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N_1-Benzenesulfonylgramine and N_1-Benzenesulfonylskatole: Novel 5-HT$_6$ Receptor Ligand Templates

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Abstract—1-Benzenesulfonyl-5-methoxy-*N*,*N*-dimethyltryptamine (**3**; $K_i = 2.3$ nM) is a 5-HT$_6$ receptor antagonist; removal of the 5-methoxy group (i.e., **6**; $K_i = 4.1$ nM) has little impact on receptor affinity. In the present study, it is shown that the aminomethyl portion of **6** can be shortened to gramine analogue **10a** ($K_i = 3.1$ nM); a related skatole derivative **11b** ($K_i = 12$ nM) also binds with high affinity indicating that the aminoethyl portion of the tryptamines is not required for binding. Compounds **10a** and **11b** represent members of novel classes of 5-HT$_6$ antagonists.

Rat and human 5-HT$_6$ receptors were first identified and cloned in the early to mid 1990s[1–3] and represent one of seven major families of serotonin receptors (5-HT$_1$-5-HT$_7$).[4] They are G-protein coupled receptors, positively coupled to an adenylate cyclase second messenger system, and are located primarily in the nucleus accumbens, striatum, hippocampus, and olfactory tubercle of the brain.[5] The exact therapeutic significance of 5-HT$_6$ receptor ligands is still under investigation, but the binding of various antipsychotics and antidepressants suggests their possible involvement in the treatment of certain mental disorders.[1,3,6] With the development of the first 5-HT$_6$ antagonists, additional pharmacological actions have been implicated including a role in cognition and convulsive disorders.[7–9] Furthermore, Slassi et al.[8] have suggested that the CNS-specific localization of 5-HT$_6$ receptors should make them attractive targets for drug development because of the low likelihood that such agents would have peripheral side effects.

The first four types of 5-HT$_6$ antagonists described in the literature were **1**–**4**. Compounds **1** (**1a**, Ro 04-6790; **1b**, Ro 63-0563) were reported by Hoffmann-La Roche,[10] and **2** (SB-271046) by SmithKline Beecham.[11] Compounds **3** (5-methoxy-N_1-benzenesulfonyl-*N*,*N*-dimethyltryptamine; MS-245) and **4** were reported from our laboratory.[12,13] Interestingly, although representing independent discoveries, three of the four types of initial 5-HT$_6$ antagonists possess a sulfonamide moiety. Furthermore, **1** and **3** were serendipitous discoveries resulting from random screening, whereas **2** was derived from structure–activity and pharmacokinetic optimization of a lead initially identified from screening of the SmithKline Beecham Compound Data Bank.[11,12,14] Most 5-HT$_6$ antagonists reported since that time are variations on these themes (e.g., sulfonamides, reversed sulfonamides, 2-substituted tryptamines).[8,9]

Because **1**–**3** each possesses an *Aryl-N-SO$_2$-Aryl'* fragment, it was initially assumed that they might bind at 5-HT$_6$ receptors in a similar manner.[12] But, with the recent discovery that reversed sulfonamide analogues of **2** retain 5-HT$_6$ receptor affinity,[15] this concept must now be questioned. Furthermore, although the sulfonamido moiety seems optimal, it has been shown that the arylsulfonamido portion of **3** can be replaced by a benzoyl or benzyl group with <10-fold decrease in affinity, and that the –SO$_2$– moiety of **3** can even be eliminated—resulting in N_1-(phenyl or substituted phenyl)-tryptamines—with <25-fold reduction in affinity.[16] It now is not clear how **3** binds relative to **1** and **2**. In fact,

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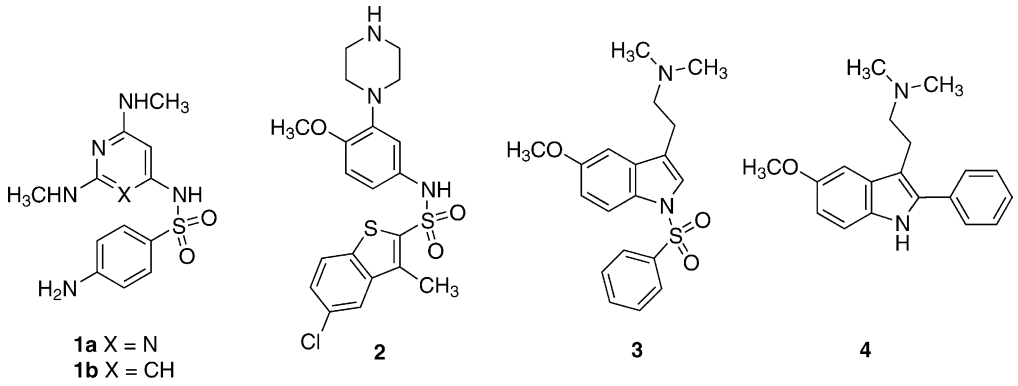


