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Synthesis and Inhibition Effects on 5-HT$_6$ Receptor of Benzothiazole Derivatives

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A novel series of aryl sulfonylpiperazine derivatives (**5-15**) were synthesized as 5-HT$_6$ ligands. *In vitro* assay was evaluated by measuring the 5-HT-induced Ca^{2+} increases using HeLa cell line expressing the cloned human 5-HT$_6$ receptor, and the compound **13** showed potent 5-HT$_6$ receptor antagonistic effect with IC_{50} value of 3.9 μM. Compound **13** also showed good selectivity on the 5-HT$_6$ over 5-HT$_4$ and 5-HT$_7$ receptors.

Key Words : Sulfonamide, *N*-Methyl piperazine, 5-HT$_6$ receptor antagonist

Introduction

The 5-HT$_6$ receptor is a member of the family of receptors that mediate the physiological effects of the neurotransmitter serotonin (5-HT).[1-3] This is one of the most recent additions to the family of serotonin receptors which was cloned in 1996[4,5] as a gene codifying a polypeptide chain of 440 amino acids[5,6] that is positively coupled to the adenylate cyclase[7-9] cascade *via* the Gs protein. In particular, it is widely reported to be located in brain regions associated with learning and memory such as the cerebral cortex, the hippocampus, and the striatum.[10] It has been demonstrated that antagonism of the 5-HT$_6$ receptor modulates the release of a wide variety of neurotransmitters including elevating extracellular levels of both glutamate and acetylcholine in brain regions such as the medial prefrontal cortex (mPFC) and the hippocampal formation (HPC).[11,12] This modulatory activity suggests potential utility for 5-HT$_6$ receptor antagonists in the treatment of cognitive impairments associated with Alzheimer's disease and Schizophrenia. Clearly, there is much evidence that the 5-HT$_6$ receptor is involved in the pathogenesis of CNS diseases [13-18] related to cognitive or eating disorders, so it appears to be an attractive therapeutic target that should be exploited for drug development. Because it is known to be expressed almost exclusively in the CNS,[19-23] it is possible that new therapeutic agents targeting this receptor might have relatively few peripheral side effects.

As an effort to identify 5-HT$_6$ antagonists, a pharmacophore model composed of two hydrophobic areas (ARs) connected with hydrogen bond acceptor (HBA), and one proton donor group (PI) was proposed by Lopez-Rodriguez.[23] The PI, a basic nitrogen, could be the primary binding site at the receptor aspartate residue, and two other aromatic sites may be involved in the secondary binding (π-staking) interactions with the receptor.

According to the literature survey, compounds containing basic ionizable cyclic amines mainly piperazine motif and hydrogen bond acceptor sulfonamide or sulfone group with indole or other heterocyclic rings as a hydrophobic group are the necessary pharmacophoric requirement for the 5-HT$_6$ receptor ligands.[24] Several diverse classes of compounds were taken up for synthesis and evaluation (Fig. 1).

Recently we have reported a novel series of benzoisothiazole and benzothiazole derivatives having the arylsulfonamides, onto which an ionizable nitrogen (PI) was introduced as *N,N*-dimethylformimiamide.[25] As our continuing efforts to identify the novel 5-HT$_6$ antagonists, we have synthesized a novel series of aryl sulfonylpiperazine derivatives (**5-15**) containing piperazine motif as a 5-HT$_6$ receptor ligand in this report.

Materials and Methods

All the melting points of the synthesized compounds were taken in Pyrex capillaries using electrothermal digital melting point apparatus (Buchi) 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.

Synthesis.

Procedure for the Preparation of 2-Chloro-6-nitrobenzo [*d*]thiazole (2): To a solution of 2-chlorobenzothiazole (1.20 g, 7.07 mmol) in concentrated H_2SO_4 (6 mL) was added HNO_3 (69% solution, 0.6 mL) dropwise at 0 °C for 20 min. The mixture was stirred at 5 °C for 3 h, poured in ice-water. The precipitate was collected and washed 5% sodium bicarbonate and water, dried *in vacuo*.

