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Bioorganic & Medicinal Chemistry Letters 16 (2006) 3793–3796
Bioorganic & Medicinal Chemistry Letters

Binding of methoxy-substituted N_1-benzenesulfonylindole analogs at human 5-HT$_6$ serotonin receptors

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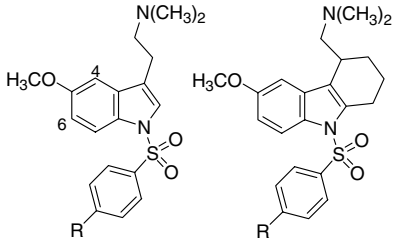
Received 23 March 2006; revised 13 April 2006; accepted 13 April 2006
Available online 18 May 2006

Abstract—Comparison of several amine-substituted and methoxy-substituted analogs of N_1-(4-aminobenzene)sulfonylindole suggests that these substituents might contribute to the 5-HT$_6$ serotonin receptor affinity of these agents via their electronic effect on the indolic nucleus. Their 1,2,3,4-tetrahydrocarbazole counterparts behave differently.

5-HT$_6$ receptors, one of seven families (5-HT$_1$–5-HT$_7$) of serotonin receptors, are of interest because of their possible involvement in certain neuropsychiatric and neurological disorders.[1–3] MS-245 (**1**; K_i = 2.1 nM) was one of the first examples of a 5-HT$_6$ receptor antagonist.[4,5] 1,2,3,4-Tetrahydrocarbazole **2** (K_i = 1.5 nM) represents an analog of MS-245 wherein the conformationally flexible side chain has been somewhat constrained.[6] The 4′-amino derivative of MS-245 (i.e., **3**; K_i = 0.8 nM) retains the affinity of its parent;[7] likewise, compound **4** (K_i = 2.0 nM) retains the affinity of **2**.[8]



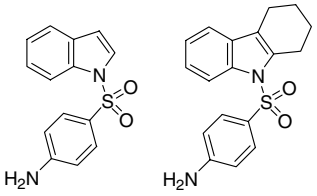
1 R = H
3 R = NH_2

2 R = H
4 R = NH_2

Both **3** and **4** can be abbreviated in structure (i.e., **5** and **6**; K_i = 10 and 29 nM, respectively) with only a small loss in affinity, but with retention of 5-HT$_6$ antagonist action.[7–9] To this extent, it appears that the tetrahydrocarbazoles behave much in the same manner as their simpler indole counterparts with respect to binding at 5-HT$_6$ receptors.

Amine-bearing analogs of **5**, such as **7** (K_i = 21 nM) and **8** (K_i = 7.0 nM), retain affinity or, as with **9** (K_i = 1.9 nM), bind with enhanced affinity at 5-HT$_6$ receptors.[9] Interestingly, when an indolic methylamine is present, the 4′-position primary amine is not required for binding (e.g., **10**; K_i = 26 nM).[9]

To account for these observations, we suggested two possibilities: in some cases one of the methylamino groups (rather than the primary amine) might interact with the amine binding site of the receptor—presumably the TM3 aspartate moiety—and/or (particularly when the primary amine is present) the methylamino group(s) might make an indirect (e.g., electronic) contribution to binding.[9]



5 **6**

Keywords: Serotonin receptors; Indole analogs; 5-HT$_6$.
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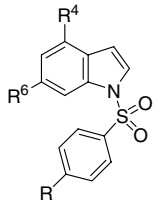
doi:10.1016/j.bmcl.2006.04.094

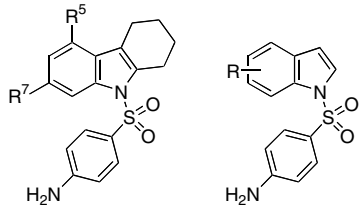
It has been concluded that indole-containing ligands need not bind at 5-HT_6 receptors with superimposable indolic nuclei, and that multiple amine groups, although possibly having an affinity-enhancing effect, are not required for binding.[9]

The purpose of the present investigation was 2-fold. First, we wished to determine if introduction of a methylamino group would have an effect on the binding of tetrahydrocarbazole **6** comparable to that seen upon conversion of **5** to **7** or **8** (i.e., **11a** and **11b**). Second, because the presence of an indolic methylamino group might influence the binding of **7**–**10** directly, by interaction with the amine binding site, or indirectly, via its electronic character, we proposed to examine several derivatives of **5** bearing an electron-donating methoxy group (i.e., **12** where R = –OMe) in place of the methylamino group.



