Binding of Sulfonyl-Containing Arylalkylamines at Human 5-HT$_6$ Serotonin Receptors

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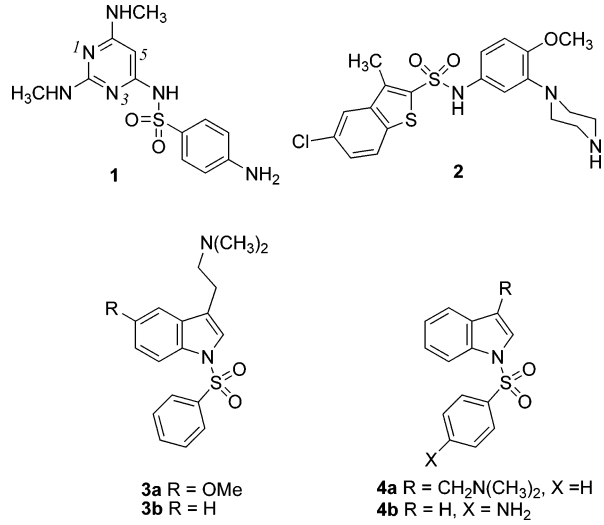
Various sulfonyl-containing compounds (e.g. sulfonamides, sulfones) bind at human 5-HT$_6$ serotonin receptors, but it has been difficult relating the binding mode(s) of such agents to one another, even though many possess a common SO_2 moiety, to identify a common pharmacophore model(s). On the basis of the hypothesis that an ergoline-type conformation might be important for the binding of some sulfonamide-containing arylalkylamines, we prepared for examination at h5-HT$_6$ receptors a series of compounds, including phenylethylamines **6**, pyrroloethylamine **7**, and phenylpiperazines **9**. The results (with K_i values ranging from about 1 nM to >1000 nM) suggest that many of these agents likely bind in a related fashion, and structure−affinity studies indicate that the benzenesulfonamide portion of the phenylethylamine and phenylpiperazine analogues can be "reversed", abbreviated to a sulfone, and moved to an adjacent position with relatively little impact on affinity. Although a benzenesulfonamide (or related arylsulfonamide) group might be common to various 5-HT$_6$ ligands, there appears to be some latitude with regard to the specific constitution and location of the sulfonamide moiety even *within* the same arylalkylamine structural framework. A pharmacophore model is presented to account for some of the current findings.

5-HT$_6$ receptors belong to the serotonin (5-HT$_1$−5-HT$_7$) receptor family. These receptors are G-protein coupled and are positively coupled to an adenylate cyclase effector system.[1−3] Much of the recent interest in 5-HT$_6$ receptors has focused on the development of agents with potential application for the treatment of CNS pathologies related to, for example, cognition, obesity, and convulsive disorders.[1−3] The first reported 5-HT$_6$ antagonist was **1** (Ro 04-6790) (K_i ca. 50 nM) (Chart 1).[4] This was soon followed by **2** (SB-271046) (K_i ca. 1 nM)[5] and, from our laboratory, **3a** (MS-245) (K_i ca. 2 nM).[6,7] Although **1**−**3a** and, since then, a variety of other structurally related agents (reviewed[2,8,9]) possess a sulfonamide moiety embedded within their structure, it has been difficult visualizing how these agents bind relative to one another upon interaction with 5-HT$_6$ receptors. Part of this problem might be associated with attempts to relate the structures of **2** and **3a** (and, now, other ligands) to that of **1**. It is still not known with any confidence which of the five basic nitrogen atoms of **1** interacts with the receptor amine-binding site (presumably the 5-HT$_6$ receptor TM3 aspartate moiety) although modeling studies suggest a bidentate interaction involving the aspartate and the protonated N3 nitrogen atom as well as its adjacent methylamino group.[10] On the other hand, certain other 5-HT$_6$ ligands possess only a single amine moiety, and the ability to relate structures back to one of these types of agents might prove informative. But even with these, the results are ambiguous. For example, although important 5-HT$_6$ binding features have been identified,[9,11] such as the terminal amine of **3**-type compounds, the amine-to-ring distance can be shortened (i.e., **4a**; K_i = 3.1 nM), and the amine can be relocated to the benzenesulfonyl group (e.g. **4b**; K_i = 10 nM) with retention of affinity (Chart 1).[12,13] Consequently, additional studies are required to determine how various 5-HT$_6$ ligands bind relative to one another.

Chart 1. Structures of Some 5-HT$_6$ Antagonists Germane to the Present Investigation



Structure−activity studies by us,[13,14] and independently by investigators at Merck,[15] showed that the 5-methoxy substituent of **3a** is not a major contributor to binding (i.e., **3b**; K_i ca. 3 nM). We also suggested that the tryptamine side-chain conformation preferred for binding likely mimics that found embedded in the ergolines because some ergolines bind at 5-HT$_6$ receptors with high affinity.[16] Support for this concept was provided by Russell et al.[15] who demonstrated that partial ergoline **5** (K_i = 7.2 nM) also binds with high affinity. As has been demonstrated for certain other 5-HT receptor populations to which ergolines bind,[e.g. 17,18] structurally simpler phenylethylamines and pyrroloethylamines, as well as tryptamines, can retain binding properties provided that other pertinent substituents are present. Hence, we prepared phenylethylamine **6a** and pyrroloethylamine

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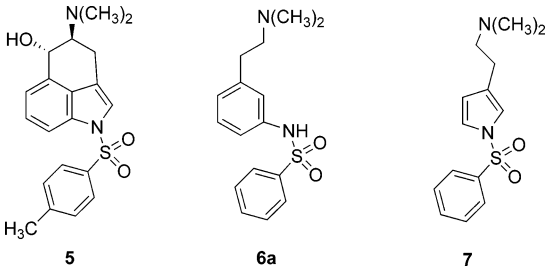
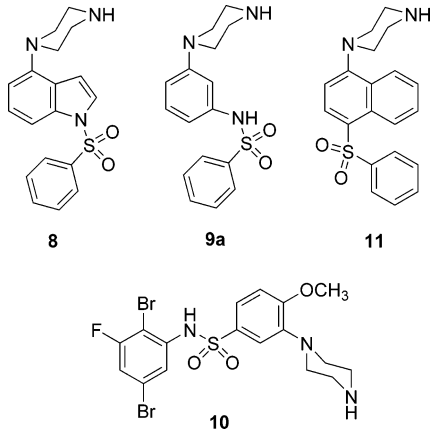


7 to determine whether these partial-structures would be sufficient for 5-HT_6 receptor binding.

Indolylpiperazine **8** (K_i ca. 1 nM) binds at 5-HT_6 receptors with high affinity.[12,19] Although **8** possesses two basic nitrogen atoms, it can be envisioned that it, too, might bind in a manner that mimics the ergolines (i.e., with the piperazine NH orienting itself in the vicinity of an ergoline basic nitrogen atom when the indolic nuclei are superimposed). Therefore, deconstructing the intact pyrrole portion of **8**, to **9** (i.e., a piperazine analogue

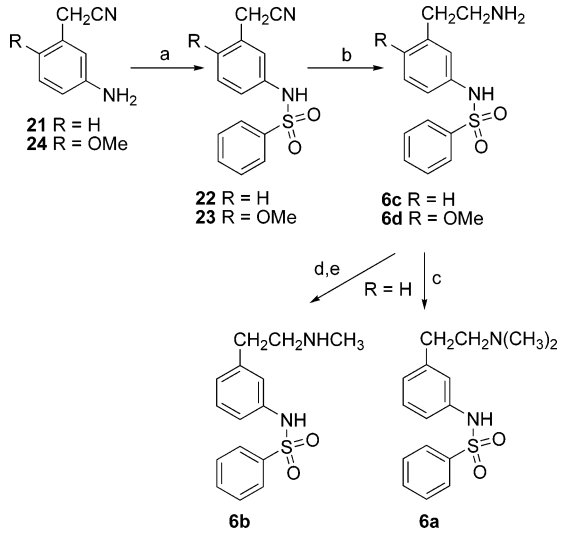


of **6**), should result in a compound that binds at 5-HT_6 receptors. Indeed, **9** bears some obvious structural similarity to **2**. However, arylpiperazine analogues such as the "reverse" sulfonamide **10** (SB-357134) (K_i ca. 3 nM)[20] and sulfone **11** (K_i = 3.8 nM)[21] also bind at 5-HT_6 receptors, further complicating structural comparisons. How are these structure-types related to compounds such as **3a** and **3b**? Another goal of the present investigation, then, was to prepare and evaluate several **9**-related arylpiperazines. It might be noted that the specific arylsulfonyl portion of various sulfonamide-containing 5-HT_6 ligands has been shown to modulate affinity over a >1000-fold range;[6] consequently, for purpose of a more strict comparison of the influence of parent structures on binding, the benzenesulfonyl moiety was held constant throughout these studies.

