Discovery of 5-Arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indole Derivatives as Potent, Selective 5-HT$_6$ Receptor Agonists and Antagonists

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Received September 16, 2004

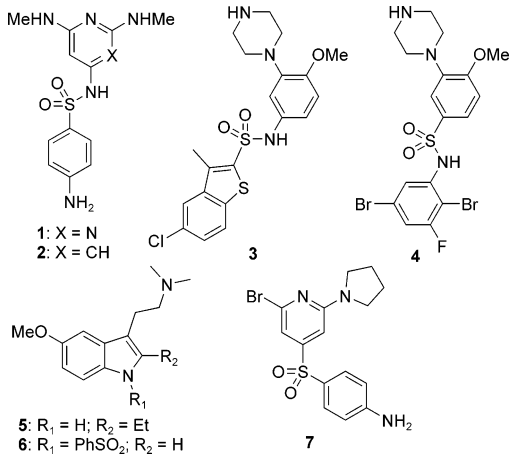
Abstract: 5-Arylsulfonylamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indoles have been identified as high-affinity 5-HT$_6$ receptor ligands. Within this class, several of the (*R*)-enantiomers were potent agonists having EC$_{50}$ values of 1 nM or less and functioning as full agonists while the (*S*)-enantiomers displayed moderate antagonist activity.

There are now approximately 15 different human serotonin (5-HT) receptors that have been cloned and divided into 7 subclasses (5-HT$_{1-7}$).[1] The 5-HT$_6$ receptor is one of the latest to have been identified and belongs to the G-protein coupled receptor (GPCR) superfamily. The rat 5-HT$_6$ receptor was first cloned in 1993 and found to consist of a 438-residue peptide chain with <40% homology with other 5-HT receptors.[2] The human receptor was cloned in 1996, shares 89% homology with the rat receptor, and is positively coupled to adenylyl cyclase.[3,4]

In situ hybridization studies indicate that the 5-HT$_6$ receptor mRNA is localized exclusively in the central nervous system, with highest densities in the cerebral cortex, nucleus accumbens, caudate-putamen, and hippocampus and with moderate densities in the thalamus and substantia nigra.[5] Binding studies have shown certain tricyclic antidepressants and antipsychotic drugs have high affinity for 5-HT$_6$ receptors.[6] The central nervous system (CNS) localization of 5-HT$_6$ receptors and their affinity for CNS drugs have created intense interest in identifying selective 5-HT$_6$ receptor modulators as tools for studying the receptor and as potential therapeutic agents.[5]

In 1998, scientists at Roche described a series of pyrimidinyl- and pyridinylsulfonamides, Ro-04-6790 (**1**) and Ro-63-0563 (**2**),[7] which were among the first selective 5-HT$_6$ receptor antagonists. A series of piperazinylbenzenesulfonamides, including SB-271046 (**3**)[8] and

Chart 1. Structures of 5-HT$_6$ Receptor Ligands



SB-357134 (**4**),[9] were subsequently revealed by Smith-Kline-Beecham. More recently, *N,N*-dimethyl-1-benzenesulfonyl-5-methoxytryptamine (**6**)[10] and the first non-sulfonamide antagonist 4-(2-bromo-6-pyrrolidine-1-yl-pyridine-4-sulfonyl)phenylamine (**7**)[11] were reported (Chart 1).

These compounds have been used to probe the therapeutic potential of 5-HT$_6$ receptor ligands. Bentley et al. showed that the 5-HT$_6$ receptor blockade with Ro-04-6790 produced a dose-dependent stretching that was blocked by the muscarinic receptor antagonist atropine suggesting that the 5-HT$_6$ receptor may regulate central cholinergic neurotransmission.[12] Ro-04-6790 also inhibited atropine- and scopolamine-induced ipsilateral rotations but not L-Dopa-induced contralateral rotations in rats with 6-OHDA lesions in the medial forebrain indicating that 5-HT$_6$ receptors may play a role in normal and dysfunctional memory.[13] While in vivo studies with Ro-04-6790, SB-271046, and SB-357134 showed no enhancement in learning, some results suggested enhanced memory retention in rats indicating that blocking 5-HT$_6$ receptor function may be involved in cognitive processes.[9,14] However, interpretation of these results has been somewhat controversial.[15] Dawson et al. demonstrated increased levels of glutamate and aspartate in rat frontal cortex and hippocampus, respectively, after treatment with SB-271046, supporting the hypothesis that the 5-HT$_6$ receptor may regulate glutamatergic neurons and that this could be involved in the no-otropic effect seen with 5-HT$_6$ receptor antagonists.[16]

Identification of selective 5-HT$_6$ receptor agonists has proven very challenging. One of the few agonists reported, 2-ethyl-5-methoxy-*N,N*-dimethyltryptamine (**6**),[17] has 16 nM affinity for the 5-HT$_6$ receptor but is only 10-, 20-, and 30-fold selective over 5-HT$_{1A}$, 5-HT$_{1D}$, and 5-HT$_7$ receptors, respectively.

