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1,2,3,4-Tetrahydrocarbazoles as 5-HT$_6$ serotonin receptor ligands

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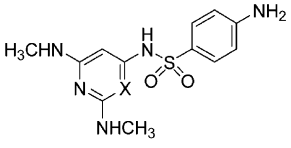
Abstract—An investigation of the structure–affinity relationships for the binding of 4-(*N*,*N*-dimethylaminomethyl)-N$_9$-arylsulfonyl-9*H*-1,2,3,4-tetrahydrocarbazoles (conformationally-constrained analogues of the benzenesulfonyltryptamine 5-HT$_6$ antagonist MS-245) at human 5-HT$_6$ receptors revealed that various arylsulfonyl substituents are tolerated and that the 4-(*N*,*N*-dimethylaminomethyl) group is not required for binding. In particular, N$_9$-(4-aminobenzenesulfonyl)-9*H*-1,2,3,4-tetrahydrocarbazole (**20**, $K_i = 29$ nM) was found to bind with high affinity and represents the first member of a new structural class of agents with 5-HT$_6$ antagonist properties (p$A_2 = 7.0$; cAMP hydrolysis assay).

5-HT$_6$ receptors represent one of seven families of serotonin receptors for the neurotransmitter 5-hydroxytryptamine (5-HT).[1,2] Evidence suggests that these receptors could play a role in certain central disorders such as schizophrenia and depression, and more recent information implicates possible involvement in cognition (but see Lindner et al.[3]), convulsive disorders and obesity.[1–4] Relatively few 5-HT$_6$ antagonists have been reported;[3] among the first were the sulfonamides Ro 04-6790 and Ro 63-0563 (**1** where X = N and CH, respectively),[5] **2**,[6] and MS-245 (**3**).[7,8] Continued investigations of these structure-types has resulted in novel analogues, improved affinity, and enhanced pharmacokinetic character.[4]



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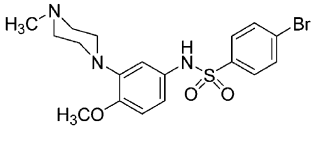

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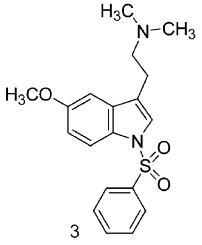

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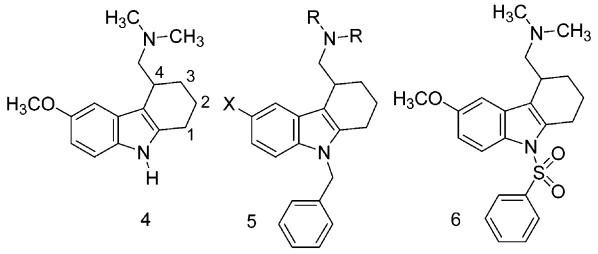

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We have previously found that tetrahydrocarbazole **4** ($K_i = 168$ nM) binds at 5-HT$_6$ receptors with an affinity approximating that of 5-HT (K_i ca. 100 nM).[9] A N$_9$-benzyl substituent is tolerated (i.e., **5**, X = OCH$_3$, R = CH$_3$; $K_i = 136$ nM), the corresponding primary amine binds with slightly reduced affinity (i.e., **5**, X = OCH$_3$, R = H; $K_i = 300$ nM), and the methoxy group is not required for binding (i.e., **5**, X = H, R = CH$_3$; $K_i = 64$ nM). More interestingly, replacement of the N$_9$-benzyl group with a benzenesulfonyl group (i.e., **6**, $K_i = 1.5$ nM) enhanced affinity by about two orders of magnitude.[9] Hence, as with the structurally simpler tryptamine analogues, introduction of a benzenesulfonyl group has a significant affinity-enhancing effect. The purpose of the present investigation was to extend the structure–affinity relationships for the binding of the tetrahydrocarbazole analogues at human 5-HT$_6$ receptors. Another reason for this endeavor is because if it can be demonstrated that the tetrahydrocarbazoles bind in a fashion similar to the benzenesulfonyltrypt-

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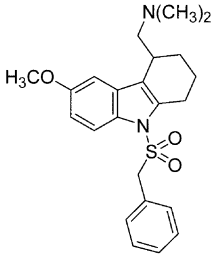
amines, they could serve as conformationally-constrained templates for future QSAR studies.