Chemistry. Primary amine **6c** was prepared by reduction of nitrile **22** with $LiAlH_4$ (Scheme 1). Secondary amine **6b** was prepared by reduction of the carbamate obtained upon reaction of **6c** (free base) with ethyl chloroformate, whereas tertiary amine **6a** was obtained from **6c** (free base) via a reductive alkylation reaction (Scheme 1). Compound **6d** was obtained in the same manner as **6c** via intermediate **23** which, in turn, was prepared from the *o*-methoxy counterpart of **21** (i.e., **24**) (Scheme 1). Pyrroloethylamine **7** was synthesized from its known[23] primary amine counterpart via reductive alkylation.

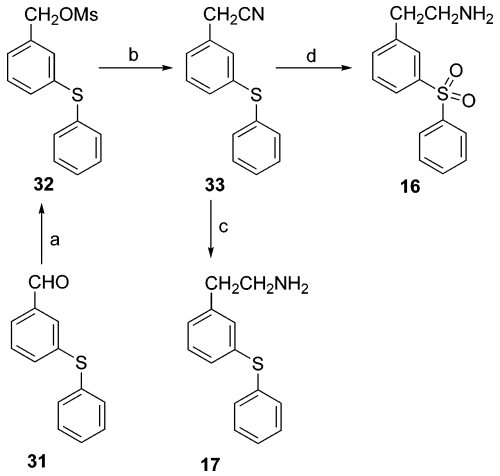
Compounds **16** and **17** were obtained from the reaction sequence shown in Scheme 2. Reduction of 3-substituted benzaldehyde **31** and mesylation of the resultant benzyl alcohol afforded **32**; displacement of the mesylate with cyanide gave intermediate nitrile **33**, and reduction of the nitrile provided **17**.

Scheme 1[a]



[a] Reagents and conditions: (a) $C_6H_5SO_2Cl$, pyridine, 60 °C, 20 h; (b) $NaBH_4$, $CoCl_2 \cdot 6H_2O$, MeOH, rt,1.5 h; (c) $NaBH_3CN$, $H_2C{=}O$, HOAc, MeOH, rt, 0.5 h; (d) $ClCO_2Et$, pyridine, DMF, rt, 2 h; (e) $LiAlH_4$, THF, reflux, 3 h.

Scheme 2[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 1 h, then, MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; (b) NaCN, DMF, 85 °C, 1.5 h; (c) Raney Ni, H_2, NH_3/MeOH, rt, 2.5 h; (d) oxone, MeOH, $NaHCO_3/Na_2CO_3$ (buffer), rt, 2 h, then, Raney Ni, H_2, NH_3/MeOH, rt, 4 h.

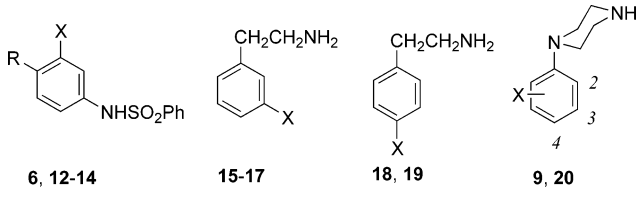
Oxidation of thioether **33** with oxone prior to reduction gave **16**. The 4-substituted phenylethylamine sulfone **19** was prepared in a manner analogous to that of **16** from 4-(phenylthio)-benzaldehyde. Several of the remaining target compounds in this series (Table 1) were synthesized in one or two simple steps via reduction of known precursor nitrile (i.e., the chain-extended analogue **12**, the chain-shortened analogue **13**, and the 4-substituted phenylethylamine sulfonamide **18**) or nitro (i.e., aniline **14** and phenylethylamine **15**) precursors.

As shown in Scheme 3, the phenylpiperazine derivatives possessing a sulfonamide moiety (**9a**, **9b**) were prepared from their corresponding N_1-Boc-protected piperazines by sulfonylation and deprotection. The sulfone analogues (i.e., **20a**−**c**) were prepared by reaction of phenyl halide **40** (where X = Br or I) with piperazine.

Results and Discussion

The ergoline partial structures, phenylethylamine **6a** (K_i = 52 nM; Table 1) and pyrroloethylamine **7** (K_i = 15 ± 3 nM),

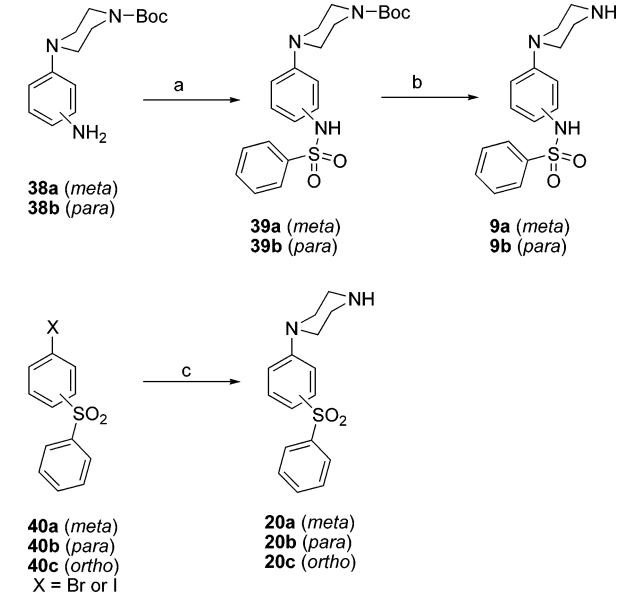
Table 1. 5-HT$_6$ Receptor Radioligand Binding Data for Target Compounds



6, **12-14** **15-17** **18**, **19** **9**, **20**

	X	R	K_i, nM	(±SEM)
6a	$CH_2CH_2N(CH_3)_2$	H	52	(12)
6b	$CH_2CH_2NHCH_3$	H	38	(13)
6c	$CH_2CH_2NH_2$	H	21	(6)
6d	$CH_2CH_2NH_2$	OMe	17	(6)
12	$CH_2CH_2CH_2NH_2$	H	230	(35)
13	CH_2NH_2	H	290	(40)
14	NH_2	H	2840	(410)
15	SO_2NHPh	- -	70	(26)
16	SO_2Ph	- -	50	(6)
17	SPh	- -	115	(15)
18	$NHSO_2Ph$	- -	38	(16)
19	SO_2Ph	- -	37	(4)
9a	3-$NHSO_2Ph$	- -	62	(13)
9b	4-$NHSO_2Ph$	- -	85	(14)
20a	3-SO_2Ph	- -	1.2	(0.2)
20b	4-SO_2Ph	- -	6.9	(0.8)
20c	2-SO_2Ph	- -	4000	(600)

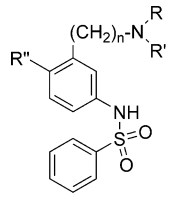
Scheme 3[a]



[a] Reagents and conditions: (a) $C_6H_5SO_2Cl$, pyridine, CH_2Cl_2, rt, 5 h; (b) HCl, EtOAc, rt, 3 h; (c) piperazine.

