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Preparation of piperazine derivatives as 5-HT$_7$ receptor antagonists

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Abstract—Twenty-four compounds of 4-methoxy-*N*-[3-(4-substituted phenyl-piperazine-1-yl)propyl] benzene sulfonamides and *N*-[3-(4-substituted phenyl-piperazine-1-yl)propyl] naphthyl sulfonamides were prepared and evaluated as 5-HT$_7$ receptor antagonists. Most of the compounds showed the IC$_{50}$ values of 12–580 nM. Four methyl branched analogues were also obtained, but the activity for methyl branched analogues was almost same as its straight chain congeners. Among the synthesized compounds, **3c** showed a good activity on 5-HT$_7$ receptors and a good selectivity on 5-HT$_{1a}$, 5-HT$_{2a}$, 5-HT$_{2c}$, and 5-HT$_6$ receptors.

1. Introduction

Serotonin is a neurotransmitter which has many important implications in the control of numerous behavioral and physiological processes both in peripheral and central nervous system. The serotonergic system is known to modulate mood, emotion, sleep, and appetite. It also participates in memory formation. In the periphery, serotonin induces both contraction and relaxation of coronary artery in various species.[1–3]

Out of the fourteen subtypes, which have been reported to date, the 5-HT$_7$ subtype is the most recently discovered one. The 5-HT$_7$ receptors belong to GPCRs, and high level of the receptors have been observed in the thalamus, hypothalamus, brainstem, and hippocampus in the brain, and blood vessels in the periphery.[2]

Even though the role of 5-HT$_7$ receptors in both CNS and periphery has not been fully clarified, biochemical and neuroanatomical studies have suggested that the 5-HT$_7$ receptors must have a role in smooth muscle relaxation, vasorelaxation, control of circadian rhythms, depression, and possibly psychosis.[4,5] Therefore agents active at 5-HT$_7$ receptor might be effective in the treatment of sleep disorders, depression, schizophrenia, coronary heart disease, migraine, and cognitive disorders.[2]

Recently, some selective 5-HT$_7$ receptor antagonists such as SB-258719 and DR 4004 were discovered from the high-throughput screening of compound libraries.[6–9] The sulfonamide derivative SB-258719 showed a modest affinity but high selectivity, whereas the teterahydrobenzindole derivative DR4004 showed a high affinity but a moderate selectivity. Structurally related SB-269970 showed the highest affinity and the best selectivity known to date to 5-HT$_7$ receptor.[10,11]

Since SB-269970 showed high activity and selectivity on 5-HT$_7$ receptor, we designed and synthesized a number of piperazine derivatives based on the structure of SB-269970 and evaluated them as 5-HT$_7$ receptor antagonists. (Fig. 1).

2. Results

2.1. Chemistry

The reported pharmacophoric hypothesis generated by catalyst suggested the minimal structural requirements for 5-HT$_7$ antagonism consisted of an aromatic ring, a

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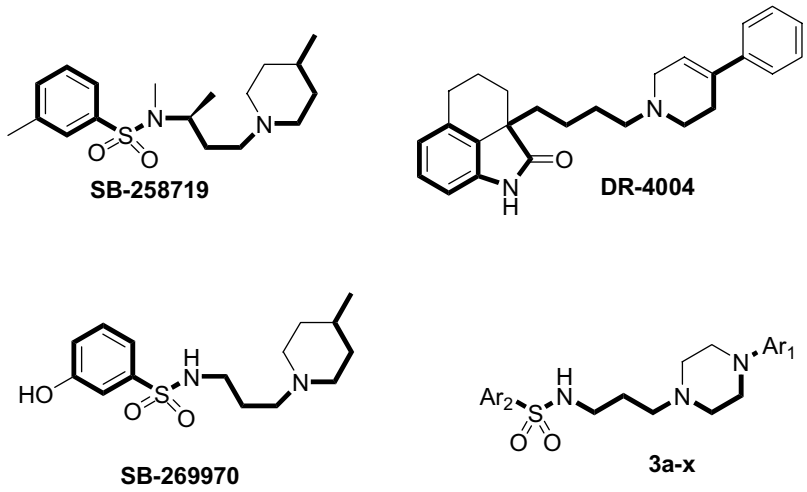


Figure 1. 5-HT_7 receptor antagonists.

basic nitrogen atom, a H-bonding acceptor group and a hydrophobic region at 4.9–5.9 Å apart from the basic center.[12] Therefore, we designed sulfonamide derivatives **3a**–**x** to possess the arylsulfonamide and piperazine moieties as well as a three carbon spacer through the structural analysis of the reported 5-HT_7 antagonists based on the pharmacophoric hypothesis.

The synthetic procedures used in the preparation of **3a**–**x** are illustrated in Scheme 1.

Substituted aryl piperazine was reacted with 1-bromo-3-chloro-propane and triethylamine to give 1-(3-chloropropyl)-4-(substituted phenyl)-piperazines **2**. Then nucleophilic displacement of chlorine of **2** by the nitrogen of *p*-methoxybenzene sulfonamide or 2-naphthylsulfonamide afforded the desired compounds **3a**–**x**, respectively. Twenty-four compounds which have different substituents such as –H, $–CF_3$, $–OCH_3$, –F, and $–Cl_2$ were prepared and the structure of the synthesized compounds is given in Table 1.

