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Identification of a series of benzoxazoles as potent 5-HT$_6$ ligands

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ABSTRACT

As part of our continuing efforts to identify therapeutics for CNS diseases such as schizophrenia and Alzheimer's disease (AD), we have been focused on the 5-HT$_6$ receptor in order to identify potent and selective ligands as a potential treatment for cognitive dysfunction. Herein we report the identification of a novel series of benzoxazole derivatives as potent 5-HT$_6$ ligands. The synthesis and detailed SAR of this class of compounds are reported. The compounds have been shown to be full antagonists in a cyclic AMP functional assay.

Cognitive dysfunction is a characteristic of various forms of dementia such as Alzheimer's disease (AD) and a core feature of schizophrenia.[1–4] Numerous therapeutic targets have been pursued in order to develop agents for cognitive enhancement in these CNS diseases.[5] As one of these emerging therapeutic targets, the 5-HT$_6$ receptor was first cloned in 1993[6,7] and is one of the most recently discovered 5-HT receptor subtypes. It is a member of the G-protein superfamily, and is positively coupled to adenylate cyclase. It is localized almost exclusively in the brain, including areas important for learning and memory, such as the cerebral cortex and hippocampus. This brain-selective localization together with the noted high affinity of therapeutically important atypical antipsychotics and tricyclic antidepressants for this receptor have stimulated significant interest in its pathophysiological function and potential therapeutic utilities in CNS diseases.[8] Numerous in vivo studies have shown that blockade of 5-HT$_6$ receptor function improves cognition in a number of rodent behavioral models. In addition, in vivo microdialysis studies have shown that 5-HT$_6$ receptor antagonism enhances neurotransmission at cholinergic and glutamatergic neurons, as well as in other pathways. Therefore, it can be proffered that antagonism of the 5-HT$_6$ receptor can potentially provide an effective treatment for cognitive impairment in AD and schizophrenia and has been the subject of intense research.[9]

In the last decade, a great number of 5-HT$_6$ ligands of both agonists and antagonists have been reported,[10–13] and many are comprised of an indole or other heterocyclic core with a basic amine and an arylsulfonyl moiety (e.g., **1**[14–16] in Fig. 1). It was rather apparent to us that the basic amine and arylsulfonyl moieties are the necessary receptor pharmacophores and the indole core serves merely as a template to hold these pharmacophores in the necessary orientation that effectively interact with the 5-HT$_6$ receptor active site residues. As part of our continued efforts in identifying novel 5-HT$_6$ ligands as potential treatments for CNS diseases,[17] we explored other heterocyclic templates as replacement of the indole core in an effort to expand our compound diversity and identify scaffolds with unique and perhaps improved drug like properties. Herein, we report identification of a novel series of benzoxazoles **3** (Fig. 1) as potent 5-HT$_6$ ligands.

The general synthesis of **4**–**7**—substituted arylsulfonylbenzoxazole **3** is depicted in Scheme 1. Diazotization of aniline **4** (vide infra) followed by reaction with KI provided iodide **5**. The

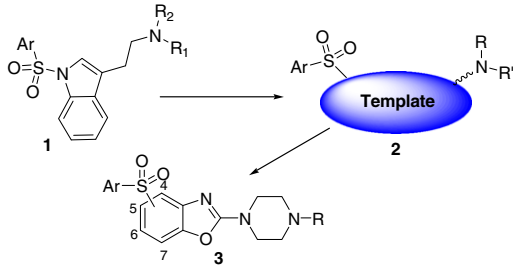

Figure 1. Design of novel 5-HT$_6$ ligands.