Russell et al.[17] have recently proposed an alternative mode of overlap where the tryptamine amino group of **3** is associated with one of the piperazine nitrogen atoms of **2**. The purpose of the present investigation was to examine more closely the terminal amine portion of **3**, and the aminoethyl group in particular, to determine their influence on 5-HT_6 receptor binding.

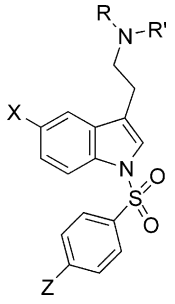
Binding Studies

5-HT_6 receptor radioligand binding[18] data are shown in Table 1. Replacement of the 5-methoxy group of **3** ($K_i = 2.3$ nM) with hydrogen has little impact on affinity (i.e., **6**; $K_i = 4.1$ nM), and *O*-demethylation to the hydroxy analogue **5** ($K_i = 28$ nM) decreases affinity by about 10-fold. While this paper was in preparation, Russell et al.[17] reported similar results for **6** and **5** ($K_i = 2.9$ and 19 nM, respectively). Apparently, the 5-methoxy group is not a major contributor to binding.

With respect to the terminal amine, the secondary amine **7** ($K_i = 23$ nM) binds with 10-fold lower affinity than its parent, **3**. The *N*,*N*-dimethyl substituents of **3** can be homologated to *N*,*N*-diethyl (**8**; $K_i = 6.2$ nM) with little effect on affinity; however, incorporation of a bulkier benzyl group, as in **9** ($K_i = 43$ nM), decreases affinity by about 20-fold.

The alkyl chain separating the terminal amine from the indole nucleus was shortened by a methylene group. Typically, such chain shortening in tryptamine analogues is not well tolerated by serotonin receptors.[19] However, in this instance, the chain-shortened analogue **10a**[20] ($K_i = 3.1 \pm 1.2$ nM) retains high affinity as compared to its tryptamine counterpart **6**. The obvious

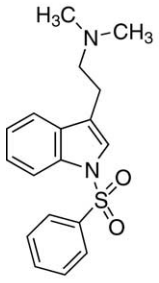
Table 1. Physicochemical and 5-HT_6 receptor binding properties of benzenesulfonyltryptamine analogues[20]



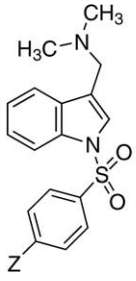
	X	R	R′	Z	Mp (°C)	Recryst. solvent[a]	% Yield	Empirical formula	K_i (nM)	(±SEM)
3[b]	$-OCH_3$	$-CH_3$	$-CH_3$	–H	—	—	—	—	2.3	
5	–OH	$-CH_3$	$-CH_3$	–H	195–197	ME	78	$C_{18}H_{20}N_2O_3S.C_2H_2O_4$	28	(6)
6	–H	$-CH_3$	$-CH_3$	–H	194–195	M	22	$C_{18}H_{20}N_2O_2S.C_2H_2O_4$[c]	4.1	(0.3)
7	$-OCH_3$	$-CH_3$	–H	–H	215	AM	83	$C_{18}H_{20}N_2O_3S.C_2H_2O_4$	23	(6)
8	$-OCH_3$	$-C_2H_5$	$-C_2H_5$	–H	170	M	54	$C_{21}H_{26}N_2O_3S.C_2H_2O_4$	6.2	(0.2)
9	$-OCH_3$	$-CH_3$	$-CH_2Ph$	–H	155–156	M	33	$C_{25}H_{26}N_2O_3S.C_2H_2O_4$	43	(15)
12	$-OCH_3$	$-CH_3$	$-CH_3$	–NHAc	201–203	M	43	$C_{21}H_{25}N_3O_4S.C_2H_2O_4$[c]	34	(6)
13	$-OCH_3$	$-CH_3$	$-CH_3$	$-NH_2$	192–194	P	78	$C_{19}H_{23}N_3O_3S.2HCl$	2.0	(0.1)
14	$-OCH_3$	$-C_2H_5$	$-C_2H_5$	–NHAc	168–169	M	32	$C_{23}H_{29}N_3O_4S.C_2H_2O_4$	230	(80)
15	$-OCH_3$	$-C_2H_5$	$-C_2H_5$	$-NH_2$	234–235	M	88	$C_{21}H_{27}N_3O_3S.HCl$	0.6	(0.2)
16	–H	$-CH_3$	$-CH_3$	–NHAc	225	AM	33	$C_{20}H_{23}N_3O_3S.C_2H_2O_4$	27	(11)
17	–H	$-CH_3$	$-CH_3$	$-NH_2$	217–218	AM/E	90	$C_{18}H_{21}N_3O_2S.2HCl$	0.8	(0.4)
18	–H	$-C_2H_5$	$-C_2H_5$	–NHAc	160–161	M	27	$C_{22}H_{27}N_3O_3S.C_2H_2O_4$[c]	90	(30)
19	–H	$-C_2H_5$	$-C_2H_5$	$-NH_2$	201–203	ME	80	$C_{20}H_{25}N_3O_2S.2HCl$	0.6	(0.2)
20	$-OCH_3$	$-CH_3$	$-CH_2Ph$	$-NH_2$	95–97	ME	20	$C_{25}H_{27}N_3O_3S.2HCl$	3.0	(1.0)

