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1-(2-Aminoethyl)-3-(arylsulfonyl)-1*H*-indoles as novel 5-HT$_6$ receptor ligands

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Abstract—Novel 1-(2-aminoethyl)-3-(arylsulfonyl)-1*H*-indoles were prepared. Binding assays indicated they are 5-HT$_6$ receptor ligands, among which *N*,*N*-dimethyl-*N*-{2-[3-(1-naphthylsulfonyl)-1*H*-indol-1-yl]ethyl}amine **8t** and *N*-methyl-*N*-{2-[3-(1-naphthylsulfonyl)-1*H*-indol-1-yl]ethyl}amine **8u** showed high affinity for 5-HT$_6$ receptors with K_i = 3.7 and 5.7 nM, respectively.
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1. Introduction

Considerable attention has been focused on the 5-HT$_6$ receptor because of its CNS localization and the therapeutic implications of its proposed role in learning and memory.[1] Intense interest in 5-HT$_6$ receptors has led to the discovery of several classes of high affinity ligands. Initial reports from Roche identified sulfonamides including Ro 04-6790 (**1**) as selective 5-HT$_6$ antagonists.[2] In 1998, scientists at SmithKline described a series of arylsulfonamide-substituted arylpiperazines from which SB-271046 (**2**) was identified as a potent, selective 5-HT$_6$ antagonist.[3] These compounds incorporate a common feature of many 5-HT$_6$ selective ligands: an arylsulfonyl group (Fig. 1).

One approach to developing novel serotonergic ligands is to reverse the relative roles of the 1- and 3-positions on the indole ring. Among the first examples of this

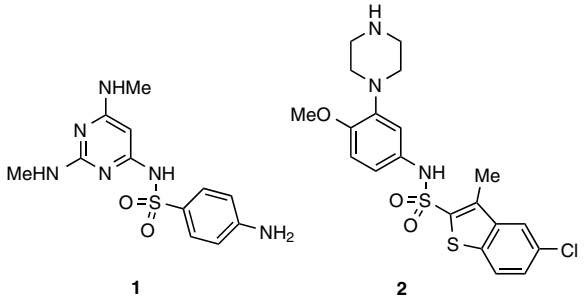

Figure 1. Early 5-HT$_6$ ligands.

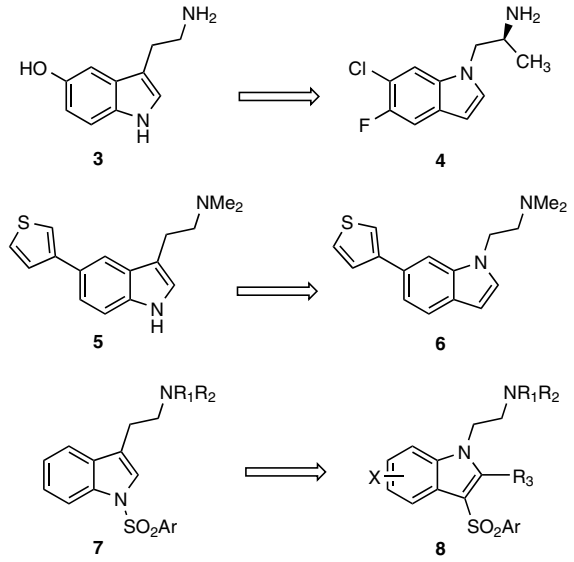

Figure 2. Examples of 'flipped' serotonergic ligands.