As part of a project to develop 5-HT$_6$ receptor modulators at Wyeth, we identified N_1-arylsulfonyltryptamine derivatives **8** as high-affinity 5-HT$_6$ receptor ligands.[10,17,18] We examined conformationally restricted aminoethyl side chains focusing on the 3-(pyrrolidin-2-ylmethyl) group.[19] Indeed, the N_1-arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indoles **9** had low-nanomolar affinity for

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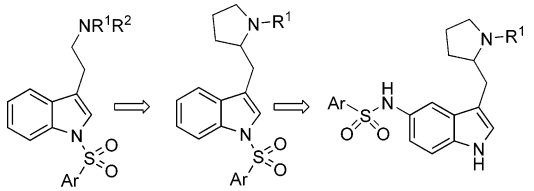
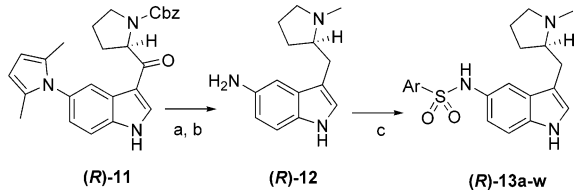
10.1021/jm049243i CCC: $30.25
Published on Web 12/21/2004

Chart 2. Design of 5-Arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indoles



Scheme 1[a]



[a] Reagents: (a) $LiAlH_4$, THF, Δ; (b) NH_4OH·HCl, Et_3N, *i*-PrOH, water, Δ; (c) $ArSO_2Cl$, Et_3N, THF.

5-HT_6 receptors. We had also found that tryptamine type cores with lipophilic groups in the 5-position, e.g., 5-benzyloxytryptamine, had high affinity for the 5-HT_6 receptor. Thus, we thought that moving the sulfonamido group from the 1- to the 5-position, as in **10** (Chart 2), might also lead to 5-HT_6 receptor ligands.

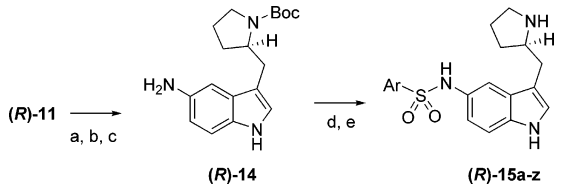
The compounds were found to have high 5-HT_6 receptor affinity and to be potent modulators of 5-HT_6 receptor dependent cyclase activity. Surprisingly, potent agonists and antagonists were identified within this single series; one enantiomeric series provided potent agonists, while compounds of the opposite chirality were potent antagonists. Herein, we describe the synthesis and remarkable biological activities of 5-arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indoles as 5-HT_6 receptor modulators.

5-Amino-3-[(*N*-methyl-pyrrolidine-2-yl)methyl]-1*H*-indole (*R*)-**12** was prepared via a literature procedure[20] by protection of 5-aminoindole as the 2,5-dimethylpyrrole, Grignard promoted coupling with Cbz-D-proline acid chloride to give (*R*)-**11**, followed by reduction with $LiAlH_4$ and deprotection of the amine to give (*R*)-**12** (Scheme 1).

This 5-aminoindole core (*R*)-**12** was converted into an array of sulfonamides (*R*)-**13a**−**w** in parallel fashion by treatment with a set of arylsulfonyl chlorides and subsequent purification by high-throughput RP-HPLC.[21] Corresponding (*S*)-enantiomers (*S*)-**13a**−**w** were prepared in similar fashion, starting from Cbz-L-proline acid chloride.