The sulfonamide derivatives which have a methyl group at the C-3 position of the three carbon spacer, as SB-258719 showed high selectivity, were synthesized using 1,3-butanediol as a spacer unit (Scheme 2). Mono tosylation of 1,3-butanediol to 1-tosyl-3-hydroxy-butane followed by reaction with substituted aryl piperazine gave 2-hydroxyl-4-(4-substituted aryl piperazinyl)butanes **4a**–**d**. Further tosylation of hydroxyl group of **4a**–**d** and substitution of tosyl group with 4-methoxybenzene sulfonamide or 2-naphthylsulfonamide was achieved to result in the desired compounds **6a**–**d**.

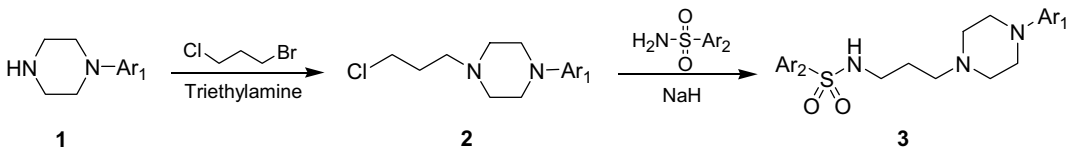
2.2. Biological evaluation

The synthesized compounds were evaluated in vitro against the human recombinant 5-HT_7 serotonin receptor from stable CHO cell line. [3H]LSD binding assay results are shown in Tables 1 and 2. Several compounds showed good activity with IC_{50} values less than 150 nM. The 5-HT_7 antagonists of synthesized compounds showed different activities depending on the substitution on piperazine or sulfonyl group. Most active compound (**3o**) showed the IC_{50} value of 12 nM, which has *m*-trifluoromethylphenyl substitution on piperazine as well as naphthyl substitution on sulfonyl group. Seven active compounds were further evaluated for their selectivity over 5-HT_{1a}, 5-HT_{2a}, 5-HT_{2c}, and 5-HT_6 receptors (Table 3).

3. Discussion

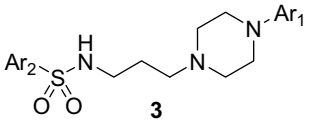
The fact that the 5-HT_7 receptor may be of value as a novel therapeutic target has spurred extensive studies on 5-HT_7 antagonists and recently many reports were made as a result.[13–15] Also it was reported that the 5-HT_7 receptor antagonists showed an antidepressant-like effect on sleep disorders and depression. The affinity of some antipsychotic drugs for the 5-HT_7 receptor led to the speculation that this 5-HT_7 receptor may mediate the therapeutic actions of these compounds.[16–18]

A few arylamides linked with a spacer to phenyl-piperazine were reported as active structure for 5-HT_7 antagonists.[18]

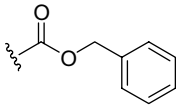
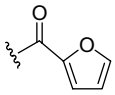


Scheme 1. Synthesis of the target compounds **3a**–**x**.

Table 1. IC_{50} values of the sulfonamide derivatives **3a**–**x** against 5-HT_7 receptor

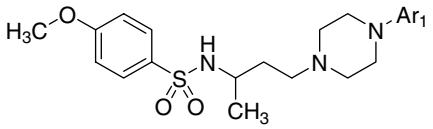


3

Compound	Ar_1	Ar_2	IC_{50} (nM)
3a	3-$CF_3C_6H_4$	4-$OCH_3C_6H_4$	89
3b	4-$CF_3C_6H_4$	4-$OCH_3C_6H_4$	384
3c	2-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	37
3d	3-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	339
3e	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$	9314
3f	2-FC_6H_4	4-$OCH_3C_6H_4$	289
3g	4-FC_6H_4	4-$OCH_3C_6H_4$	47
3h	3,4-$Cl_2C_6H_3$	4-$OCH_3C_6H_4$	103
3i	$C_6H_5CH_2$	4-$OCH_3C_6H_4$	949
3j	C_6H_5	4-$OCH_3C_6H_4$	>10,000
3k	4-$NO_2C_6H_4$	4-$OCH_3C_6H_4$	>10,000
3l	4-$COCH_3C_6H_4$	4-$OCH_3C_6H_4$	>10,000
3m		4-$OCH_3C_6H_4$	>10,000
3n		4-$OCH_3C_6H_4$	>10,000
3o	3-$CF_3C_6H_4$	$C_{10}H_7$	12
3p	4-$CF_3C_6H_4$	$C_{10}H_7$	567
3q	2-$OCH_3C_6H_4$	$C_{10}H_7$	20
3r	3-$OCH_3C_6H_4$	$C_{10}H_7$	223
3s	4-$OCH_3C_6H_4$	$C_{10}H_7$	3241
3t	2-FC_6H_4	$C_{10}H_7$	140
3u	4-FC_6H_4	$C_{10}H_7$	53
3v	3,4-$Cl_2C_6H_3$	$C_{10}H_7$	124
3w	$C_6H_5CH_2$	$C_{10}H_7$	476
3x	C_6H_5	$C_{10}H_7$	681

The 5-HT_7 antagonists of synthesized compounds showed a different activity depending on the substitution on piperazine. The introduction of carbonyl group (**3l**, **3m**, and **3n**) resulted in the complete loss of activity. Compounds which have $–CF_3$, $–OCH_3$, or –F substituted phenyl group on piperazine showed a high activity with IC_{50} values ranging in 12–375 nM. The position of substituents on phenyl also affected the activity as shown in **3c**–**e** and **3q**–**s**. For these methoxyphenyl substituted analogues, the order was *o*->*m*->*p*- and *o*-methoxy compounds (**3c** and **3q**) showed 200–300 times higher activity than *p*-methoxy congeners (**3e** and **3s**), respectively. Similarly *m*-CF_3 substituted compounds showed higher activity than *p*-CF_3 congeners (**3a** > **3b** and **3o** > **3p**). However, in the case of fluorine, the above postulated trend failed, and *p*-F substituted compounds (**3g** and **3u**) showed higher activity than *o*-F substituted congeners (**3f** and **3t**).

