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A regiospecific synthesis of a series of 1-sulfonyl azepinoindoles as potent 5-HT_6 ligands

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ABSTRACT

A regiospecific synthesis of a series of 1-sulfonyl azepinoindoles as potent 5-HT6 ligands is reported.

The 5-HT_6 receptor was first cloned in 1993 and is one of the most recently discovered 5-HT receptor subtypes.[1,2] Its brain selective location, together with high affinity of therapeutically important atypical antipsychotics and tricyclic antidepressants at this receptor has stimulated significant interest in its pathophysiological function and potential therapeutic utility as CNS therapeutics. The 5-HT_6 receptor has been implicated in a range of diseases including anxiety, depression, schizophrenia, epilepsy, obesity, abnormal feeding behavior, and cognitive dysfunctions. Research efforts in this area have led to the discovery of a number of potent and selective 5-HT_6 agonists and antagonists.[3,4]

As part of our continued efforts in identifying novel 5-HT_6 ligands as potential treatments for CNS diseases, we continued our earlier strategy[5,6] of elaborating the simplified substituted tryptamine scaffold **1** (Fig. 1). Tryptamine derivatives **1** bearing a sulfonyl group at indole N1 position have been reported to be potent 5-HT_6 ligands by Glennon,[7] Russell,[8] and Cole.[5] We were interested in rigidifying the molecule by tethering the amino side chain to the 2-position of the indole core with the hope that the novel constrained 1-sulfonyl azepinoindole derivatives **2** may provide better selectivity against other 5-HT subtypes than their acyclic counterparts.[7]

For an efficient synthesis of **2**, the azepinoindole intermediate **3** (Fig. 2) with a protecting group on the basic amine was required. This intermediate would allow for the facile derivatization at the 3- and 6-positions of the azepinoindole core. Traditional synthesis of azepinoindoles (Fig. 2) involves Fischer indole synthesis from arylhydrazines such as **4** and hexahydroazepin-4-one **5**.[9] This non-regioselective synthesis provides a mixture of the desired

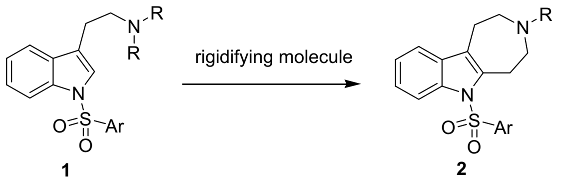

Figure 1. Design of novel 5-HT_6 ligands from substituted tryptamine template.

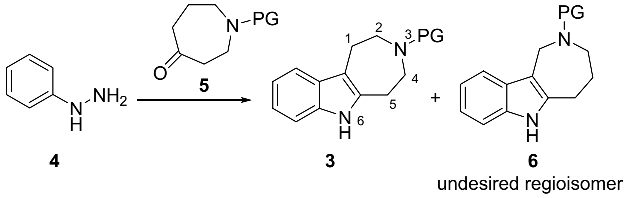

Figure 2. Traditional synthesis of azepinoindoles.

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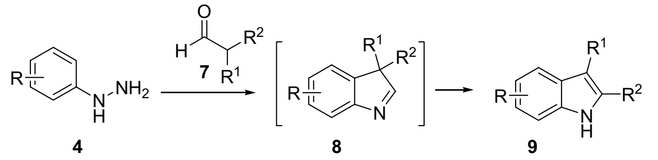


Figure 3. Synthesis of 2,3-substituted indoles via rearrangement of 3,3-disubstituted indolenines.[10]

product **3** and its regioisomer **6**, the desired product generally being isolated in poor yields.

Recently, we reported the synthesis of 2,3-substituted indoles **9** from 3,3-disubstituted indolenines **8** via acid-catalyzed rearrangement (Fig. 3).[10] Indolenines **8** could be conveniently synthesized from arylhydrazines **4** and α-branched aldehydes **7** via Fischer indole-type synthesis.[11,10] As part of our efforts in applying this methodology to synthesis of biologically interesting compounds for CNS diseases, we developed a novel and directed synthesis of azepinoindoles, which is reported here.

Our approach to the construction of the azepinoindole core is depicted in Figure 4. The synthesis involves heating equimolar amounts of the common phenylhydrazine **4** and the commercially available N-Cbz protected aldehyde **10** in HOAc. The Cbz protecting group was chosen in preference to an acid labile Boc protecting group due to the commonly utilized acidic conditions of the Fischer indole reaction. In practice, the reaction components are heated for 2 h at 70 °C, whereupon complete formation of the indolenine derivative is verified by LCMS. The reaction temperature is then increased to 110 °C for an extended time (10–16 h), to effect rearrangement to the tricyclic azepinoindole **12** which is isolated in 50–70% yields after chromatographic purification.[12] Additional work is being conducted to explore the scope and limitations of this methodology, the results of which will be reported in due course.

After intermediate **12** was successfully prepared, the remaining elaboration of the core **12** to the desired 5-HT$_6$ ligands **2** was straightforward, and depicted in Figure 5. Simple basic treatment of the indole and commercially available arylsulfinyl chlorides in DMF afforded the 1-substituted derivates **13** in good yields (60–70%). Removal of the Cbz protecting group affords the secondary amines **2a**–**n** without incident. Further elaboration to the substituted tertiary amines **2o**–**v** can be easily performed under a variety of reductive amination or alkylation conditions.