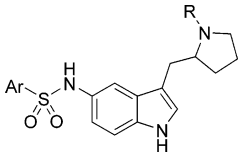
A somewhat modified route was used to prepare the N−H pyrrolidinyl analogues (Scheme 2). The 2-(5-amino-1*H*-indol-3-ylmethyl)-*N*-Boc-pyrrolidine core (*R*)-**14** was synthesized by selective reduction of (*R*)-**11** with lithium borohydride in refluxing THF. This milder reducing agent effected the keto-to-methylene transformation while leaving the Cbz group intact. A Boc for Cbz protecting group exchange was achieved in a single pot by hydrogenation over palladium hydroxide in the presence of di-*tert*-butyl dicarbonate in ethanol. Deprotection of the 5-amino group then gives the Boc-protected core (*R*)-**14**. Sulfonamide array synthesis is accomplished as for the *N*-methyl series. The Boc group

Scheme 2[a]



[a] Reagents: (a) $LiBH_4$, THF, Δ; (b) H_2, $Pd(OH)_2$, $(Boc)_2O$, EtOH; (c) NH_4OH·HCl, Et_3N, *i*-PrOH, water, Δ; (d) $ArSO_2Cl$, Et_3N, THF; (e) HCl, dioxane.

Table 1. 5-HT_6 Receptor Binding Affinity of 5-Arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indoles



		K_i (nM)[a]			
		R = Me		R = H	
	Ar	(*R*)-**13**	(*S*)-**13**	(*R*)-**15**	(*S*)-**15**
a	Ph	1.0 ± 0.3	16 ± 2	4.0 ± 0.4	
b	2-F-Ph	1.0 ± 0.1		4.0 ± 0.4	
c	2-Cl-Ph	1.0 ± 0.0	22 ± 2	3.0 ± 0.4	
d	2-Br-Ph		5 ± 1		
e	2-I-Ph			1.0 ± 0.1	
f	3-Cl-Ph	0.4 ± 0.1	11 ± 1	2.0 ± 0.2	36 ± 1
g	3-CF3-Ph	1.0 ± 0.2	12 ± 2	4 ± 1	
h	4-F-Ph	1.0 ± 0.2		4 ± 1	74%[b]
i	4-Cl-Ph			3 ± 1	
j	4-Br-Ph		9 ± 1	3.0 ± 0.2	57 ± 6
k	4-I-Ph	0.3 ± 0.0		1.0 ± 0.1	
l	4-Me-Ph	1.0 ± 0.0		4 ± 1	
m	4-MeO-Ph	1.0 ± 0.1	34 ± 4		64%[b]
n	4-CF3-Ph	0.4 ± 0.0	10 ± 2		
o	4-CF3O-Ph	1.0 ± 0.2	8 ± 2	5 ± 1	
p	4-(2-Pr)-Ph	1.0 ± 0.2	3.0 ± 0.2	1.0 ± 0.1	
q	2-Naph	1.0 ± 0.1	1.0 ± 0.2		
r	2-(3-Me-5-Cl-benzothiophene)		2.0 ±0.2		
s	2,4-diF-Ph			8 ± 1	131 ± 19
t	2-Cl-4-F-Ph		35 ± 5	9 ± 2	
u	3,4-diCl-Ph	1.0 ± 0.2	7 ± 1	3.0 ± 0.3	
v	3-Cl-6-MeO-Ph		24 ± 3		
w	4-(3,5-diMe-isoxazole)	1.0 ± 0.2			

[a] Displacement of [^{3}H]-LSD binding to cloned h5-HT_6 receptors stably expressed in HeLa cells. K_i values were determined in triplicate. [b] % inhibition at 1000 nM.

was then removed by treatment with HCl in dioxane, affording the sulfonamide array (*R*)-**15a**−**w**. The (*S*)-enantiomers were prepared analogously starting from Cbz-L-proline, acid chloride.

Many 5-HT_6 receptor antagonists (e.g., **1**−**4)** share a pharmacophore consisting of a sulfonamide separated from a basic amine by an aryl group and linker. Indeed, our initial targets, *N*-sulfonyl-3-pyrrolidin-2-ylmethyl-1*H*-indoles (**9**), contained this pharmacophore and had high affinity for 5-HT_6 receptors (data not shown). Gratifyingly, moving the sulfonamide from the indole N_1-position to the 5-amino position also provided high-affinity 5-HT_6 receptor ligands **13** and **15** (Table 1). In general, the (*S*)-enantiomers in **13** and **15** have significantly weaker affinity compared to the corresponding (*R*)-enantiomers with a single exception: (*R*)-**13q** and (*S*)-**13q** in which Ar = 2-naphthyl were equipotent at 5-HT_6 receptors (K_i = 1 nM).

