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Further studies on the binding of N_1-substituted tryptamines at h5-HT$_6$ receptors

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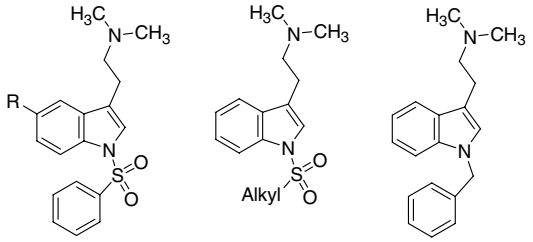
Abstract—N_1-Arylsulfonyl-substituted analogs of *N*,*N*-dimethyltryptamine bind at 5-HT$_6$ receptors. Replacement of the aryl moiety with similarly hydrophobic alkyl substituents results in decreased affinity, as does replacement of a benzenesulfonyl moiety with a benzyl group. Current findings indicate that an aryl (or substituted aryl) sulfonyl (rather than alkylsulfonyl or benzyl) moiety is optimal for high-affinity binding, and further suggest that the N_1-benzenesulfonyl- and their corresponding N_1-benzyltryptamine counterparts bind in a different fashion.

Adenylate cyclase linked G-protein-coupled 5-HT$_6$ serotonin receptors have generated considerable recent interest because of their possible involvement in obesity, certain neuropsychiatric disorders, and cognition.[1–6] Among the early 5-HT$_6$ receptor antagonists was the N_1-arylsulfonyltryptamine MS-245 (**1**; K_i = 2.1 nM) and its *des*-methoxy counterpart **2a** (K_i = 4.1 nM).[7,8] Despite structure-affinity studies by us,[8] and others[9–11] (reviewed[5,12]), a number of questions remain unanswered. For example, a structural feature common to these arylsulfonyltryptamines is an 'aryl' moiety. Yet, it has not been established that an aryl group is essential for binding. That is, if the aryl group binds at the receptor via a hydrophobic type of interaction, its replacement by an alkyl group of similar or greater hydrophobicity could result in retention of affinity. Consequently, in this study we prepared and evaluated several analogs of **2a** (i.e., **3**) where the phenyl ring is replaced by an alkyl group. Another feature that has not been fully explored is the necessity of the sulfonyl group. It is generally thought that the sulfonamido portion of **1** and **2a** is important for binding. But, it has been shown that the benzenesulfonyl group of **2a** can be replaced by a benzyl group (**4a**; K_i = 6.0 nM) with relatively little impact on 5-HT$_6$ receptor affinity.[13] Because the 5-HT$_6$ receptor affinities of N_1-benzyltryptamines have not been well investigated, we now examine several substituted analogs of **4a**. In some instances, their corresponding benzenesulfonyl counterparts were prepared for the purpose of comparison.



1: R = OMe
2a: R = H

3:

4a

Synthesis of most of the target compounds (Scheme 1) was achieved by sulfonylation or alkylation of the *N*,*N*-dimethyltryptamine (**5**) anion, generated using *t*-BuOK (for **2** and **3**, except **3d** and **3f**) or NaH (for **3d** and **3f**, and generally, for **4**), with the appropriate arylsulfonyl- alkylsulfonyl- or benzyl halide (Table 1) as previously described for the synthesis of **1** and **2a**.[8,14] Attempts to prepare amine analog **4d** using a sim-

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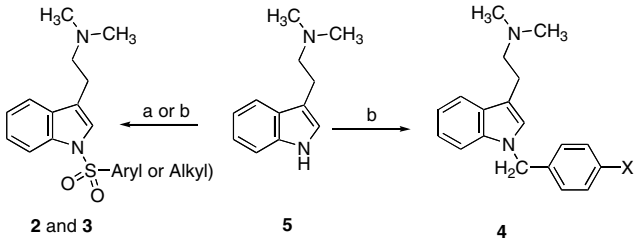
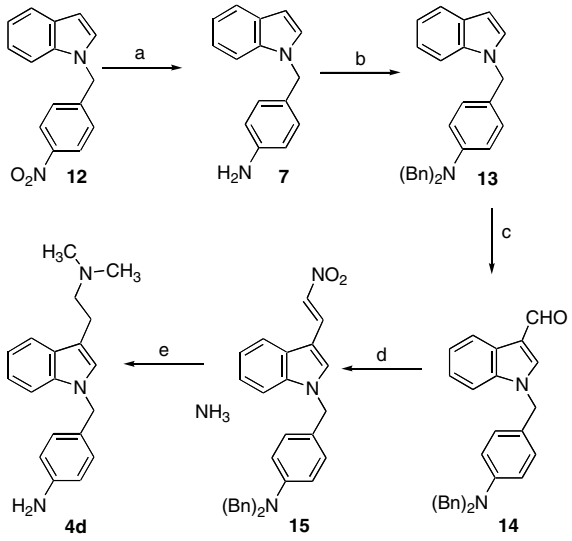


