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3-(Arylsulfonyl)-1-(azacyclyl)-1*H*-indoles are 5-HT$_6$ receptor modulators

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ABSTRACT

Novel 3-(arylsulfonyl)-1-(azacyclyl)-1*H*-indoles **6** were synthesized as potential 5-HT$_6$ receptor ligands, based on constraining a basic side chain as either a piperidine or a pyrrolidine. Many of these compounds had good 5-HT$_6$ binding affinity with K_i values <10 nM. Depending on substitution, both agonists (e.g., **6o**: EC_{50} = 60 nM, E_{max} = 70%) and antagonists (**6y**: IC_{50} = 17 nM, I_{max} = 86%) were identified in a 5-HT$_6$ adenylyl cyclase assay.

Modulation of the human serotonergic system has long been investigated for the treatment of mood disorders including anxiety and depression. Recently, the human 5-HT$_6$ receptor has been targeted because of its CNS localization and the therapeutic implications of its proposed role in learning and memory.[1] Scientists at Roche identified sulfonamides including Ro 04-6790 (**1**) as selective 5-HT$_6$ antagonists[2] while researchers at SmithKline prepared arylsulfonamide-substituted arylpiperazines including SB-271046 (**2**) as selective antagonists (Fig. 1).[3] These compounds incorporate a common feature of many 5-HT$_6$ selective ligands: an arylsulfonyl group.

More recent efforts at identifying novel 5-HT$_6$ ligands have highlighted so-called 'flipped' indoles in which the regiochemical relationship of the basic side chain and the arylsulfonyl group are reversed from earlier indole-containing ligands. Typical of this approach are 1-aminoalkyl-3-arylsulfonyl-1*H*-indoles **4**,[4] which are based on earlier 1-arylsulfonyl-tryptamines **3**[5] (Fig. 2). Derivatives of type **4** had affinity for 5-HT$_6$ receptors, which was generally similar to that of the substituted tryptamines, though they were often only moderately potent agonists in a 5-HT$_6$ in vitro functional assay.

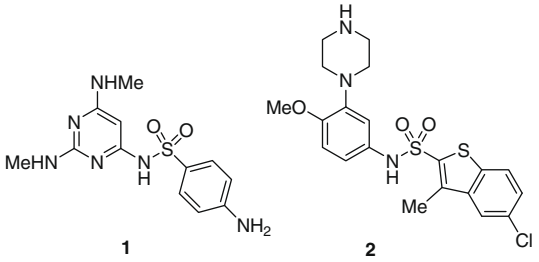

Figure 1. Early 5-HT$_6$ antagonists.

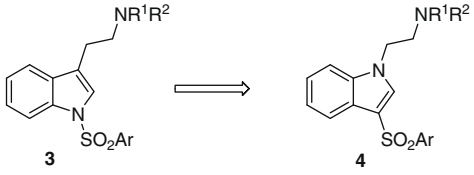

Figure 2. An example of a 'flipped' serotonergic ligand.

The affinity of these flipped ligands **4** for 5-HT$_6$ receptors prompted us to examine analogs in which the aminoalkyl side chain is constrained as an azacycle such as pyrrolidine and

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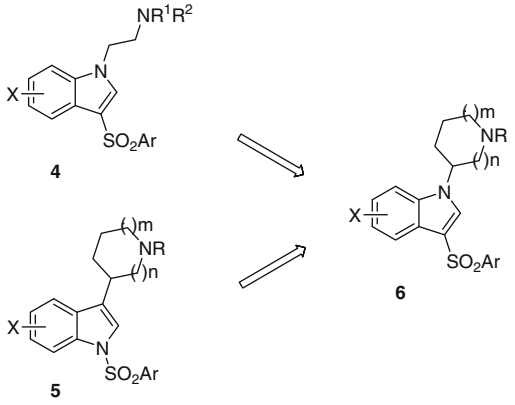
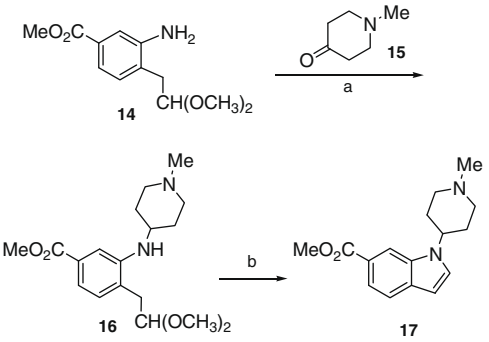


Figure 3. Design of 1-(azacyclyl)-3-arylsulfonyl-1*H*-indoles **5** as constrained 5-HT_6 ligands.