Similarly, there is a trend in which the *N*-methylpyrrolidines (*R*)-**13** have ∼4-fold higher affinity relative to

Table 2. Antagonism of cAMP Production[a]

	Ar	IC_{50} (nM)	I_{max} (%)
(*S*)-**13d**	2-Br-Ph	0.8 ± 0.2	75 ± 1
(*S*)-**13g**	3-CF3-Ph	14.1 ± 4.7	78 ± 1
(*S*)-**13j**	4-Br-Ph	1.6 ± 0.1	85 ± 1
(*S*)-**13n**	4-CF3-Ph	21.6 ± 0.6	78 ± 1
(*S*)-**13o**	4-CF3O-Ph	25.8 ± 0.3	85 ± 1
(*S*)-**13p**	4-(2-Pr)-Ph	21.1 ± 2.7	76 ± 1
(*S*)-**13q**	2-Naph	10.4 ± 0.4	95 ± 0
(*S*)-**13r**	2-(3-Me-5-Cl-benzothiophene)	1.1 ± 0.1	91 ± 1

[a] Antagonism of 5-HT stimulated cAMP production in HeLa cells stably transfected with human 5-HT_6 receptors. IC_{50} and I_{max} values were determined in triplicate.

Table 3. Agonism of cAMP Production[a]

	Ar	EC_{50} (nM)	E_{max} (%)
(*R*)-**13b**	2-F-Ph	1.3 ± 0.1	91 ± 1
(*R*)-**13c**	2-Cl-Ph	1.1 ± 0.2	100 ± 0
(*R*)-**13f**	3-Cl-Ph	1.6 ± 0.2	100 ± 0
(*R*)-**13g**	3-CF3-Ph	3.2 ± 0.8	90 ± 1
(*R*)-**13h**	4-F-Ph	1.1 ± 0.1	85 ± 5
(*R*)-**13k**	4-I-Ph	2.7 ± 0.5	72 ± 2
(*R*)-**13l**	4-Me-Ph	1.3 ± 0.0	79 ± 7
(*R*)-**13m**	4-MeO-Ph	2.2 ± 0.2	83 ± 2
(*R*)-**13n**	4-CF3-Ph	4.5 ± 0.6	85 ± 2
(*R*)-**13o**	4-CF3O-Ph	2.9 ± 0.7	94 ± 2
(*R*)-**13w**	4-(3,5-diMe-isoxazole)	0.8 ± 0.1	77 ± 1
(*S*)-**13o**	4-CF3O-Ph	180 ± 3	68 ± 1
(*R*)-**15a**	Ph	1.4 ± 0.0	73 ± 0
(*R*)-**15c**	2-Cl-Ph	1.3 ± 0.4	100 ± 1
(*R*)-**15e**	2-I-Ph	0.4 ± 0.1	100 ± 0
(*R*)-**15f**	3-Cl-Ph	1.0 ± 0.2	92 ± 1
(*R*)-**15g**	3-CF3-Ph	5.8 ± 0.9	77 ± 1
(*R*)-**15i**	4-Cl-Ph	4.5 ± 1.2	99 ± 1
(*R*)-**15o**	4-CF3O-Ph	4.2 ± 0.8	86 ± 2
(*R*)-**15s**	2,4-diF-Ph	5.2 ± 0.4	78 ± 2

[a] Agonism of cAMP production in HeLa cells stably transfected with human 5-HT_6 receptors. IC_{50} and I_{max} values were determined in triplicate.

the corresponding N−H analogues (*R*)-**15**. More subtle effects on 5-HT_6 receptor affinities can also be discerned. For example, *N*-[3-(1-methylpyrrolidin-2-ylmethyl)-1*H*-indol-5-yl]benzenesulfonamide (*R*)-**3a** with no substitution on the phenyl group binds with 1 nM affinity. Substitution on the phenyl at the 2-, 3-, or 4-position with small groups, e.g., halogen, methyl, methoxy, resulted in similar or modestly increased receptor affinity. Some disubstituted phenyl groups were also tolerated. Replacing the phenyl group with lipophilic heterocycles such as 4-(3,5-dimethylisoxazole ((*R*)-**13w**) also afforded high-affinity ligands, as did bicyclic aromatic groups ((*R*)-**13q** and (*R*)-**13r**).