Scheme 1. Reagents and conditions: (a) i—NaH, DMF, 100 °C; ii—$ArSO_2Cl$; (b) *t*-BuOK, 18-crown-6, THF, RCH_2X, rt.

ilar approach (i.e., utilizing a 4-nitro- or 4-acetamido-substituted benzyl halide) were unsuccessful. Subsequently, compounds **4d** and **7**[14] were prepared via a common route from **12**[15] as shown in Scheme 2.

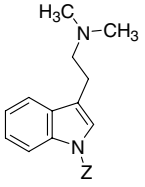
Human 5-HT_6 receptor binding data are shown in Table 1. Several analogs **3** were prepared where the alkyl group ranged in length from *n*-propyl (**3b**; K_i = 280 nM) to *n*-octyl (**3e**; K_i = 440 nM); some analogs possessed branched alkyl groups such as *i*-propyl analog **3a** (K_i = 590 nM) and cyclohexyl analog **3f** (K_i = 210 nM). Yet, none of the alkylsulfonyl analogs displayed the affinity of the simple benzenesulfonyltryptamine **2a** (K_i = 4.1 nM). The results show that an arylsulfonyl group at the tryptamine N_1-position is preferred, relative to an alkylsulfonyl group, for 5-HT_6 receptor affinity. Even cyclohexyl analog **3f**, which is simply a reduced version of **2a**, binds with 50-fold lower affinity than **2a** itself.



Scheme 2. Reagents and conditions: (a) $SnCl_2{\cdot}2H_2O$, EtOH; (b) BnBr, NEt_3, CH_2Cl_2; (c) $POCl_3$/DMF; (d) $MeNO_2$, $AcONH_4$; (e) i—$LiAlH_4$, THF; ii—$NaBH_3CN$, $H_2C=O$; iii—Pd/C, $HCOONH_4$, MeOH.

A small series of N_1-benzyl analogs **4** was examined. Substituents selected for evaluation included several electron-donating and electron-withdrawing groups. Only 4-substituted benzyl analogs were examined to reduce any potential complications in data interpretation that might arise from rotameric binding. 5-HT_6 receptor affinities ranged from 20 to >400 nM. But, none of the benzyl analogs retained the affinity of the

Table 1. Physicochemical properties and h5-HT_6 receptor affinities for target compounds



Compound	*Z*	Melting point[a] (°C)	Recryst solvent	Empirical formula[a]	K_i[b], nM (±SEM)
3a	–SO_2-*i*-propyl	175–178	MeOH/Et_2O	$C_{15}H_{22}N_2O_2S$ $(COOH)_2$	590 (110)
3b	–SO_2-*n*-propyl	144–145	MeOH/Et_2O	$C_{15}H_{22}N_2O_2S$ $(COOH)_2$	280 (40)
3c	–SO_2-*n*-butyl	162–163	MeOH/Et_2O	$C_{16}H_{24}N_2O_2S$ $(COOH)_2$	135 (20)
3d	–SO_2-*n*-amyl	167–169	MeOH/Et_2O	$C_{17}H_{26}N_2O_2S$ $(COOH)_2$	220(30)
3e	–SO_2-*n*-octyl	138–139	MeOH/Et_2O	$C_{20}H_{32}N_2O_2S$ $(COOH)_2$	440(65)
3f	–SO_2-cyclohexyl	173–175	MeOH/Et_2O	$C_{18}H_{26}N_2O_2S$ $(COOH)_2$	210(30)
2a	–SO_2-phenyl	—	—	—	4.1
2b	–SO_2-(4-Me)phenyl	191–193	Acetone	$C_{19}H_{22}N_2O_2S$ $(COOH)_2$	2.5(0.6)
2c	–SO_2-(4-OMe)phenyl	164–166	Acetone	$C_{19}H_{22}N_2O_3S$ $(COOH)_2$	13 (3)
2d	–SO_2-(4-NH_2)phenyl	—	—	—	0.8
2e	–SO_2-(4-CF_3)phenyl	176–179	Acetone	$C_{19}H_{19}F_3N_2O_2S$ $(COOH)_2$	1.9 (0.4)
2f	–SO_2-(4-Cl)phenyl	180–182	Acetone	$C_{19}H_{22}ClN_2O_2S$ $(COOH)_2$	94 (25)
4a	–CH_2-phenyl	—	—	—	6.0
4b	–CH_2-(4-Me)phenyl	179–182	MeOH/Et_2O	$C_{20}H_{22}N_2$ $(COOH)_2$	29 (3)
4c	–CH_2-(4-OMe)phenyl	172–173	MeOH/Et_2O	$C_{20}H_{22}N_2O$ $(COOH)_2$	132 (25)
4d	–CH_2-(4-NH_2)phenyl	157–159	MeOH/Et_2O	$C_{19}H_{24}N_3{\cdot}2HCl{\cdot}0.5H_2O$	44 (7)
4e	–CH_2-(4-CF_3)phenyl	162–163	MeOH/Et_2O	$C_{20}H_{21}F_3N_2$ $(COOH)_2$	445 (50)
4f	–CH_2-(4-Cl)phenyl	170–172	MeOH/Et_2O	$C_{19}H_{21}ClN_2$ $(COOH)_2$	20 (5)