Table 2. IC_{50} values of the sulfonamide derivatives **6a**–**d** against 5-HT_7 receptor



6

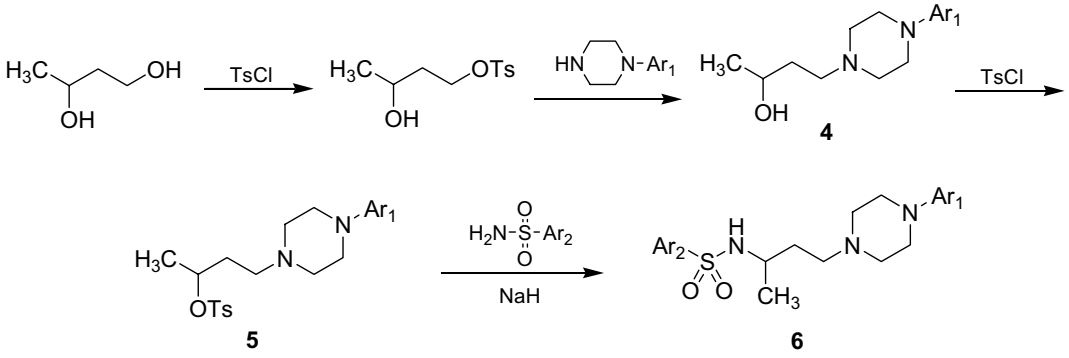
Compound	Ar_1	IC_{50} (nM)
6a	3-$CF_3C_6H_4$	107
6b	2-$OCH_3C_6H_4$	580
6c	4-FC_6H_4	373
6d	C_6H_5	377

Table 3. IC_{50} values of the selected sulfonamide derivatives against 5-HT receptors

Compound	Binding affinity, IC_{50} (nM)			
	5-HT_{1a} receptor	5-HT_{2a} receptor	5-HT_{2c} receptor	5-HT_6 receptor
3a	44	352	57	2839
3c	272	5168	9665	>10,000
3g	39	74	4886	>10,000
3o	29	95	91	1956
3q	4.6	85	241	2634
3v	215	19	215	768
6a	39	1824	1349	6925

Only two substitutions on the sulfonyl group were compared, though the study on the effect of substitution on sulfonyl group was not conclusive. General 2-naphthyl substituted compounds showed a little higher activity than 4-methoxyphenyl substituted compounds.

All the four compounds with methyl branch on three carbon spacer showed a good activity as shown in Table 2. But it showed very limited effect on the introduction



Scheme 2. Synthesis of the target compounds **6a**–**d**.

of methyl group, and only one compound (**6d**) was more active than its straight chain congener (**3j** and **3x**).

Since SB-258719 showed a modest affinity but high selectivity, the methyl branch on the three carbon spacer could be useful for the selectivity over different 5-HT receptors.

Seven compounds with high 5-HT_7 activity were further evaluated for their selectivity on 5-HT_{1a}, 5-HT_{2a}, 5-HT_{2c}, and 5-HT_6 receptors. Most of the evaluated compounds showed good selectivity over 5-HT_6 receptors, but poor selectivity over 5-HT_{1a} receptors. Among the synthesized compounds, **3c** showed good activity over 5-HT_7 (IC_{50} = 37 nM) and good selectivity over 5-HT_{1a} (IC_{50} = 272 nM), 5-HT_{2a} (5168 nM), 5-HT_{2c} (9665 nM), and 5-HT_6 (>10,000 nM). Compound **3o** showed a poor selectivity but good activity for the most of receptors with IC_{50} values of 12, 29, 95, and 91 nM for 5-HT_7, 5-HT_{1a}, 5-HT_{2a}, and 5-HT_{2c} receptors, respectively. The methyl branched compound **6a** showed moderate selectivity for 5-HT_{2a}, 5-HT_{2c}, and 5-HT_6 receptors.

4. Conclusion

Twenty-eight arylamides linked with a spacer to phenylpiperazine were synthesized and evaluated as 5-HT_7 antagonists. The synthesized compounds showed different activity depending on the substitution on piperazine. Compounds which have $–CF_3$, $–OCH_3$, or –F substituted phenyl group on piperazine showed good activity with IC_{50} values 12–375 nM. Among the synthesized compounds, **3c** showed good activity on 5-HT_7 (IC_{50} = 37 nM) and good selectivity on 5-HT_{1a} (IC_{50} = 272 nM), 5-HT_{2a} (5168 nM), 5-HT_{2c} (9665 nM), and 5-HT_6(>10,000 nM).

5. Experimental

5.1. Materials and methods

All the melting points of the synthesized compounds were taken in Pyrex capillaries using electrothermal digital melting point apparatus (Büchi) and were not corrected. ^{1}H NMR spectra were recorded on a 400 MHz Varian FT-NMR using tetramethylsilane as an internal standard. Mass spectra data were obtained on a Jeol JMS 700 high resolution mass spectrometer at the Korea Basic Science Institute (Daegu). Most of the reagents were purchased from Aldrich Chemical Company and Merck Company.