7 R^4 = NHMe, R^6 = H, R = NH_2
8 R^4 = H, R^6 = NHMe, R = NH_2
9 R^4 = R^6 = NHMe, R = NH_2
10 R^4 = R^6 = NHMe, R = H

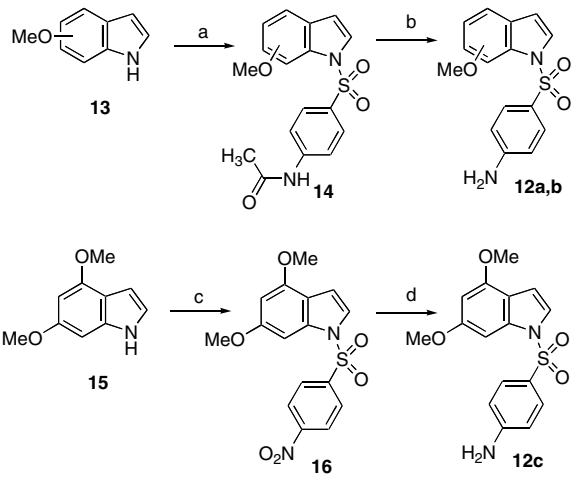
Compounds **12a** and **12b** were obtained (Scheme 1) by reaction of *N*-acetylsulfanilyl chloride with the appropriately substituted methoxyindolyl anion. The protected amide intermediates **14** were hydrolyzed to the target amines with dilute ethanolic HCl. An attempt to prepare **12c** in the same manner was unsuccessful. Subsequently, 4,6-dimethoxyindole (**15**)[10] was converted to its anion and allowed to react with 4-nitrobenzenesulfonyl chloride, followed by reduction of the nitro intermediate **16** to the desired product (Scheme 1).



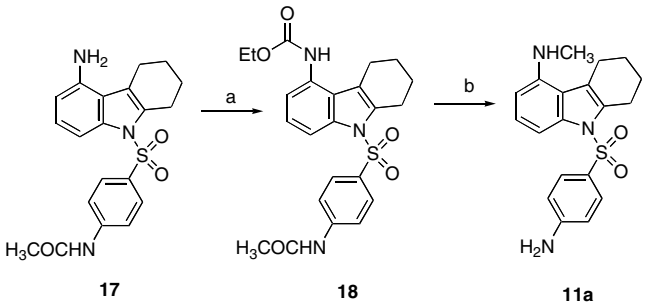
11a R^5 = NHMe, R^7 = H
11b R^5 = H, R^7 = NHMe
11c R^5 = R^7 = OMe

12

Dimethoxycarbazole **11c** was prepared in the same manner employed for the synthesis of **12a** and **12b** beginning with 5,7-dimethoxy-1,2,3,4-tetrahydrocarbazole.[11] The two methylamino carbazole analogs, **11a** and **11b**, were prepared in a common manner as shown for **11a** in Scheme 2. The requisite nitro compound[12] was reduced ($SnCl_2{\cdot}2H_2O$) to amine **17**, and **17** was reacted with ethyl chloroformate to afford intermediate **18**. Careful hydrolysis of the amide followed by lithium aluminum hydride reduction afforded the target compound **11a**. Compound **11b** was prepared from the known 7-nitro counterpart.[12] Both products were isolated as their oxalate salts, but it was not possible to remove all traces of Et_2O from the salts obtained.



Scheme 1. Reagents and conditions: (a) i—NaH (60%), DMF, 80 °C/1 h; ii—*N*-acetylsulfanilyl chloride, 0 °C/16 h; (b) 10% ethanolic HCl, Δ/3 h; (c) i—50% NaOH, $(n\text{-Bu})_4NHSO_4$, CH_2Cl_2, rt/20 min; ii—4-nitrobenzenesulfonyl chloride, rt/16 h; (d) $SnCl_2{\cdot}2H_2O$, absolute EtOH, Δ/3 h.

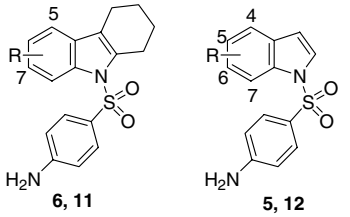


Scheme 2. Reagents and conditions: (a) ClCOOEt, pyridine, DMF, −10 °C, 45 min; (b) i—10% ethanolic HCl, reflux, 2 h; ii—$LiAlH_4$, THF, reflux, 5 h.

All of the compounds examined displayed nanomolar affinity for 5-HT_6 receptors (Table 1). However, neither methylaminotetrahydrocarbazole **11a** (K_i = 165 nM) nor **11b** (K_i = 205 nM) showed an affinity comparable to that of the unsubstituted tetrahydrocarbazole **6** (K_i = 29 nM). Unlike what was seen with the simpler indole derivatives, introduction of the methylamino group was not well tolerated and resulted in about 5- to 10-fold reduced affinity.

