

Interaction of chiral MS-245 analogs at h5-HT₆ receptors

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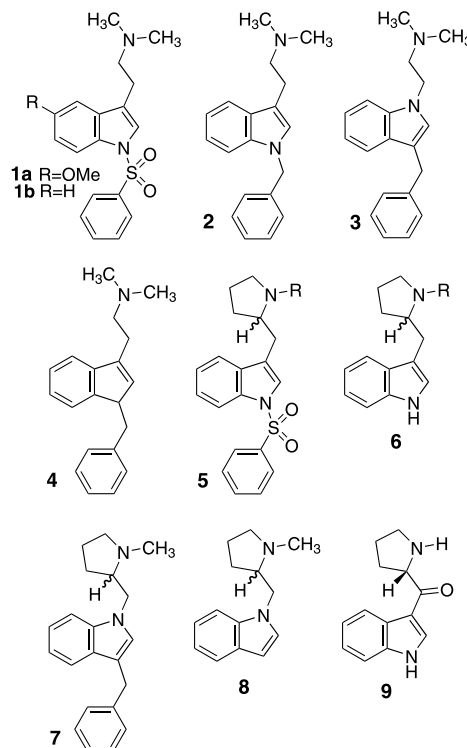
Abstract—Optically active pyrrolidinylmethylindole analogs related in structure to the benzenesulfonyltryptamine 5-HT₆ receptor antagonist MS-245 were evaluated and their *R*-isomers were found to bind with affinity higher than their *S*-enantiomers.
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5-HT₆ receptors are members of the serotonin receptor family (5-HT₁–5-HT₇) and are of potential therapeutic interest due to their possible involvement in neuropsychiatric disorders, such as depression and psychosis.^{1–6} This receptor population was first identified about 10 years ago, but only in the past few years have 5-HT₆ 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-HT₆ 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 N₁ 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 N₁ 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-HT₆ receptors differently depending upon whether or not they possess an N₁ (e.g., a benzenesulfonyl or benzyl) substituent.

If the presence or absence of an N₁ substituent dictates how tryptamine analogs interact with 5-HT₆ receptors,

it was reasoned that chiral analogs of N₁-unsubstituted tryptamines might bind differently than N₁-substituted tryptamines and that isomeric comparisons could prove to be informative. In an extreme case, optical isomers of N₁-substituted tryptamines might even display opposite enantioselectivity for binding, as compared to their corresponding N₁-unsubstituted counterparts.



Keywords: Serotonin; Pyrrolidinylmethylindoles.

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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-HT₆ 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-HT₁) serotonin receptor populations^{12,13}, we prepared the optical isomers of **5** (where R = H or Me) for binding comparisons with their N₁-unsubstituted analogs **6**. To evaluate this hypothesis further, we also prepared the isomers of isotryptamine **7** for comparison with their (C₃) unsubstituted counterparts **8**.

Compounds **6a** and **6b** were previously reported in the patent literature as 5-HT₁ 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 LiBH₄ 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

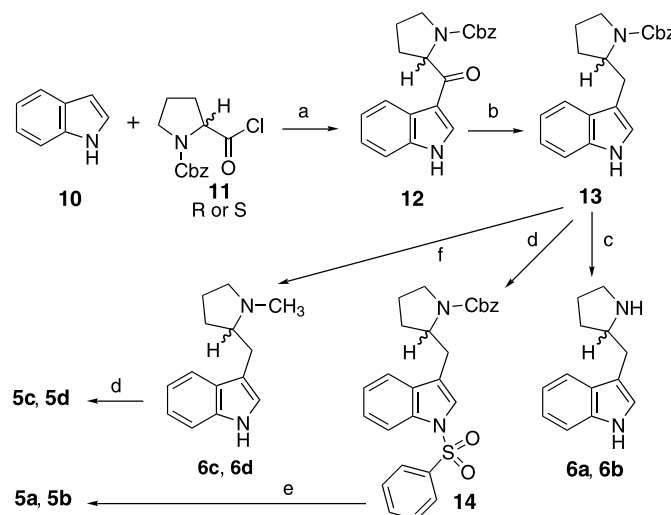
Both isomers of **13** were treated with sodium bis(trimethylsilyl)amide to form the corresponding anions that were allowed to react with benzenesulfonyl chloride to afford intermediates **14**; deprotection of **14** was performed, as described for **13**, to afford isomers **5a** and **5b** (Scheme 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**.