5.2. General procedure for the preparation of 4-methoxy-N-{3-[4-(substituted phenyl)-piperazin-1-yl]-propyl}-benzenesulfonamides (3a–x)

To a suspension of 1-(4-substituted aryl) piperazine (0.5 mmol, 1 equiv) and triethylamine (0.75 mmol, 1.5 equiv) in dichloromethane was added 1-bromo-3-chloro-propane (1.0 mmol, 2 equiv). The reaction mixture was stirred at rt for 16 h. The reaction mixture was made basic to pH 9 with saturated $NaHCO_3$ solution, and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography to give 1-(3-chloro-propyl)-4-Ar_1-piperazine (dichloromethane/methanol = 20:1).

For the further conversion to sulfonamides, NaH (0.5 mmol, 1 equiv) was added to a suspension of arylbenzenesulfonamide (0.5 mmol, 1 equiv) in DMF (15 mL). After stirring at 60 °C for 30 min under nitrogen, 1-(3-chloro-propyl)-4-Ar_1-piperazine (0.5 mmol, 1 equiv) in DMF (10 mL) was added. The reaction mixture was stirred at 80 °C for 16 h. After cooling, the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography to give Ar_2-N-[3-(4-Ar_1-piperazin-1-yl)-propyl]-sulfonamide (ethyl acetate/*n*-hexane/methanol = 10:1:1).

5.2.1. 4-Methoxy-*N*-{3-[4-(*m*-trifluoromethylphenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3a). Pale yellow solid, 11 mg (5%), mp 93–95 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.35 (m, 1H), 7.07 (m, 3H), 6.97 (m, 2H), 3.87 (s, 3H), 3.25 (s, 4H), 3.08 (t, J = 11.6 Hz, 2H), 2.59 (s, 4H), 2.49 (t, J = 12.0 Hz, 2H), 1.70 (m, 2H). HR-FABMS Calcd for $C_{21}H_{27}F_3N_3O_3S_1$ (M^++H): 458.1725, Found: 458.1726.

5.2.2. 4-Methoxy-*N*-{3-[4-(*p*-trifluoromethylphenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3b). Yellow solid, 7 mg (3%), mp 105–106 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.49 (d, J = 8.4 Hz, 2H), 6.97 (m, 2H), 6.92 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H), 3.29 (s, 4H), 3.08 (t, J = 11.6 Hz, 2H), 2.57 (s, 4H), 2.48 (t, J = 11.6 Hz, 2H), 1.70 (m, 2H). HR-FABMS Calcd for $C_{21}H_{27}F_3N_3O_3S_1$ (M^++H): 458.1725, Found: 458.1722.

5.2.3. 4-Methoxy-*N*-{3-[4-(*o*-methoxyphenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3c). Yellow oil, 83 mg (43%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 9.2 Hz, 2H), 6.91 (m, 5H), 3.79 (s, 3H), 3.20 (s, 3H), 3.04 (m, 6H), 2.56 (m, 4H), 2.42 (t, J = 6.4 Hz, 2H), 1.61 (m, 2H). HR-FABMS Calcd for $C_{21}H_{30}N_3O_4S$ (M^++H): 420.1957, Found: 420.1953.

5.2.4. 4-Methoxy-*N*-{3-[4-(*m*-methoxyphenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3d). Pale yellow solid, 61 mg (26%), mp 97–99 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.17 (t, J = 16.4 Hz, 1H), 6.97 (m, 2H), 6.52 (d, J = 10.8 Hz, 1H), 6.46 (s, 1H), 6.44 (d, J = 10.8 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.20 (s, 4H), 3.08 (t, J = 11.6 Hz, 2H), 2.56 (s, 4H), 2.47 (t, J = 11.6 Hz, 2H), 1.68 (m, 2H). HR-FABMS Calcd for $C_{21}H_{30}N_3O_4S$ (M^++H): 420.1957, Found: 420.1959.

5.2.5. 4-Methoxy-*N*-{3-[4-(*p*-methoxyphenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3e). Pale yellow solid, 35 mg (17%), mp 116–119 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 6.96 (m, 2H), 6.91 (m, 2H), 6.84 (m, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.09 (m, 6H),

2.58 (s, 4H), 2.47 (t, J = 11.6 Hz, 2H), 1.67 (m, 2H). HR-FABMS Calcd for $C_{21}H_{30}N_3O_4S$ (M^++H): 420.1957, Found: 420.1956.

5.2.6. 4-Methoxy-*N*-{3-[4-(*o*-fluorophenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3f). Yellow oil, 58 mg (16%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.05 (m, 2H), 6.96 (m, 4H), 3.87 (s, 3H), 3.12 (s, 4H), 3.08 (t, J = 11.6 Hz, 2H), 2.60 (s, 4H), 2.48 (t, J = 11.6 Hz, 2H), 1.67 (m, 2H). HR-FABMS Calcd for $C_{20}H_{27}FN_3O_3S$ (M^++H): 408.1757, Found: 408.1752.

5.2.7. 4-Methoxy-*N*-{3-[4-(*p*-fluorophenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3g). Pale yellow solid, 45 mg (22%), mp > 300 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.2 Hz, 2H), 6.87–6.92 (m, 4H), 6.79–6.83 (m, 2H), 3.79 (s, 3H), 3.08–3.10 (m, 4H), 2.99–3.03 (m, 2H), 2.52–2.58 (m, 4H), 2.42–2.48 (m, 2H), 1.62–1.68 (m, 2H). HR-FABMS Calcd for $C_{20}H_{27}FN_3O_3S$ (M^++H): 408.1757, Found: 408.1759.