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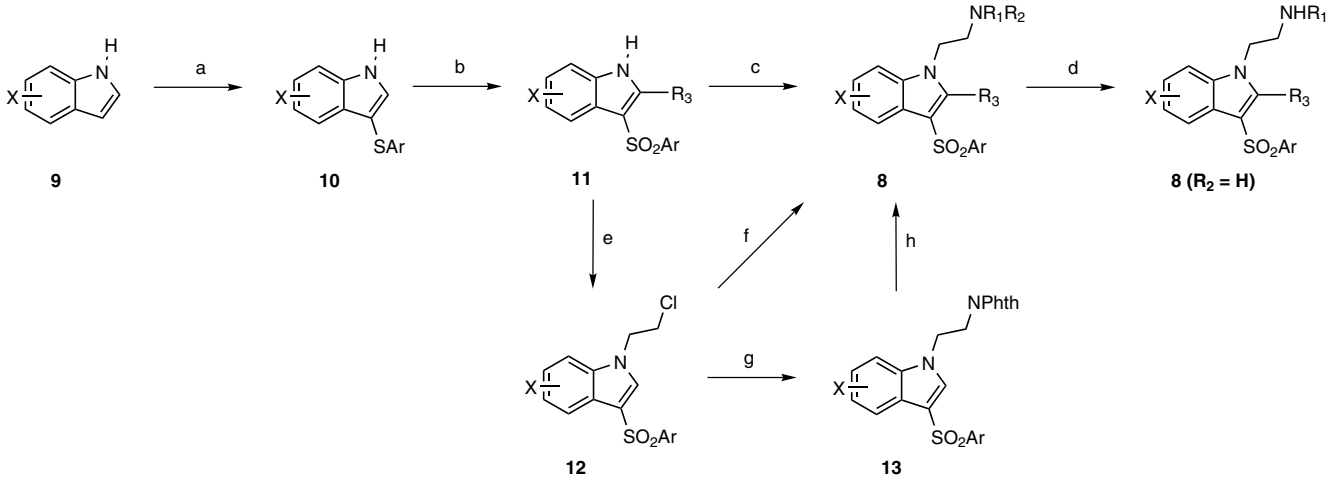
approach is 5-HT_{2C} agonist **4**, described by Roche.[4a] In this ligand, the location of the aminoethyl side chain is 'flipped' from the 3-position of the indole ring as in serotonin (**3**) to the indole nitrogen. A similar approach was used by NPS to develop novel 5-HT_{1D} ligands including **6** based on **5**.[4b] We have adopted a similar approach to develop novel 5-HT_6 ligands. Glennon and others have identified 1-arylsulfonyl-tryptamines **7** as 5-HT_6 ligands (Fig. 2).[5] These reports led us to synthesize a series of 1-(2-aminoethyl)-3-arylsulfonyl-1*H*-indoles **8** in which the positions of the arylsulfonyl group and basic side chain are exchanged (or 'flipped') relative to each other and to investigate their 5-HT_6 affinity.

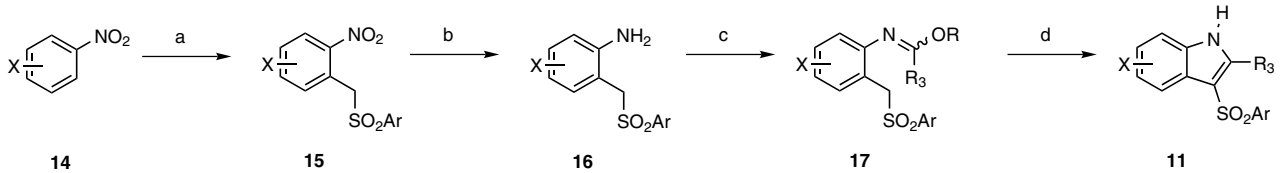
2. Chemistry

Direct alkylation of 3-arylsulfonyl-1*H*-indoles should provide compound **8**. The requisite 3-RSO_2-1*H*-indoles for this approach were prepared by two routes. The first introduced a 3-arylthio substituent on indole **9** by reaction with a thiol (ArSH) in the presence of iodine and potassium iodide as described by Beveridge and Harris[6] to give substituted indoles **10** (Scheme 1). Oxidation with Oxone™ in acetone/aqueous sodium bicarbonate[7] or with *m*CPBA afforded 3-arylsulfonyl-1*H*-indoles **11** in good yield. In the presence of base, direct alkylation with aminoethylchlorides or bromides, that is, $R_1R_2N(CH_2)_nHal$, generally as HCl salts, provided targets **8**.[8] Secondary amines could be prepared from tertiary amines by refluxing **8** (R_1, $R_2 \neq H$) with 1-chloroethylchloroformate (ACE–Cl) as described by Olofson et al.[9] Alternatively, the basic side chain was introduced by reacting **11** with 1,2-dichloroethane and a base under phase-transfer conditions to give **12**. Heating **12** with an amine (R_1R_2NH) provided compounds **8**. Primary amines were initially obtained by Gabriel synthesis, displacing the chlorine in **12** with potassium phthalimide to give **13**, which was in turn treated with hydrazine to give **8** (R_1, $R_2 = H$). Alternatively, the phase-transfer conditions of Alvarez-Builla and coworkers allowed direct, one-step introduction of the primary aminoethyl group onto **11** using 2-aminochloroethane and base.[10]

