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1-Sulfonylindazoles as potent and selective 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 an attempt to identify ligands as a potential treatment for cognitive dysfunction. Herein we report the identification of a novel series of 1-sulfonylindazole derivatives as potent and selective 5-HT$_6$ antagonists. The synthesis and SAR of this class of compounds are reported. Several potent compounds in both binding and cyclase functional assays also display good selectivity, microsomal stability, solubility, and brain penetration as well as low cytochrome P450 inhibition. One compound exemplified in this series showed 24% oral bioavailability and in vivo efficacy in a NOR cognition model at 10 mg/kg following an oral administration in rats.

Cognitive dysfunction is a increasingly recognized 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 and other 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. 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.[8–11]

As part of our continued efforts in identifying potent and selective 5-HT$_6$ ligands for cognitive impairment, we continued our earlier strategy[12,13] in order to identify novel heterocyclic scaffolds based on our pharmacophore model (**1**, Fig. 1). The basis of our hypothesis is that the basic amine and arylsulfonyl moieties of 5-HT$_6$ ligands are the necessary receptor pharmacophores and the indole and other heterocyclic cores serve merely as a template to hold these pharmacophores in the necessary orientation. In doing so they effectively interact with the 5-HT$_6$ receptor active site residues. Herein, we report identification of a novel series of indazole derivatives **2** as potent and selective 5-HT$_6$ antagonists.

The general synthesis of 1-sulfonylindazole derivatives **2** is depicted in Scheme 1. Commercially available 4-, 5-, or 6-NO$_2$ indazoles **3** were sulfonylated with an appropriate arylsulfonyl chloride in the presence of KO*t*Bu or NaH to provide **4** in good yields. Occasionally, the reaction also provided the 2-arylsulfonyl indazole regioisomer as a minor product, but this could be separated easily from **4** by chromatography or crystallization. Sulfonylation of the regioisomeric 7-NO$_2$-indazole was also attempted but

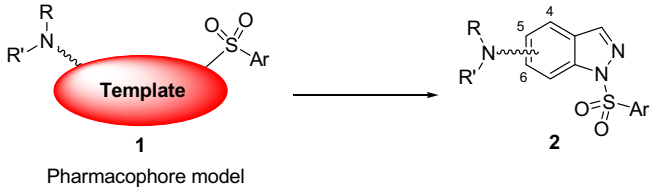

Figure 1. Design of novel 5-HT$_6$ ligands.

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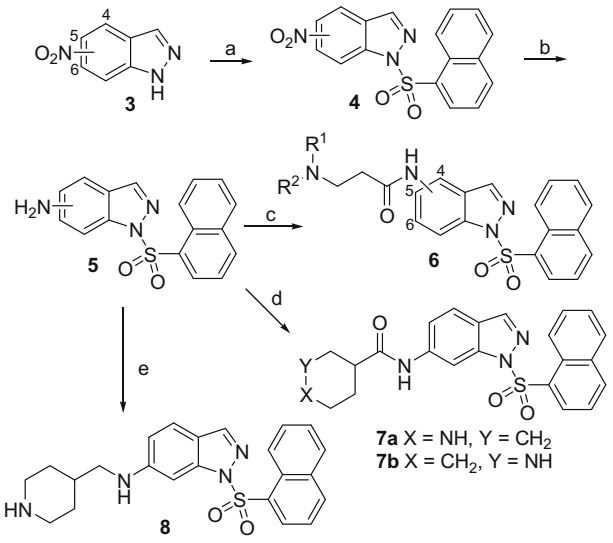

Scheme 1. Reagents and conditions: (a) 1-Naphthalenesulfonyl chloride, KO*t*Bu, DMF, 59–95%; (b) H_2, Pd/C or $SnCl_2$, EtOH, 83–95%; (c) *N*,*N*-substituted amino acids, EDC, CH_3CN; (d) (i) Boc-amino acids, EDC, CH_3CN; (ii) TFA; (e) (i) Boc-amino aldehydes, $NaBH(OAc)_3$, 1,2-dichloroethane; (ii) TFA.

to no avail. One could postulate that this reduced activity is a consequence of the increased steric hindrance from the adjacent 7-NO_2 group. Nitro group reduction of the successfully elaborated 4, 5, and 6-nitroindazoles by catalytic hydrogenation or with $SnCl_2$ provided anilines **5** in excellent yields. Derivatization of **5** with various amino acids through amide bond formation or with amino aldehydes through reductive amination by well known procedures provided final compounds **6–8**.

