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Interaction of chiral MS-245 analogs at h5-HT$_6$ receptors

Carmen Abate,[a] Renata Kolanos,[a] Malgorzata Dukat,[a] Vince Setola,[b] Bryan L. Roth[b,c] and Richard A. Glennon[a,*]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298-0540, USA*
[b]*Department of Biochemistry, Case Western Reserve University, USA*
[c]*Department of Psychiatry and Neurosciences, School of Medicine, Case Western Reserve University, USA*

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Abstract—Optically active pyrrolidinylmethylindole analogs related in structure to the benzenesulfonyltryptamine 5-HT$_6$ receptor antagonist MS-245 were evaluated and their *R*-isomers were found to bind with affinity higher than their *S*-enantiomers.
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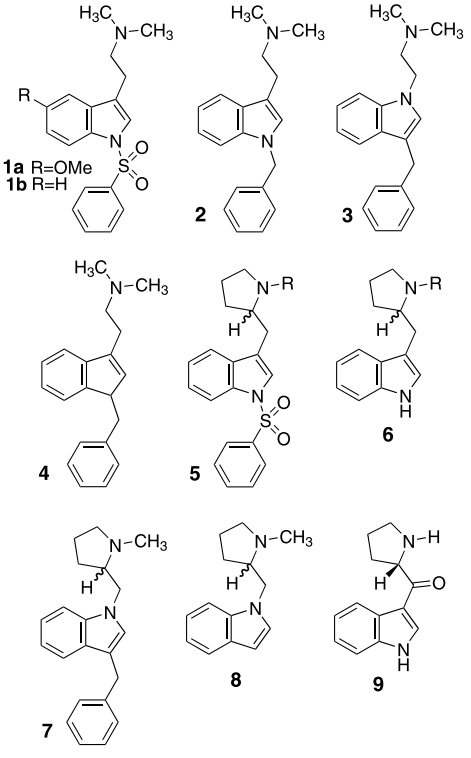
5-HT$_6$ receptors are members of the serotonin receptor family (5-HT$_1$–5-HT$_7$) and are of potential therapeutic interest due to their possible involvement in neuropsychiatric disorders, such as depression and pyschosis.[1–6] This receptor population was first identified about 10 years ago, but only in the past few years have 5-HT$_6$ receptor antagonists been described (reviewed[5,6]). We identified MS-245 (**1a**; K_i ca. 2 nM) as one of the first examples of a 5-HT$_6$ receptor antagonist.[7,8] Subsequent pharmacophoric studies have revealed that the 5-methoxy group of **1a** is not required for binding (i.e., **1b**; K_i = 4 nM), that the benzenesulfonyl moiety can be replaced by a benzyl group (**2**; K_i = 6 nM) with retention of antagonist action,[5] and that the indole N$_1$ nitrogen atom is not required for binding, as evidenced by the high affinity of, for example, isotryptamine **3** (K_i = 32 nM) and indene **4** (K_i = 3 nM) for this receptor population.[9]

Various tryptamines lacking an N$_1$ substituent generally bind with reduced affinity and, like 5-hydroxytryptamine (i.e., serotonin; K_i ca. 100 nM), can display agonist character.[5] On the basis of comparative structure–affinity and receptor modeling studies,[8,10] we have proposed that tryptamine analogs, although likely utilizing a common aspartate moiety, bind at 5-HT$_6$ receptors differently depending upon whether or not they possess an N$_1$ (e.g., a benzenesulfonyl or benzyl) substituent.

If the presence or absence of an N$_1$ substituent dictates how tryptamine analogs interact with 5-HT$_6$ receptors, it was reasoned that chiral analogs of N$_1$-unsubstituted tryptamines might bind differently than N$_1$-substituted tryptamines and that isomeric comparisons could prove to be informative. In an extreme case, optical isomers of N$_1$-substituted tryptamines might even display opposite enantioselectivity for binding, as compared to their corresponding N$_1$-unsubstituted counterparts.



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* Corresponding author. Tel.: +1 804 828 8487; fax: +1 804 828 7404; e-mail: glennon@hsc.vcu.edu

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Introduction of substituents α to the terminal amine of tryptamine analogs (e.g., an α-methyl or α-ethyl group) to create a chiral center has been shown to result in somewhat reduced 5-HT_6 receptor affinity.[11] Nevertheless, it was thought that reduced affinity might be an acceptable trade-off if it allowed enantiomeric potency comparisons to be made. Rather than examining isomers of α-methyl- or α-ethyltryptamines, however, we opted to examine their cognate pyrrolidinylmethylindole counterparts. That is, because necessary optically active starting materials with defined absolute configuration were readily available, and because pyrrolidinylmethylindoles have been previously shown to bind at other (i.e., 5-HT_1) serotonin receptor populations[12,13], we prepared the optical isomers of **5** (where R = H or Me) for binding comparisons with their N_1-unsubstituted analogs **6**. To evaluate this hypothesis further, we also prepared the isomers of isotryptamine **7** for comparison with their (C_3) unsubstituted counterparts **8**.