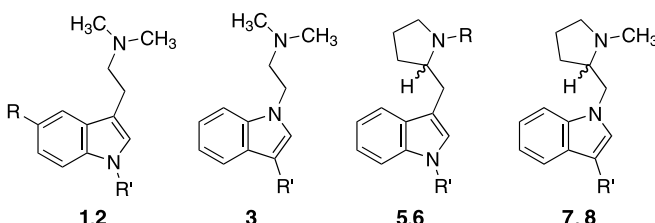
The isomers of **7** and **8** (Table 1) were conveniently synthesized by reaction of the indolyl anion (generated by treatment with NaH in DMF) of indole or 3-benzylindole¹⁶, with the known optical isomers of 2-(chloromethyl)-1-methylpyrrolidine hydrochloride.¹⁷

Radioligand binding¹⁸ data for the target compounds are shown in Table 1. As with structurally simpler *N,N*-dialkyltryptamines,⁵ introduction of an N₁-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 N₁-substituted and N₁-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** ($\rightarrow$ **6c**) and **6b** ($\rightarrow$ **6d**) by about 5-fold, methylation enhanced the affinity of **5a** ($\rightarrow$ **5c**) and **5b** ($\rightarrow$ **5d**) by 25-fold. Clearly, there are differences between the N₁-unsubstituted and N₁-substituted series.



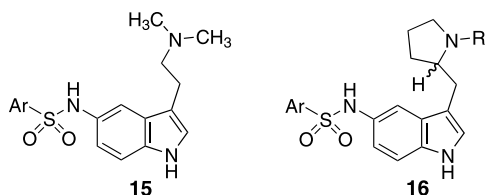
Scheme 1. (a) EtMgBr; (b) LiBH₄, Δ ; (c) H₂, 10% Pd/C, absolute EtOH, 35–40 psi/3 h; (d) i. [(CH₃)₃Si]₂NNa, THF, –78 °C, ii. PhSO₂Cl, rt; (e) H₂, 10% Pd/C, absolute EtOH/MeOH, 35 psi/12 h; and (f) LiAlH₄, THF, Δ /4 h.

Table 1. Radioligand binding data for reference compounds **1–3**, and physicochemical properties and 5-HT₆ 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 ₂ Ph	—	—	—	2
1b	H	SO ₂ Ph	—	—	—	4
2	H	CH ₂ Ph	—	—	—	6
3	—	CH ₂ Ph	—	—	—	32
6a	H	H	<i>S</i> (+)	203–205 ^c	C ₁₃ H ₁₆ N ₂ HCl	2400 (±400)
6b	H	H	<i>R</i> (–)	204–205 ^c	C ₁₃ H ₁₆ N ₂ HCl	60 (±10)
5a	H	SO ₂ Ph	<i>S</i> (+)	182–184 ^c	C ₁₉ H ₂₀ N ₂ SO ₂ C ₂ H ₂ O ₄	46 (±6)
5b	H	SO ₂ Ph	<i>R</i> (–)	179–181 ^c	C ₁₉ H ₂₀ N ₂ SO ₂ C ₂ H ₂ O ₄ ^d	7.8 (±1.4)
6c	Me	H	<i>S</i> (–)	216–218 ^c	C ₁₄ H ₁₈ N ₂ HCl	640 (±110)
6d	Me	H	<i>R</i> (+)	216–217 ^c	C ₁₄ H ₁₈ N ₂ HCl	9.1 (±0.8)
5c	Me	SO ₂ Ph	<i>S</i> (–)	145–147 ^c	C ₂₀ H ₂₂ N ₂ SO ₂ C ₂ H ₂ O ₄	1.7 (±0.3)
5d	Me	SO ₂ Ph	<i>R</i> (+)	145–147 ^c	C ₂₀ H ₂₂ N ₂ SO ₂ C ₂ H ₂ O ₄ ^d	0.3 (±0.1)
8a	—	H	<i>S</i> (+)	157–158 ^e	C ₁₄ H ₁₈ N ₂ HCl	8750 (±2200)
8b	—	H	<i>R</i> (–)	157–158 ^e	C ₁₄ H ₁₈ N ₂ HCl	550 (±110)
7a	—	CH ₂ Ph	<i>S</i> (+)	124–125 ^e	C ₂₁ H ₂₄ N C ₄ H ₄ O ₄	29 (±5)
7b	—	CH ₂ Ph	<i>R</i> (–)	124–125 ^e	C ₂₁ H ₂₄ N C ₄ H ₄ O ₄	9.9 (±1.3)

^a All compounds analyzed within 0.4% of theory for C, H, and N. C₂H₂O₄, oxalate salt; C₄H₄O₄, 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 H₂O.^e Recrystallization solvent = CH₂Cl₂/Et₂O.

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-HT₆ 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-HT₆ 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 N₁-substituted tryptamine-related analogs might bind differently than their N₁-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-HT₆ receptors, and that some are 5-HT₆ 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-HT₆ antagonists, whereas the *R*-isomers displayed agonist action.²¹

Acknowledgment

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