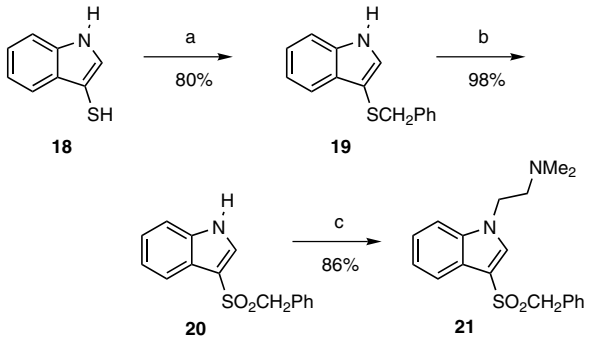
A second route to 3-arylsulfonyl-1*H*-indoles **11** followed the vicarious nucleophilic substitution (VNS) approach developed by Wojciechowski and Makosza.[11] Nitrobenzenes **14** were reacted with $ArSO_2CH_2Cl$[12] in the presence of base under conditions, which favored *ortho*-substitution to provide **15** (Scheme 2).[13] Nitro reduction provided aniline **16**. Heating **16** with excess *ortho*-ester and catalytic *p*-TsOH hydrate in 1,2-dichloroethane followed by concentration in vacuo gave crude iminoether **17**, which was dissolved in THF and treated with a slight excess of 1.0 M KO^{t}Bu/THF to afford **11**. This one-pot approach avoided an aqueous workup of **17** and generally provided good yields of indoles **11**.[14]



Scheme 1. Synthesis of 1-(2-aminoethyl)-3-(arylsulfonyl)-1*H*-indoles **8**. Reagents and conditions: (a) ArSH/I_2·KI/EtOH/H_2O; (b) Oxone™/aq $NaHCO_3$/acetone, or *m*CPBA/CH_2Cl_2; (c) $R_1R_2N(CH_2)_2Hal$/NaH/DMF, or $H_2NCH_2CH_2Cl$; (d) $CH_3CH(Cl)C(O)Cl/ClCH_2CH_2Cl$/reflux, then EtOH/reflux; (e) $ClCH_2CH_2Cl$/aq NaOH/1,2-DCE/PTC; (f) R_1R_2NH, heat; (g) PhthK/DMF; (h) H_2NNH_2/EtOH/reflux.



Scheme 2. Vicarious nucleophilic substitution route to 3-(arylsulfonyl)-1*H*-indoles **11**. Reagents and conditions: (a) $ArSO_2CH_2Cl$/THF/KO^{t}Bu/−65 to −20 °C/1 h, then AcOH quench; (b) Sn (4.4 equiv)/4 M aq HCl/MeOH/45 °C/4–6 h; (c) $HC(OEt)_3$ or $CH_3C(OCH_3)_3$ (5 equiv)/*p*-TsOH·H_2O (0.1 equiv)/$ClCH_2CH_2Cl$/reflux; (d) 1.0 M KO^{t}Bu/THF (1.3–1.5 equiv)/THF/rt/5–30 min.



Scheme 3. Reagents and conditions: (a) NaH/$PhCH_2Br$/DMF; (b) Oxone™/aq $NaHCO_3$/acetone; (c) $Me_2NCH_2CH_2Cl$/NaH/DMF.

A one-carbon homolog with an additional methylene between the phenyl ring and the sulfonyl group was also prepared (Scheme 3). 3-Thio-1*H*-indole (**18**)[15] was alkylated with benzylbromide to provide **19**, which was oxidized to **20**. Alkylation provided compound **21**.

3. Results and discussion

Final compounds were tested for 5-HT_6 affinity in a standard radioligand binding assay[16] using human-cloned 5-HT_6 receptors stably transfected in HeLa cells (Table 1). Comparison of 3-(aminoethyl)-1-phenylsulfonyl-1*H*-indole **7a** to 1-(aminoethyl)-3-phenylsulfonyl-*1H*-indole **8a** showed 'flipping' the relative locations of the basic side chain and phenylsulfonyl resulted in only a modest decrease in affinity for the 5-HT_6 receptor. Generally some loss in affinity accompanied most substitution of the phenyl portion of the indole ring, that is, **8b–d**, though 5-F substitution (**8e**) had no effect on affinity. Secondary amine **8f** had somewhat weaker affinity for the 5-HT_6 receptor compared to the nonflipped analog **7b** but had slightly improved affinity relative to the primary amine (**8a**). The tertiary amine (**8g**) was similar to the primary. Consistent with the trends for the primary amines, substitution of the indole phenyl ring in the tertiary amines did not improve and was often deleterious to receptor affinity. While sterically more demanding basic side chains such as **8o** lost affinity for the receptor, 2-methyl substitution of the indole was tolerated (**8p**). Substitution of the arylsulfonyl ring (**8q–s**) was generally tolerated regardless of position. The most significant improvement in affinity occurred when 1-naphthylsulfonyl was substituted for phenylsulfonyl on the 3-position of the indole ring. Tertiary amine **8t** had excellent affinity for 5-HT_6 receptors (K_i = 3.7 nM) while the corresponding secondary amine **8u** was nearly as good. In contrast, increasing the distance between the phenyl ring and the sulfonyl group with a methylene (**21**) resulted in a 50-fold loss in receptor affinity.