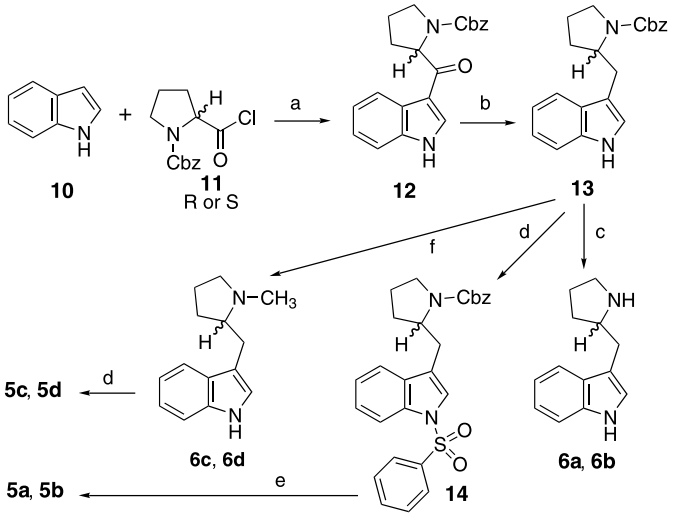
Compounds **6a** and **6b** were previously reported in the patent literature as 5-HT_1 ligands;[12] and the synthesis of their 5-methoxy analogs has also been described by Macor and co-workers.[13,14] Compounds **6a** and **6b** were prepared using the same methodology (Scheme 1). Ketones **12** were obtained by the reaction of indole (**10**) with either the commercially available *R*- or *S*-isomer of **11**; isomers **12** were reduced with $LiBH_4$ to protected amine **13**, which was deprotected via catalytic hydrogenation to the desired targets **6a** and **6b** (Table 1). In one instance, (−)**12** was subjected to direct catalytic reduction and resulted in ketone derivative *S*(−)**9**.[15]

Both isomers of **13** were treated with sodium bis(trimethylsilyl)amide to form the corresponding anions that were allowed to react with benzenesulfonyl chloride to afford intermediates **14**; deprotection of **14** was performed, as described for **13**, to afford isomers **5a** and **5b** (Scheme 1). Direct treatment of **13** with lithium aluminum hydride led to **6c** and **6d**, and these were subsequently converted to their corresponding benzenesulfonyl analogs **5c** and **5d**.

The isomers of **7** and **8** (Table 1) were conveniently synthesized by reaction of the indolyl anion (generated by treatment with NaH in DMF) of indole or 3-benzylindole[16], with the known optical isomers of 2-(chloromethyl)-1-methylpyrrolidine hydrochloride.[17]

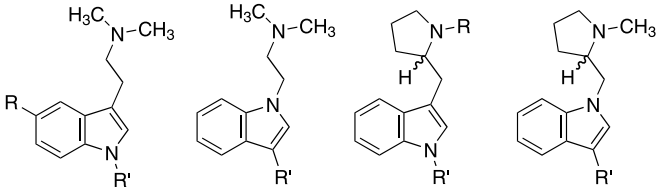
Radioligand binding[18] data for the target compounds are shown in Table 1. As with structurally simpler *N*,*N*-dialkyltryptamines,[5] introduction of an N_1-benzenesulfonyl moiety led to enhanced affinity (comparing pyrrolidinylmethylindoles **5a** with **6a**, **5b** with **6b**, **5c** with **6c**, and **5d** with **6d**) (Table 1). Likewise, in the isotryptamine series, benzyl analogs **7a** and **7b** displayed affinity higher than those of their parents, **8a** and **8b**, respectively. In fact, the pyrrolidinylmethylindoles bind with affinities higher than those of their simpler *N*,*N*-dimethyltryptamine counterparts; for example, compound **5d** binds with more than 10 times the affinity of **1b** and **7b** binds with 3 times the affinity of **3**.

In the absence of enantioselectivity reversal, it is not possible to conclude that the N_1-substituted and N_1-unsubstituted compounds are binding in a different fashion. Nevertheless, there is some tantalizing evidence in support of this possibility. For example, there is greater enantioselectivity in the absence of the benzenesulfonyl group (40- and 70-fold for **6a/6b** and **6c/6d**, respectively) than in its presence (<6-fold for **5a/5b** and **5c/5d**). A similar, but somewhat less pronounced, trend is seen with the isotryptamines. Furthermore, N-methylation has dissimilar effects in the unsubstituted and substituted series; whereas N-methylation enhanced the affinity of **6a** (→**6c**) and **6b** (→**6d**) by about 5-fold, methylation enhanced the affinity of **5a** (→**5c**) and **5b** (→**5d**) by 25-fold. Clearly, there are differences between the N_1-unsubstituted and N_1-substituted series.



Scheme 1. (a) EtMgBr; (b) $LiBH_4$, Δ; (c) H_2, 10% Pd/C, absolute EtOH, 35–40 psi/3 h; (d) i. $[(CH_3)_3Si]_2NNa$, THF, −78 °C, ii. $PhSO_2Cl$, rt; (e) H_2, 10% Pd/C, absolute EtOH/MeOH, 35 psi/12 h; and (f) $LiAlH_4$, THF, Δ/4 h.

