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N_1-(Benzenesulfonyl)tryptamines as Novel 5-HT_6 Antagonists†

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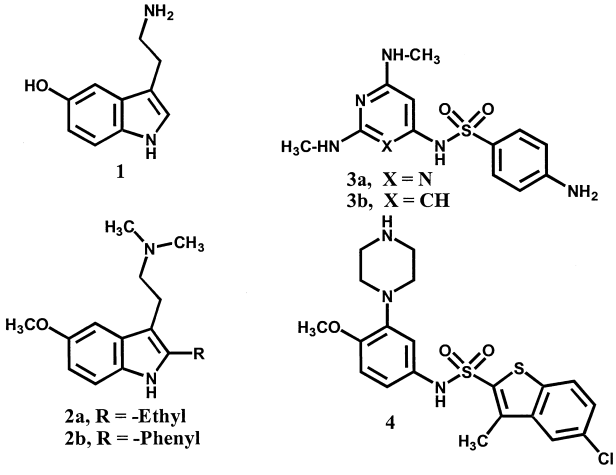
Abstract—N_1-Benzenesulfonyl-5-methoxy-*N,N*-dimethyltryptamine (BS/5-OMe DMT; **5**) was shown to bind at human 5-HT_6 serotonin receptors with high affinity ($K_i = 2.3$ nM) relative to serotonin ($K_i = 78$ nM). Structural variation failed to result in significantly enhanced affinity. BS/5-OMe DMT acts as an antagonist of 5-HT-stimulated adenylate cyclase ($pA_2 = 8.88$ nM) and may represent the first member of a novel class of 5-HT_6 antagonists. © 2000 Elsevier Science Ltd. All rights reserved.

Seven families of serotonin (**1**) receptors have been identified: 5-HT_1–5-HT_7,[1,2] and one of the newest of these are the 5-HT_6 receptors.[3] 5-HT_6 receptors belong to the G-protein superfamily of receptors and are positively coupled to an adenylate cyclase second messenger system.[4] Although the exact clinical implications of 5-HT_6 receptors remain to be identified, it is of significance that these receptors are found primarily in the central nervous system. Importantly, various typical and atypical antipsychotic agents and antidepressants have been demonstrated to bind with high affinity at 5-HT_6 receptors (i.e., with K_i values of < 100 nM)[5–7] suggesting that these receptors be targeted for the development of novel psychotherapeutic agents. Evidence also suggests that 5-HT_6 receptors might modulate cholinergic neurotransmission and GABA function leading to speculation that 5-HT_6 agents could play a role in memory impairment, anxiety, mood-dependent behavior, and related disorders.[8–13]

To date, relatively few 5-HT_6-selective agents have been reported. EMDT (**2a**) represents the first agonist showing selectivity for 5-HT_6 receptors.[14] Ro 04-6790 (**3a**), Ro 63-0563 (**3b**),[15,16] and SB-271046 (**4**)[17] represent the first 5-HT_6-selective antagonists. The 2-phenyl counterpart of EMDT (i.e., PMDT; **2b**) also displays 5-HT_6 antagonist character.[14]



The sulfonamide-containing antagonist compounds **3** and **4** are structurally distinct from the tryptamine-containing agonists 5-HT (**1**) and EMDT (**2a**). However, PMDT (**2b**) is a 5-HT_6 antagonist indicating that antagonist activity can be associated with a tryptamine scaffold. In the course of the synthesis of certain EMDT-related compounds, a benzenesulfonyl group was employed to protect the indole N_1-position during

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functionalization of the C_2-position.[14] As a matter of routine, some of these N_1-benzenesulfonyl-protected tryptamine derivatives were examined in radioligand binding assays and were found to bind at 5-HT_6 receptors. Upon this discovery, our intent was to optimize affinity by investigating analogues where the substitution pattern in the benzenesulfonamide moiety was varied, to subsequently vary the position of the tryptamine methoxy group, and to then select a member of the series for further evaluation in a functional assay. Disclosure of **3** and **4** prompted us to report our findings. In particular, we posed the following questions: (1) Do the N_1-benzenesulfonyl analogues of tryptamines possess activity as 5-HT_6 agonists or antagonists? (2) Is the mode of binding of **3** and **4** related to the mode of binding of these benzenesulfonyltryptamines?

Chemistry

All compounds were prepared by a simple one-step acylation reaction of the anion of a methoxy-substituted *N,N*-dimethyltryptamine derivative with the appropriate benzenesulfonyl chloride. Physicochemical properties of the target compounds are provided in Table 1.

