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Identification of a novel series of 3-piperidinyl-5-sulfonylindazoles as potent 5-HT$_6$ ligands

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ABSTRACT

Cognitive dysfunction is a characteristic of various forms of dementia such as Alzheimer's disease (AD) and a core feature of schizophrenia. As part of our continuing efforts to develop agents for cognitive enhancement, we have been focused on the 5-HT$_6$ receptor—one of the emerging therapeutic targets in this area. Herein, we report the identification of a novel series of 3-piperidinyl-5-sulfonylindazole derivatives as potent 5-HT$_6$ antagonists. The synthesis and SAR of this class of compounds are 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 the high affinity of therapeutically important atypical antipsychotics and tricyclic antidepressants at this receptor have stimulated significant interest in its pathophysiological function and potential therapeutic utility. Thus, the 5-HT$_6$ receptor has been implicated in a range of diseases including anxiety, depression, schizophrenia, epilepsy, obesity, abnormal feeding behavior, and most notably cognitive dysfunctions.[1,3] Research efforts in this area have led to the discovery of a number of potent and selective 5-HT$_6$ agonists and antagonists, for example, **1–5** (Chart 1).[4–8] Currently a number of compounds are believed to be active in phase I and II clinical trials for cognitive impairment in AD and schizophrenia.[4,7,8]

As part of our continued efforts in identifying novel 5-HT$_6$ ligands as potential treatments for CNS diseases,[9,10] we explored other heterocyclic templates as replacement of the indole core while retaining the ArSO$_2$ and basic amine pharmacophores in an effort to expand our compound diversity and identify scaffolds with unique and perhaps improved druglike properties. Herein, we report identification of a novel series of 3-piperidinyl-5-sulfonylindazole derivatives **6** (Chart 1) as potent 5-HT$_6$ ligands.

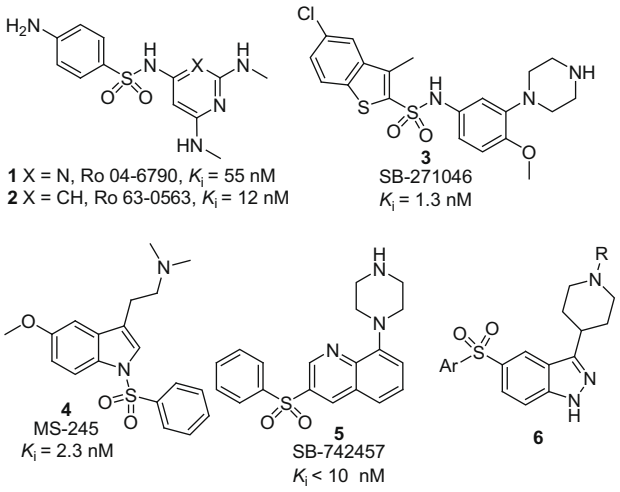

Chart 1. Structures of 5-HT$_6$ ligands.

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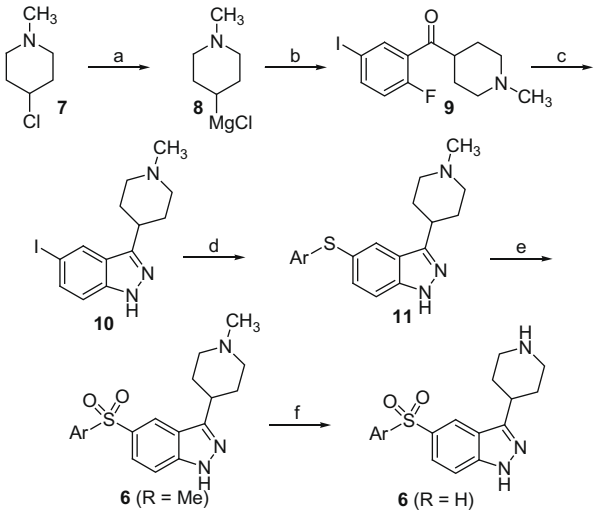
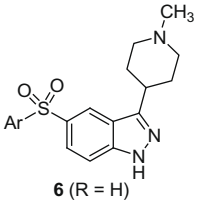


Scheme 1. Reagents and conditions: (a) Mg turnings, THF; (b) 2-fluoro-5-iodo-benzoyl chloride, 53% (2-step); (c) NH_2NH_2, DMSO, 81%; (d) ArSH, CuI, K_2CO_3, ethylene glycol, *i*PrOH, 60–95%; (e) (i) HCl, MeOH; (ii) Oxone, MeOH/H_2O, 90–100%; (f) (i) ACECl, 1,2-dichloroethane; (ii) MeOH, H_2O, KOH, 30–80%.