Scheme 2. Reagents and conditions (from Coe[10]): (a) Na_2SO_4, AcOH, then $NaBH(OAc)_3$ and (b) 1 M HCl, MeOH, heat.

piperidine, that is, **6** (Fig. 3). These compounds may be viewed as 'flipped' analogs of 1-arylsulfonyl-3-(azacyclyl)-1*H*-indoles **5** described by Cole et al.[6] We report here the synthesis of a series of indoles **6** and the biological activity of these compounds at the 5-HT_6 receptor.

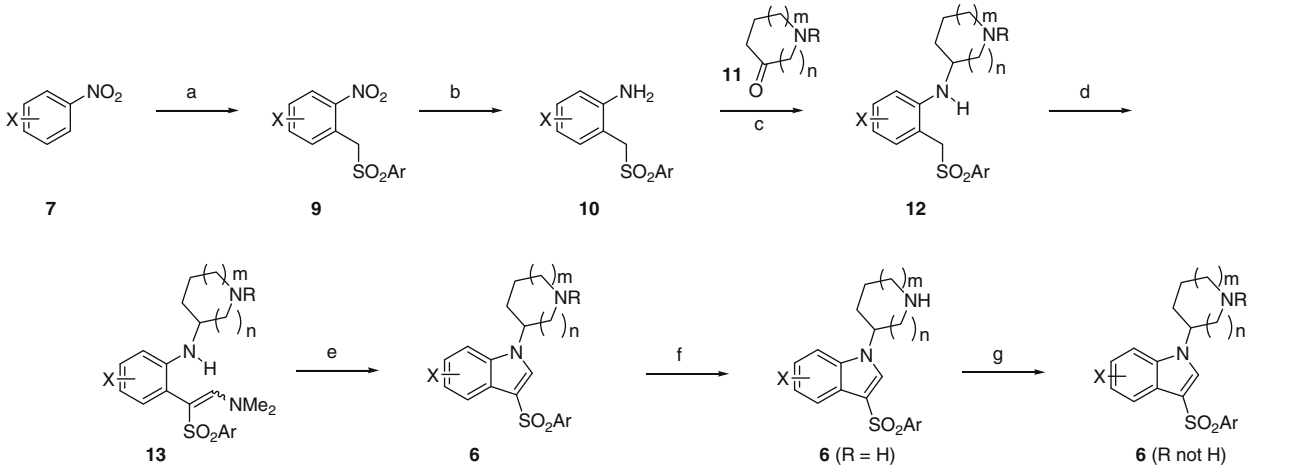
Initial attempts to synthesize **6** centered on the alkylation of 3-arylsulfonylindoles with halopiperidines and halopyrrolidines, and by Mitsunobu reactions of 3-arylsulfonylindoles with hydroxypiperidines and hydroxypyrrolidines. Unfortunately, these methods generally provided low yields or no product at all. Suspecting there may be steric problems too difficult to overcome, especially in light of potential competing elimination, another preparative route was sought.

An alternative approach used a reductive amination to introduce the key azacycles. The requisite arylsulfonylmethylene-substituted anilines **10** were obtained by a vicarious nucleophilic substitution (VNS) approach starting with nitrobenzenes **7** (Scheme 1).[7] Thus, treatment of nitrobenzenes **7** and chloromethylsulfones **8** with KO^{t}Bu in THF at low temperatures (conditions that favor ortho-substitution) provided **9**.[8] Noncommercial compounds **8** were readily prepared by a one-pot method from the corresponding arylsulfonyl chlorides.[9] Nitro reduction, generally using tin in hydrochloric acid, gave desired anilines **10**. Coe et al. developed an approach to 1-azacyclyl-1*H*-indoles **17** incorporating an azacycle by reductive amination of a ketone (e.g., **15**) with aniline **14** to give **16** followed by cyclization under acidic conditions (Scheme 2).[10] Coe's reductive amination conditions applied to **10** and keto-azacycles **11** gave **12** in high yield.

Cyclization of **12** was initially problematic. Attempts to form the indole by reaction with orthoformates did not give the desired enol ethers needed for ring formation. However, prolonged heating of **12** with dimethylformamide dimethylacetal and *para*-toluenesulfonic acid gave enamines **13**, often accompanied by small amounts (~20%) of desired cyclization product **6**. The enamines were conveniently converted to **6** by further treatment with ethanolic acid, typically from the crude mixture of **6** and **13**. Secondary amines could then be easily prepared by dealkylation of the tertiary amines **6** using 1-chloroethyl chloroformate in high yields (**6**, R = H).[11] With these in hand, diversity was achievable by reaction with alkylhalides. By appropriate choice of starting nitrobenzene **7**, chloromethylarylsulfone **8**, keto-azacycle **11** and alkylating agent, we were able to vary X, Ar, R, and azacycles found in compounds **6**.