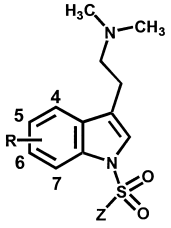
Results and Discussion

N_1-Benzenesulfonyl-5-methoxy-*N,N*-dimethyltryptamine (BS/5-OMe DMT; **5**) binds at 5-HT_6 receptors with high affinity ($K_i = 2.3$ nM), and with an affinity higher than that of 5-HT (**1**; $K_i = 78 \pm 6$ nM) itself. Table 1 shows that introduction of an electron-withdrawing 4-chloro group (i.e., **6**) or electron-donating methoxy substituents (i.e., **7** and **8**) has little effect on 5-HT_6 receptor affinity. Replacement of the N_1-benzenesulfonyl group with the sterically larger 2-naphthalenesulfonyl (i.e., **9**) or 1-naphthalenesulfonyl (i.e., **10**) groups also had little effect. The affinities of these derivatives were not more than four times greater than, or less than, that of **5**. The indole 5-methoxy substituent of **8** was moved to the 4-, 6-, and 7-positions. With the exception of the 7-methoxy analogue (**15**; $K_i = 183$ nM), which binds with about 140-fold reduced affinity, affinity was only slightly decreased when **8** ($K_i = 1.3$ nM) is compared with **11** ($K_i = 7.4$ nM) and **12** ($K_i = 9.5$ nM).

In the absence of the N_1-benzenesulfonyl group, moving the 5-methoxy group of 5-methoxy-*N,N*-dimethyltryptamine ($K_i = 16$ nM) to the 4-, 6-, or 7-position reduces affinity by about 10-fold, 500-fold, and 1225-fold, respectively.[18] Because the affinity of the 7-methoxy analogue **15** was higher than expected, we examined several additional 7-methoxy-substituted compounds. The 4-chloro ($K_i = 45$ nM) and 4-methoxy ($K_i = 93$ nM) derivatives **13** and **14**, respectively, displayed higher affinity than **15**, but lower affinity than **5** ($K_i = 2.3$ nM). Interestingly, the affinity of the N_1-(2-naphthalenesulfonyl) derivative **16** ($K_i = 5.0$ nM) was in the same range as that of **5**.

Compound **5**, the parent member of the series, was examined both as an agonist and as an antagonist in an adenylate cyclase assay. Compound **5** lacked agonist character at a concentration of 10,000 nM. However, this single concentration completely blocked 5-HT-stimulated cyclase activity. Subsequent testing showed that **5** produced inhibition of adenylate cyclase activity in a dose-dependent manner ($pA_2 = 8.88 \pm 0.2$ nM).

Table 1. Physicochemical and 5-HT_6 serotonin receptor binding properties of N_1-(arylsulfonyl)-*N,N*-dimethyltryptamine derivatives



	R	Z	Yield[a] (%)	Mp (°C)	Empirical formula	K_i, (nM) (±SEM)[b]
5	5-OMe	Ph	61	224–226	$C_{19}H_{22}N_2O_3S \cdot C_2H_2O_4$	2.3 (±0.5)
6	5-OMe	4-Cl Ph	37	218–220	$C_{19}H_{21}ClN_2SO_3 \cdot C_2H_2O_4$	3.1 (±0.1)
7	5-OMe	4-OMe Ph	16	172–174	$C_{20}H_{24}N_2SO_4 \cdot C_2H_2O_4$	8.0 (±0.4)
8	5-OMe	2,5-diOMe Ph	30	172–174	$C_{21}H_{26}N_2SO_5 \cdot C_2H_2O_4$	1.3 (±0.2)
9	5-OMe	2-Naphthyl	33	174–176	$C_{23}H_{24}N_2SO_3 \cdot C_2H_2O_4$	1.6 (±0.3)
10	5-OMe	1-Naphthyl	15	172–174	$C_{23}H_{24}N_2SO_3 \cdot C_2H_2O_4$[c]	0.9 (±0.2)
11	4-OMe	2,5-diOMe Ph	14	167–168	$C_{21}H_{26}N_2SO_5 \cdot C_2H_2O_4$[d]	7.4 (±0.2)
12	6-OMe	2,5-diOMe Ph	24	178–181	$C_{21}H_{26}N_2SO_5 \cdot C_2H_2O_4$	9.5 (±0.6)
13	7-OMe	4-Cl Ph	12	168–170	$C_{19}H_{21}ClN_2SO_3 \cdot C_2H_2O_4$	45 (±7)
14	7-OMe	4-OMe Ph	17	164–166	$C_{20}H_{24}N_2SO_4 \cdot C_2H_2O_4$[e]	93 (±7)
15	7-OMe	2,5-diOMe Ph	4	207–208	$C_{21}H_{26}N_2SO_5 \cdot C_2H_2O_4$	183 (±32)
16	7-OMe	2-Naphthyl	16	191–193	$C_{23}H_{24}N_2SO_3 \cdot C_2H_2O_4$[d]	5.0 (±0.6)