Compounds with K_i < 15 nM were further evaluated for their ability to modulate 5-HT_6 receptor function in a cyclase assay measuring production of cyclic AMP (cAMP) at various concentrations of ligand. None of the (*S*)-enantiomers (*S*)-**13** or (*S*)-**15** had significant intrinsic (agonist) activity at 5-HT_6 receptors, with the exception of the weak partial agonist (*S*)-**13o**. However, when these compounds were tested for the ability to block serotonin-induced stimulation of cAMP, several of the (*S*)-enantiomers (*S*)-**13** were antagonists with low nanomolar IC_{50} values and I_{max} = 75−95% (Table 2).

In contrast, the (*R*)-enantiomers proved to be potent *agonists* at 5-HT_6 receptors (Table 3). Pyrrolidine N-substitution had little effect on intrinsic activity because (*R*)-**13** (N−Me) and (*R*)-**15** (N−H) analogues have similar activity (compare (*R*)-**13c** vs (*R*)-**15c** and (*R*)-**13f** vs (*R*)-**15f**). Many compounds behave as essentially full agonists with EC_{50} values in the low-nanomolar or even subnanomolar range.

Table 4. Selectivity Binding Affinity for Serotonin and Dopamine Receptors, K_i (nM)[a]

receptor	(*R*)-**13c**	(*R*)-**13f**	(*R*)-**15c**	(*R*)-**15e**
5-HT_6	1 ± 0	0.4 ± 0.1	3.0 ± 0.4	1.0 ± 0.1
5-HT_{1A}	170 ± 17	200 ± 28	552 ± 63	234 ± 35
5-HT_{1B}	15 ± 5	4.3 ± 1.2	88 ± 10	9.3 ± 8.5
5-HT_{1D}	29.5[b]	4.7[b]	>1000	65 ± 28
5-HT_{1F}	16 ± 10	2.7 ± 1.7	12.3 ± 0.9	17.8 ± 2.5
5-HT_{2A} (agonist)	367 ± 43	269 ± 33	ND[d]	42%[c]
5-HT_{2c}	289 ± 39	231 ± 18	566 ± 4	235 ± 1
5-HT_7	74 ± 12	24 ± 2	ND[d]	329 ± 42
D2	>2000	>2000	>5000	>2000
D3	>1000	930 ± 46	>5000	>5000
D4	>5000	>5000	>5000	>5000

[a] Receptors were all human clones stably expressed in CHO cells (5-HT receptors) or CHO-K1 cells (D receptors). Radioligands were as follows. 5-HT_{1A}: 8-hydroxy-[^{3}H]-DPAT. 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F}, 5-HT_{2C}: [^{3}H]-5-HT. 5-HT_{2A}: [^{125}I]DOI. 5-HT_6, 5-HT_7: [^{3}H]-LSD. Dopamine D_2, D_3, and D_4: [^{3}H]spiperone. K_i values were determined in triplicate except for those indicated by footnote b. [b] K_i values were determined with n = 1. [c] % inhibition at 1000 nM. [d] ND = not determined.

(*R*)-**13c**, (*R*)-**13f**, (*R*)-**15c**, and (*R*)-**15e** were examined further for selectivity against several serotonergic and dopaminergic receptors (Table 4). All four compounds were greater than 50-fold selective over 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_7, and dopamine (D_2, D_3, and D_4) receptors but show significant affinity for the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors.

In summary, our exploration of the SAR of N_1-arylsulfonyltryptamine derivatives relative to the 5-HT_6 receptor led to the finding that the aminoethyl group of the tryptamine could be replaced with the conformationally restricted pyrrolidin-2-ylmethyl group. Further structural manipulations led to the important finding that the indole N_1-arylsulfonyl group could be moved to a 5-amino substitutent on the indole, providing 5-arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indoles **13** and **15** as high-affinity 5-HT_6 receptor ligands. Surprisingly, while the (*R*)- and (*S*)-enantiomer series had good affinity for 5-HT_6 receptors, they had essentially opposite functional activity. Specifically, (*S*)-enantiomers showed moderate antagonist activity while many of the (*R*)-enantiomers function as essentially full agonists with several compounds having EC_{50} values of 1 nM or less. Some of the highest affinity agonists are relatively selective against several other 5-HT and dopamine receptors. This new series of 5-HT_6 receptor modulators, especially the agonists, may be useful tools in elucidating potential therapeutic uses for 5-HT_6 receptor ligands.

Acknowledgment. We thank Mario D. Gonzalez, Organix, Inc., for synthesis of intermediates, and we thank Xidong Feng, Michael Kelly, and Mairead Young for HRMS, LCMS, and chiral HPLC and SFC analysis.

Supporting Information Available: Experimental details for the binding and functional assays and the synthetic procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM049243I