1-Sulfonylindazole derivatives **6–8** were evaluated for their binding affinity to human 5-HT_6 receptor in a standard competition binding assay[14] and the results are summarized in Table 1. A range of arylsulfonyl groups were explored in order to establish the SAR for this chemical series (data not shown) and in particular the 1-naphthalenesulfonyl group was identified to be one of the optimal sulfonyl groups. Target analogs (**6a–c**) were then synthesized with an acyclic amino alkyl group at the 4–6 positions of the indazole in order to identify the optimal amine regiochemistry for this core. Clearly, the data shows that substitution of the 6-position is preferred as exemplified by compound **6c** with potency of 0.5 nM at the 5-HT_6 receptor. Further substitution on the basic nitrogen appendage of **6c** was then explored (**6d–g**) in order to further elucidate the SAR of the amine moiety. Although small alkyl substitution (**6d–f**) affords minimal loss of potency (by 2–4-fold), larger alkyl groups (e.g., **6g**) reduce affinity significantly (by >30-fold). In addition, compounds with a cyclic amino moiety were prepared and both the 3- and 4-piperidinyl derivatives (**7a** and **7b**) displayed excellent affinity (K_i = 2.3 and 1.3 nM, respectively). The reduced analog **8a** was prepared and exhibited a >8-fold loss in potency compared to the amide **7a**. This would suggest that the hydrogen bonding properties of the amide are making a key interaction in the receptor site contributing to increased 5-HT_6 affinity. Alternatively, the amide bond of **7a** and **7b** may have provided a favorable conformational change for 5-HT_6 affinity.

Selected compounds were further evaluated for their functional activity in a 5-HT_6 receptor cyclase assay.[14] All of the indazole derivatives evaluated showed full antagonism as determined by blockage of 5-HT induced cyclic AMP (cAMP) formation. The data is summarized in Table 2.

Compounds **6c**, **7a**, and **7b** which displayed excellent potency in both binding and cyclase functional assays were further profiled for their selectivity against a panel of receptors including several other 5-HT receptor subtypes, adrenergic α2A and dopamine D_2 receptors and the data is summarized in Table 3. In general, all three compounds showed >500-fold selectivity over all the receptors with the exception of 5-HT_{2B}. Since 5-HT_{2B} agonism activity has been associated with adverse cardiovascular effects,[15] the compounds were then screened for their potential agonist activity in a FLIPR assay.[16] To our satisfaction, no activity was observed for all three compounds at concentrations of 0.1 nM–10 μM in this functional assay.

Table 4 summarizes the solubility, cytochrome P450 inhibition and in vitro PK properties of **6c**, **7a**, and **7b**. All three compounds have excellent water solubility (>100 μg/mL @ pH 7.4), good human and modest rat microsomal stability, and good brain penetration. In addition, no major P450 inhibition was observed for these compounds.

In male Sprague–Dawley rats, while compounds **6c** and **7a** displayed poor bioavailability following oral administration at 10 mg/kg (*F* = 7% and 5%, respectively), **7b** showed acceptable bioavailability (*F* = 24%). In a behavioral assay of cognitive retention-novel object recognition (NOR),[17] compound **7b** fully reversed a 24-h delay induced retention deficit in rats following acute oral administration at 10 mg/kg. Racemic **7b** was then resolved by chiral chromatography and the (*S*)- and (*R*)-enantiomers were shown to have almost equal potency (K_i = 3.2 and 4.0 nM, respectively) and full 5-HT_6 antagonist activity.

In summary, we have identified a novel series of indazole derivatives as potent 5-HT_6 ligands. Synthesis and SAR of this class of compounds have been reported. The compounds were shown to be full antagonists in a cyclic AMP functional assay. Several potent compounds in both binding and cyclase functional assays also display good selectivity, good microsomal stability and brain penetration, low P450 inhibition, and excellent solubility. The potential utility of this class of compounds was exemplified by demonstration of efficacy in a NOR cognition model in rats following an oral

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

Compound	Position	R^1	R^2	K_i (nM)
6a	4	H	H	7.9
6b	5	H	H	50
6c	6	H	H	0.5
6d	6	CH_3	H	1.2
6e	6	CH_3	CH_3	1.8
6f	6	CH_3CH_2	CH_3CH_2	2.1
6g	6	$-CH_2CH_2CH_2CH_2CH_2-$		15
7a	6	—	—	2.3
7b	6	—	—	1.3
8	6	—	—	18

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors stably expressed in HeLa cells.[14] K_i values were determined in triplicate.