[a]All compounds were recrystallized from a MeOH–anhydrous Et_2O mixture.
[b]K_i values were determined in triplicate. Clozapine ($K_i = 4.8 \pm 0.6$ nM) was employed as control.
[c]Crystallized with 1 equiv of H_2O.
[d]Crystallized with 0.25 equiv of H_2O.
[e]Crystallized with 0.5 equiv of H_2O.

The structure of **5** was modeled using SYBYL, and three families of low-energy conformations were identified. The families possessed C_{7a}–N_1–S–C_ϕ torsion angles (τ) of approximately 60°, 180°, or 300°, and members within each family varied with respect to S–C_ϕ rotation angle α. The lowest energy conformer of **5** (22.33 kcal/mol; $\tau = 300.8°$, $\alpha = 323.4°$, Family 3) was energetically similar to the two lowest energy conformers from the other two families (Family 1: 22.41 kcal/mol, $\tau = 60.8°$, $\alpha = 213.4$C; Family 2: 22.87 kcal/mol, $\tau = 180.8°$, $\alpha = 88.4°$). Similar results were obtained with **3b** (where τ is defined as $C_{py\text{-}4}$–N–S–C_ϕ). The lowest-energy conformers in each family are as follows; Family 1: −6.49 kcal/mol, $\tau = 59.8°$, $\alpha = 212.4°$; Family 2: −5.29 kcal/mol, $\tau = 179.8°$, $\alpha = 87.4°$, and Family 3: −6.30 kcal/mol, $\tau = 299.8°$, $\alpha = 322.4°$. The lowest energy conformers for the three families of **3b** and **5** were superimposed and resulted in rmsd values of 0.176 in all three cases. This is shown for the Family 2 pair in Figure 1. It would seem theoretically possible for members of the three conformational families of **5** to superimpose with the corresponding members of families of **3b**. Because Family 2 of **5** places the benzenesulfonyl aromatic moiety the greatest distance from the indole 7-position, this might be a favored conformational family for ligand–receptor interaction. Alternatively, the higher than anticipated affinities seen with the 7-substituted derivatives **13**–**16**, as compared with **5**, and in particular with **16** relative to **13**–**15**, might reflect a shift in τ or α angles.

The goal of this investigation was not the development of novel 5-HT_6-selective receptor antagonists; rather, it was our intention to determine whether compounds such as **5** possess agonist or antagonist action and, due to structural similarities between **5** and recently reported **3**, to determine whether such compounds might bind in a similar manner. Nevertheless, given the high affinity of BS/5-OMe DMT (**5**) for h5-HT_6 receptors, we examined the binding of this compound at several other 5-HT receptor populations. Compound **5** displayed low affinity for h5-HT_{1A} ($K_i = 702 \pm 154$ nM), h5-HT_{1B} ($K_i = 9210 \pm 3960$ nM), h5-HT_{1E} ($K_i = 4220 \pm 420$ nM), h5-HT_3 ($K_i = 2390 \pm 60$ nM), and h5-HT_7 ($K_i = 600 \pm 180$ nM) receptors. In contrast, **5** displayed higher affinity for r5-HT_{2A} ($K_i = 130 \pm 65$ nM) and r5-HT_{2C} ($K_i = 23 \pm 5$ nM) receptors. This latter finding is not unexpected. It is known that tryptamines bearing N_1-substituents are tolerated by 5-HT_2 receptors.[1]

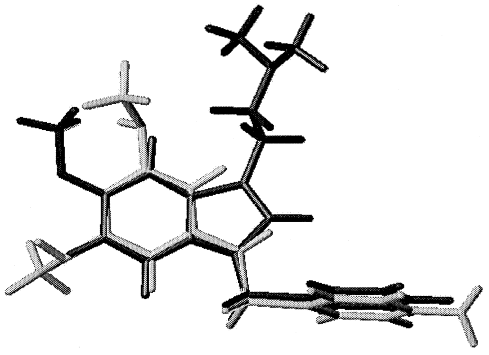


Figure 1. Superimposition of the lowest-energy Family 2 conformers of **3b** (light-shaded structure) and **5** (dark-shaded structure) (rmsd = 0.176).