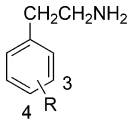
bind at 5-HT$_6$ receptors with 10-fold and 4-fold lower affinity, respectively, than **3b** (K_i = 4.1 nM), indicating that the intact tryptamine nucleus of **3b** might be optimal for binding.

A limited structure−affinity study was conducted with **6a**. Replacement of one (i.e., **6b**; K_i = 38 nM) or both (i.e., **6c**; K_i = 21 nM) of the terminal-amine methyl groups by a hydrogen atom had relatively little impact on affinity, with the primary amine **6c** binding only with twice the affinity of **6a**. This is consistent with what has been previously reported for **3**-type analogues. Lengthening the alkyl side-chain from two to three methylene groups decreased affinity by 10-fold (**12**; K_i = 230 nM), as did shortening the chain by one methylene group (**13**; K_i = 290 nM). Further shortening of the chain to aniline **14** (K_i = 2840 nM), a compound now bearing greater resemblance to **1** than to **2**, resulted in 100-fold reduced affinity relative to **6c**. As mentioned earlier, the presence of the methoxy group of **3a** has little impact on affinity when compared with **3b**. Introduction of what should be the corresponding methoxy group to **6c** (i.e., **6d**; K_i = 17 nM) also had little effect on affinity.



6a n = 2, R = R' = Me, R" = H
6b n = 2, R = Me, R' = R" = H
6c n = 2, R = R' = R" = H
6d n = 2, R = R' = H, R" = OMe
12 n = 3, R = R' = R" = H
13 n = 1, R = R' = R" = H
14 n = 0, R = R' = R" =H

It has been demonstrated for certain sulfonamide-containing 5-HT$_6$ antagonists that the sulfonamide moiety can be "reversed" (e.g. **10**), or that the NH portion of the sulfonamide can be eliminated altogether to afford sulfone analogues.[9,22] Compound **15** (K_i = 70 nM), the reverse sulfonamide analogue of **6c**, and the corresponding sulfone **16** (K_i = 50 nM), had 2- to 3-fold reduced affinity for 5-HT$_6$ receptors. In this regard, the behavior of the sulfonamidophenylethylamines is reminiscent of other sulfonamido 5-HT$_6$ ligands. There has been discussion about a possible interaction of the sulfonamido (or sulfonyl) oxygen atoms with receptor-associated features (e.g. participation in hydrogen-bond formation).[8,10] This was directly evaluated by examining compound **17**. Thioether **17** (K_i = 115 nM) displayed half the affinity of its sulfone counterpart **16**, indicating that the oxygen atoms might play a small contributory role. Alternatively, it could be the difference in the −S− vs −SO_2− bond angle that accounts for this small difference in affinity. It might be noted that compound **17** is the first thioether shown to bind at 5-HT$_6$ receptors and represents the first direct test of the effect of sulfonyl oxygen atoms on the binding of these types of compounds. It would appear that the SO_2 moiety is not an absolute requirement for binding.



15 R = 3-SO_2NH-Ph
16 R = 3-SO_2-Ph
17 R = 3-S-Ph
18 R = 4-$NHSO_2$-Ph
19 R = 4-SO_2-Ph

To determine if the effects of the sulfonamide/sulfone moieties are position-specific, we prepared and examined compounds **18** and **19**. These compounds are analogues of **6c** and **16** where the sulfonamide or sulfone moiety was moved from the 3- to the 4-position (from the meta to the para position), respectively. Interesting is that **18** (K_i = 38 nM) and **19** (K_i = 37 nM) bind with comparable affinity, once again indicating that the NH is not required for binding. More interesting is that these compounds displayed affinities comparable to their 3-substituted positional isomers **6c** and **16**, respectively. Evidently, there is some latitude with respect to substituent location.

Although we have presented evidence that some N_1-arylsulfonylindoles might bind at 5-HT$_6$ receptors in such a manner that their indolic nuclei are not superimposed,[12] at this time it is not known how indolylpiperazines such as **8** bind relative to **3**-type compounds. Piperazines **9** might be viewed as analogues of **8** where the pyrrole portion of the molecule has been disrupted. Compound **9a** (K_i = 62 nM) binds with reduced affinity relative to **8** (K_i ca. 1 nM) but with affinity comparable to phenylethylamine **6a** (K_i = 52 nM), supporting the concept that the entire indolic nucleus might be optimal for binding. Furthermore, as seen with the phenylethylamine derivatives, the sulfonamide moiety can be moved from the 3- to the 4-position

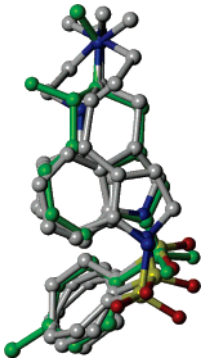


Figure 1. Superimposition of tryptamine **3b**, phenylethylamine **6a**, and piperazinylindole **8** with the partial ergoline structure **5** (molecule shown in green) showing the relationship between common structural features (i.e., terminal amine, phenyl or fused phenyl ring, and the bensenezulfonamide phenyl ring). The rms is <0.2 for individual superimpositions with **5**. Numerous low-energy conformers (rotamers) are possible for the benzenesulfonyl group; a common low-energy conformer was selected for each, but the results are not meant to imply that the conformer shown is the preferred conformer for binding.

(i.e., **9b**; K_i = 85 nM) with little effect on affinity. Also, as seen with the phenylethylamines, the sulfonamide can be abbreviated to a sulfone (i.e., **20a**; K_i = 1.2 nM); however here, this structural modification results in 50-fold enhanced affinity. The sulfone moiety can be effectively moved from the 3- to the 4-position with retention of affinity (**20b**; K_i = 6.9 nM), whereas moving the substituent to the 2-position (**20c**; K_i = 4000 nM) resulted in >3000-fold reduced affinity.

The general results of the present investigation support the possibility that ligands such as **2**, **3**, **5**−**9** bind in a roughly similar manner upon interaction with 5-HT_6 receptors and might utilize some common binding features. Added support comes from molecular superimposition studies where the tryptamine **3b** (rms = 0.184), phenylethylamine **6a** (rms = 0.062), and indolylpiperazine **8** (rms = 0.119) are able to superimpose with partial ergoline **5** (Figure 1). The results also indicate that the benzenesulfonamide moiety of the phenylethylamines can be "reversed" (comparing **6c** with **15**) or abbreviated to the corresponding sulfone (comparing **6c** with **16**), and moved from the 3- to the 4-position (comparing **6c** with **18**). The phenylpiperazines behave in a similar fashion, and the 3-benzenesulfonamide moiety can be moved from the 3- to the 4-position (comparing **9a** with **9b**) and converted to a sulfone (comparing **9a** with **20a**, and **9b** with **20b**). The latter finding is informative in that it helps explain the high affinity previously reported[21] for the 4-substituted naphthylpiperazine **11**.

Attempts have been made to demonstrate how various, apparently disparate, sulfonamide-containing 5-HT_6 ligands relate to one another in order to formulate 5-HT_6 binding pharmacophores.[9] A sulfonyl moiety, being a common component of many such agents, frequently, and not unexpectedly, serves as a beacon in such comparisons. The present studies indicate, however, that 5-HT_6 receptors can accommodate a sulfonyl group in more than one position in the same parent molecule when, for example, **9a** is compared with **9b**, or **20a** is compared with **20b**. Likewise, the binding of pyrroloethylamine **7** and piperazine analogue **20a** indicates that although a bicyclic structure can be accommodated by the receptor, it is certainly not required.