[a]Recrystallization solvents: M = MeOH, AM = aqueous MeOH; ME = MeOH/anhydrous Et_2O; P = *n*PrOH.
[b]Binding data for compound **3** was previously reported.[12]
[c]Compounds **6** and **18** crystallized with 0.5 mol H_2O.

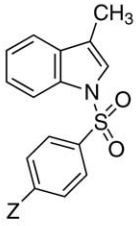
question at this point is whether or not this amine is even required for binding. Removal of the amine of **10a** would result in skatole analogue **11a**, a compound that lacks aqueous solubility.[21] Hence, in order to examine the need for an aminoalkyl group at the indole 3-position, it was necessary to locate a position on the molecule that would tolerate a solubilizing group. An amino group was selected because a water-soluble salt could be formed. It was already known from earlier studies that both electron donating and electron withdrawing substituents are tolerated in the benzenesulfonyl ring of **3**; depending upon the specific substituent, the affinity of the resulting compound is either slightly enhanced or slightly decreased.[12] Consequently, we prepared and examined several aryl amine derivatives of **3**, **6**, and **8** to determine if the amine would be tolerated. The corresponding acetamido analogues were used as controls.



6



10a Z = -H
10b Z = -NH_2



11a Z = -H
11b Z = -NH_2

Compound **13** ($K_i = 2.0$ nM), the 4′-amino analogue of **3**, binds with the same affinity as its parent, **3**. Likewise, the affinities of amino analogues **15**, **17**, and **19** ($K_i = 0.6$, 0.8, and 0.6 nM, respectively) are also quite high and indicate that the amino group is tolerated at this position. In compound **20** ($K_i = 3.0$ nM), the presence of the amino group actually increases affinity by nearly 15-fold relative to its parent, **9**. Furthermore, the affinity of **17** and **19** again indicate that the presence of a 5-methoxy group is not required for binding. The lower affinities of the corresponding acetamido derivatives **12**, **14**, **16**, and **18** show that affinity is not directly related simply to the presence of an NH substituent on the aryl ring. As a further test of the tolerance of the *para* amino substituent, compound **10b**[20] was examined. The affinity of **10b** ($K_i = 6.9 \pm 0.3$ nM) was similar to that of **10a**.

On the basis that a *para* amino group is tolerated by 5-HT_6 receptors, compound **11b** was prepared and examined. Compound **11b** ($K_i = 12 \pm 9$ nM) retains affinity for 5-HT_6 receptors. Even though its affinity is about 3-fold lower than tryptamine derivative **6**, it, like **10**, represents a novel type of 5-HT_6 receptor ligand.

Functional Studies

Benzenesulfonylgramine (1-BSG; **10a**) and the amino benzenesulfonylskatole derivative **11b** (AminoBSK) were examined for functional activity by measuring their ability to either stimulate cAMP accumulation in HEK cells, or to antagonize 5-HT-induced cAMP production.[22] Both compounds failed to behave as agonists, but both antagonized the actions of 5-HT (data not shown). Calculated IC_{50} values for the inhibition of 5-HT-stimulated cAMP production in HEK-5-HT_6 cells by **10a** and **11b** were 880 (±35) and 320 (±10) nM, respectively. Schild analysis for **11b** provided a pA_2 of 7.0 (±0.2). Evidently, both compounds behave as 5-HT_6 antagonists.