2-Chloro-6-nitrobenzo[*d*]thiazole (2): Pale yellow solid (58%): ^{1}H NMR ($CDCl_3$) δ 9.10 (d, J = 2.4 Hz, 1H), 8.44 (dd, J = 2.4 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H).

Procedure for the Preparation of 2-(4-Methylpiperazin-1-yl)-6-nitrobenzo[*d*] thiazole (3): To a refluxing mixture of the 4-methylpiperazine (0.21 mL, 1.86 mmol) and sodium bicarbonate (0.31 g, 3.73 mmol) in 8 mL of 80% isopropyl alcohol a solution of 2-chloro-6-nitrobenzo[*d*]thiazole (**2**)

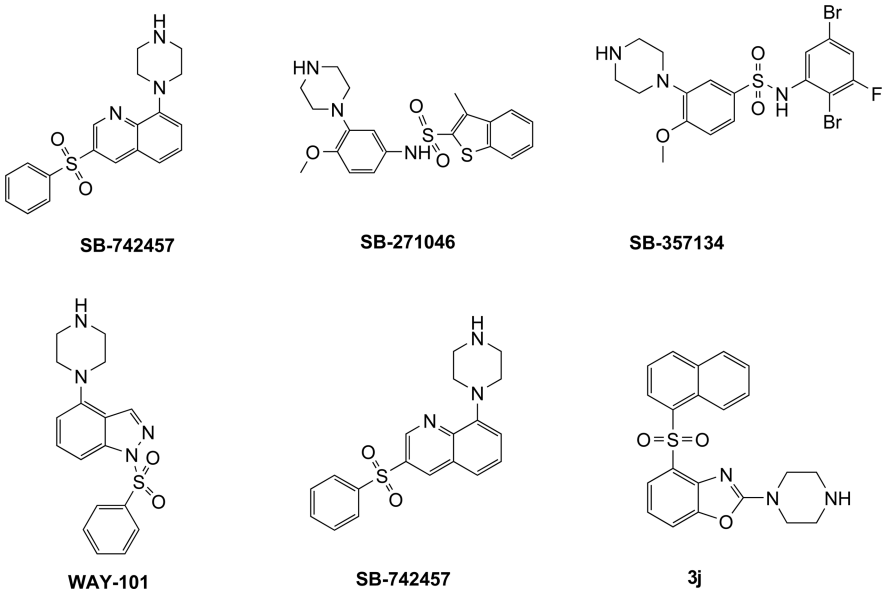


Figure 1. Structures of piperazine containg 5-HT_6 receptor antagonists.

(0.2 g, 0.93 mmol) in 5 mL of isopropyl alcohol was added drop wise. The mixture was refluxed 48 h. The solvent was evaporated under reduced pressure, and the sticky oil residue was suspended 10 mL of water. After stirring for 5 min, the mixture was extracted with methylene chloride, and the solvent was removed *in vacuo*.

2-(4-Methylpiperazin-1-yl)-6-nitrobenzo[*d*]thiazole (3): Orange solid (81%): ^{1}H NMR ($CDCl_3$) δ 8.51 (d, *J* = 2.4 Hz, 1H), 8.23 (dd, *J* = 2.4 Hz, 1H), 7.51 (d, *J* = 3.2 Hz, 1H), 3.74 (t, *J* = 5.2 Hz, 4H), 2.56 (t, *J* = 5.2 Hz, 4H), 2.37 (s, 3H).

Procedure for the Preparation of 2-(4-Methylpiperazin-1-yl)benzo[*d*]thiazol-6-amine (4). A solution of 2-(4-methylpiperazin-1-yl)-6-nitrobenzo[*d*]thiazole (**3**) (0.1 g, 0.36 mmol) in MeOH (10 mL) was subjected to hydrogenation using H_2 and 5% Pd-C (0.200 g). The catalyst was filtered on a bed of Celite, washed with MeOH, and the filtrate was concentrated *in vacuo*.