5.2.8. 4-Methoxy-*N*-{3-[4-(3,4-dichlorophenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3h). Yellow oil, 43.9 mg (10.6%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 9.2 Hz, 1H), 7.25–7.28 (m, 2H), 6.94–6.98 (m, 2H), 6.72 (d, J = 12.0 Hz, 1H), 3.86 (s, 3H), 3.13–3.20 (m, 6H), 2.54 (t, J = 10.0 Hz, 4H), 2.39 (t, J = 14.4 Hz, 2H), 1.76–1.80 (m, 2H) HR-FABMS Calcd for $C_{20}H_{26}Cl_2N_3O_3S$ (M^++H): 458.1072, Found: 458.1074.

5.2.9. 4-Methoxy-*N*-[3-(4-benzyl-piperazin-1-yl)-propyl]-benzenesulfonamide (3i). Yellow oil, 16.4 mg (4.5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 9.2 Hz, 2H), 7.32 (d, J = 4.4 Hz, 4H), 6.96 (d, J = 9.2 Hz, 2H), 3.87 (s, 3H), 3.52 (s, 2H), 3.04 (t, J = 11.2 Hz, 2H), 2.42–2.56 (m, 4H), 2.40 (t, J = 11.6 Hz, 4H), 1.59–1.62 (m, 2H) HR-FABMS Calcd for $C_{21}H_{30}N_3O_3S$ (M^++H): 404.2008, Found: 404.2007.

5.2.10. 4-Methoxy-*N*-[3-(4-phenyl-piperazin-1-yl)-propyl]-benzenesulfonamide (3j). Pale yellow solid, 92 mg (48%), mp > 300 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 9.2 Hz, 2H), 7.18–7.22 (m, 2H), 6.85–9.92 (m, 4H), 6.81 (tt, J = 7.2 and 0.8 Hz, 1H), 3.79 (s, 3H) 3.14–3.17 (m, 4H), 3.00–3.03 (m, 2H), 2.50–2.56 (m, 4H), 2.42–2.45 (m, 2H), 1.62–1.65 (m, 2H). HR-FABMS Calcd for $C_{20}H_{27}N_3O_3S$ (M^++H): 390.1851, Found: 390.1846.

5.2.11. 4-Methoxy-*N*-{3-[4-(*p*-nitrophenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3k). Brown oil, 57.8 mg (26%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 9.2 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 3.86 (s, 3H), 3.44–3.50 (m, 4H), 3.09 (t, J = 6.0 Hz, 2H), 2.54–2.68 (m, 6H), 1.72–1.80 (m, 2H). HR-FABMS Calcd for $C_{20}H_{27}N_4O_5S$ (M^++H): 435.1702, Found: 435.1706.

5.2.12. 4-Methoxy-*N*-{3-[4-(4-acetophenyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3l). Pale yellow solid, 31.2 mg (29%), mp > 300 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 9.2 Hz, 2H), 7.80 (d, J = 9.2 Hz, 2H), 6.98 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 9.2 Hz, 2H), 3.87 (s, 3H), 3.37–3.40 (m, 4H), 3.07–3.10 (m, 2H), 2.56–2.64 (m, 4H), 2.52–2.54 (m, 2H), 2.51 (s, 3H), 1.70–1.74 (m, 2H). HR-FABMS Calcd for $C_{22}H_{30}N_3O_4S$ (M^++H): 432.1957, Found: 432.1953.

5.2.13. Benzyl-4-(4-methoxyphenyl sulfonylaminopropyl)-piperazine-1-carboxylate (3m). Red brown oil, 37.7 mg (19%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.8 Hz, 2H), 7.32–7.38 (m, 5H), 6.97 (d, J = 8.8 Hz, 2H), 5.13 (s, 2H), 3.87 (s, 3H), 3.50–3.52 (m, 4H), 3.05–3.08 (m, 2H), 2.36–2.48 (m, 6H), 1.60–1.70 (m, 2H). HR-FABMS Calcd for $C_{22}H_{30}N_3O_5S$ (M^++H): 448.1906, Found: 448.1910.

5.2.14. 4-Methoxy-*N*-{3-[4-(furan-2-yl-methanoyl)-piperazin-1-yl]-propyl}-benzenesulfonamide (3n). Brown oil, 27.7 mg (13%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 6.8 Hz, 2H), 7.80 (d, J = 6.8 Hz, 2H), 7.48 (dd, J = 2.0 and 0.8 Hz, 1H), 6.97 (dd, J = 2.0 and 0.8 Hz, 1H), 6.48 (dd, J = 4.0 and 2.0 Hz, 1H), 3.87 (s, 3H), 3.07–3.10 (m, 2H), 2.46–2.51 (m, 8H), 1.65–1.75 (m, 2H), 0.85–0.88 (m, 2H). HR-FABMS Calcd for $C_{19}H_{26}N_3O_5S$ (M^++H): 408.1593, Found: 408.1591.