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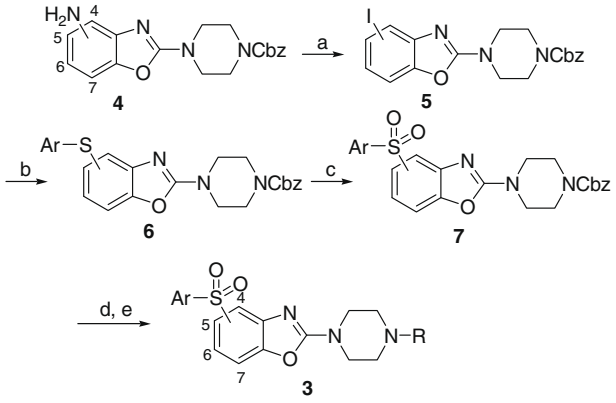


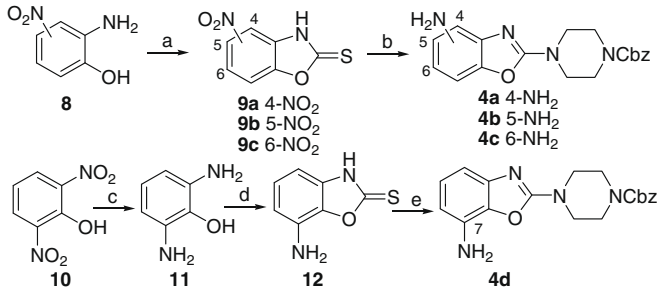
Scheme 1. Reagents and conditions: (a) i—$NaNO_2$, HCl, MeOH; ii—KI, 50–60%; (b) ArSH, CuI, $(CH_2OH)_2$, *i*-PrOH, 60–90%; (c) mCPBA, $CHCl_3$, 90–100%; (d) HBr in HOAc, 70–95%; (e) R′CHO, $NaBH(OAc)_3$, 40–95%.

arylsulfonyl group was then introduced to the molecule by first coupling of **5** with a thiol, using a procedure reported by Buchwald,[18] followed by oxidation with mCPBA. The Cbz protecting group of **7** was then removed by treatment with HBr in HOAc to furnish the benzoxazole core ligands **3** (R = H), which were further alkylated on the piperazine nitrogen via reductive amination under standard conditions.

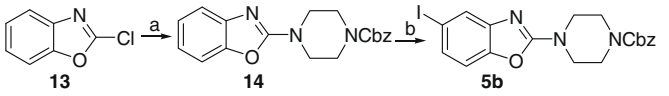
Synthesis of aniline intermediates **4** is depicted in Scheme 2. For **4**–**6** substituted analogs, the commercially available nitro substituted 2-aminophenols **8** were employed as starting materials. Reaction of these aminophenols with CS_2 in the presence of KOH provided benzoxazol-2-thiones **9.** Subsequent nucleophilic substitution with Cbz-protected piperazine followed by reduction with $SnCl_2$ provided **4a–c**. For 7-substituted analogs, commercially available **10** was employed as the starting material and a similar synthetic sequence was followed to provide **4d**.

Alternatively, the iodo intermediate **5b**, for synthesis of the 5-sulfonylbenzoxazoles **3**, can be more efficiently synthesized from commercially available 2-chlorobenzoxazole **13**. Aromatic nucleophilic substitution with Cbz-protected piperazine followed by direct iodination at the 5-position affords the desired intermediate (Scheme 3).

The final products, **3**, were evaluated for their binding affinity to human 5-HT_6 receptor[16] and the results are summarized in Table 1. For the range of 4-arylsulfonyl *N*-unsubstituted benzoxazole derivatives (**3a–j**, R = H) synthesized, the optimal sulfonyl group identified was the 1-naphthalenesulfonyl group (**3j**). Analogs with this 1-naphthalenesulfonyl group at the alternate positions (**3k–m**) were prepared in order to identify the optimal position for this moiety. While the 7-(1-naphthalenesulfonyl) derivative **3m** (K_i = 7.1 nM) was comparable in potency to its 4-substituted counterpart **3j**, alternates were significantly less potent (6-substitution in particular) with a 15- to 60-fold reduction in affinity. This underscores our

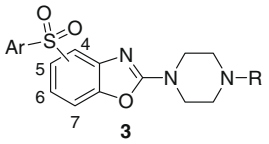


Scheme 2. Reagents and conditions: (a) CS_2, KOH, 35–79%; (b) i—benzyl 1-piperazinecarboxylate, xylenes, reflux; ii—$SnCl_2$, HCl, EtOH, 24–50%; (c) H_2, Pd/C, 89%; (d) CS_2, KOH; (e) benzyl 1-piperazinecarboxylate, xylenes, reflux.