Because incorporation of various substituents into the N_1-benzenesulfonyl ring of **3**, or replacement of the N_1-benzenesulfonyl group by an N_1-(1- or (2-naphthalenesulfonyl) group, is tolerated (i.e., such substitution generally results in <10-fold change in affinity),[9] it was of interest to determine if corresponding structural changes would have a similar effect on derivatives of **6**. It was also of interest to determine if the N_9-benzenesulfonyl group of **6** could be replaced by an N_9-benzylsulfonyl group. Accordingly, we prepared and examined benzylsulfonyl derivative **7** and substituted arylsulfonyl derivatives **8**–**16** (Table 1).[10]



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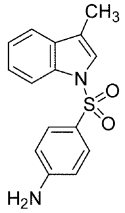

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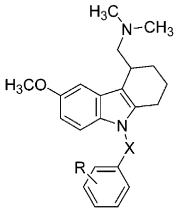
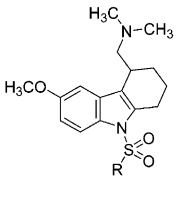
The aryl- and benzylsulfonyl derivatives were readily prepared by acylation of the appropriate carbazole in the presence of base (Table 1). In the case of amine-bearing arylsulfonyl substituents, the acylation step was performed using a protected amine (i.e., acetamide) followed by hydrolysis to the desired product.

The affinity of **6** was re-determined ($K_i = 2.3$ nM, Table 1) and found consistent with the value reported earlier.[9] Insertion of a methylene group between the benzene and sulfonyl groups of **6** reduced affinity by nearly 100-fold (**7**, $K_i = 200$ nM) indicating that such extension is not favorable for binding. As with derivatives of **3**, a variety of benzenesulfonyl substituents was tolerated (e.g., **8**–**14**) and, with the exception of 4-methoxy derivative **11**, affinity varied <10-fold as compared to tetrahydrocarbazole **6**. The 2,5-dimethoxybenzenesulfonyl analogue **12** ($K_i = 0.3$ nM) displayed the highest affinity of the compounds examined. Also, as with **3**, there seems to be a certain amount of bulk tolerance associated with this portion of the receptor in that replacement of the benzenesulfonyl group of **6** with naphthyl- or 8-quinolylsulfonyl moieties (i.e., **14**–**16**) was accommodated. The general conclusion of these studies is that the N_9-benzenesulfonyl moiety of **6** can bear various substituents or can be replaced with slightly larger ring systems, as was the case for derivatives of **3**, with

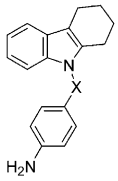
Table 1. Physicochemical and 5-HT_6 receptor binding properties of tetrahydrocarbazole and carbazole derivatives