The results of the present study indicate that **5** binds at 5-HT_6 receptors with high affinity ($K_i = 2.3$ nM). Structure–affinity studies show that the introduction of 4-chloro, 4-methoxy, or 2,5-dimethoxy substituents into the benzenesulfonamide moiety have little effect on affinity. Even replacement of the benzenesulfonyl with the more bulky 1-naphthalene- or 2-naphthalenesulfonyl groups had little influence on affinity. Unlike what was seen for *N,N*-dimethyltryptamines lacking an N_1-substituent, moving the 5-methoxy group to the 4- or 6-position was tolerated. This lack of parallel behavior between N_1-unsubstituted tryptamines and N_1-benzenesulfonamides suggest that the two series might be binding in a different manner at the receptors. Even the 7-methoxy compound **15** binds with higher affinity than expected, and **16** binds with an affinity comparable to that of **5**. In contrast, molecular modeling studies indicate that the arylbenzenesulfonamide portions of **5** and the antagonist **3b** are superimposable suggesting that the N_1-arylsulfonyltryptamines might be binding in a manner related to that of the antagonists. Supporting this contention, **5** was shown to be a 5-HT_6 antagonist. In conclusion, the N_1-benzenesulfonyltryptamine **5** represents the first member of a novel class of reasonably selective tryptamine-based 5-HT_6 receptor antagonists.

Experimental

Chemistry

Flash column chromatography was performed using silica gel (220–440 mesh). Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Proton NMR spectra were obtained using a Varian Gemini 300 MHz spectrometer with tetramethylsilane as an internal standard and infrared spectra were measured using a Nicolet 5ZDX FT-IR spectrophotometer. Elemental analysis was performed by Atlantic Microlab (Norcross, GA) and determined values were within 0.4% of theory. All compounds were prepared by the simple reaction of the appropriate methoxytryptamine anion with the requisite sulfonyl chloride as exemplified for the preparation of **6**. 4-Methoxy-,[19] 6-methoxy-,[20] and 7-methoxy-*N,N*-dimethyltryptamine[21] were prepared according to literature procedures. 5-Methoxy-*N,N*-dimethyltryptamine was available in our laboratory as the result of previous studies.

1-4-(Chlorobenzenesulfonyl)-5-methoxy-*N,N*-dimethyltryptamine oxalate (6). A mixture of 5-methoxy-*N,N*-dimethyltryptamine (220 mg, 1.0 mmol) and an unwashed 60% suspension of NaH in mineral oil (40 mg) was heated at 100 °C under an N_2 atmosphere until melted. The cooled homogeneous mixture was dissolved in dry DMF (2 mL). A solution of 4-chlorobenzenesulfonyl chloride (230 mg, 1.1 mmol) in dry DMF (1 mL) was added in a dropwise manner at 0 °C, and the reaction mixture was allowed to stir at room temperature overnight (about 16 h). Saturated $NaHCO_3$ solution (12 mL)

was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic portion was washed with brine and solvent was removed under reduced pressure to afford an oil. The oil was purified by flash chromatography (silica gel) using CH_2Cl_2:MeOH (20:1) as eluent to give 220 mg of a homogeneous oil. The oil in dry acetone (4 mL) was added all at once to a saturated solution of oxalic acid to yield a white precipitate. The product was collected by filtration and recrystallized from an anhydrous MeOH/anhydrous Et_2O mixture to give 180 mg (37%) of **6** as a white solid, mp 218–220 °C. ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6H, 2×CH_3), 2.56–2.61 (t, 2H, CH_2), 2.77–2.82 (t, 2H, CH_2), 3.82 (s, 3H, OCH_3), 6.92–6.94 (m, 2H, ArH), 7.26–7.38 (m, 3H, ArH), 7.73–7.86 (m, 3H, ArH). IR (film) 1371 and 1176 cm^{-1}. Anal. ($C_{19}H_{21}ClN_2SO_4 \cdot C_2H_2O_4$) C, H, N.