Scheme 3. Reagents and conditions: (a) benzyl 1-piperazinecarboxylate, K_2CO_3, DMF, 77%; (b) ICl, HOAc, 65%.

Table 1
5-HT_6 binding affinity of benzoxazole derivatives[a]



Compound	Position	Ar	R	K_i (nM)
3a	4	Ph	H	41
3b	4	3-F-Ph	H	54
3c	4	4-F-Ph	H	64
3d	4	3-Cl-Ph	H	31
3e	4	4-iPr-Ph	H	22
3f	4	3-CF3-Ph	H	22
3g	4	4-CF3-Ph	H	33
3h	4	3-MeO-Ph	H	25
3i	4	2,5-diCl-Ph	H	13
3j	4	1-Naph	H	3.1
3k	5	1-Naph	H	52
3l	6	1-Naph	H	196
3m	7	1-Naph	H	7.1
3n	4	1-Naph	Me	9.7
3o	4	1-Naph	Et	12
3p	4	1-Naph	*n*-Pr	36
3q	4	1-Naph	*i*-Pr	13
3r	4	1-Naph	*n*-Bu	88
3s	4	1-Naph	*i*-Bu	176
3t	4	1-Naph	$Ph(CH_2)_3$	127
3u	4	1-Naph	*c*-Bu	72
3v	4	1-Naph	*c*-Pen	79

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors stably expressed in HeLa cells.[16] K_i values were determined in triplicate.

hypothesis that the relative positions of the key basic amine and the arylsulfonyl pharmacophores for effective interaction with the 5-HT_6 receptor site are paramount. The 'symmetry' of affinity between the 4- and 7-positions (K_i = 3.1 and 7.1 nM, respectively) and between the 5- and 6-positions (K_i = 52 and 196 nM, respectively) further supports this and is the basis of the design of this class of compounds as 5-HT_6 ligands. One should not ignore the need for the proper heterocyclic core and its ability to positively interact with the receptor site. However, our experience with these and other 5-HT_6 specific ligands supports the notion that the core heterocycle serves as a template to hold the pharmacophores in the required positions for effective interaction with the receptor in order to achieve optimal affinity.

With that in mind, and maintaining the 1-naphthalenesulfonyl group in the optimal 4-position, a number of *N*-substituted benzoxazole derivatives (**3n–v**, Table 1) were then prepared in order to further explore the SAR of this series. While small alkyl substitutions (R = Me, Et, *i*-Pr) are tolerated, larger alkyl groups significantly reduce the potency. This tread is consistent with the SAR of the azepinoindole 5-HT_6 ligands we recently reported.[13] The reason for this, although unclear, is possibly that the conformational rigidity of both the benzoxazoles and azepinoindoles and the change of pK_a of the basic amine upon alkylation contribute to this SAR.

Selected compounds were further evaluated for their functional activity in a 5-HT_6 receptor cyclase assay.[16] All of the benzoxazole derivatives **3** evaluated showed full antagonism as determined by blockage of 5-HT induced cyclic AMP (cAMP) formation. The data is summarized in Table 2.

Table 2
Cyclase functional activity of selected benzoxazole derivatives[a]

Compound	IC_{50} (nM)	I_{max} (%)
3f	120	96
3h	100	92
3i	117	92
3j	96	97
3m	77	96
3n	105	83
3o	248	89

[a] Antagonism of 5-HT stimulated cAMP formation in HeLa cells stably transfected with human 5-HT_6 receptors.[16] IC_{50} and I_{max} values were determined in triplicate.

In summary, we have identified a novel series of benzoxazole derivatives as potent 5-HT_6 ligands. Synthesis and detailed SAR of this class of compounds have been reported. The compounds were shown to be full antagonists in a cyclic AMP functional assay. Further profiling of this class of compounds will be detailed in subsequent reports.

Acknowledgments

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