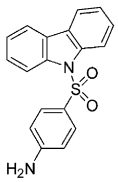
6–13



14–16



18-20



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	X	R	Recryst. Solvent	Percent Yield	Melting Point (°C)	Empirical Formula[a]	K_i, nM	(±SEM)
6	$-SO_2-$	H	—	—	—	—	2.3	(0.4)
7	$-SO_2-CH_2-$	H	MeOH/Et_2O	60%	188–189	$C_{23}H_{28}N_2O_3S{\cdot}1.75C_2H_2O_4$	200	(50)
8	$-SO_2-$	4-Cl	MeOH/Et_2O	71%	218–220	$C_{22}H_{25}ClN_2O_3S{\cdot}C_2H_2O_4$[b]	5.0	(2.0)
9	$-SO_2-$	4-I	MeOH/Et_2O	83%	201–203	$C_{22}H_{25}IN_2O_3S{\cdot}C_2H_2O_4$[c]	2.4	(0.8)
10	$-SO_2-$	4-Me	MeOH/Et_2O	64%	201–203	$C_{23}H_{28}N_2O_3S{\cdot}C_2H_2O_4$	9.4	(2.4)
11	$-SO_2-$	4-OMe	MeOH/Et_2O	64%	208–210	$C_{23}H_{28}N_2O_4S{\cdot}C_2H_2O_4$	47	(10)
12	$-SO_2-$	2,5-Di OMe	MeOH/Et_2O	67%	202–204	$C_{24}H_{30}N_2O_5S{\cdot}C_2H_2O_4$[b]	0.3	(0.1)
13	$-SO_2-$	4-NH_2	MeOH/Et_2O	61%	172–174	$C_{22}H_{27}N_3O_3S{\cdot}2HCl$[d]	2.0	(0.5)
14	—	1-Naphthyl	MeOH/Et_2O	57%	162–164	$C_{26}H_{28}N_2O_3S{\cdot}C_2H_2O_4$[b]	14	(3)
15	—	2-Naphthyl	MeOH/Et_2O	60%	174–176	$C_{26}H_{28}N_2O_3S{\cdot}C_2H_2O_4$[d]	5.1	(1.6)
16	—	8-Quinolinyl	MeOH/Et_2O	57%	162–164	$C_{25}H_{27}H_3O_3S{\cdot}C_2H_2O_4$[e]	7.6	(1.2)
18	$-CH_2-$	—	Acetone	68%	164–165	$C_{19}H_{20}N_2{\cdot}C_2H_2O_4$[b]	6000	(2000)
19	$-C(=O)-$	—	Acetone	66%	151–153	$C_{19}H_{18}N_2O{\cdot}C_2H_2O_4$[b]	6000	(1000)
20 (JCF-177)	$-SO_2-$	—	MeOH/Et_2O	53%	179–181	$C_{18}H_{18}N_2O_2S{\cdot}1.5C_2H_2O_4$	29	(4)
21	—	—	EtOAc	25%	169–170	$C_{18}H_{14}N_2O_2S{\cdot}HCl$	49	(8)

[a] Products, isolated either as their oxalate or hydrochloride salts, analyzed within 0.4% of theory for C, H, N.
[b] Crystallized with 0.5 mol H_2O.
[c] Crystallized with 1.0 mol H_2O.
[d] Crystallized with 1.5 mol H_2O.
[e] Crystallized with 0.25 mol H_2O.

relatively little effect (with the exception of 4-methoxy derivative **11**) on 5-HT$_6$ receptor affinity. The nature of the specific type of contribution these substituent groups make to receptor affinity will require a more systematic investigation of additional analogues.

It might be noted that the affinity of the benzenesulfonyl analogue **6** ($K_i = 2.3$ nM) is >100-fold higher than that of its corresponding benzyl counterpart **5**; it would appear, then, that the presence of the sulfonyl moiety seems to be contributing to the binding of **6**. Nevertheless, it remains to be determined if the sulfonyl group interacts directly with receptor-associated features or whether it contributes indirectly by influencing the electronic character of other portions of the molecule that might be important for binding. In addition, because various sulfones have been demonstrated to bind at 5-HT$_6$ receptors, for example,[11] the presence of the indolic nitrogen atom might not be required for binding; this, too, requires further study.