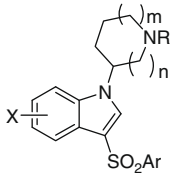
All target compounds were tested for human-cloned 5-HT_6 receptor affinity in a standard radioligand binding assay[12] (Table 1). Early results led to some obvious conclusions about the SAR of this class of compounds. Compounds **6a** and **6b** had relatively weak affinity, attributed to the 4-piperidinyl isomer.

Higher 5-HT_6 affinity was observed for both the 3-piperidinyl (**6c–6m**) and 3-pyrrolidinyl analogs (**6n–6dd**). However, the



Scheme 1. (a) **8** (1.0 equiv), THF, −0 °C, then 1 M KO^{t}Bu/THF (1.1 equiv), −30 °C, 1 h, AcOH quench (X = H, Ar = Ph, 81%); (b) Sn (4.4 equiv), concd HCl, MeOH, 45–50 °C, 4–6 h (X = H, Ar = Ph, 89%); (c) **11** (2.0 equiv), Na_2SO_4 (10 equiv), AcOH, 15–45 min, then $NaBH(OAc)_3$ (3.0 equiv), 2–5 h; (d) $Me_2NCH(OMe)_2$ (as solvent), *para*-toluenesulfonic acid hydrate (0.02–0.05 equiv), reflux, 2–5 d; (e) 2 M aqueous HCl, EtOH, 20 °C, 1–4 h; (f) $CH_3CH(Cl)C(O)Cl$ (2–3 equiv), DCE, reflux, 2–5 h, concentrate, then MeOH or EtOH, reflux, 2–24 h; and (g) RBr or RI (1.1 equiv), K_2CO_3 (1–2 equiv), DMF, 50–80 °C.

Table 1
5-HT_6 binding and adenylyl cyclase activity for indoles **6**[a]



6

Compd	Azacycle	Ar	X	R	5-HT_6 K_i (nM)	5-HT_6 cAMP accumulation assay	
						EC_{50} or IC_{50} (nM)	E_{max} or I_{max} (%)
6a	4-Piperidinyl	Ph	H	CH_2Ph	49 (±6)	nt	nt
6b	4-Piperidinyl	Ph	H	H	91 (±4)	nt	nt
6c	3-Piperidinyl	Ph	H	CH_2Ph	122 (±16)	nt	nt
6d	3-Piperidinyl	Ph	H	H	13 (±1)	82 (±3)	99 (±0.4)
6e	3-Piperidinyl	Ph	H	Et	7.3 (±0.9)	31 (±4)	52 (±2)
6f	3-Piperidinyl	3-FPh	H	H	6.0 (±0.6)	56 (±21)	78 (±5)
6g	3-Piperidinyl	3-FPh	5-OMe	H	10.7 (±0.3)	73 (±12)	75 (±1)
6h	3-Piperidinyl	3-FPh	5-OMe	Me	68 (±3)	nt	nt
6i	3-Piperidinyl	3-FPh	5-OMe	Et	16 (±1)	203 (±73)	50 (±0.4)
6j	3-Piperidinyl	3-FPh	5-F	H	4.0 (±0.3)	18 (±3) (ant)	85 (±0) (ant)
6k	3-Piperidinyl	1-Naphthyl	H	H	21 (±1)	nt	nt
6l	3-Piperidinyl	1-Naphthyl	H	Me	7.1 (±0.5)	107 (±7) (ant)	87 (±1) (ant)
6m	3-Piperidinyl	8-Quinolinyl	H	H	5.6 (±0.3)	592 (±5)	71 (±0.3)
6n	3-Pyrrolidinyl	Ph	H	CH_2Ph	113 (±2)	nt	nt
6o	3-Pyrrolidinyl	Ph	H	H	5.0 (±0.3)	60 (±7)	70 (±0.3)
6p	3-Pyrrolidinyl	3-FPh	H	H	4.7 (±0.1)	68 (±5)	38 (±0.4)
6q	3-Pyrrolidinyl	3-FPh	H	Me	3.5 (±0.7)	398 (±47)	49 (±0.7)
6r	3-Pyrrolidinyl	3-FPh	4-F	H	18 (±1)	nt	nt
6s	3-Pyrrolidinyl	3-FPh	5-F	H	9.6 (±1.4)	38 (±4)	50 (±0.4)
6t	3-Pyrrolidinyl	3-FPh	5-F	Me	5.0 (±0.5)	94 (±2) (ant)	70 (±1) (ant)
6u	3-Pyrrolidinyl	3-FPh	6-F	H	18 (±2)	nt	nt
6v	3-Pyrrolidinyl	3-FPh	5-Cl	H	15 (±1)	nt	nt
6w	3-Pyrrolidinyl	3-FPh	6-Cl	H	72 (±5)	nt	nt
6x	3-Pyrrolidinyl	3-ClPh	H	H	3.2 (±0.9)	125 (±10)	48 (±1)
6y	3-Pyrrolidinyl	3-ClPh	H	Me	1.3 (±0.1)	17 (±2) (ant)	86 (±0) (ant)
6z	3-Pyrrolidinyl	3-ClPh	6-OMe	H	4.6 (±0.4)	80 (±11) (ant)	100 (±0) (ant)
6aa	3-Pyrrolidinyl	1-Naphthyl	H	H	23.3 (±0.3)	107 (±10) (ant)	100 (±0) (ant)
6bb	3-Pyrrolidinyl	1-Naphthyl	H	Me	6.0 (±0.6)	60 (±12) (ant)	98 (±10) (ant)
6cc	3-Pyrrolidinyl	8-Quinolinyl	H	H	1.5 (±0.1)	82 (±13) (ant)	64 (±0) (ant)
6dd	3-Pyrrolidinyl	8-Quinolinyl	H	Me	2.8 (±0.2)	76 (±24) (ant)	97 (±2) (ant)