Those QSAR studies that have focused on a single structure-type,[25] or that have employed methods that do not require specific molecular alignments,[26] have met with some success. But even these studies might be confounded by the lack of

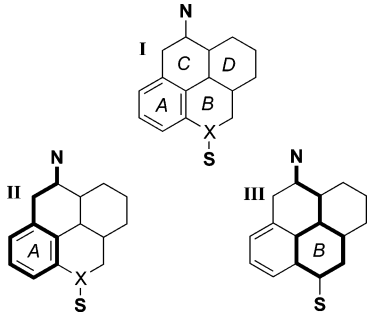
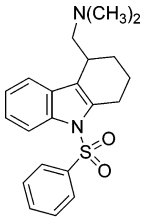


Figure 2. A stylized composite of possible interaction modes for various arylalkylamines with 5-HT_6 receptors (I). Depending upon the nature and location of aryl substituents, ligands can orient using both ring A and ring B (e.g. tryptamines **3** and partial ergoline **5**), ring A (e.g. as shown with phenylethylamine **6**, II), or with ring B (e.g. as shown with phenylethylamine **16**, III). Group X can be a nitrogen atom, whereas S represents the sulfur atom of a sulfonamide or sulfone. See text for further discussion.

available structure−activity data. For example, in one study in which two different binding models were proposed, one model implicates the secondary amine of piperazine-type compounds as making a negative contribution to binding, whereas the second model suggests that the piperazine tertiary amine (i.e., aryl-N) makes a positive contribution.[26] While these models might be correct for explaining the binding of certain compounds, consideration of aniline **14** (K_i = 2840 nM), or 4-substituted arylpiperazines such as **11** (K_i = 3.8 nM) and **20b** (K_i = 6.9 nM) might have afforded slightly different results.

A fairly simplistic manner in which alteration/translocation of the sulfur-containing substituents can be envisioned is shown in Figure 2. In the stylized representation, rings A and B (I, Figure 2) could represent a tryptamine or related bicyclic nucleus; introduction of ring C would begin to approach ergoline-type structures such as **5**. A somewhat similar representation has been very recently suggested by Holenz et al.[9] The receptors seem to tolerate an additional ring D. For example, compound **41** (K_i = 1.5 nM) binds with high affinity.[14]



41

The monocyclic 3-substituted phenylethylamines **6** could bind in a manner that utilizes the A site, whereas the 4-substituted phenylethylamines might utilize the B site (Figure 2, II and III, respectively). This fairly simple concept would also account for the binding of pyrroloethylamine **7** and could be further extended to certain 3- and 4-substitutd arylpiperazines, including the bicyclic naphthylpiperazine **11**. While it might not adequately explain all of the findings, the pharmacophore model accounts for the binding of monocyclic, bicyclic, and tricyclic compounds and provides testable hypotheses that can be evaluated in the future.

So, in addition to examining the binding of several novel sulfonamides and sulfones, the present investigation identified two new structure-types, phenylethylamines and pyrroloethylamines, as potential scaffolding for the development of novel 5-HT_6 ligands. Some of the targets displayed good affinity, but

it should be realized that because the nature (i.e., ring system, substituents) of the arylsulfonyl portion of arylsulfonamides and aryl sulfones can modulate affinity over a broad range, the affinity of these structure-types should not yet be considered optimized. The present study also extends the scope of compounds and substitution patterns that will need to be considered in future QSAR studies.

Experimental Section

Chemistry. Melting points were taken in glass capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. ^{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 calculated values, except where otherwise noted. Chromatographic separations were performed on silica gel columns (Kieselgel 40, 0.040−0.063 mm, Merck). Reactions and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates.

***N*-[3-(2-Dimethylaminoethyl)phenyl]benzenesulfonamide Hydrochloride (6a).** Sodium cyanoborohydride (0.24 g, 3.76 mmol) was added portionwise (over 10 min) to a stirred solution of **6c** (free base; 0.65 g, 2.35 mmol) and 37% aqueous formalin (0.95 g, 11.8 mmol) in MeOH (10 mL) at room temperature. After 30 min the reaction mixture was neutralized with a few drops of HOAc, and stirring was continued for another 2 h. Sodium hydroxide solution (1 N, 10 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined extract was washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 35 g) using CH_2Cl_2/MeOH (4:1) to afford a pale-yellow semisolid product (0.26 g, 36%). Gaseous HCl was bubbled through a small amount of the product in MeOH/Et_2O, and the crude product was recrystallized from MeOH/Et_2O to give pale-yellow crystals of **6a**: mp 163−165 °C; ^{1}H NMR (DMSO-d_6) δ 2.74 (s, 6H, CH), 2.90 (t, J = 4.5, 2H, CH), 3.12 (t, J = 5.4, 2H, CH), 6.92−7.01 (m, 3H, ArH), 7.13−7.18 (m, 1H, ArH), 7.49−7.61 (m, 3H, ArH), 7.73−7.76 (m, 2H, ArH). Anal. ($C_{16}H_{20}N_2O_2S$·HCl) C, H, N.

***N*-[3-(2-Methylaminoethyl)phenyl]benzenesulfonamide Hydrochloride (6b).** Ethyl chloroformate (0.22 mL, 2.35 mmol) was added to a stirred solution of **6c** (free base; 0.44 g, 1.57 mmol) and pyridine (0.25 mL, 3.14 mmol) in DMF (5 mL) at −10 °C under N_2. The reaction mixture was allowed to stir at room temperature for 2 h, followed by removal of solvent under reduced pressure. The residue was diluted with CH_2Cl_2 (25 mL), washed with H_2O (15 mL) and brine (15 mL), and dried (Na_2SO_4), and solvent was removed under reduced pressure. The carbamate ester intermediate was purified by column chromatography (silica gel, 15 g) using hexane/EtOAc (7:3) as eluent to obtain a yellow oil (0.50 g, 90%). The intermediate (0.50 g, 1.42 mmol) in dry THF (10 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (0.22 g, 5.68 mmol) in THF (20 mL) at 0 °C under N_2. The reaction mixture was heated at reflux for 3 h, cooled to room temperature, and placed in an ice bath. Water (1 mL) was carefully added followed by NaOH (15%, 2 mL), and the resulting mixture was allowed to stir for 30 min. The supernatant was removed. The solid material was washed with hot THF (5 × 30 mL), combined with the supernatant, and filtered, and solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 10 g) using CH_2Cl_2/MeOH (4:1) as eluent to afford 0.36 g of the free base of **6b** as a pale-yellow semisolid material: mp 53−55 °C. Gaseous HCl was bubbled through a solution of the base in MeOH/Et_2O and the salt was recrystallized from MeOH/Et_2O to afford beige crystals of **6b** (0.33 g, 84%): mp 140−142 °C; ^{1}H NMR (DMSO-d_6) δ 2.81 (t, J = 7.8, 2H, CH), 2.96 (t, J = 4.6, 2H, CH), 3.33 (s, 3H, CH), 6.89−6.98 (m, 3H, ArH), 7.13−7.18 (m, 1H, ArH), 7.50−7.59 (m, 3H, ArH), 7.74−7.76 (m, 2H, ArH). Anal. ($C_{15}H_{18}N_2O_2S$·HCl·0.25H_2O) C, H, N.

***N*-[3-(2-Aminoethyl)phenyl]benzenesulfonamide Oxalate (6c).** Benzenesulfonyl chloride (1.20 g, 6.17 mmol) was added to a mixture of **21** (1.00 g, 7.56 mmol) and pyridine (1.00 g, 12.64 mmol) under an N_2 atmosphere and heated at reflux for 2 h. The reaction mixture was allowed to cool to room temperature, and solvent was removed under reduced pressure. The residue was washed with H_2O and extracted with EtOAc (4 × 50 mL). The organic portion was dried ($MgSO_4$), and solvent was removed under reduced pressure to give an oil. The oil was purified by flash chromatography (hexane/EtOAc, 20:1) to give 1.62 g (79%) of the sulfonamide which was used without further characterization.