Molecular modeling

The structures of **3b** and **5** were constructed from standard bond lengths and angles using the SKETCH MOLECULE command in version 6.6 of SYBYL. The structures were energy minimized with the Tripos force field and charges were calculated using the Gasteiger Huckel algorithm as implemented in SYBYL. A full conformational search was performed using the SYSTEMATIC SEARCH command; rotatable bonds (two in each compound) were rotated in 5°-increments including the starting conformation. The results were analyzed with the SEARCH routine of the SYBYL program. Superimpositions were performed on the conformers of **3b** and **5** with the FIT-ATOMS command using the $C_{py\text{-}2}$, N_S and S atoms and the C_4, N_1 and S atoms of **3b** and **5**, respectively.

Radioligand binding assay

The binding assay was conducted as previously described.[14] Human 5-HT_6 receptors stably transfected to HEK 293 human embryonic kidney cells were used and [^{3}H]lysergic acid diethylamide (70 Ci/mmol; DuPont NEN) was employed as the radioligand. All assays were conducted in triplicate using polypropylene 1 mL/well plates (Anachemia). The radioligand was diluted in incubation buffer in borosilicate glass vials and protected from light. Competing agents (1 mM stock solutions) were dissolved in DMSO or saline and stored at −20 °C in 1.2-mL polypropylene tubes (ElKay). Dilutions of compounds were made using incubation buffer in 96-well polypropylene plates and mixed by multichannel pipetting >25 times. Serial dilutions (1 in 4) started at a final concentration of 10,000 nM. Final concentrations >10,000 nM were individually prepared from the 1 mM stock solution. Nonspecific binding was defined by 100 μM serotonin creatinine sulfate (Research Biochemicals) prepared fresh in incubation buffer at the time of each determination, and protected from light. Reactions volumes were as follows: 200 μL incubation buffer (50 mM Tris, 0.5 mM EDTA, 10 mM $MgCl_2$, pH 7.4 at 22 °C), 100 μL test agent or serotonin (100 μM) or buffer (for total binding), 100 μL [^{3}H]lysergic acid diethylamide (2 nM final concentration), and 100 μL membrane preparation (15 μg protein). The incubation was initiated by the addition of membrane homogenate and the plates vortexed (Baxter S/P Multitube Mixer). The plates were incubated, with protection from light, by shaking (Gyrotop Water Bath/Shaker Model G76, speed 2) at 37 °C for 60 min. The binding reaction was stopped by filtration. The samples were filtered under vacuum over 96 well glass fiber filters (Packard Unifilter GF/B), presoaked in 0.3% PEI in 50 mM Tris buffer (4 °C, pH 7.4) for at least 1 h, and then washed six times with 1 mL of cold 50 mM Tris buffer (pH 7.4) using the Packard Filtermate 196 Harvester. The Unifilter plates were dried overnight in a 37 °C dry incubator. The Unifilter bottoms were sealed and 35 μL of Packard MicroScint-0 was added. The plates were allowed to equilibrate for 1 h and were then sealed using a Packard TopSeal P with the Packard Plate Micromate 496. Plates were counted in a Packard TopCount 4.1 by liquid scintillation spectrometry. Each well was counted for 3 min. The test agents were initially assayed at 1000 and 100 nM. If the compound was active (defined as causing at least 80% inhibition of [^{3}H]lysergic acid diethylamide binding at 1000 nM), they were further tested for determination of a K_i value. The range of concentrations was chosen such that the middle concentration would produce approximately 50% inhibition.

Methods employed for obtaining the binding profile are described at the NIMH Psychoactive Drug Screening Program website: http://pdsp/cwru.edu/pdsp.htm

Adenylate cyclase assay

h5-HT_6 receptors stably expressed in HEK-293 cells were grown in 24-well plates to near-confluency and 18 h prior to assay the medium was replaced with DMEM containing dialyzed 10% fetal calf serum. For the assay, the medium was aspirated and replaced with fresh DMEM without serum and incubated with various concentrations of test agent in a total volume of 0.5 mL for 15 min. The assay was terminated by aspiration and the addition of 10% trichloroacetic acid (TCA). The TCA extract was used for cAMP determinations. Data represent the mean of n = four separate determinations. For pA_2 determinations, cells were incubated with increasing concentrations of 5-HT ± four different concentrations of test agents. Calculation of pA_2 values using a Schild analysis was as previously described.[22] Data represent mean ± SEM of three different pA_2 determinations.

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