In contrast, the affinity of **5** (K_i = 10 nM) was enhanced upon introduction of a methoxy group at either the 4-position (**12a**; K_i = 3.3 nM) or 6-position (i.e., **12b**; K_i = 1.8 nM). As a consequence, the 4,6-dimethoxy-substituted analog **12c** (K_i = 0.8 nM) was prepared and found to bind with >10 times higher affinity than **5**. As a further comparison between the indoles and tetrahydrocarbazoles, the corresponding dimethoxy tetrahydrocarbazole **11c** was examined. Compound **11c** (K_i = 210 nM) displayed an affinity comparable to methylaminotetrahydrocarbazoles **11a** and **11b**, and nearly 10-fold lower than the parent tetrahydrocarbazole **6** (K_i = 29 nM).

Table 1. Physicochemical and 5-HT_6 receptor binding properties of target compounds



	R	Recrystallization solvent	Melting point (°C)	Empirical formula[a]	K_i, nM (±SEM)[13]
6[b]	–H	—	—	—	29
11a	5-NHMe	CH_2Cl_2	135–137	$C_{19}H_{21}N_3O_2S$ 1.25 $C_2H_2O_4$[c]	165 (24)
11b	7-NHMe	CH_2Cl_2	151–152	$C_{19}H_{21}N_3O_2S$ 2.0 $C_2H_2O_4$[d]	205 (20)
11c	5,7-Di OMe	MeOH	199–200	$C_{20}H_{22}N_2O_4S$ 0.25 H_2O	210 (30)
5[b]	–H	—	—	—	10
12a	4-OMe	EtOH	151	$C_{15}H_{14}N_2O_3S$	3.3 (0.4)
12b	6-OMe	EtOH	143–145	$C_{15}H_{14}N_2O_3S$	1.8 (0.5)
12c	4,6-Di OMe	MeOH	200–201	$C_{16}H_{16}N_2O_4S$	0.8 (0.1)
12d[b]	4,6-Di NO_2	—	—	—	980

[a] All compounds were homogeneous as determined using thin-layer chromatography, assigned structures are consistent with ^{1}H NMR spectra, and compounds analyzed within 0.4% of theory for C, H, and N. $C_2H_2O_4$ = oxalate salt.
[b] Binding data for **5**,[9] **6**,[8] and **12d**[9] were previously reported.
[c] Crystallized with 0.5 mol Et_2O.
[d] Crystallized with 0.25 mol Et_2O.

These new data show that replacement of the methylamino group of **7** and **8** by methoxy (i.e., **12a** and **12b**, respectively) was not only tolerated, but resulted in slightly enhanced affinity. In addition, the dimethoxy compound **12c** displayed an affinity similar to that of its dimethylamino counterpart **9**, and >10 times the affinity of its parent indole **5**.

Because the electron-donating methoxy groups do not likely contribute directly to an interaction with the amine binding site, it would appear that they influence binding indirectly either by their electronic character or their ability to form a hydrogen bond with some receptor-associated binding feature. These results are also consistent with the earlier finding that the presence of electron withdrawing groups decreases the affinity of **5**. For example, 4,6-dinitro-N_1-benzenesulfonylindole (**12d**, K_i = 980 nM)[9] binds at 5-HT_6 receptors with >500- to 1000-fold lower affinity than **8** and **12c**. On this basis, it would not seem that the secondary amine groups of **7**–**9** interact directly with the amine binding site. However, this conclusion may not apply to compound **10** which lacks any other amine function for binding.

Despite their structural similarity, and the similar affinity of **1** with **2**, and **5** with **6**, the results indicate that the tetrahydrocarbazoles **11** do not necessarily behave in a manner comparable to that of the structurally simpler N_1-benzenesulfonylindoles **12** upon introduction of a methylamino group (viz. **11a** and **11b**) or a dimethoxy group (viz. **11c**). That is, in the presence of the partially saturated benzenoid ring, introduction of these aromatic substituents tends to decrease 5-HT_6 receptor affinity. In contrast, it has been demonstrated that there are a number of binding similarities between analogs of **1** and **2**.[8] Differences are evident primarily when the compounds possess a 4′-amino group rather than an indolic alkylamine as their sole amine substituent. Whereas evidence suggests that analogs of **1** and **2** might bind in a similar fashion,[8] and although analogs of **11** and **12** may or may not bind similarly to one another, they might not bind in a manner common to that of **1** and **2**. Given this supposition, it would seem that the region of the receptor into which **6** binds does not readily accommodate indole substituents such as found in **11**.

Overall, then, it would appear that analogs of **5** and **6** might not always bind in a similar fashion at 5-HT_6 receptors despite their structural similarity, and that when an amino group is present at the benzenesulfonyl ring 4-position, the indolic methylamino group(s) of **5**-derived compounds **7**–**9** can be replaced by a methoxy group without unfavorable effect on affinity. Such information should contribute to investigations aimed at identification of pharmacophore models for 5-HT_6 receptor binding.

Acknowledgments

This work was funded in part by MH 60599 (R.A.G.), and U.S. was supported by a Werner Lowenthal Neurological Sciences Award.

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