These azepinoindole derivatives **2** were then evaluated for their 5-HT$_6$ affinity over several serotonin subtype receptors. The results are summarized in Table 1. For the range of 3-unsubstituted azepinoindole derivatives (**2a–n**, R = H) synthesized, the optimal sulfonyl group identified was 3-methoxylbenzenesulfonyl group. A number of 3-*N*-alkyl-6-(3-methoxybenzenesulfonyl) analogs (**2o–v**, R ≠ H) were prepared in order to further explore the SAR for this chemical series. Although small alkyl substitution (R = Me, Et) affords little loss of potency, larger alkyl groups abrogate affinity quite effectively. This trend is not very consistent with the SAR observed previously with other classes of 5-HT$_6$ ligands[13] in which the substitution on the basic amine is oftentimes tolerated. The reasons for this are not apparent, but one may hypothesize that the azepinoindole derivatives with rigidified structures bind to the 5-HT$_6$ receptor in a constrained conformational mode, projecting this alkyl group unfavorably into the peptide backbone of the receptor. Alternatively, the change in the pK_a of the basic amine, the required 5-HT binding appendage, upon alkylation, is not tolerated by the key aspartic or glutamic acid residue, ubiquitous in the 5-HT G-protein coupled receptors. Unfortunately, this class of compounds did not show improved selectivity as initially expected against other closely related 5-HT subtypes examined (e.g., 5-HT$_{2C}$ K_i = 14 nM for **2l**).

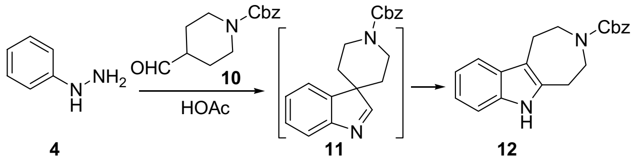


Figure 4. Regiospecific synthesis of azepinoindoles.

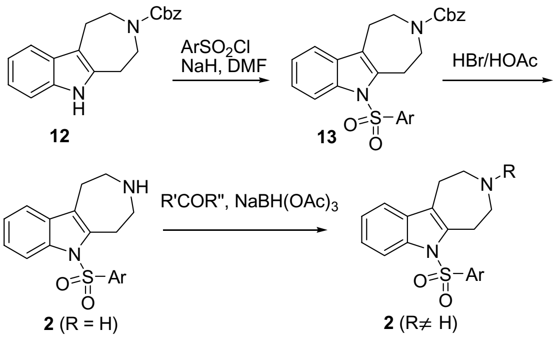
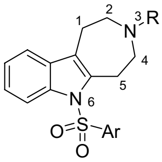


Figure 5. Synthesis of azepinoindoles as 5-HT$_6$ ligands.

Table 1
5-HT$_6$ binding affinity of 1-sulfonyl azepinoindole derivatives



2

Compound	Ar	R	K_i[a] (nM)
2a	Ph	H	193
2b	3-F-Ph	H	33
2c	4-F-Ph	H	23
2d	2-Cl-Ph	H	19
2e	3-Cl-Ph	H	41
2f	4-Cl-Ph	H	18
2g	3-Me-Ph	H	68
2h	4-Me-Ph	H	29
2i	3-CF$_3$-Ph	H	89
2j	4-CF$_3$-Ph	H	46
2k	5-Cl-Naph	H	24
2l	2-MeO-Ph	H	19
2m	4-MeO-Ph	H	33
2n	3-MeO-Ph	H	12
2o	3-MeO-Ph	Me	19
2p	3-MeO-Ph	Et	50
2q	3-MeO-Ph	*n*-Pr	124
2r	3-MeO-Ph	*i*-Pr	85
2s	3-MeO-Ph	Bn	319
2t	3-MeO-Ph	PhCH$_2$CH$_2$	504
2u	3-MeO-Ph	*c*-Pentyl	324
2v	3-MeO-Ph	*c*-Hexyl	253
1	Ph	Et	12

[a] Displacement of [^{3}H]-LSD binding to cloned h5-HT$_6$ receptors stably expressed in HeLa cells.[6] K_i values were determined in triplicate.

Selected compounds were evaluated for their 5-HT$_6$ functional activity by measuring their ability to produce cyclic AMP (cAMP) through modulation of 5-HT$_6$ receptor function in a cyclase assay. In all cases, these azepinoindoles derivatives were shown to be antagonists with modest functional affinity for the target receptor (e.g., IC$_{50}$ = 162 nM for **2l**).

In summary, we have reported a novel facile synthesis of 3-arylsulfonyl azepinoindoles that possess good affinity for the 5-HT$_6$ receptor. These analogs are prepared in 2–3 steps, depending on the elaboration of the basic amine moiety, in a regiospecific manner and moderate yields. Noted examples are antagonists at the target receptor, with minimal selectivity versus closely related serotonin subtype receptors.

Acknowledgments

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12. *Procedure.* A mixture of phenylhydrazine **4** (1.50 g, 13.9 mmol) in AcOH (93 mL) was stirred at 70 °C for 1 h. Additional HOAc (184 mL) was added and the mixture was heated at reflux overnight, concentrated, and purified by chromatography with 10–100% EtOAc/Hex to provide **12** (2.5 g, 56%).
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