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Interaction of N_1-unsubstituted and N_1-benzenesulfonyltryptamines at h5-HT$_6$ receptors

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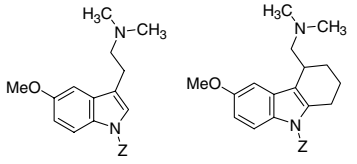
Abstract—Despite possessing a common tryptaminergic scaffold, examination of 28 (i.e., 14 pairs of) compounds suggests that N_1-unsubstituted and N_1-benzenesulfonyltryptamines likely bind at h5-HT$_6$ receptors in a dissimilar manner ($r^2 = 0.201$). Additionally, an examination of two rotationally constrained N_1-benzenesulfonyltryptamine analogs indicates that a non-coplanar relationship between the two aryl groups might be preferred for interaction with the receptors.

5-HT$_6$ receptors represent one of seven major populations of receptors for the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT).[1,2] They are G-protein coupled and positively linked to an adenylate cyclase second messenger system.[1–3] The receptors are of potential clinical interest due to their possible involvement in obesity and certain neuropsychiatric disorders such as depression, pyschosis, and cognition.[1–5] More recently, 5-HT$_6$ receptors have been implicated as playing a role in neuronal plasticity.[6] Although this receptor population was first identified about 10 years ago, only within the past few years have 5-HT$_6$-selective agonists and antagonists been identified (reviewed[5,7]).

Simple tryptamine derivatives, such as serotonin itself, bind at 5-HT$_6$ receptors with modest affinity, and ordinarily do so with little to no selectivity.[5] However, we[8,9] and later others[10] found that introduction of an N_1-arylsulfonyl substituent to the tryptamine nucleus can result in substantially (10- to >100-fold) enhanced affinity. For example, the affinity of 5-OMe DMT (**1a**; $K_i = 16$ nM) is enhanced upon introduction of an N_1-benzenesulfonyl group (MS-245, **1b**; $K_i = 2$ nM), as is that of carbazole **2a** ($K_i = 168$ nM) to **2b** ($K_i = 1.5$ nM).[9,11,12] Furthermore, these benzenesulfonyl-substituted tryptamine analogs (e.g., **1b** and **2b**) behaved as 5-HT$_6$ receptor antagonists.[9,11] On the basis of radioligand binding and modeling studies of the receptor, we have suggested that simple N_1-unsubstituted tryptamines and N_1-substituted tryptamines might bind differently at 5-HT$_6$ receptors.[9,13] In the present investigation, we empirically address this issue.



1a: Z = H
1b: Z = SO_2Ph
2a: Z = H
2b: Z = SO_2Ph

It is commonly thought, when two series of agents are binding in a similar manner, that parallel structural changes between the two series will typically result in parallel affinity shifts. In the present investigation we compared the h5-HT$_6$ receptor affinities of 28 (i.e., 14 pairs of) N_1-unsubstituted tryptamines and their N_1-benzenesulfonyl-substituted counterparts to determine if such is the case. If the affinities of the two series parallel one another, this might be taken as evidence that the two series are binding somewhat similarly at the receptor.

Another goal of this study was to examine a conformationally (i.e., rotamerically) constrained analog of the

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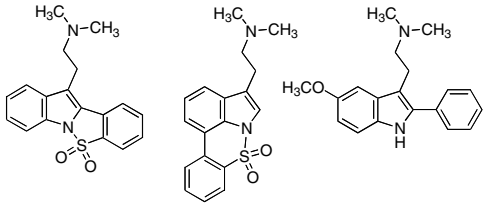
N_1-benzenesulfonyltryptamines to determine rotational preference for binding. Previous molecular modeling studies with **1b** showed that there are three families of energetically similar low-energy rotameric populations when rotation (torsion angle τ) about the C_{7a}–N_1–S–Cϕ bond is considered. Two of these families position the benzenesulfonyl moiety nearly perpendicular to the plane of the indole nucleus (τ ca. 60° and 300°), whereas the other family is more 'in-plane' (τ ca. 180°).[9] Compound **3** is a structurally constrained analog of des-methoxy **1b** (i.e., **6b**) that should allow us to determine the importance of this latter conformation. Compound **4** was prepared for comparison because it represents the opposite rotational extreme (τ approximating 0°) and might not be expected to bind with high affinity. Compound **3** was of particular interest because it represents a structural hybrid of **1b** and the 5-HT_6 antagonist PMDT (**5**; K_i = 20 nM).[8]