2-(4-Methylpiperazin-1-yl)benzo[*d*]thiazol-6-amine (4): Brown solid (51%): ^{1}H NMR ($CDCl_3$) δ 7.21 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 2.4 Hz, 1H), 3.49 (t, *J* = 5.2 Hz, 4H), 3.31 (s, 2H), 2.45 (t, *J* = 5.2 Hz, 4H), 2.26 (s, 3H).

General Procedure for the Preparation of 2-(4-Methylpiperazin-1-yl)-6-Ar-sulfonamido benzo[*d*]thiazol (5-15). For the further conversion to sulfonamides, sodium hydride (1 mmol) was added to a suspension of 2-(4-methylpiperazin-1-yl)benzo[*d*]thiazol-6-amine (**4**) (0.5 mmol) in DMF (5 mL). After stirring at 60 °C for 30 min under nitrogen, arylsulfonyl chloride (0.75 mmol) in DMF (5 mL) was added. The reaction mixture was stirred at 100 °C for 16 h. After cooling, the mixture was poured in to cold water and extracted three times with ethyl acetate (50 mL). 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 using ethyl acetate: methanol (2:1) as eluent.

2-(4-Methylpiperazin-1-yl)-6-phenylsulfonamidobenzo[*d*]thiazol (5): Light brown solid (43%), mp 248-250 °C: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.46 (s, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 4.4 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.25 (s, 1H), 3.63 (t, *J* = 5.2 Hz, 4H), 2.52 (t, *J* = 5.2 Hz, 4H), 2.35 (s, 3H). HR-FABMS Calcd for $C_{18}H_{21}N_4O_2S_2$ $[M+H]^+$: 389.1106, Found: 389.1107.

2-(4-Methylpiperazin-1-yl)-6-(4-methylphenyl)sulfonamidobenzo[*d*]thiazol (6): Pale yellow solid (31%), mp 208-210 °C: ^{1}H NMR ($CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.47 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.22 (s, 1H), 3.63 (t, *J* = 5.0 Hz, 4H), 2.52 (t, *J* = 5.0 Hz, 4H), 2.35 (d, *J* = 6.8 Hz, 6H). HR-FABMS Calcd for $C_{19}H_{23}N_4O_2S_2$ $[M+H]^+$: 403.1262, Found: 403.1265.

2-(4-Methylpiperazin-1-yl)-6-(4-methoxyphenyl)sulfonamidobenzo[*d*]thiazol (7): Yellow solid (20%), mp 156-159 °C: ^{1}H NMR ($CDCl_3$) δ 7.59 (d, *J* = 9.2 Hz, 2H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 9.2 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.20 (s, 1H), 3.81 (s, 3H), 3.63 (t, *J* = 5.2 Hz, 4H), 2.52 (t, *J* = 5.0 Hz, 4H), 2.35 (s, 3H). HR-FABMS Calcd for $C_{19}H_{23}N_4O_3S_2$ $[M+H]^+$: 419.1212, Found: 419.1211.

2-(4-Methylpiperazin-1-yl)-6-(4-isopropylphenyl)sulfonamidobenzo[d]thiazol (8): Brown solid (19%), mp 185-188 °C: ^{1}H NMR ($CDCl_3$) δ 7.58 (d, *J*= 8.4 Hz, 2H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.25-7.23 (m, 2H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.25 (s, 1H), 3.63 (t, *J* = 5.2 Hz, 4H), 2.95-2.88 (m, 1H), 2.52 (t, *J* = 5.2 Hz, 4H), 2.35 (s, 3H), 1.27-1.21 (m, 6H). HR-FABMS Calcd for $C_{21}H_{27}N_4O_2S_2$ $[M+H]^+$: 431.1575, Found: 431.1579.