Up to this point, structural modification of the tetrahydrocarbazoles seems to have an effect on 5-HT$_6$ binding resembling that seen with **3**. We have previously shown that the dimethylaminomethyl portion of **3** is not required for 5-HT$_6$ binding. For example, **17** ($K_i = 12$ nM) binds at 5-HT$_6$ receptors and acts as a 5-HT$_6$ antagonist ($pA_2 = 7.0$).[12] To determine if the tetrahydrocarbazoles behave in a similar fashion, several truncated carbazole analogues were prepared where the aminomethyl side chain was removed. Because a 4′-amino group was shown to be tolerated (i.e., see **13**, Table 1), the abbreviated carbazole analogues retained this moiety; the presence of the amino group also allowed for the preparation of a water soluble salt. Aminobenzyl compound **18** ($K_i = 6000$ nM; Table 1), which can be viewed as structurally related to **5**, displayed low affinity for 5-HT$_6$ receptors; its aminobenzoyl counterpart **19** ($K_i = 6000$ nM) also displayed little affinity. However, 4-aminobenzenesulfonyl analogue **20** ($K_i = 29$ nM) displayed higher affinity. Thus, once again (comparing **20** with **18** and **19**), it seems that the specific presence of the sulfonyl moiety imparts enhanced affinity. Aromatization of tetrahydrocarbazole **20** to carbazole **21** ($K_i = 49$ nM) halved affinity.

Functional studies were conducted with tetrahydrocarbazole **20** to determine if it is a 5-HT$_6$ agonist or antagonist by measuring its ability to either stimulate cAMP accumulation in HEK cells, or to antagonize 5-HT-induced cAMP production.[13] Compound **20** failed to behave as agonist (to 10,000 nM), but competitively antagonized the actions of 5-HT (data not shown); Schild analysis for **20** provided a pA_2 of 7.0 (± 0.1), which is identical to that reported for **17**.[12]

Several tetrahydrocarbazole analogues were examined as 5-HT$_6$ receptor ligands and structural modification seemed to influence affinity in a manner that generally paralleled that seen upon structural modification of MS-245 (**3**). For example, an indolic methoxy group is not required for binding, various benzenesulfonyl substituents were tolerated, and replacement of the benzenesulfonyl group with bulkier arylsulfonyl groups had minimal impact on affinity. Also, as with **3**, the aminoalkyl side chain was not essential for 5-HT$_6$ receptor binding or antagonist activity. That is, removal of the tetrahydrocarbazole *N*,*N*-dimethylaminomethyl substituent resulted in **20** ($K_i = 29$ nM) which behaved as a competitive 5-HT$_6$ antagonist in a cAMP hydrolysis assay. As such, tetrahydrocarbazole **20** appears to represent a member of a novel class of agents with 5-HT$_6$ antagonist character that is structurally related to MS-245 (**3**). The present results suggest that **20** might serve as a lead structure for the further development of new 5-HT$_6$ antagonists; efforts are currently underway to improve its 5-HT$_6$ receptor affinity and, once achieved, binding profiles of the resulting compounds will be examined. This study also indicates that the benzenesulfonyl tetrahydrocarbazoles likely bind at 5-HT$_6$ receptors in a manner similar to the benzenesulfonyltryptamines and, as such, provide conformationally-constrained analogues that can be used as templates for the structural alignment of compounds in QSAR studies.

Acknowledgements

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10. Radioligand Binding Assay: The h5-HT$_6$ radioligand binding assays were performed as previously described.[7] In brief, h5-HT$_6$ cDNA was transiently expressed in COS-7 cells using the DEAE-dextran technique.[7] Seventy-two hours after transfection, cells were harvested by scraping and centrifugation from medium containing 10% dialyzed fetal calf serum. Cells were then washed by centrifugation and resuspension once in phosphate buffered saline (pH = 7.40; PBS) and then frozen as tight pellets at

−80 °C until use. Binding assays were performed at room temperature for 90 min in binding buffer (50 mM Tris–Cl, 10 mM $MgCl_2$, 0.1 mM EDTA, pH = 7.40) with [^{3}H]LSD (1 nM final concentration) using 10 μM clozapine for non-specific binding. Various concentrations of unlabeled test agent (1–10,000 nM) were used for K_i determinations with K_i values calculated using the LIGAND program. Specific binding represented 80–90% of total binding. K_i values are the result of triplicate determinations.

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