Those compounds with excellent 5-HT_6 affinity (generally, K_i < 20 nM) were tested in a cyclase assay to determine whether the ligands were able to modulate 5-HT_6 function in vitro.[17] A few compounds possessed weak, partial agonist activity. Others at least partially blocked the effect of serotonin on cyclic AMP levels. Of note was **8t**, essentially a full antagonist (I_{max} = 97%) with good potency (IC_{50} = 47 nM).

In summary, novel 1-(2-aminoethyl)-3-(arylsulfonyl)-1*H*-indoles were prepared. These compounds invert

Table 1. Biological activities of 1-(aminoethyl)-3-(RSO_2)-1*H*-indole monohydrochlorides (**8**, **21**)[16,17]

Compound	Ar	R_1	R_2	R_3	X	5-HT_6 K_i (nM)	*c*AMP assay for 5-HT_6	
							IC_{50} (nM)	I_{max} (%)
7a	Ph	H	H	—	—	10.3		
7b	Ph	Me	H	—	—	5.0 (±0.5)		
8a	Ph	H	H	H	—	25 (±2)	Weak partial agonist	
8b	Ph	H	H	H	6-MeO	78% (1 μM)		
8c	Ph	H	H	H	6-Cl	141 (±14)		
8d	Ph	H	H	H	5-MeO	86% (1 μM)		
8e	Ph	H	H	H	5-F	27 (±3)		
8f	Ph	Me	H	H	—	15.5 (±0.5)		
8g	Ph	Me	Me	H	—	20 (±0.2)	Weak partial agonist	
8h	Ph	Me	Me	H	6-MeO	23 (±1)		
8i[a]	Ph	Me	Me	H	6-F	46 (±7)		
8j[a]	Ph	Me	Me	H	6-Cl	42 (±4)		
8k	Ph	Me	Me	H	6-CN	42% (1 μM)		
8l	Ph	Me	Me	H	4-F	98 (±6)		
8m[a]	Ph	Me	Me	H	5-F	44 (±7)		
8n	Ph	Me	Me	H	7-MeO	25 (±5)	23 (±2.5)	80.5 (±0.35)
8o	Ph	–$(CH_2)_5$–		H	5-MeO	55% (1 μM)		
8p	Ph	Me	Me	Me	—	18 (±1)		
8q	4-MePh	Me	Me	H	—	57 (±3)		
8r	3-FPh	Me	Me	H	—	13 (±0.6)	Weak partial agonist	
8s	2-CF_3OPh	Me	Me	H	—	16 (±2)	792 (±16)	100 (±0)
8t	1-Naphthyl	Me	Me	H	—	3.7 (±0.4)	47 (±9)	97 (±2)
8u	1-Naphthyl	Me	H	H	—	5.7 (±0.1)	359 (±109)	97 (±2)
21	CH_2Ph	Me	Me	—	—	1011 (±102)		

[a] Isolated and tested as the free amines.

the relative positions of the basic side chains and arylsulfonyl group in known 5-HT_6 ligands and represent one of the earliest applications of this approach to 5-HT_6 receptors. Binding assays indicated these compounds have high affinity for the target receptors, especially **8t** and **8u** with K_i values of 3.7 and 5.7 nM, respectively. Compound **8t** was essentially a full antagonist of moderate potency (IC_{50} = 47 nM, I_{max} = 97%) in a 5-HT_6 functional (cyclase) assay.

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16. Binding assays were run using [^{3}H]-LSD as the radioligand. Compounds were all tested as the monohydrochloride salts except for **8i**,**8j**, and **8m** which were tested as the free amines. For conditions see: Bernotas, R. C.; Lenicek, S. E.; Antane, S. A.; Zhou, P.; Li, Y.; U.S. Patent 6,727,246.
17. Cyclase assay: HeLa cells transfected with the human 5-HT_6 receptor were washed with Krebs buffer and incubated at 37 °C in Krebs supplemented with 500 μM IBMX for 5 min at 37 °C. Cells were then stimulated with test compound in the concentration range 0.1–10,000 nM for an additional 10 min at 37 °C. The assay was terminated with the addition of 0.5 M perchloric and intracellular *c*AMP levels were determined by radioimmunoassay with the *c*AMP Scintillation Proximity Assay System (Amersham).