2-(4-Methylpiperazin-1-yl)-6-(4-fluorophenyl)sulfonamidobenzo[d]thiazol (9): Light brown solid (47%), mp 213-215 °C: ^{1}H NMR ($CDCl_3$) δ 7.89-7.64 (m, 2H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.09-7.05 (m, 2H),

6.78 (d, *J* = 8.4 Hz, 1H), 6.26 (s, 1H), 3.64 (t, *J* = 5.0 Hz, 4H), 2.53 (t, *J* = 5.2 Hz, 4H), 2.35 (s, 3H). ^{13}C NMR (DMSO): 167.99, 165.45, 162.95, 149.93, 135.64, 130.95, 130.77, 129.76, 129.67, 120.84, 118.65, 116.42, 116.20, 114.88, (13C, aromatic), 53.70, 47.86 (4C, piperazine), 45.65 (1C, *N*-methyl) HR-FABMS Calcd for $C_{18}H_{20}FN_4O_2S_2$ $[M+H]^+$: 407.1012, Found: 407.1012.

2-(4-Methylpiperazin-1-yl)-6-(4-chlorophenyl)sulfonamidobenzo[*d*]thiazol (10): Gray solid (12%), mp 183-184 °C: ^{1}H NMR ($CDCl_3$) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.38-7.34 (m, 3H), 6.78 (dd, *J* = 8.8 Hz, 1H), 6.29 (s, 1H), 3.64 (t, *J* = 4.2 Hz, 4H), 2.53 (t, *J* = 4.2 Hz, 4H), 2.35 (s, 3H). HR-FABMS Calcd for $C_{18}H_{20}ClN_4O_2S_2$ $[M+H]^+$: 423.0716, Found: 423.0712.

2-(4-Methylpiperazin-1-yl)-6-(4-trifluoromethylphenyl)-sulfonamidobenzo[*d*]thiazol (11): Brown solid (24%), mp 189-190 °C: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.53 (s, 1H), 3.64 (t, *J* = 5.2 Hz, 4H), 2.53 (t, *J* = 5.2 Hz, 4H), 2.35 (s, 3H). HR-FABMS Calcd for $C_{19}H_{20}F_3N_4O_2S_2$ $[M+H]^+$: 457.0980, Found: 457.0982.

2-(4-Methylpiperazin-1-yl)-6-(4-nitrophenyl)sulfonamidobenzo[*d*]thiazol (12): Light brown solid (41%), mp 235-238 °C: ^{1}H NMR ($CDCl_3$) δ 8.25 (d, *J* = 9.2 Hz, 2H), 7.83 (d, *J* = 9.2 Hz, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 3.64 (t, *J* = 5.2 Hz, 4H), 2.53 (t, *J* = 5.0 Hz, 4H), 2.35 (s, 3H). ^{13}C NMR (DMSO): 168.15, 150.23, 149.72, 144.86, 131.01, 130.15, 128.30, 124.51, 121.19, 118.74, 115.35 (13C, aromatic), 53.69, 47.86 (4C, piperazine), 45.63 (1C, N-methyl). HR-FABMS Calcd for $C_{18}H_{20}N_5O_4S_2$ $[M+H]^+$: 434.0957, Found: 434.0960.

2-(4-Methylpiperazin-1-yl)-6-(1-naphthalenyl)sulfonamidobenzo[*d*]thiazol (13): Dark brown solid (10%), mp 154-156 °C: ^{1}H NMR ($CDCl_3$) δ 8.68 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.70-7.66 (m, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.56 (d, *J* = 8.6 Hz, 2H), 3.59 (t, *J* = 5.2 Hz, 4H), 2.49 (t, *J* = 5.2 Hz, 4H), 2.33 (s, 3H). HR-FABMS Calcd for $C_{22}H_{23}N_4O_2S_2$ $[M+H]^+$: 439.1262, Found: 439.1259.

2-(4-Methylpiperazin-1-yl)-6-(8-quinolinyl)sulfonamidobenzo[*d*]thiazol (14): Pale yellow solid (11%), mp 239-240 °C: ^{1}H NMR ($CDCl_3$) δ 9.17 (d, 1H), 8.29 (t, *J* = 8.8 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.70 (q, *J* = 3.2 Hz, 1H), 7.63 (q, *J* = 4.4 Hz, 1H), 7.54-7.51 (m, 2H), 7.44 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 3.56 (t, *J* = 5.2 Hz, 4H), 2.47 (t, *J* = 5.0 Hz, 4H), 2.31 (s, 3H). HR-FABMS Calcd for $C_{21}H_{22}N_5O_2S_2$ $[M+H]^+$: 440.1215, Found: 440.1212.