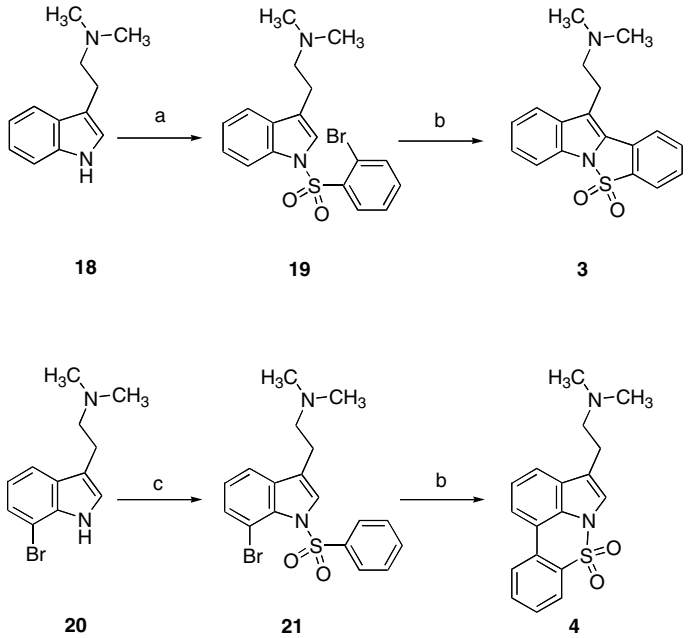
3 **4** **5**

Some of the compounds required for the comparative study had been synthesized earlier in our laboratories. The targets not already on-hand were obtained by reaction of the appropriately substituted *N*,*N*-dialkyltryptamine with benzenesulfonyl chloride as previously described.[9,11]

Compound **3** was obtained by cyclization of **19** which, in turn, was obtained by the sulfonylation of *N*,*N*-dimethyltryptamine (**18**) using (2-bromo)benzenesulfonyl chloride (Scheme 1). Compound **4** (Scheme 1) was obtained in a similar manner from **21**, beginning with 7-bromo-*N*,*N*-dimethyltryptamine (**20**).[14] The free bases of compounds **3** and **4** (but not binding data) were recently reported in the patent literature.[15]

Binding data for certain of the compounds utilized in the comparative analysis had already been published by our laboratory and are shown, together with the appropriate literature citations, in Table 1. In the comparative analysis utilizing 14 pairs of tryptamines, it was found that there was little correspondence (r^2 = 0.201; Fig. 1) between the 5-HT_6 receptor affinities of the examined pairs. The results show that the N_1-unsubstituted tryptamines and their N_1-benzenesulfonyltryptamine counterparts behaved differently when parallel structural changes were made, and support our earlier hypothesis[9] that the two series might be binding (i.e., orienting) differently at the receptor. It might be parenthetically noted that Russell et al.[10] have previously reported a lower affinity (K_i = 320 nM) than that reported by us for **13b**; use of their affinity data did not improve the correlation (results not shown).

Tetracyclic compounds **3** and **4** represent structurally constrained conformational (rotational) extremes of compound **6b** (K_i = 4.1 nM). As expected, compound **3** (K_i = 143 nM) displayed higher affinity than **4** (K_i = 4500 nM) (Table 1). Nevertheless, **3** still showed nearly 35-fold lower affinity than its conformationally more flexible **6b**. It might be argued that the reduced affinity of **3** relative to **6b** is due to intolerance by the

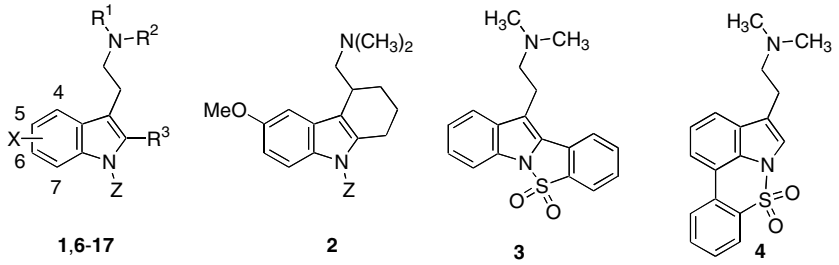


18 **19** **3**

20 **21** **4**

Scheme 1. Reagents and conditions: (a) *t*-BuOK, 18-crown-6, (2-Br)$PhSO_2Cl$, THF; (b) $[Pd(Ph_3)P]_4$, KOAc, DMF, 100 °C; (c) *t*-BuOK, 18-crown-6, $PhSO_2Cl$, THF.

Table 1. Radioligand binding data for reference compounds, and physicochemical properties and h5-HT_6 receptor affinities of the target compounds



Compound	X	R^1	R^2	R^3	Melting point (°C)[a]	Empirical formula[b]	h5-HT_6 K_i[c] nM		Reference[d]
							a: Z = H	b: Z = SO_2Ph	
6	H	Me	Me	H	—	—	30	4.1	18
7a	H	Et	Et	H	106–108	$C_{14}H_{20}N_2$ $(COOH)_2$	575 (±25)	—	—
7b	H	Et	Et	H	189–190	$C_{20}H_{24}N_2O_2S$ HCl	—	14 (±3)	—
8a	4-OMe	Me	Me	H	—	—	154	—	17
8b	4-OMe	Me	Me	H	226–228	$C_{19}H_{22}N_2O_3S$ HCl	—	11 (±1)	—
1	5-OMe	Me	Me	H	—	—	13 (±2)[e]	2.0	9
9	5-OMe	Et	Et	H	—	—	48	6.2	18
10a	5-OMe	Me	Bn	H	152–153	$C_{19}H_{22}N_2O$ $(COOH)_2$	106 (±22)	—	—
10b	5-OMe	Me	Bn	H	—	—	—	43	18
11	5-OMe	Me	Me	Et	—	—	52	5.5	11
12	5-OMe	Me	Me	*n*Pr	—	—	185	2.5	11
13	5-OCH_2Ph	Me	Me	H	—	—	18	14	11
14	5-$O(CH_2)_5Ph$	Me	Me	H	—	—	6.3	17	11
15	5-SO_3CF_3	Me	Me	H	—	—	220	2.3	11
16a	6-OMe	Me	Me	H	—	—	8000	—	17
16b	6-OMe	Me	Me	H	208–210	$C_{19}H_{22}N_2O_3S$ HCl	—	15 (±1)	—
17a	7-OMe	Me	Me	H	—	—	19600	—	17
17b	7-OMe	Me	Me	H	240–242	$C_{19}H_{22}N_2O_3S$ HCl	—	138 (±30)	9
2	—	—	—	—	—	—	168	1.5	11
3	—	—	—	—	282–283	$C_{18}H_{18}N_2O_2S$ HCl[f]	143 (±30)		—
4	—	—	—	—	275–277	$C_{18}H_{18}N_2O_2S$ HCl[g]	4500 (±580)		—