A solution of **22** (1.00 g, 3.67 mmol) in dry THF (25 mL) was added in a dropwise manner to a stirred suspension of $LiAlH_4$ (0.63 g, 16.55 mmol) in THF (50 mL). The reaction mixture was heated at reflux for 5 h under N_2 and then cooled to 0 °C. Excess hydride was decomposed by the dropwise addition of H_2O until H_2 evolution ceased, and then 15% NaOH (0.50 mL) was added. The resulting white solid was collected by filtration and washed with THF (30 mL). The solvent from the combined filtrate and washings was evaporated under reduced pressure to give a yellow oil that was purified by column chromatography (CH_2Cl_2/MeOH, 9:1) and converted to an oxalate salt. The salt was recrystallized from MeOH and anhydrous Et_2O to give 0.72 g (71%) of the title compound: mp 211−213 °C. ^{1}H NMR (DMSO-d_6) δ 2.61 (t, 2H, CH_2), 2.90 (t, 2H, CH_2), 6.89−7.01 (m, 4H, ArH), 7.12−7.18 (t, 1H, ArH), 7.48 (m, 2H, ArH), 7.73 (m, 2H, ArH). Anal. ($C_{14}H_{16}N_2O_3S$·0.9$C_2H_2O_4$) C, H, N.

***N*-[3-(2-Aminoethyl)-4-methoxyphenyl]benzenesulfonamide Oxalate (6d).** Benzenesulfonyl chloride (1.20 g,6.17 mmol) was added to a mixture of 2-methoxy-3-aminophenylacetonitrile (**24**)[27] (1.00 g, 6.17 mmol) and pyridine (1.00 g, 12.64 mmol) under N_2 and heated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue was washed with H_2O and extracted with EtOAc (4 × 50 mL). The organic portion was dried ($MgSO_4$), and solvent was removed under reduced pressure to give an oil. The oil was purified by flash chromatography (hexane/EtOAc, 20:1) to give 1.50 g (82%) of sulfonamide **23** which was used without further characterization.

A solution of **23** (1.00 g, 3.31 mmol) in dry THF (25 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (0.63 g, 16.55 mmol) in THF (50 mL). The reaction mixture was heated at reflux for 5 h under N_2 and then cooled to 0 °C. Excess hydride was decomposed by the dropwise addition of H_2O (0.50 mL) and then 15% NaOH (0.50 mL). The white solid was collected by filtration and washed with dry THF (30 mL). The solvent from the combined filtrate and washings was evaporated under reduced pressure to give a yellow oil that was purified by column chromatography (CH_2Cl_2/MeOH, 9:1) and converted to an oxalate salt. The oxalate salt was recrystallized from MeOH and anhydrous Et_2O to give 0.60 g (58%) of the title compound: mp 165−167 °C. ^{1}H NMR ($CDCl_3$, free base) δ 2.9 (t, 2H, CH_2), 3.1 (t, 2H, CH_2), 3.90 (s, 3H, OCH_3), 6.6 (s, 1H, ArH), 6.7 (d, 1H, ArH), 6.8 (d, 1H, ArH), 7.4−7.6 (m, 5H, ArH). Anal. ($C_{15}H_{18}N_2O_3S$·$C_2H_2O_4$) C, H, N.

***N,N*-Dimethyl-2-[1-(benzenesulfonyl)-1*H*-pyrrol-3-yl]-1-aminoethane Hydrochloride (7).** The free base of the primary amine counterpart of **7** was prepared as reported by Clark et al.,[23] as a clear oil. Sodium cyanoborohydride (0.37 g, 5.84 mmol) was added portionwise to a stirred solution of the amine (0.73 g, 2.92 mmol) and 37% aqueous formalin (1.5 mL, 20.14 mmol) in MeOH (10 mL) at room temperature. The reaction mixture was allowed to stir at room temperature for 1 h, and H_2O (20 mL) and brine (10 mL) were consecutively added. The mixture was extracted with CH_2Cl_2 (4 × 30 mL), the combined extracts were washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using CH_2Cl_2 followed by CH_2Cl_2/MeOH

(4:1) to afford the dimethylated free base as a pale-yellow oil (0.70 g, 86%). Gaseous HCl was bubbled through a solution of the free base in MeOH/Et_2O. Recrystallization from MeOH/Et_2O afforded **7** as a white solid (0.42 g): mp 189−191 °C; ^{1}H NMR ($CDCl_3$) δ 2.82 (s, 3H, CH), 2.84 (s, 3H, CH), 3.01−3.08 (m, 2H, CH), 3.13−3.18 (m, 2H, CH), 6.20 (dd, J = 3.0, 1.5, 1H, ArH), 7.03−7.05 (m, 1H, ArH), 7.13−7.15 (m, 1H, ArH), 7.51−7.57 (m, 2H, ArH), 7.62−7.67 (m, 1H, ArH), 7.85−7.86 (m, 1H, ArH), 7.87−7.88 (m, 1H, ArH). Anal. ($C_{14}H_{18}N_2O_2S$·HCl) C, H, N.

4-(3-Benzenesulfonamidophenyl)piperazine Hydrochloride (9a). A saturated solution of HCl (g) in dry EtOAc (25 mL) was added in a dropwise manner to a solution of 1-Boc-4-(3-benzenesulfonamidophenyl)piperazine (2.85 g, 5.0 mmol) (**39a**) in dry EtOAc (25 mL). The reaction mixture was allowed to stir for 3 h, and solvent was evaporated under reduced pressure to give a brown semisolid material. The crude product was purified by flash chromatography (silica gel; CH_2Cl_2/MeOH, 4:1) to give a gray-brown solid that was subsequently recrystallized from *i*PrOH/Et_2O to afford 1.26 g (69%) of **9a** as a gray powder: mp 141−143 °C (dec); ^{1}H NMR (DMSO-d_6) δ 3.13 (m, 4H, CH_2), 3.22 (m, 4H, CH_2), 6.57−6.70 (m, 3H, ArH), 7.06 (m, 1H, ArH), 7.52−7.61 (m, 3H, ArH), 7.77 (m, 2H, ArH), 9.54 (br.s., 2H, piperazinyl NH_2^+, D_2O exchangeable). Anal. ($C_{16}H_{19}N_3O_2S$·HCl·0.7H_2O) C, H, N.

4-(4-Benzenesulfonamidophenyl)piperazine Hydrochloride (9b). A solution of benzenesulfonyl chloride (2.20 g, 12.5 mmol) in dry CH_2Cl_2 (10 mL) was added in a dropwise manner to a mixture of 1-Boc-4-(4-aminophenyl)piperazine[28] (**38b**) (2.77 g, 10.0 mmol) and pyridine (1.18 g, 1.5 mmol) in dry CH_2Cl_2 (25 mL) at room temperature under an N_2 atmosphere. The reaction mixture was allowed to stir for 5 h and solvent was evaporated under reduced pressure. A solution of the residue in CH_2Cl_2 (100 mL) was washed with 5% NaOH (2 × 25 mL), then brine (3 × 50 mL), dried ($MgSO_4$), and solvent was evaporated under reduced pressure. The resultant crude product was recrystallized from EtOAc/hexane to give 3.58 g (86%) of **39b** as a white solid: mp 180−181 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H, CH_3), 3.11 (m, 4H, CH_2), 3.59 (m, 4H, CH_2), 6.28 (br.s., 1H, $NHSO_2$, D_2O exchangeable), 6.82 (m, 2H, ArH), 6.98 (m, 2H, ArH), 7.48 (m, 2H, ArH), 7.54 (m, 1H, ArH), 7.73 (m, 2H, ArH).

A saturated solution of HCl (g) in dry EtOAc (25 mL) was added in a dropwise manner to a stirred solution of **39b** (2.85 g, 5 mmol) in dry EtOAc (25 mL). The reaction mixture was allowed to stir for 3 h and concentrated under reduced pressure, and solids were removed by filtration. The grayish-white solid was recrystallized from MeOH/Et_2O to afford 1.62 g (92%) of **9b** as a gray powder: mp >205 °C (dec). ^{1}H NMR (DMSO-d_6) δ 3.17 (m, 4H, CH_2), 3.25 (m, 4H, CH_2), 6.85 (d, J = 9.3 Hz, 2H, ArH), 6.95 (d, J = 8.7 Hz, 2H, ArH), 7.58 (m, 3H, ArH), 7.71 (m, 2H, ArH), 9.04 (br.s., 2H, piperazinyl NH_2^+, D_2O exchangeable), 9.92 (br.s., 1H, $NHSO_2$, D_2O exchangeable). Anal. ($C_{16}H_{19}N_3O_2S$·HCl·1.5H_2O) C, H, N.