2-(4-Methylpiperazin-1-yl)-6-(thiophen-2-yl)sulfonamidobenzo[d]thiazol (15): Yellow solid (46%), mp 232-233 °C: ^{1}H NMR ($CDCl_3$) δ 7.78 (d, *J* = 5.0 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 4.0 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.12-7.07 (m, 2H), 3.59 (t, *J* = 5.2 Hz, 4H), 2.47 (t, *J* = 5.2 Hz, 4H), 2.27 (s, 3H). ^{13}C NMR (DMSO): 168.00, 150.02, 139.75, 133.14, 132.21, 130.88, 130.80, 127.50, 120.88, 118.61, 114.85 (11C, aromatic), 53.70, 47.86 (4C, piperazine), 45.65 (1C, *N*-methyl). HR-FABMS Calcd for $C_{16}H_{19}N_4O_2S_3$ $[M+H]^+$: 395.0670, Found: 395.0667.

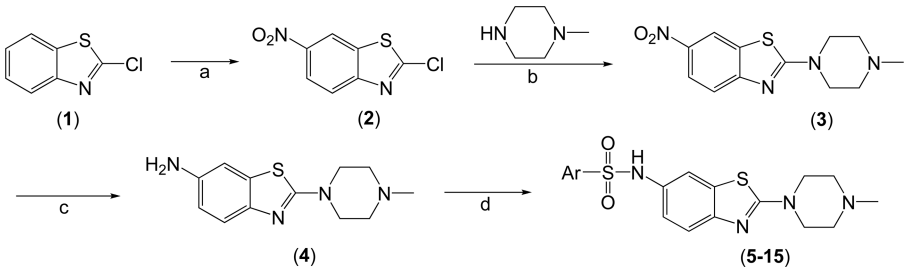
Functional Assays.

Cell Culture and Transfection: HeLa and HEK293 cells were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, penicillin (100 units/mL), and streptomycin (100 μg/mL) at 37 °C in a humidified atmosphere of 5% CO_2 and 95% air. For 5-HT$_6$R activity, HEK293 or HeLa cell lines stably expressing the human 5-HT$_6$R, were used. For 5-HT$_4$R or 5-HT$_7$R activity, human 5-HT$_4$R or 5-HT$_7$R receptor gene was transiently expressed in HEK293 cells and the receptor activity assayed using the FDSS6000 system.

Assay of 5-HT Receptors Using the FDSS6000 System: We measured 5-HT-induced Ca^{2+} increases using a promiscuous Ga_{15} protein that facilitates coupling of Ga_S-coupled receptors to phospholipase C and consequent intracellular Ca^{2+} release, which is subsequently detected using an FDSS6000 96-well fluorescence plate reader as previously reported.[30] Briefly, HeLa or HEK293 cells were loaded with the Ca^{2+} indicator dye Fluo-4-AM (5 μM) and 0.001% Pluronic F-127 (Molecular Probes, Eugene, OR) and incubated in a HEPES-buffered solution (150 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 10 mM HEPES, 10 mM glucose, 2 mM $CaCl_2$) for 1 h at 37 °C. Then, the cells were washed three times with a HEPES-buffered solution and maintained with a volume of 80 μL/well in 96-well plates. For antagonist experiments, cells were pre-incubated with compounds for 15 min before the addition of an agonist. The fluorescence intensity (F), and the initial fluorescence intensity (F_0) were measured at 480 nm. All data were collected and analyzed using the FDSS6000 system and related software (Hamamatsu Photonics, Japan).