nt = not tested.
[a] ant after the data in the cyclase assay indicates the tested compound was an antagonist and IC_{50} values and I_{max} values are given.

relatively narrow range of binding K_i values made some SAR trends difficult to discern. Large substituents on the azacycle nitrogen (i.e., benzyl) reduced affinity while smaller groups (H, Me, Et) were well tolerated. Similarly, larger groups (X) on the indole ring reduced affinity, for example, **6w**.

Furthermore, larger arylsulfonyl groups such as naphthyl and quinolinyl ring systems were acceptable and, in the case of the quinolinyl analogs **6cc** and **6dd**, even among the highest affinity ligands. Other high affinity compounds included **6q**, **6x**, and **6y**, with K_i values <4 nM. Those compounds with excellent 5-HT_6 affinity (generally K_i < 20 nM) were tested in an adenylyl cyclase assay to determine whether the ligands were able to modulate 5-HT_6 function, based on the intracellular concentration of cAMP.[12] Some of the compounds tested demonstrated agonist activity, especially the 3-piperidinyl analogs, while the 3-pyrrolidinyl analogs were more often antagonists. Effects on functional activity from substituents on the indole and the arylsulfonyl rings were often subtle, though in general larger arylsulfonyl groups such as naphthyl and quinolylsulfonyl resulted in antagonists (**6l**, **6aa**–**6dd**). However, quinoline **6m** was an agonist though rather weakly so. Even chlorophenylsulfonyl-containing compounds (**6y**, **6z**) were more likely to be antagonists compared to the smaller phenylsulfonyl (**6d**–**6e**, **6o**) and fluorophenylsulfonyl analogs (**6f**–**g**, **6i**, **6p**–**q**, **6s**). Some exceptions to this general trend can be explained by the increased steric requirements from alkylation of the pyrrolidine nitrogen, as seen by comparing **6s** to **6t** and **6x** to **6y**. In both analogous pairs, methylation of the pyrrolidine converted agonists in the cyclase assay into antagonists. Overall, notable antagonists include **6j**, a potent antagonist (IC_{50} = 18 nM) which largely blocked the effects of 5-HT_6 in the adenylyl cyclase assay (I_{max} = 85%), and **6y**, which had an essentially identical antagonist profile.[13]

A series of 3-(arylsulfonyl)-1-(azacyclyl)-1*H*-indoles was designed and synthesized as 5-HT_6 ligands using azacycles as constrained replacements for an aminoethyl moiety. Binding assays demonstrated compounds **6** are high affinity 5-HT_6 receptor ligands, many with K_i values less than 10 nM. In general, the 3-piperidinyl analogs were more likely to be agonists while the 3-pyrrolidinyl analogs were more often antagonists in a 5-HT_6 adenylyl cyclase functional assay.