***N*-[3-(3-Aminopropyl)phenyl]benzenesulfonamide Oxalate (12).** Benzenesulfonyl chloride (2.1 g, 11.7 mmol) was added to a solution of 2-(3-aminophenyl)acrylonitrile (**25**)[29] (1.4 g, 9.7 mmol) in pyridine (20 mL), and the solution was allowed to stir at 60 °C overnight (18 h). Pyridine was removed under reduced pressure, HCl (1 N, 50 mL) was added to the residue, and the mixture was extracted with EtOAc (4 × 20 mL). The combined organic portion was washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was diluted with EtOAc (20 mL), and upon addition of hexane, benzenesulfonamide **26** precipitated out as a beige solid (2.2 g, 80%): mp 188−190 °C; ^{1}H NMR ($CDCl_3$) δ 5.84 (d, J = 8.4, 1H, CH═CH), 7.12−7.34 (m, 6H, ArH), 7.46−7.62 (m, 3H, ArH), 7.81 (d, J = 4.2, 1H, CH═CH).

Raney Ni (0.05 g of 2800 Ni slurry in H_2O, 0.9 mmol) was added to a solution of **26** (0.5 g, 1.8 mmol) in NH_3/MeOH (2 M, 20 mL). The mixture was hydrogenated at ca. 50 psi overnight (12 h), and the solid material was removed by filtration. Solids were washed with CH_2Cl_2 (5 × 10 mL). The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using CH_2Cl_2/MeOH (4:1) as eluent to afford the free base of **12** as a pale yellow solid (0.15 g): mp 176−177 °C. Oxalic acid was added to a solution of the free base in acetone, and the salt was collected and recrystallized from acetone to give **12** as a white solid (0.1 g, 48%): mp 206−208 °C; ^{1}H NMR (CD_3OD) δ 1.88 (s, 2H, CH), 2.61 (s, 2H, CH), 2.86 (s, 2H, CH), 6.93 (m, 3H, ArH), 7.12 (m, 1H, ArH), 7.47−7.57 (m, 3H, ArH), 7.75(m, 2H, ArH). Anal. ($C_{15}H_{18}N_2O_2S$·$C_2H_2O_4$) C, H, N, except that N_{calc} = 7.36%, N_{found} = 7.77%.

***N*-[(3-Aminomethyl)phenyl]benzenesulfonamide Oxalate (13).** The free base of **13** was prepared from *N*-(3-cyanophenyl)-benzenesulfonamide (**27**)[30] using the procedure of Satoh and Suzuki.[31] The crude free base was purified by column chromatography (silica gel, 30 g) using CH_2Cl_2/MeOH (4:1) and converted to its oxalate salt to give **13** (0.15 g, 53%) as white crystals following recrystallization from acetone: mp 153−154 °C. ^{1}H NMR (DMSO-d_6) δ 3.95 (s, 2H, CH), 7.10 (dd, J = 4.05, 13.65, 2H, ArH), 7.27 (t, J = 7.8, 2H, ArH), 7.52−7.62 (m, 3H, ArH), 7.80 (d, J = 4.2, 2H, ArH). Anal. ($C_{13}H_{14}N_2O_2S$·1.25$C_2H_2O_4$) C, H, N.

***N*-(3-Aminophenyl)benzenesulfonamide Hydrochloride (14).** A mixture of *N*-(3-nitrophenyl)benzenesulfonamide (**28**)[32] (1.50 g, 5.39 mmol) and $SnCl_2$·2H_2O (6.09 g, 26.98 mmol) in absolute EtOH (50 mL) was heated at reflux until all the starting material disappeared (30 min). The reaction mixture was allowed to cool to room temperature and poured onto a small amount of ice, and the solution was made slightly basic (pH 8−9) by the addition of saturated $NaHCO_3$ solution. Solid NaCl (ca. 4−5 g) was added to the solution, and the solution was extracted with EtOAc (3 × 100 mL). The organic portion was thoroughly washed with brine (3 × 50 mL) and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The free base of the title compound was obtained as a brown solid (1.20 g, 90%). The hydrochloride salt was prepared in anhydrous MeOH and recrystallized from MeOH/Et_2O to give **14** as brown-colored crystals: mp 226−227 °C. ^{1}H NMR (DMSO-d_6) δ: 6.95 (d, J = 8.1 Hz, 1H, CH); 7.03 (dd, J = 8.1 Hz, J = 2.1 Hz, 1H, CH) 7.16 (d, J = 2.1 Hz, 1H, CH); 7.28 (dd, J = 8.1 Hz, J = 8.1 Hz, 1H, 1CH); 7.51−7.70 (m, 3H, 3CH); 7.80−7.83 (m, 2H, 2CH); 10.70 (s, 1H, NH). Anal. ($C_{12}H_{12}N_2O_2S$·HCl) C, H. N.

***N*-Phenyl-3-(2-aminoethyl)benzenesulfonamide Oxalate (15).** A mixture of nitromethane (100 mL), *N*-phenyl-(3-formyl)benzenesulfonamide **29** (2.0 g, 7.64 mmol[33] and NH_4OAc (0.65 g, 8.41 mmol) was heated at reflux overnight (20 h) under N_2. Water (20 mL) was added, the organic portion was extracted with EtOAc (4 × 10 mL), the combined organic extract was washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. Column chromatography (silica gel, 30 g) of the residue using hexane/EtOAc (7:3) afforded intermediate nitrostyrene **30** as a yellow oil in a quantitative yield. ^{1}H NMR ($CDCl_3$) δ 7.12−7.18 (m, 2H, ArCH═CH), 7.24−7.32 (m, 3H, ArH), 7.41−7.46 (m, 1H, ArH), 7.54−7.60 (m, 1H, ArH), 7.68−7.78 (m, 1H, ArH), 7.88−8.00 (m, 3H, ArH).

Nitrostyrene **30** (0.80 g, 2.61 mmol) in dry THF (10 mL) was slowly added to a suspension of $LiAlH_4$ (0.40 g, 10.44 mmol) in THF (30 mL) at 0 °C under N_2. The reaction mixture was heated at reflux for 3 h, allowed to cool to room temperature, and placed in an ice bath. Water (1 mL) was carefully added to the reaction mixture followed by the dropwise addition of NaOH (15%, 2 mL). The mixture was allowed to stir for 20 min, and the supernatant was removed. The solid material was washed with hot THF (5 × 30 mL). Solvent was removed from the combined supernatant fractions and washings under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using CH_2Cl_2/MeOH (4:1) to afford the free base of **15** as a white solid (0.44 g, 61%): mp 140−142 °C. Oxalic acid was added to a solution of the free base in acetone to obtain **15** as a white solid following recrystallization from acetone: mp 179−181 °C; ^{1}H NMR (DMSO-d_6) δ 2.83−2.95 (m, 4H, CH), 6.96−7.06 (m, 3H, ArH), 7.16−7.21 (m, 2H, ArH), 7.43−7.50 (m, 2H, ArH), 7.58−7.62 (m, 2H, ArH). Anal. ($C_{14}H_{16}N_2O_2S$·$C_2H_2O_4$) C, H, N.