Results

Chemistry. The aryl sulfonylpiperazine derivatives (**5-15**) were designed to possess a sulfonamide group (SO_2NH-) and a piperazine moiety as well as a hydrophobic aromatic ring through the structural analysis of the 5-HT$_6$ receptor antagonists as shown in Figure 1. In all the structures of 5-HT$_6$ receptor antagonists, three moieties are common such as piperazine ring, hydrophobic aromatic ring and sulfonamide group. Particularly, the designed compounds have a characteristic *N*-methyl piperazine and different aryl sulfonamides which are linked at position number two and five to the hydrophobic benzothiazole ring. The arylsulfonylpiperazine derivatives **5-15** were synthesized from 2-chlorobenzothiazole **1** in four steps, respectively (Scheme 1). In the first step, the nitration of 2-chlorobenzohiazole in presence of *conc*. HNO_3 and H_2SO_4 at 5 °C temp to give 2-chloro-6-nitrobenzothiazole in good yield. In the second step of the reaction, the 2-chloro-6-nitrobenzothiazole was treated with *N*-methyl piperazine at reflux temperature to afford the 2-(4-methylpiperazine-1-yl)-6-nitrobenzothiazole, which on reduction in presence of Pd/C gave 2-(4-methylpiperazine-1-yl)benzothiazol-6-amine in the third step of the reaction.



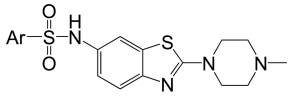
Scheme 1. General method for the synthesis of 2-(4-methylpiperazin-1-yl)-6-Ar-sulfonamido benzo[*d*]thiazol (**5-15**).
Reagent and conditions: (a) H_2SO_4, HNO_3, 5 °C, 3 h (b) aq. $NaHCO_3$, isopropyl alcohol, reflux, 48 h. (c) H_2/Pd-C, rt, overnight (d) NaH, DMF arylsulfonyl chloride, 100 °C, overnight.

Coupling of 2-(4-methyl-piperazine-1-yl)benzothiazol-6-amine with different aryl sulfonyl chloride in presence of NaH at 100 °C gave the different aryl sulfonamide derivatives (**5-15**) in moderate yield in the last step of the synthesis. Each compound synthesized was characterized by ^{1}H NMR, and high resolution MS.

Biological Evaluation. All the synthesized compounds were evaluated *in vitro* against the human recombinant 5-HT_6 serotonin receptor. The functional efficacy of each compound was evaluated by measuring the 5-HT-induced Ca^{2+} increases using HeLa cell line expressing the cloned human 5-HT_6 receptor (Table 1).[26] The SB258585 was used as reference compound, having IC_{50} = 66.8 nM in our experiment. The selected compounds were further evaluated for their selectivity on the 5-HT_6 over the 5-HT_4 and 5-HT_7 receptors which belong to the same Gs protein family (Table 2).

Among the compounds **5-15**, compound **8** and **13** (IC_{50} = 14 μM and 3.9 μM, respectively) having substituted 4-isopropylphenyl and 1-naphthyl sulfonamide group at C-5 position of benzothiazole ring respectively, showed significant inhibition of the 5-HT-induced Ca^{2+} increases than other derivatives. Compounds having phenyl, 4-methyl phenyl, 4-methoxy phenyl, 4-flurophenyl, 4-chlorophenyl, 4-trifluromethykphenyl, 4-nitrophenyl, 8-quinoinyl and thiophene-2-yl sulfonamide groups at C-5 position of benzothiazole ring showed less than 50% inhibition at 10 μM concentration of each compound. The compound with 4-nitrophenyl (**12**) showed the lowest activity. When two active compounds, **8** and **13**, were examined further for functional assay toward other serotonergic receptors (Table 2), the compound **13** displayed higher selectivity for the serotonin 5-HT_6 receptor than for the serotonin 5-HT_4 and 5-HT_7 receptors, showing 15.8 and 21.2% inhibition.