5.2.15. Naphthalene-2-sulfonic acid {3-[4-(3-trifluoromethylphenyl)-piperazin-1-yl]-propyl}-amide (3o). Pale yellow solid, 105 mg (20%), mp 86–88 °C: ^{1}H NMR (400 MHz, DMSO d_6) δ 8.44 (s, 1H), 8.14 (m, 2H), 8.04 (m, 1H), 7.90 (d, J = 10.4 Hz, 1H), 7.84 (d, J = 10.8 Hz, 1H), 7.68 (m, 3H), 7.46 (s, 1H), 7.05 (m, 1H), 3.05 (s, 4H), 2.84 (m, 2H), 2.32 (m, 4H), 2.25 (t, J = 13.6 Hz, 2H), 1.55 (m, 2H). HR-FABMS Calcd for $C_{24}H_{26}F_3N_3O_2S$ (M^++H): 478.1776, Found: 478.1773.

5.2.16. Naphthalene-2-sulfonic acid {3-[4-(4-trifluoromethylphenyl)-piperazin-1-yl]-propyl}-amide (3p). White solid, 205 mg (66%), mp 136–139 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.96 (m, 2H), 7.91 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 10.4 Hz, 1H), 7.63 (m, 2H), 7.48 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.28 (s, 4H), 3.14 (t, J = 11.6 Hz, 2H), 2.55 (s, 4H), 2.46 (t, J = 11.6 Hz, 2H), 1.70 (m, 2H). HR-FABMS Calcd for $C_{24}H_{27}F_3N_3O_2S$ (M^++H): 478.1776, Found: 478.1777.

5.2.17. Naphthalene-2-sulfonic acid {3-[4-(2-methoxyphenyl)-piperazin-1-yl]-propyl}-amide (3q). Yellow solid, 27 mg (5%), mp 100–102 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.70 (m, 2H), 6.88 (m, 4H), 3.75 (s, 3H), 3.23 (t, J = 14.8 Hz, 2H), 2.88 (s, 4H), 2.40 (s, 4H), 2.29 (t, J = 13.6 Hz, 2H), 1.66 (m, 2H). HR-FABMS Calcd for $C_{24}H_{30}N_3O_3S$ (M^++H): 440.2008, Found: 440.2004.

5.2.18. Naphthalene-2-sulfonic acid {3-[4-(3-methoxyphenyl)-piperazin-1-yl]-propyl}-amide (3r). Brown oil, 11 mg (5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.20 (d, J = 8.0 Hz, 2H), 8.14 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 10.4 Hz, 1H), 7.70 (m, 2H), 7.09 (t, J = 16.4 Hz, 1H), 6.40 (m, 3H), 3.71 (s, 3H), 3.20 (m, 2H), 3.04 (s, 4H), 2.37 (s, 4H),

2.27 (t, J = 14.0 Hz, 2H), 1.65 (m, 2H). HR-FABMS Calcd for $C_{24}H_{30}N_3O_3S$ (M^++H): 440.2008, Found: 440.2005.

5.2.19. Naphthalene-2-sulfonic acid {3-[4-(4-methoxyphenyl)-piperazin-1-yl]-propyl}-amide (3s). Pale brown solid, 26 mg (8%), mp 150–153 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.14 (t, J = 18.8 Hz, 2H), 8.05 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 10.8 Hz, 1H), 7.69 (m, 2H), 6.80 (s, 4H), 3.67 (s, 3H), 3.31 (m, 2H), 2.83 (m, 4H), 2.25 (m, 4H), 2.23 (t, J = 13.6 Hz, 2H), 1.54 (m, 3H). HR-FABMS Calcd for $C_{24}H_{30}N_3O_3S$ (M^++H): 440.2008, Found: 440.2009.

5.2.20. Naphthalene-2-sulfonic acid {3-[4-(2-fluorophenyl)-piperazin-1-yl]-propyl}-amide (3t). Dark brown oil, 130 mg (31%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.95–7.98 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 10.4 Hz, 1H), 7.61–7.66 (m, 2H), 6.90–7.07 (m, 4H), 3.29 (t, J = 15.2 Hz, 2H), 3.06 (s, 4H), 2.55 (s, 4H), 2.39 (t, J = 14.0 Hz, 2H), 1.67–1.82 (m, 2H). HR-FABMS Calcd for $C_{23}H_{27}FN_3O_2S$ (M^++H): 428.1808, Found: 428.1805.

5.2.21. Naphthalene-2-sulfonic acid {3-[4-(4-fluorophenyl)-piperazin-1-yl]-propyl}-amide (3u). Pale yellow solid, 28 mg (7.2%), mp 143–145 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.96 (d, J = 11.2 Hz, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 10.4 Hz, 1H), 7.61–7.65 (m, 2H), 6.98 (t, J = 17.6 Hz, 2H), 6.86–6.89 (m, 2H), 3.13 (t, J = 10.4 Hz, 6H), 2.56 (t, J = 10.0 Hz, 4H), 2.46 (t, J = 11.6 Hz, 2H), 1.65–1.71 (m, 2H). HR-FABMS Calcd for $C_{23}H_{27}FN_3O_2S$ (M^++H): 428.1808, Found: 428.1805.

5.2.22. Naphthalene-2-sulfonic acid {3-[4-(3,4-dichlorophenyl)-piperazin-1-yl]-propyl}-amide (3v). Pale yellow solid, 113 mg (23%), mp 146–148 °C: ^{1}H NMR (400 MHz, DMSO d_6) δ 8.44 (s, 1H), 8.15 (m, 2H), 8.04 (t, J = 13.2 Hz, 1H), 7.85 (m, 1H), 7.69 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.03 (s, 1H), 6.85 (d, J = 12 Hz, 1H), 3.00 (m, 4H), 2.84 (m, 2H), 2.30 (s, 4H), 2.23 (t, J = 13.6 Hz, 2H), 1.53 (m, 2H). HR-FABMS Calcd for $C_{23}H_{26}Cl_2N_3O_2S$ (M^++H): 478.1123, Found: 478.1119.