2-(3-Benzenesulfonyl)phenyl-1-aminoethane Hydrochloride

(16). A solution of oxone (6.10 g, 9.93 mmol) in H_2O (16 mL) was added to nitrile **33** (0.7 g, 3.31 mmol) in MeOH at 0 °C. The reaction mixture was adjusted to pH 5 with $NaHCO_3/Na_2CO_3$ (0.2M buffer) and allowed to stir at room temperature for 2 h. Water (50 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (4 × 30 mL); the combined extract was washed with brine (30 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure to afford a white solid product (0.84 g). Raney Ni (1.62 g, 27.62 mmol) was added to a solution of this material (0.84 g, 3.45 mmol) in methanolic ammonia (2 M NH_3 in MeOH, 40 mL). The reaction mixture was hydrogenated at ca. 50 psi for 4 h and then filtered. Solvent was removed from the filtrate under reduced pressure, and the residue was purified by column chromatography (silica gel, 15 g) using CH_2Cl_2/MeOH (4:1) as eluent; the free base of **16** was obtained as a white semisolid material (0.61 g, 71%). A portion of the free base in dry MeOH/anhydrous Et_2O was converted to a salt using HCl (g). After recrystallization from MeOH/Et_2O, **16** was obtained as a white solid: mp 241−243 °C; ^{1}H NMR (DMSO-d_6) δ 2.83−3.01 (m, 2H, CH), 3.05−3.10 (m, 2H, CH), 7.56−7.73 (m, 4H, ArH), 7.83−8.04 (m, 5H, ArH). Anal. ($C_{14}H_{15}NO_2S$·HCl) C, H, N.

2-(3-Phenylthio)phenyl-1-aminoethane Hydrochloride (17). Raney Ni (1.33 g, 22.72 mmol) was added to **33** (0.60 g, 2.84 mmol) in a solution of NH_3 (2 M) in MeOH (40 mL). The reaction mixture was hydrogenated at ca. 50 psi for 2.5 h and then filtered. The filtrate was collected, and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using CH_2Cl_2/MeOH (4:1), and the free base, obtained as a pale-yellow oil (0.38 g, 52%), in dry MeOH/anhydrous Et_2O was converted to a salt using HCl (g). After recrystallization from MeOH/Et_2O, **17** (0.3 g) was obtained as a white solid: mp 193−195 °C; ^{1}H NMR (DMSO-d_6) δ 2.83−2.88 (m, 2H, CH), 2.96−3.01 (m, 2H, CH), 7.14−7.39 (m, 9H, ArH), 8.12 (s, 3H, NH). Anal. ($C_{14}H_{15}NS$·HCl) C, H, N.

***N*-[4-(2-Aminoethyl)phenyl]benzenesulfonamide Oxalate (18).** Sodium borohydride (1.4 g, 37 mmol) was slowly added (over 15 min) to a stirred solution of 4-(*N*-benzenesulfonyl)aminophenylacetonitrile (**34**)[34] (1.0 g, 3.7 mmol) and $CoCl_2$·$6H_2O$ (1.7 g, 7.4 mmol) in anhydrous MeOH (20 mL). During addition, H_2 evolved and a black precipitate formed. The reaction mixture was allowed to stir at room temperature for 1.5 h, and then HCl (3 N, 20 mL) was added with continued stirring until the precipitate dissolved. Solvent was removed under reduced pressure, the aqueous portion was basified with 15% aqueous NaOH, and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic portion was washed with brine (50 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using CH_2Cl_2/MeOH (4:1) as eluent. Oxalic acid was added to the pale-yellow solid in acetone, and the precipitate was collected and recrystallized from acetone to give **18** (0.2 g, 68%) as a white solid: mp 174−175 °C; ^{1}H NMR (DMSO-d_6) δ 2.76 (t, J = 8.7, 2H, CH), 2.97 (t, J = 8.7, 2H, CH), 7.04−7.14 (dd, J = 4.2, 4.2, 4H, ArH), 7.53−7.60 (m, 3H, ArH), 7.77 (d, J = 4.35, 2H, ArH); Anal. ($C_{14}H_{16}N_2O_2S$·$C_2H_2O_4$) C, H, N. The compound has been previously reported[35] but without characterization.

2-[4-(Benzenesulfonyl)phenyl]-1-aminoethane Hydrochloride (19). Sodium borohydride (0.9 g, 23.34 mmol) was added portionwise to a solution of 4-phenylthiobenzaldehyde (**35**)[36] (2.5 g, 11.67 mmol) in MeOH (30 mL). The reaction mixture was allowed to stir at room temperature for 1 h, H_2O (30 mL) was added, and the mixture was extracted with EtOAc (4 × 30 mL). The combined extract was washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using hexane followed by hexane/EtOAc (7:3) as eluent to afford a white solid in quantitative yield: mp 47−49 °C. Triethylamine (1.6 mL, 11.48 mmol) was added to a solution of the solid (2.0 g, 9.25 mmol) in dry CH_2Cl_2 at 0 °C under N_2. After 5 min, MsCl (2.1 mL, 27.02 mmol) was added in a dropwise manner, and the reaction mixture was allowed to stir at 0 °C for 2 h, and then at room temperature for 27 h. Water (20 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined extract was washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using hexane followed by hexane/EtOAc (9:1) as eluent to afford **36** as a clear oil (2.1 g, 77%). This unstable material was used immediately in the following step; **36** (1.9 g, 6.45 mmol) in dry DMF (5 mL) was added to a solution of NaCN (1.0 g, 20.40 mmol) in DMF (25 mL) under positive N_2 pressure. The reaction mixture was allowed to stir at 90 °C for 30 min and cooled to room temperature, and H_2O (300 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined extract was washed with brine (30 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using hexane followed by hexane/EtOAc (9:1) as eluent to afford the nitrile intermediate as a pale-yellow oil (1.33 g, 98%). A solution of oxone (11.35 g, 18.46 mmol) in H_2O (32 mL) was added to the nitrile (1.3 g, 6.15 mmol) in MeOH (32 mL) at 0 °C. The reaction mixture was adjusted to pH 5 with $NaHCO_3/Na_2CO_3$ (0.2M buffer) and allowed to stir at room temperature for 2 h. Water (100 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined extract was washed with brine (30 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using CH_2Cl_2 to afford **7** as a white solid (1.4 g, 93%): mp 143−145 °C; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 2H, CH), 7.28−7.61 (m, 5H, ArH), 7.95−8.01 (m, 4H, ArH).

Raney Ni, 2800 Ni slurry in H_2O (2.97 g, 50.50 mmol), was added to **37** (1.3 g, 5.05 mmol) in a solution of NH_3 (2 M) in MeOH (40 mL) and hydrogenated at ca. 50 psi for 5 h. Solids were removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using CH_2Cl_2/MeOH (4:1) as eluent to obtain the free base of **19** as a white solid (1.10 g, 83%): mp 95−97 °C. A solution of the free base in dry MeOH/anhydrous Et_2O was treated with HCl (g) to afford **19** (0.59 g, 76%) as a white solid after recrystallization from MeOH/Et_2O: mp 189−191 °C (lit.[37] mp 184−185 °C); ^{1}H NMR (DMSO-d_6) δ 2.95−3.06 (m, 4H, CH), 7.51−7.53 (d, J = 8.4, 2H, ArH), 7.59−7.71 (m, 3H, ArH), 7.90−7.97 (m, 4H, ArH), 8.18 (br.s., 1H, NH_2^+).

4-(3-Benzenesulfonylphenyl)piperazine hydrochloride (20a) was prepared from 3-phenylsulfonylbromobenzene[38] (**40a**) and piperazine in 50% yield in the same manner described for the preparation of **20b**. The product was isolated as a white solid: mp 246−247 °C (free base: mp 113−114 °C); ^{1}H NMR (DMSO-d_6) δ 3.24 (m, 4H, CH_2), 3.46 (m, 4H, CH_2), 7.27−7.49 (m, 4H, ArH), 7.59−7.70 (m, 3H, ArH), 7.98 (m, 2H, ArH), 9.07 (br.s, 2H, NH_2^+, D_2O exchangeable). Anal. ($C_{16}H_{18}N_2O_2S$·HCl) C, H, N. The title compound has been cited in the patent literature[38] but was not characterized.