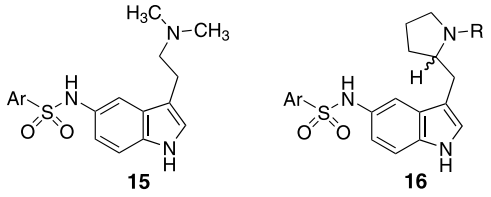
Table 1. Radioligand binding data for reference compounds **1**–**3**, and physicochemical properties and 5-HT_6 receptor affinities of the target compounds



	R	R′	Isomer	Melting point (°C)	Empirical formula[a]	h5-HT_6 K_i, nM (±SEM)[b]
1a	OMe	SO_2Ph	—	—	—	2
1b	H	SO_2Ph	–	—	—	4
2	H	CH_2Ph	—	—	—	6
3	—	CH_2Ph	—	—	—	32
6a	H	H	*S*(+)	203–205[c]	$C_{13}H_{16}N_2$ HCl	2400 (±400)
6b	H	H	*R*(−)	204–205[c]	$C_{13}H_{16}N_2$ HCl	60 (±10)
5a	H	SO_2Ph	*S*(+)	182–184[c]	$C_{19}H_{20}N_2SO_2$ $C_2H_2O_4$	46 (±6)
5b	H	SO_2Ph	*R*(−)	179–181[c]	$C_{19}H_{20}N_2SO_2$ $C_2H_2O_4$[d]	7.8 (±1.4)
6c	Me	H	*S*(−)	216–218[c]	$C_{14}H_{18}N_2$ HCl	640 (±110)
6d	Me	H	*R*(+)	216–217[c]	$C_{14}H_{18}N_2$ HCl	9.1 (±0.8)
5c	Me	SO_2Ph	*S*(−)	145–147[c]	$C_{20}H_{22}N_2SO_2$ $C_2H_2O_4$	1.7 (±0.3)
5d	Me	SO_2Ph	*R*(+)	145–147[c]	$C_{20}H_{22}N_2SO_2$ $C_2H_2O_4$[d]	0.3 (±0.1)
8a	—	H	*S*(+)	157–158[e]	$C_{14}H_{18}N_2$ HCl	8750 (±2200)
8b	—	H	*R*(−)	157–158[e]	$C_{14}H_{18}N_2$ HCl	550 (±110)
7a	—	CH_2Ph	*S*(+)	124–125[e]	$C_{21}H_{24}N$ $C_4H_4O_4$	29 (±5)
7b	—	CH_2Ph	*R*(−)	124–125[e]	$C_{21}H_{24}N$ $C_4H_4O_4$	9.9 (±1.3)

[a] All compounds analyzed within 0.4% of theory for C, H, and N. $C_2H_2O_4$, oxalate salt; $C_4H_4O_4$, maleate salt.
[b] K_i values were determined, at least in triplicate, as previously described.[18,22] Binding data for **1**–**3** have been previously reported[5,8,9] and are shown here for comparison.
[c] Recrystallization solvent = anhydrous MeOH/absolute EtOH.
[d] Crystallized with 0.25 mol H_2O.
[e] Recrystallization solvent = CH_2Cl_2/Et_2O.

It was shown that *R*-pyrrolidinylmethylindoles bind with higher affinity than their *S*-enantiomers and that **5d** (K_i = 0.3 nM) binds with nearly 10-fold higher affinity than MS-245 (**1**). Interestingly, a recent review of the patent literature revealed that **5d** had been previously described as a 5-HT_6 antagonist; although the compound was not physically characterized and though no enantiomeric potency comparison was provided (because its *S*-enantiomer was not prepared), **5d** was reported to bind at 5-HT_6 receptors with a K_i < 10 nM.[19]



Although the present results cannot be used as evidence for different modes of binding, they are not inconsistent with the concept that N_1-substituted tryptamine-related analogs might bind differently than their N_1-unsubstituted counterparts. The results further identify *R*-pyrrolidinylmethylindole analogs of MS-245 (**1a**) as binding with affinity higher than their *S*-enantiomers. While this manuscript was under preparation, Holenz et al.[20] showed that 5-arylsulfonamido analogs of tryptamines (e.g., **15**) bind at 5-HT_6 receptors, and that some are 5-HT_6 antagonists, whereas others are agonists. At this time, however, it is not known how **15** binds relative to the compounds described herein. Nevertheless, Cole et al.,[21] coincidentally, reported on the pyrrolidinylmethylindole counterparts of such agents (i.e., **16**). In the latter investigation, there was a trend for the *R*-isomers of **16** (where R = Me) to bind with about 4-fold higher affinity, relative to the corresponding NH analogs, and even more fascinating is that the *S*-enantiomers generally behaved as 5-HT_6 antagonists, whereas the *R*-isomers displayed agonist action.[21]

Acknowledgment

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