 2.58-2.76 (m, 6H, CH_2-N-pip, $2CH_2$-pip), 3.19-3.32 (m, 4H, $2CH_2$-pip), 3.60 (t, 2H, CH_2-N-amide), 6.55-7.53 (m, 9H, ArH), 8.70 (s, 1H, NH), 12.60 (s, 1H, OH). *Anal.* Calcd. for $C_{20}H_{25}N_3O_2 \cdot HCl \cdot 0.5H_2O$ (384.90): C, 62.41; H, 7.07; N, 10.92. Found: C, 62.28; H, 7.02; N, 11.03.

***N*-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-2-hydroxybenzamide** (**3b**). Base; ir (KBr): ν 759, 1237, 1489, 1596, 1641, 2835, 2943, 3197 cm^{-1}; ^1H nmr: δ 1.83-1.97 (m, 2H, CH_2), 2.67-2.74 (m, 6H, CH_2-N-pip, $2CH_2$-pip), 3.19-3.31 (m, 4H, $2CH_2$-pip), 3.56 (t, 2H, CH_2-N-amide), 6.56-7.48 (m, 8H, ArH), 8,63 (s, 1H, NH), 12,59 (s, 1H, OH). *Anal.* Calcd. for $C_{20}H_{24}ClN_3O_2 \cdot 2HCl$ (446.80): C, 53.76; H, 5.87; N, 9.40. Found: C, 53.75; H, 5.92; N, 9.25.

***N*-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-2-hydroxybenzamide** (**3c**). Base; ir (KBr): ν 750, 1243, 1500, 1596, 1643, 2823, 2945, 3188, 3431 cm^{-1}; ^1H nmr: δ 1.84-1.98 (m, 2H, CH_2), 2.64-2.83 (m, 6H, CH_2-N-pip, $2CH_2$-pip), 3.13-3.24 (m, 4H, $2CH_2$-pip), 3.52 (t, 2H, CH_2-N-amide), 3.87 (s, 3H, OCH_3), 6.65-7.63 (m, 8H, ArH), 9,00 (s, 1H, NH), 12,60 (s, 1H, OH). *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, 56.87; H, 6.66; N, 9.35.

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