4-(4-Benzenesulfonylphenyl)piperazine Hydrochloride (20b). A mixture of 4-(phenylsulfonyl)iodobenzene (**40b**) (0.668 g, 2.0 mmol), piperazine (0.689 g, 8.0 mmol), sodium *tert*-butoxide (0.268 g, 2.8 mmol), and dichlorobis(tri-*o*-tolylphosphine)palladium(II) (0.047 g, 0.06 mmol) in dry toluene (15 mL) was heated at reflux for 12 h under an N_2 atmosphere. The reaction mixture was allowed to cool to room temperature and filtered through a Celite pad. The filtrate was evaporated under reduced pressure to give a solid residue which was purified by flash chromatography (silica gel; CH_2Cl_2/MeOH, 9:1) to give the free base of **20b** as a white solid: mp 169−170 °C. A solution of the product in anhydrous MeOH (10 mL) was treated with a saturated solution of HCl (g) in MeOH (10 mL), the reaction mixture was concentrated under reduced pressure, and the solid material was collected by filtration to yield a product that was recrystallized from MeOH/Et_2O to afford 0.325 g (48%) of **20c** as a white solid: mp >250 °C (dec); ^{1}H NMR (DMSO-d_6) δ 3.14 (m, 4H, CH_2), 3.51 (m, 4H, CH_2), 7.09 (d, J = 9.3 Hz, 2H, ArH), 7.61 (m, 3H, ArH), 7.75 (d, J = 9.0 Hz, 2H, ArH), 7.90 (m, 2H, ArH). Anal. ($C_{16}H_{18}N_2O_2S$·HCl·0.75H_2O) C, H, N.

4-(2-Benzenesulfonylphenyl)piperazine Hydrochloride (20c).

Compound **20c** was prepared from 2-phenylsulfonylbromobenzene (**40c**) and piperazine in 45% yield in the same manner described for the preparation of **20b**. The product was isolated as a white solid: mp >263 °C (dec) (free base: mp 124−125 °C); ^{1}H NMR (DMSO-d_6) δ 2.84 (m, 4H, CH_2), 2.92 (m, 4H, CH_2), 7.44−7.47 (m, 1H, ArH), 7.56−7.61 (m, 3H, ArH), 7.67−7.69 (m, 1H, ArH), 7.77−7.82 (m, 3H, ArH), 8.18−8.21 (m, 1H, ArH), 9.13 (br.s, 2H, NH_2^+, D_2O exchangeable). Anal. ($C_{16}H_{18}N_2O_2S$·HCl) C, H, N.

(3-Phenylthio)phenylacetonitrile (33). Sodium borohydride (1.41 g, 37.33 mmol) was added portionwise to a solution of 3-(phenylthio)benzaldehyde (**31**)[39] (4.0 g, 18.67 mmol) in MeOH (30 mL), and the reaction mixture was allowed to stir at room temperature for 1 h. Water (30 mL) was added, and the reaction mixture was extracted with EtOAc (4 × 30 mL). The combined extract was washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure, leaving behind the crude intermediate product as a clear oil in quantitative yield. Triethylamine (1.61 mL, 11.56 mmol) was added to the above intermediate (2.5 g, 11.56 mmol) in dry CH_2Cl_2 at 0 °C, under N_2. After 5 min, MsCl (2.24 mL, 28.90 mmol) was added in a dropwise manner, and the reaction mixture was allowed to stir at 0 °C for 2 h. Water (20 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic portion was washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using hexane followed by hexane/EtOAc (9:1) to afford the *O*-mesyl derivative **32** as a white solid (2.5 g, 73): mp 43−45 °C. ^{1}H NMR ($CDCl_3$) δ 2.94 (s, 3H, CH), 5.20 (s, 2H, CH), 7.27−7.43 (m, 9H, ArH). Sodium cyanide (1.0 g, 20.38 mmol) was added, under positive N_2 pressure, to a solution of **32** (2.0 g, 6.79 mmol) in dry DMF (40 mL), and the reaction mixture was allowed to stir at 85 °C for 1.5 h. Water (300 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined extract was washed with brine (20 mL) and dried (Na_2SO_4), and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g) using hexane followed by hexane/EtOAc (9.5:0.5) to afford **33** as a homogeneous pale-yellow oil in quantitative yield. The nitrile was used without further characterization in the preparation of **16** and **17**. Compound **33** has been previously reported,[40] but, with the exception of its ^{1}H NMR spectrum, was uncharacterized.

1-Boc-4-(3-Benzenesulfonamidophenyl)piperazine (39). A solution of benzenesulfonyl chloride (2.20 g, 12.5 mmol) in dry CH_2Cl_2 (10 mL) was added in a dropwise manner to a mixture of 1-Boc-4-(3-aminophenyl)piperazine[41] (**38**) (2.77 g, 10.0 mmol) and pyridine (1.18 g, 1.5 mmol) in CH_2Cl_2 (25 mL) at room temperature under an N_2 atmosphere. The reaction mixture was allowed to stir for 5 h, and solvent was evaporated under reduced pressure to give a solid residue. A solution of the residue in CH_2Cl_2 (100 mL) was washed with brine (3 × 50 mL) and dried ($MgSO_4$), and solvent was evaporated under reduced pressure. The resultant crude product was purified by flash chromatography (silica gel; EtOAc/hexane, 1:1) to give 3.67 g (50%) of **39** as a grayish-brown solid: mp 139−140 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H, CH_3), 3.06 (m, 4H, CH_2), 3.51 (m, 4H, CH_2), 6.47 (br.s., 1H, $NHSO_2$, D_2O exchangeable), 6.67 (m, 3H, ArH), 7.06 (m, 1H, ArH), 7.40 (m, 2H, ArH), 7.53 (m, 1H, ArH), 7.75 (m, 2H, ArH).

2-(Benzenesulfonyl)bromobenzene (40c) was prepared in the same manner as described for the preparation of 3-(benzenesulfonyl)bromobenzene[38] (**40a**) in 78% yield: mp 112−113 °C (lit.[42] mp 117−119 °C).

Binding Assay. The *h*5-HT_6 radioligand binding assays were performed as previously described.[43] In brief, *h*5-HT_6 cDNA was transiently expressed in HEK-293 cells using Fugene6 according to the manufacturer's recommendations. Twenty-four hours after transfection, the medium was replaced; 24 h later, medium containing dialyzed serum (to remove 5-HT) was added. At 75 h after transfection, cells were harvested by scraping and centrifugation. Cells were then washed, centrifuged resuspended 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 nonspecific binding. Various concentrations of unlabeled test agent were used for K_i determinations, with K_i values calculated using the program LIGAND. Specific binding represented 80−90% of total binding. K_i values represent a minimum of triplicate determinations.

Molecular Modeling. The computational studies were performed on a Silicon Graphics workstation using SYBYL (SYBYL Molecular Modeling Package, Version 7.1, 2005; Tripos Inc., St. Louis, MO) software. The 3-D model of compound **5** was built using standard bond lengths and angles within the BUILD/SKETCH molecule command in SYBYL followed by molecular mechanics minimization (MINIMIZE) and calculation of charges by the Gasteiger−Hückel algorithm.[44] The 3-D models of analogues **3b**, **6a**, and **8** were constructed by modification of structure **5** using this same BUILD/SKETCH algorithm, and their geometry was subsequently optimized using the Tripos force field, analogously to that used for **5**. A flexible fit between template **5** and molecules **3b**, **6a**, and **8** was performed using the COMPUTE/MULTIFIT command, including the electrostatics calculated from the Gasteiger−Hückel atomic charges. The resulting conformers of **3b**, **6a**, and **8** then were individually superimposed (FIT-ATOM) on template **5** to perform a least-squares fit. Three linearly independent points (phenyl centroid, benzfused centroid, and N-terminal) were used in both MULTIFIT and FIT.

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Supporting Information Available: Elemental analysis results. This information is available free of charge via the Internet at http://pubs.acs.org.

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