5.2.23. Naphthalene-2-sulfonic acid [3-(4-benzyl-piperazin-1-yl)-propyl]-amide (3w). Yellow solid, 40 mg (31%), mp 110–113 °C: ^{1}H NMR (400 MHz, DMSO d_6) δ 8.37 (s, 1H), 8.10 (m, 2H), 7.99 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 10.4 Hz, 1H), 7.63 (m, 2H), 7.26 (m, 2H), 7.18 (d, J = 6.8 Hz, 1H), 3.30 (s, 2H), 2.75 (m, 2H), 2.27 (m, 2H), 2.12 (m, 8H), 1.42 (m, 2H). HR-FABMS Calcd for $C_{24}H_{30}N_3O_2S$ (M^++H): 424.2059, Found: 424.2061.

5.2.24. Naphthalene-2-sulfonic acid [3-(4-phenyl-piperazin-1-yl)-propyl]-amide (3x). Yellow oil 13 mg (5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.97 (d, J = 9.6 Hz, 2H), 7.80 (m, 2H), 7.58 (t, J = 15.2 Hz, 2H), 7.29 (t, J = 16.4 Hz, 1H), 7.25 (m, 2H), 6.88 (m, 2H), 3.51 (m, 2H), 3.21 (m, 4H), 2.87 (m, 4H), 2.72 (m, 2H), 0.86 (m, 2H). HR-FABMS Calcd for $C_{23}H_{28}N_3O_2S$ (M^++H): 410.1902, Found: 410.1901.

5.3. General procedure for the preparation of 4-methoxy-*N*-{3-[4-(*m*-trifluoromethylphenyl)-piperazin-1-yl]-1-methyl-propyl}-benzenesulfonamide (6a–d)

Tosyl chloride (14.1 g, 74 mmol) in 30 mL of pyridine was added dropwise to the solution of 1,3-butanediol (6.2 g, 68 mmol) in 20 mL pyridine at −20 °C. The mixture was stirred at −25 °C for 1 h. Water was added, and the mixture was stirred for 20 min. The reaction mixture was extracted with chloroform, and the organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and the solvent was removed in vacuo. After column chromatography on silica gel (*n*-hexane/ethyl acetate = 3:2), 1-tosyl-3-hydroxy-butane was obtained in ca. 40% yield.

2-Hydroxy-4-tosyl-butane (0.5 mmol, 1 equiv) and 4-Ar_1-piperazine (0.75 mmol, 1.5 equiv) were refluxed in acetonitrile (25 mL) for 16 h under nitrogen. On cooling to rt, the solvent was removed in vacuo, the residue was extracted with dichloromethane. The organic layer was washed with water, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude oil was purified by column chromatography (methylene chloride/methanol = 9:1). Tosyl chloride (0.75 mmol, 1.5 equiv) in 10 mL of pyridine was added to a pyridine solution of 2-hydroxy-4-(4-Ar_1-piperazine)-butane (0.5 mmol, 1 equiv) at rt. The mixture was stirred at rt for 16 h. To the reaction mixture, water (2 mL) was added and stirred for 20 min. The reaction mixture was extracted with chloroform. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 3:2) to give 2-tosyl-4-(4-Ar_1-piperazine)-butane.

For the further conversion to sulfonamides, NaH (0.5 mmol, 1 equiv) was added to a solution of 4-methoxy-benzenesulfonamide (0.5 mmol, 1 equiv) in DMF (15 mL), and the reaction mixture was stirred at 60 °C for 30 min. under nitrogen. 2-Tosyl-4-(4-Ar_1-piperazine)-butane (0.5 mmol, 1 equiv) in DMF (10 mL) was added slowly to the reaction mixture. The mixture was stirred at 60° Covernight under nitrogen. After cooling, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography (ethyl acetate/*n*-hexane/methanol = 10:1:1).

5.3.1. 4-Methoxy-*N*-{3-[4-(*m*-trifluoromethylphenyl)-piperazin-1-yl]-1-methyl-propyl}-benzenesulfonamide (6a). Pale yellow oil, 90 mg (40%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.32 (t, J = 13.2 Hz, 1H), 7.06 (m, 3H), 6.96 (m, 2H), 3.84 (s, 3H), 3.25 (m, 6H), 2.63 (m, 4H), 1.69 (m, 2H), 1.00 (s, 2H). HR-FABMS Calcd for $C_{22}H_{29}F_3N_3O_3S$ (M^++H): 472.1882, Found: 472.1883.

5.3.2. 4-Methoxy-*N*-{3-[4-(*o*-methoxyphenyl)-piperazin-1-yl]-1-methyl-propyl}-benzen sulfonamide (6b). Yellow oil, 10 mg (6%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76

(m, 2H), 6.97 (m, 2H), 6.91 (m, 2H), 6.82 (d, J = 9.2 Hz, 2H), 3.85 (s, 6H), 3.28 (m, 1H), 3.06 (m, 6H), 2.73 (m, 2H), 2.63 (m, 4H), 1.00 (s, 2H). HR-FABMS Calcd for $C_{22}H_{32}N_3O_4S$ (M^++H): 434.2114, Found: 434.2111.