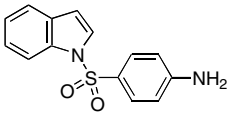
[a] Compounds were homogeneous to thin layer chromatography, analyzed within 0.4% of theory for C, H, and N, and assigned structures are consistent with ^1H NMR spectra.

[b] K_i values (±SEM for new results) were determined at least in triplicate[25] as previously described.[26] SEM are not shown for previously reported binding data. Binding data for **2a**, **2d**, and **4a** have been previously published from our laboratories.[13]

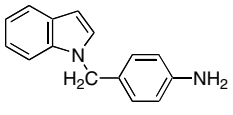
unsubstituted benzyl analog **4a** (K_i = 6.0 nM) or its benzenesulfonyl counterpart **2a** (K_i = 4.1 nM).

One explanation for the reduced affinity of **4b–f**, compared with **4a**, is that the receptor does not tolerate substituents on the benzylic nucleus. This seems unlikely because certain analogs of **1** bearing benzenesulfonyl substituents have been previously shown to bind with affinities comparable to that of **1** itself.[8] However, with regard to these latter compounds, each possesses a methoxy group on the indolic ring. In order to make a more strict comparison, the benzenesulfonyl counterparts of **4b–f** (i.e., **2b–f**) were prepared and examined. The results (Table 1) show that 5-HT_6 receptors tolerate aryl substituents, and that the 4-methyl, 4-amino, and 4-trifluoromethyl analogs (**2b**, **2d**, **2e**; K_i = 2.5, 0.8, and 1.9 nM, respectively) bind at least as well as their unsubstituted parent **2a**. The results indicate that even though N_1-benzyl-substituted analogs bind at 5-HT_6 receptors, they bind with reduced affinity relative to their corresponding N_1-benzenesulfonyl counterparts, and further suggest that the two series might bind in a somewhat different fashion. It is commonly held that two series of compounds might be binding in a similar manner when parallel structural changes result in parallel shifts in affinity. However, a comparison of the affinities of the series **4** compounds with the series **2** compounds (r^2 = 0.048; n = 6) shows little correspondence between the two.

As a further test to determine if the N_1-benzyl- and benzenesulfonyl analogs behave in a similar manner, we compared **6** with **7**. It has been shown, when an amino group is present at the 4-position of the benzenesulfonyl moiety, that the *N*,*N*-dimethylaminoethyl portion of the tryptamines can be removed with only a slight decrease in affinity.[14,16] For example, compound **6** (K_i = 10 nM)[16] binds with an affinity similar to that of **2a**. Interestingly, compound **7** (K_i = 8200 ± 800 nM) was found to bind with >1000-fold lower affinity than its tryptamine counterpart **4a**. Here, then, is another example of where a parallel structural change resulted in a dissimilar effect on 5-HT_6 receptor affinity.