Summary

The present investigation demonstrates that the aminoalkyl portion of N_1-benzenesulfonyltryptamine is, unexpectedly, not a requirement for 5-HT_6 receptor binding. N_1-Benzenesulfonylgramines such as **10a** and **10b** ($K_i = 3.1$ and 6.9 nM, respectively), derivatives of **3** (more specifically, derivatives of **6**; $K_i = 4.1$ nM) in which the *N*,*N*-dimethylaminoethyl portion of the molecule was shortened to an *N*,*N*-dimethylaminomethyl group, retain affinity. Even more interesting is that the *N*,*N*-dimethylamine portion of **10b** could be eliminated (**11b**; $K_i = 12$ nM). Both **10a** and **11b** behaved as antagonists of 5-HT-induced cAMP accumulation. These studies, then, extend the structure–affinity and structure–activity relationships of the N_1-benzenesulfonyltryptamines as 5-HT_6 antagonists and identified two novel classes of 5-HT_6 antagonists: N_1-benzenesulfonylgramines and N_1-benzenesulfonylskatoles. Furthermore, the affinities of these novel analogues question the manner in which they interact at 5-HT_6 receptors relative to **2**; that is, if the amino group of **3**-type compounds is not required for binding, it seems unlikely that this amino group must mimic one of the piperazine nitrogen atoms of **2**. Additional investigations with these classes of compounds are currently underway.