5.3.3. 4-Methoxy-*N*-{3-[4-(*p*-fluorophenyl)-piperazin-1-yl]-1-methyl-propyl}-benzenesulfonamide (6c). Brown oil, 24 mg (6%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 2H), 6.93 (m, 4H), 6.86 (m, 3H), 3.84 (s, 3H), 3.26 (m, 1H), 3.09 (m, 4H), 2.60 (m, 4H), 1.76 (m, 1H), 1.59 (m, 1H), 1.00 (s, 2H). HR-FABMS Calcd for $C_{21}H_{29}FN_3O_3S$ (M^++H): 422.1914, Found: 422.1902.

5.3.4. 4-Methoxy-*N*-[3-(4-phenyl-piperazin-1-yl)-1-methyl-propyl]-benzenesulfonamide (6d). Pale brown solid, 30 mg (15%), mp 92–94 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.27 (m, 2H), 6.96 (m, 4H), 6.88 (m, 1H), 3.85 (s, 3H), 3.20 (m, 4H), 2.96 (m, 2H), 2.76 (m, 4H), 2.53 (m, 2H), 1.74 (m, 1H), 1.44 (m, 1H), 0.95 (s, 2H). HR-FABMS Calcd for $C_{21}H_{30}N_3O_3S$ (M^++H): 404.2008, Found: 404.2004.

5.4. Radioligand binding assays[19]

5.4.1. [^{3}H]LSD binding to serotonin 5-HT$_7$ receptor. Membranes from stable CHO cell line expressing the human recombinant 5-HT$_7$ serotonin receptor (PerkinElmer Life and Analytical Sciences, Boston, USA) were used. For 5-HT$_7$ receptor binding assay, cell membrane, 3 nM [^{3}H]LSD and appropriate concentrations of test compounds were added to 0.25 mL of 50 mM Tris·HCl (pH 7.4) buffer containing 10 mM $MgCl_2$ and 0.5 mM EDTA. The mixture was incubated for 90 min at 27 °C, and the reaction was terminated by rapid filtration through Whatman GF/C glass fiber filter presoaked in 0.3% polyethylenimine. The filter was covered with MeltiLex, sealed in a sample bag followed by drying in the microwave oven, and counted by MicroBeta Plus (Wallac, Finland). Nonspecific binding was determined in the presence of 0.5 μM methiothepin. Competition binding studies were carried out with 7–8 varied concentrations of the test compounds run in duplicate tubes, and isotherms from three assays were calculated by computerized nonlinear regression analysis (GraphPad Prism Program, San Diego, USA) to yield inhibition values (IC_{50}).

5.4.2. [^{3}H]8-OH-DPAT binding to serotonin 5-HT$_{1a}$ receptor. Membranes from stable CHO-K1 cell line expressing the human recombinant 5-HT$_{1a}$ serotonin receptor were used. For the binding assay, aliquots of receptor membranes, 0.5 nM [^{3}H]8-OH-DPAT and appropriate concentrations of test compounds were added to 0.25 mL of 50 mM Tris·HCl (pH 7.4) buffer containing 1 mM EDTA and 2.5 mM $MgCl_2$.

Nonspecific binding was determined using 0.5 AM methiothepin. Incubations were carried out for 30 min at 37 °C saturated, and these were terminated by rapid filtration using an Inotech cell harvester through Whatman GF/C glass fiber filter presoaked in 0.3% polyethylenimine. The filter was covered with MeltiLex, sealed in a sample bag followed by drying in the microwave oven, and counted by MicroBeta Plus.

5.4.3. [^{3}H]Ketanserin binding to serotonin 5-HT$_{2a}$ receptor. For serotonin 5-HT$_{2a}$ binding, an aliquot of frozen membrane from CHO-K1 cell line expressing the human recombinant 5-HT$_{2a}$ receptor and [^{3}H]Ketanserin (1 nM) were used in the presence of mianserin (0.5 AM) as nonspecific. The reaction mixture was incubated for 15 min at 37 °C using 50 mM Tris·HCl (pH 7.4) buffer, and harvested through Whatman GF/C glass fiber filter presoaked in 0.05% Brij.

5.4.4. [^{3}H]Mesulergine binding to serotonin 5-HT$_{2c}$ receptor. Frozen membranes from stable CHO-K1 cell line expressing the human recombinant 5-HT$_{2c}$ receptor were used. For the binding assay, [^{3}H]Mesulergine (1 nM), receptor membrane and test compounds were added into 50 mM Tris·HCl (pH 7.7) buffer containing 0.1% ascorbic acid and 10 AM pargyline. Nonspecific binding was determined using 0.5 AM mianserin. The incubations were performed for 30 min at 37 °C, and these were terminated by rapid filtration through Whatman GF/C glass fiber filter presoaked in 1% BSA.

5.4.5. [^{3}H]LSD binding to serotonin 5-HT$_6$ and 5-HT$_7$ receptor. For receptor binding assays, human 5-HT$_6$ and 5-HT$_7$ serotonin receptor expressed in HeLa cells were used. Frozen membrane, 1.8 nM [^{3}H]LSD and appropriate concentrations of test compounds were added to 0.25 mL of assay buffer. Incubations were carried out for 60 min at 37 °C, and these were terminated by rapid filtration through Whatman GF/C glass fiber filter presoaked in 0.3% polyethylenimine. Methiothepin and 50 mM Tris·HCl (pH 7.4) containing 10 mM $MgCl_2$ and 0.5 mM EDTA, were used as the nonspecific ligand or assay buffer, respectively.

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