References and notes

1. For reviews on 5-HT_6 receptor modulators and their potential therapeutic applications, see: Russell, M. G. N.; Dias, R. *Curr. Top. Med. Chem.* **2002**, *2*, 643; Glennon, R. A. *J. Med. Chem.* **2003**, *46*, 2795; Holenz, J.; Pauwels, P. J.; Diaz, J. L.; Merce, R.; Codony, X.; Buschmann, H. *Drug Discovery Today* **2006**, *11*, 283; Liu, K. G.; Robichaud, A. J. *Drug Dev. Res.* **2009**, *70*, 145; Witty, D.; Ahmed, M.; Chuang, T. T. *Prog. Med. Chem.* **2009**, *48*, 163.
2. Sleight, A. J.; Boess, F. G.; Bos, M., et al *Brit. J. Pharmacol.* **1998**, *124*, 556.
3. Bromidge, S. M.; Clarke, S. E.; Gager, T.; Griffith, K.; Jeffrey, P.; Jennings, A. J.; Joiner, G. F.; King, F. D.; Lovell, P. J.; Moss, S. F.; Newman, H.; Riley, G.; Rogers,

D.; Routledge, C.; Serafinowska, H.; Smith, D. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 55. and references cited therein.
4. Bernotas, R. C.; Lenicek, S.; Antane, S.; Zhang, G. M.; Smith, D.; Coupet, J.; Harrison, B.; Schechter, L. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5499.
5. For N-sulfonylindoles as 5-HT_6 ligands, see: Russell, M. G. N.; Baker, R. J.; Barden, L.; Beer, M. S.; Bristow, L.; Broughton, H. B.; Knowles, M.; McAllister, G.; Patel, S.; Castro, J. L. *J. Med. Chem.* **2001**, *44*, 3881; Tsai, Y.; Dukat, M.; Slassi, A.; MacLean, N.; Demchyshyn, L.; Savage, J. E.; Roth, B. L.; Hufesein, S.; Lee, M.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2295; Lee, M.; Rangisetty, J. B.; Dukat, M.; Slassi, A.; Maclean, N.; Lee, D. K. H.; Glennon, R. A. *Med. Chem. Res.* **2000**, *10*, 230; Isaac, M.; Slassi, A.; Xin, T.; MacLean, N.; Wilson, J.; McCallum, K.; Wang, H.; Demchyshyn, L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1719.
6. Cole, D. C.; Ellingboe, J.; Lennox, W.; Zhang, G. M.; Smith, D.; Coupet, J.; Schechter, L. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 379.
7. All new compounds provided satisfactory ^{1}H NMR (300 or 400 MHz) and MS data. Compounds (**6a**–**6dd**) were isolated as hydrochlorides and generally provided satisfactory CHN analysis, though often as partial hydrates. For additional details, including synthetic procedures and analytical data, see: Bernotas, R. C.; Lenicek, S. E. US patent 6,995,176, 2006.
8. Wojciechowski, K.; Makosza, M. *Synthesis* **1986**, 651; Wojciechowski, K.; Makosza, M. *Tetrahedron Lett.* **1984**, *25*, 4793.
9. Antane, S.; Bernotas, R.; McDevitt, R.; Yan, Y.; Li, Y. *Synth. Commun.* **2004**, *34*, 2443.
10. Coe, J. W.; Vetelino, M. G.; Bradlee, M. J. *Tetrahedron Lett.* **1996**, *37*, 6045.
11. Olofson, R. A.; Martz, Jonathan T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
12. Binding assays were performed using cloned human 5-HT_6 receptors stably transfected into HeLa cells using [^{3}H]-LSD as the radioligand. For the adenylyl cyclase assay, HeLa cells transfected with the human 5-HT_6 receptor were used. The % efficacy is relative to serotonin. For detailed assay conditions, see: Cole, D. C.; Stock, J. R.; Lennox, W. J.; Bernotas, R. C.; Ellingboe, J. W.; Boikess, S.; Coupet, J.; Smith, D. L.; Leung, L.; Zhang, G. M.; Feng, X. D.; Kelly, M. F.; Galante, R.; Huang, P. Z.; Dawson, L. A.; Marquis, K.; Rosenzweig-Lipson, S.; Beyer, C. E.; Schechter, L. *J. Med. Chem.* **2007**, *50*, 5535.
13. While compounds **6c**–**6dd** were tested as their racemates, a related 7-azaindole series of 5-HT_6 modulators showed comparable binding and functional activity for the separated enantiomers. Elokdah, H.; Li, D.; McFarlane, G.; Bernotas, R. C.; Robichaud, A. J.; Magolda, R. L.; Zhang, G.-M.; Smith, D.; Schechter, L. E. *Bioorg. Med. Chem.* **2007**, *15*, 6208.