Acknowledgements

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18. Radioligand binding assay. The h5-HT_6 radioligand binding assays were performed as previously described.[3,6] In brief, h5-HT_6 cDNA was transiently expressed in COS-7 cells using the DEAE-dextran technique.[6] Seventy-two hours after transfection, cells were harvested by scraping and centrifugation from medium containing 10% dialyzed fetal calf serum. Cells were then washed by centrifugation and resuspension once in phosphate buffered saline (pH 7.40; PBS) and then frozen as tight pellets at −80 °C until use. Binding assays were performed at room temperature for 90 min in binding buffer (50 mM Tris–Cl, 10 mM $MgCl_2$, 0.1 mM EDTA, pH 7.40) with [^{3}H]LSD (1 nM final concentration) using 10 μM clozapine for non-specific binding. Various concentrations of unlabeled test agent (1 to 10,000 nM) were used for K_i determinations with K_i values calculated using the LIGAND program.[23] Specific binding represented 80–90% of total binding. K_i values are the result of triplicate determinations.
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20. Synthesis: Melting points (uncorrected) were obtained with a Thomas Hoover apparatus. ^{1}H NMR spectra were recorded with a Varian EM-390 spectrometer, and peak positions are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Microanalyses were performed by Atlantic Microlab (GA) for the indicated elements, and the results are within 0.4% of theory. Reactions and product mixtures were routinely monitored by thin-layer chromatography on silica gel precoated F_{254} Merck plates. The free base of compound **10a** was reported earlier by a different method of synthesis.[21] Compounds in Table 1 were prepared by a procedure similar to that employed for the synthesis of **10b** using the appropriate tryptamine derivative in place of gramine. **1-Benzenesulfonyl-3-(*N*,*N*-dimethylaminomethyl)indole oxalate (1-benzenesulfonylgramine; 10a).** A mixture of gramine (0.50 g, 2.87 mmol) and 60% NaH (0.13 g, 3.16 mmol) was heated at 130 °C under N_2 until the evolution of the H_2 gas ceased. The resultant mass was dissolved in anhydrous DMF (7 mL) and benzenesulfonyl chloride (0.56 g, 3.15 mmol) in anhydrous DMF (3 mL) was added in a dropwise manner at 0 °C. The reaction mixture was allowed to stir at room temperature overnight. At 0 °C ice was added to the reaction mixture to decompose the excess NaH followed by H_2O (15 mL); the crude mixture was dissolved in CH_2Cl_2 (30 mL) and washed with H_2O (4×50 mL). The organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH; 10:1) to give 0.21 g (23%) of an oil. ^{1}H NMR (CD_3OD) δ 2.65 (s, 6H, $2CH_3$), 4.27 (s, 2H, CH_2), 7.15 (dd, J=7.6 Hz, J=7.7 Hz, 1H, CH), 7.23 (dd, J=7.6 Hz, J=7.9 Hz, 1H, CH), 7.31 (s, 1H, CH), 7.35 (d, J=7.9 Hz, 1H, CH), 7.41–7.47 (m, 1H, CH), 7.55 (d, J=7.7 Hz, 1H, CH), 7.77–7.84 (m, 4H, 4CH). An oxalate salt was prepared in anhydrous MeOH and recrystallized from MeOH/Et_2O: mp 198 °C. Anal. calcd for ($C_{17}H_{18}N_2O_2S{\cdot}C_2H_2O_4$) C, H, N. **1-(4-Aminobenzenesulfonyl)-3-(*N*,*N*-dimethylaminomethyl)indole hydrochloride (10b).** A mixture of gramine (1.00 g, 5.73 mmol) and 60% NaH (0.26 g, 6.32 mmol) was heated at reflux in DMF (25 mL) under N_2 for 2 h. *N*-Acetylsulfanilyl chloride (1.60 g, 6.88 mmol) in DMF (5 mL) was added in a dropwise manner at 0 °C, and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was extracted with CH_2Cl_2 (2×50 mL); the combined CH_2Cl_2 fraction was washed with H_2O (4×50 mL) and the organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH; 19:1) to give 1.10 g (52%) of a white solid: mp 65–67 °C. Hydrochloric acid (36%; 5 mL) was added to a solution of the solid acetamide (0.50 g, 1.35 mmol) in absolute EtOH (25 mL) and heated at reflux for 2 h. The reaction mixture was cooled to 0 °C, 40% NaOH solution was added to pH 12, and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic portion was dried (Na_2SO_4) and solvent was removed under reduced pressure to give 0.40 g (90%) of **10b** as the free base. ^{1}H NMR (DMSO-d_6) δ 2.72 (d, J=4.2 Hz, 6H, $2CH_3$), 3.53 (bs, 2H, NH_2), 4.42 (d, J=4.2 Hz, 2H, CH_2), 6.55 (d, J=8.9 Hz, 2H, 2CH), 7.31 (dd, J=7.5 Hz, J=7.7 Hz, 1H, CH), 7.38 (dd, J=7.5 Hz, J=7.8 Hz 1H, CH), 7.60 (d, J=8.9 Hz, 2H, 2CH), 7.84 (d, J=7.8 Hz, 1H, CH), 7.88 (d, J=7.7 Hz, 1H, CH), 8.05 (s, 1H, CH). The HCl salt was prepared in anhydrous MeOH and recrystallized from MeOH/Et_2O: mp 215-217 °C. Anal. calcd for ($C_{17}H_{19}N_3O_2S{\cdot}HCl$) C, H, N. **1-(4-Aminobenzenesulfonyl)-3-methylindole hydrochloride (1-[(4-amino)benzenesulfonyl]skatole; 11b).** A mixture of 3-methylindole (0.50 g, 3.81 mmol) and 60% NaH (0.24 g, 6.00 mmol) was heated at 110 °C under N_2 until the evolution of the H_2 gas ceased. At 0 °C, anhydrous DMF (7 mL) was added with stirring followed by the dropwise addition of 4-nitrobenzenesulfonyl chloride (0.93 g, 4.19 mmol) in DMF (3 mL). The reaction mixture was allowed to stir at room temperature overnight. Ice and then H_2O (25 mL) were added at 0 °C to decompose excess NaH. The crude product was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (4×50 mL). The organic portion was dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc; 19:1) to give 0.22 g (18%) of a solid, mp 173 °C, after recrystallization from acetone/petroleum ether. Raney nickel in MeOH (~0.8 g) was added to a methanolic (20 mL) solution of this material (0.20 g, 0.632 mmol) in a Parr bottle, and the reaction mixture was flushed several times with H_2 and then maintained under H_2 at a delivery pressure of 12 psi for 4 h. Catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give 0.17 g (59%) of a solid. ^{1}H NMR (CD_3OD) δ 2.03 (d, J=1.4 Hz, 3H, CH_3),

7.00-7.14 (m, 3H, 3CH), 7.09 (d, $J=8.8$ Hz, 2H, 2CH), 7.19 (d, $J=1.4$ Hz, 1H, CH), 7.27 (d, $J=7.0$ Hz, 1H, CH), 7.74 (d, $J=8.8$ Hz, 2H, 2CH). The HCl salt was prepared in CH_2Cl_2: mp 195-196 °C. Anal. calcd for ($C_{15}H_{14}N_2O_2S$·HCl) C, H, N.

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