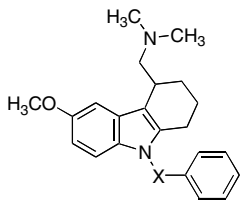


6

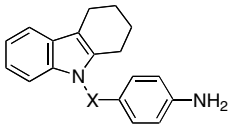


7

The present results help explain some findings previously published from our laboratory.[17] A (partially) conformationally constrained analog of **1** (i.e., **8**; K_i = 1.5 nM) binds at 5-HT_6 receptors with high affinity. However, replacement of the benzenesulfonyl group with a benzyl group (i.e., **9**; K_i = 136 nM) resulted in decreased affinity—results that were difficult to explain at that time given the similar affinity of **2a** and **4a**. Furthermore, whereas **10** (K_i = 29 nM) binds, its benzyl counterpart **11** (K_i = 6000 nM) displayed much lower affinity.[17] In this respect, the earlier results are consistent with the present findings. It would appear, then, that the similar affinity of **2a** and **4a** might be merely coincidental.



8 X = SO_2
9 X = CH_2



10 X = SO_2
11 X = CH_2

General findings of the present investigation are that replacement of the benzenesulfonyl group of MS-245-like (i.e., **1**-like or **2a**-like) benzenesulfonyltryptamines with either an alkylsulfonyl group or a benzyl group results in diminished affinity for h5-HT_6 receptors. The alkylsulfonyl derivatives **3** differed with respect to chain length, shape, and hydrophobicity, but none retained the affinity of the simplest MS-245-like compound **2a**. It would seem that electronic or π–π interactions better account for the binding of these compounds than do simple hydrophobic interactions.

The N_1-benzyl-substituted compounds **4** bind at 5-HT_6 receptors but typically do so with affinities somewhat lower than their benzenesulfonyl counterparts **2**. Evidence suggests that the two series (i.e., **2** and **4**) are probably binding differently and, because the only structural difference between the two series is a sulfonyl versus methylene group, it would seem that the sulfonyl group determines the manner of binding. That is, the presence of the sulfonyl group results in a somewhat higher affinity. The phenyl–SO_2–N bond angle of *N*-benzenesulfonylpyrrole[18] and related benzenesulfonylindoles[19,20] (ca. 105–106°) is only slightly less than the bond angle of a tetrahedral carbon atom. Furthermore, the N_1–S bond length (ca. 1.6–1.7 Å) found in such compounds is only slightly longer than the N_1–C bond length (ca. 1.5 Å) of N_1-benzylindoles.[18–23] So, it is unlikely that geometry plays a substantial role in the affinity differences observed between the benzenesulfonyltryptamines and their benzyltryptamine counterparts.[24] Thus, although it cannot be concluded that the sulfonyl group is essential for binding, it would appear that its presence is optimal when similarly substituted pairs of compounds are examined, and that the oxygen atoms might form an anchoring interaction with some receptor-associated feature. An alternative explanation for the observed affinity differences between the two series involves the electronic effects of benzenesulfonyl versus benzyl substituents. That is, in the benzenesulfonyl series, the N_1-substituent is conjugated with the indole nucleus and benzenesulfonyl substituents might exert a greater effect on the electronic character of the indole ring than they would if appended to a non-conjugated N_1-benzyl moiety. This remains to be further examined. The results also suggest, if the two series are binding differently, that structure-affinity findings from the N_1-benzenesulfonyl series cannot be extrapolated to the N_1-benzyl series (e.g., compare **2e** and **4e**). Hence, because N_1-benzyltryptamines bind at 5-HT_6 receptors, additional studies will be required to optimize their affinity.

Acknowledgment

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24. It might be noted, however, that the presence of the sulfonyl oxygen atoms might influence rotation about the S–C bond. For example, in the solid state, the N–S–C_{1Ar}–C_{2Ar} torsion angle of an N_1-benzenesulfonylindole is about −92°, whereas for its N_1-benzyl counterpart the corresponding angle was found to be −155°.[20,23]
25. The h5-HT_6 radioligand binding assay was performed as previously described.[26] In brief, h5-HT_6 cDNA was transiently expressed in HEK-293 cells using Fugene6 according to the manufacturer's recommendations; 24 h after transfection, the medium was replaced, and 24 h later, medium containing dialyzed serum (to remove 5-HT) was added. At 72 h after transfection, cells were harvested by scraping and centrifugation. Cells were then washed by centrifugation and resuspension in phosphate-buffered saline (pH 7.40; PBS) and 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 $MgCl_2$, and 0.1 mM EDTA, pH 7.40) with [^{3}H]LSD (1 nM final concentration) using 10 μM clozapine for non-specific binding. Concentrations of unlabeled test agent were used for K_i determinations with K_i values calculated using the program GraphPad Prizm (V4.0). Specific binding represented 80–90% of total binding. K_i values are the result of triplicate determinations.
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