[a] Compounds were recrystallized from an MeOH/anhydrous Et_2O mixture.
[b] Compounds not previously reported were homogeneous to thin layer chromatography, analyzed within 0.4% of theory for C, H, and N, and assigned structures are consistent with ^1H NMR spectra.
[c] K_i values (±SEM for new results) were determined at least in triplicate[19] as previously described.[20] SEM are not shown for previously reported binding data.
[d] Literature reference for binding data previously published from our laboratories.
[e] K_i value re-determined; previously published K_i = 16 nM.[17]
[f] Hemihydrate.
[g] Monohydrate.

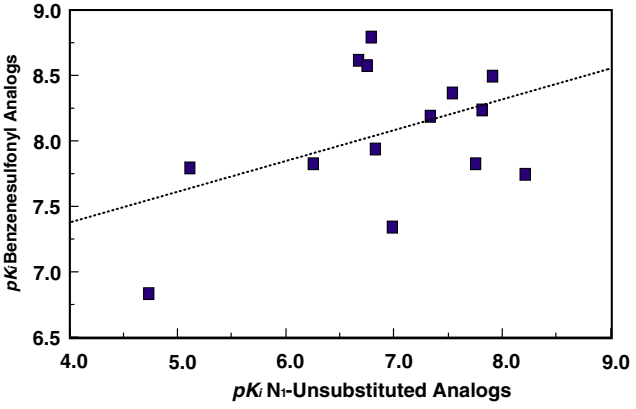


Figure 1. Relationship between the 5-HT_6 receptor affinities (pK_i values) of 14 N_1-unsubstituted tryptamines and their corresponding N_1-benzenesulfonyl counterparts (r^2 = 0.201). Included are compounds **1**, **2**, and **6**–**17**.

receptor for an indole 2-position substituent. However, the high affinity of 2-substituted compounds such as **11b** and **12b** indicates that 2-position substituents are tolerated when compared with **1b**. Furthermore, a 2-phenyl substituent has been shown to be tolerated as with PMDT (**5**).[8] Thus, a conclusion that can be reached is that this rotamer does not reflect that which might be optimal for binding. However, other explanations are possible. For example, in **6b** the benzenesulfonyl moiety is relatively free to rotate about the S–Cϕ bond;[9] this is not the case with **3**. Consequently, the reduced affinity of **3** relative to **6b** could be due to an unfavorable positioning of the phenyl group. The affinity of **4** is >1000-fold lower than that of **6b**. Here too, low affinity could be ascribed to the intolerance by the receptor of substitution at the indolic 7-position. This remains a possibility because the 7-methoxy derivative **17b** (K_i = 138 nM) binds with considerably lower affinity than **6b** (K_i = 4.1 nM)

itself. Nevertheless, **4** represents a rotamer that was not calculated to be of low energy. This is probably a more reasonable explanation for the observed low affinity of **4**.

Overall then, the results of this investigation (on compounds with K_i values spanning a >10,000-fold range) support the prior suggestion that N_1-unsubstituted and N_1-benzenesulfonyl-substituted tryptamines are probably binding in a dissimilar fashion upon interaction with 5-HT_6 receptors. It is, perhaps, a quirk of human nature (and not an unreasonable one)[16] to intuit that agents sharing a common structural scaffold will likely bind in a common fashion. This does not appear to be the case, however, with the compounds examined in the present investigation. Future SAR and QSAR studies, particularly with the types of compounds described here, should take this into account, and consider also that agonists and antagonists, despite structural similarity, need not bind in a similar manner. In addition, the higher affinity of **3** relative to **4**—structurally constrained rotational extremes of the benzenesulfonyl group of **6b**—suggests that **3**, more so than **4**, represents a favorable conformation for binding. But, because the affinity of **3** is still lower than that of more conformationally flexible N_1-benzenesulfonyltryptamines (such as **6b**), it would seem that the 'out-of-plane' rotamers (i.e., those where τ is closer to 60° or 300°) might be preferred for an optimal interaction with the receptor.

Acknowledgment

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