The general synthesis of 3-piperidinyl-5-sulfonylindazole derivatives **6** is depicted in Scheme 1. Grignard reagent **8**, which was prepared from commercially available chloride **7** under standard conditions, was reacted with 2-fluoro-5-iodo-benzoyl chloride at low temperatures (−78 °C to 0 °C) to provide 2-fluoro-benzophenone intermediate **9**. Subsequent reaction with NH_2NH_2 in DMSO afforded 5-iodo-indazole **10**, a key common intermediate, for efficient synthesis of final target compounds. A variety of thiols were then utilized for coupling with **10,** using a procedure reported by Buchwald,[11] to provide sulfides **11**. Our initial attempts to oxidize sulfides **11** to their corresponding sulfones **6** with a number of oxidants such as *m*CPBA and H_2O_2 under a variety of reaction conditions were not very fruitful. The resultant complex reaction mixtures, over-oxidized products and low yields of desired products necessitated a broadening of our search. Fortunately, we found that oxidation with Oxone went smoothly and efficiently after pretreatment of **11** with 1 equiv of HCl. This is presumably due to obviating the oxidation of the piperidine nitrogen by protonation and preventing many of these side products from complicating the reaction mixture. Absence of the acid in this procedure led to the expected over-oxidized complex mixtures. Demethylation of **6** (R = Me) with 1-chloroethyl chloroformate afforded the unsubstituted piperidines **6** (R = H) which can then be further substituted with other alkyl groups to expand the SAR investigation.

Table 1
5-HT_6 binding affinity of 3-piperidinyl-5-sulfonylindazoles[a]



Compound	Ar	K_i (nM)
6a	Ph	55
6b	3-F-Ph	93
6c	3-Cl-Ph	19
6d	3-Me-Ph	50
6e	4-F-Ph	66
6f	4-CF_3-Ph	46
6g	4-*i*Pr-Ph	14
6h	4-CF_3O-Ph	48
6i	4-MeO-Ph	123
6j	1-Naph	3.8
6k	2-Naph	9.6

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors stably expressed in HeLa cells.[12] K_i values were determined in triplicate.

Table 2
Cyclase functional activity of selected compounds[a]

Compound	IC_{50} (nM)	I_{max} (%)
6c	754	95
6g	108	100
6j	251	100
6k	102	100

[a] Antagonism of 5-HT stimulated cAMP formation in HeLa cells stably transfected with human 5-HT_6 receptors.[12] IC_{50} and I_{max} values were determined in triplicate.

The 3-piperidinyl-5-sulfonylindazole final compounds were evaluated for their binding affinity to human 5-HT_6 receptor in a standard competition binding assay[12] and the results are summarized in Table 1. For *N*-Me derivatives **6** (R = H), a range of arylsulfonyl groups were explored in order to establish the SAR for this chemical series. The unsubstituted benzenesulfonyl derivative **6a** has a potency of 55 nM. Meta- and para-substitution (**6b–i**) of the $PhSO_2-$ moiety with a variety of groups including neutral, electron-withdrawing, and electron-donating groups did not appear to significantly affect the potency. Nonetheless, para-substitution with the bulkier *i*-Pr group did provide compound **6g** with slightly improved potency. This trend of SAR was further observed with more dramatically improved potency of compounds with the much larger 1-naphthalenesulfonyl (**6j**) and 2-naphthalenesulfonyl (**6k**) groups (K_i = 3.8 and 9.6 nM, respectively). It was also observed that in general demethylated piperidine analogs **6** (R = H) have comparable or slightly less affinity as compared to their *N*-Me counterparts **6** (data not shown).

Selected compounds were further evaluated for their functional activity in a 5-HT_6 receptor cyclase assay.[12] All of the 3-piperidinyl-5-sulfonylindazole derivatives evaluated showed full antagonism as determined by blockage of 5-HT induced cyclic AMP (cAMP) formation. The data is summarized in Table 2.

In summary, we have identified a novel series of 3-piperidinyl-5-sulfonylindazole derivatives as potent 5-HT_6 ligands. Synthesis and SAR of this class of compounds has 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.

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