Table 1. % Inhibition and IC_{50} values of the sulfonamide derivatives **5a-5k** against 5-HT_6 receptor



5-15

Compound	Ar	% Inhibition (10 μM)	IC_{50} (μM)
5	Phenyl	37.1 ± 1.8	
6	4-methylphenyl	20.4 ± 2.8	
7	4-methoxyphenyl	23.2 ± 6.7	
8	4-isopropylphenyl	47.9 ± 3.6	14
9	4-fluorophenyl	33.0 ± 4.2	
10	4-chlorophenyl	28.3 ± 4.9	
11	4-trifluromethylphenyl	25.2 ± 2.7	
12	4-nitrophenyl	3.4 ± 1.6	
13	1-naphthyl	81.0 ± 2.1	3.9
14	8-quinolinyl	17.5 ± 4.6	
15	Thiophen-2-yl	28.9 ± 3.2	

Table 2. % Inhibition of the selected sulfonamide derivatives against 5-HT receptors

Compound	%Inhibition (10 μM) (n = 3)		
	5-HT_4	5-HT_6	5-HT_7
8	13.2 ± 5.2	49.7 ± 4.5	16.9 ± 5.3
13	15.8 ± 2.2	82.2 ± 2.4	21.2 ± 10.2

Discussion

Serotonin (5-HT) research is now more than 50 years old but still represents one of the most attractive areas in medicinal chemistry.

The reported pharmacophore model of 5-HT_6 receptor antagonist has four key pharmacophore elements: A positive ionizable atom (PI), an aromatic ring (AR), a hydrogen bond acceptor group (HBA), and a hydrophobic site (HYD).[23] Based on the pharmacophore model, recently we have reported a novel series of benzoisothiazole and benzothiazole derivatives having the arylsulfonamides, in which an ionizable nitrogen (PI) was introduced as *N,N*-dimethylformimiamide.[25] All of these synthesized compounds were evaluated *in vitro* against the human recombinant 5-HT_6 serotonin receptor. The functional efficacy of each compound was evaluated by measuring the 5-HT-induced Ca^{2+} increases using HeLa cell line expressing the cloned human 5-HT_6 receptor. In the series, compounds with 4-methylphenyl and 2-naphthyl group showed good activities (IC_{50} = 0.36 μM and 0.44 μM, respectively).

Therefore, we have prepared a series of similar compounds (Figure 1(a)) that contain a methyl piperazine ring as a PI,

while the AR feature is a benzothiazole system. In the new compounds, the methyl piperazine ring is attached to the benzothiazole system at the position two and -SO_2Ar system is attached at the position number five. In terms of structure activity relationship, it seems that biological activity depends upon electron donating and withdrawing group. Compounds **11** and **12** showed decreased biological activity may be due to the presence of strong electron withdrawing groups (trifluoro and nitro) at the para position of phenyl ring. Presence of a weak electron withdrawing group like fluoro and chloro in compounds **9** and **10** also showed very poor in biological activity. Compounds **6** and **7** having methyl and methoxy, electron donating groups at para position of phenyl ring also showed increased biological activity as compared to compounds **9**, **10**, and **11** having fluoro, chloro and trifluoro groups at para position of phenyl ring. Compound **8** having 4-isopropyl group (ring activating group), and compound **13** having 1-naphthyl showed good activity with IC_{50} values 14 and 3.9 μM, respectively, When these were compared to **6** and **7** having methyl and methoxy groups at para position of phenyl ring, the size of substituents, in addition to the electronic factor, may play an important role in the biological activity of synthesized compounds. Compounds **14** and **15** both have heteroaromatic rings (quinoline and thiophene) did not show any meaningful biological activity.

The 5-HT$_6$ inhibitory activities of this piperazine containing series were slightly lower than the *N,N*-dimethylformimiamide containing series we had reported before. But it showed selectivity over other 5-HT receptors, too. The compound **13** displayed higher selectivity for the serotonin 5-HT$_6$ receptor than for the serotonin 5-HT$_4$ and 5-HT$_7$ receptors, showing 15.8 and 21.2% inhibition, respectively.

Conclusion

A new series of sulfonylpiperazine derivatives (**5-15**) were synthesized as 5-HT$_6$ ligands. All the synthesized compounds were evaluated by measuring the 5-HT-induced Ca^{2+} increases using HeLa cell line expressing the cloned human 5-HT$_6$ receptor. The results showed that compound **13** was a potent 5-HT$_6$ receptor antagonist with the selectivity over 5-HT$_4$ and 5-HT$_7$ receptors.

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