Table 2
Cyclase functional activity of selected 1-sulfonylindazoles[a]

Compound	IC_{50} (nM)	I_{max} (%)
6c	11	100
6d	26	100
6e	53	100
6f	260	100
6g	170	100
7a	8	100
7b	10	100

[a] Antagonism of 5-HT stimulated cAMP formation in HeLa cells stably transfected with human 5-HT_6 receptors.[14] IC_{50} and I_{max} values were determined in triplicate.

Table 3
Selectivity of selected 1-sulonfylindazole derivatives[a]

Compound	5-HT_{1a} (nM)	5-HT_{1b} (nM)	5-HT_{1d} (nM)	5-HT_{2b} (nM)	5-HT_{2c} (nM)	5-HT_7 (nM)	α2a (nM)	D_2 (nM)
6c	6400	>2000	>2000	155	>2000	5100	>2000	>2000
7a	8500	>2000	>2000	130	>2000	6900	>2000	>2000
7b	5600	1800	>2000	174	>2000	5800	>2000	>2000

[a] K_i values were determined in triplicate.

Table 4
Solubility and in vitro PK and P450 profile of selected 1-sulonfylindazole derivatives[a]

Compound	Solubility @7.4 (μg/mL)	Microsomal stability $t_{1/2}$ (min)[b]		Major P450 inhibition IC_{50} (μM)			BBB P_e ($\times 10^{-6}$), cm/s[c]
		Human	Rat	3A4	2D6	2C9	
6c	>100	>30	28	30	200	7	4.3
7a	>100	>30	11	61	350	370	1.6
7b	>100	>30	8	260	110	140	3.8

[a] Values were determined in triplicate.
[b] Microsomal protein concentration: 0.5 mg/mL.[18]
[c] BBB P_e: blood brain barrier effective permeability.[19]

administration at 10 mg/kg. Further profiling of this class of compounds will be detailed in subsequent reports.

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References and notes

1. Peuskens, J.; Demily, C.; Thibaut, F. *Clin. Ther.* **2005**, *27*, S25.
2. Bowie Christopher, R.; Jaga, K. *Expert. Rev. Neurother.* **2007**, *7*, 281.
3. Kuperberg, G.; Heckers, S. *Curr. Opin. Neurobiol.* **2000**, *10*, 205.
4. Galletly, C. A.; Clark, C. R.; MacFarlane, A. C. *J. Psychiatry Neurosci.* **2000**, *25*, 117.
5. Robichaud, A. J. *Curr. Top. Med. Chem.* **2006**, *6*, 553.
6. Monsma, F. J., Jr.; Shen, Y.; Ward, R. P.; Hamblin, M. W.; Sibley, D. R. *Mol. Pharmacol.* **1993**, *43*, 320.
7. Ruat, M.; Traiffort, E.; Arrang, J. M.; Tardivel-Lacombe, J.; Diaz, J.; Leurs, R.; Schwartz, J. C. *Biochem. Biophys. Res. Commun.* **1993**, *193*, 268.
8. Woolley, M. L.; Marsden, C. A.; Fone, K. C. F. *Curr. Drug Targets CNS Neurol. Disord.* **2004**, *3*, 59.
9. Glennon, R. A. *J. Med. Chem.* **2003**, *46*, 2795.
10. Holenz, J.; Pauwels, P. J.; Diaz, J. L.; Merce, R.; Codony, X.; Buschmann, H. *Drug Discov. Today* **2006**, *11*, 283.
11. Liu, K. G.; Robichaud, A. J. *Drug Develop. Res.* **2009**, *70*, 145.
12. Liu, K. G.; Lo, J. R.; Comery, T. A.; Zhang, G. M.; Zhang, J. Y.; Kowal, D. M.; Smith, D. L.; Di, L.; Kerns, E. H.; Schechter, L. E.; Robichaud, A. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3929.
13. Liu, K. G.; Lo, J. R.; Comery, T. A.; Zhang, G. M.; Zhang, J. Y.; Kowal, D. M.; Smith, D. L.; Di, L.; Kerns, E. H.; Schechter, L. E.; Robichaud, A. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1115.
14. Cole, D. C.; Lennox, W. J.; Lombardi, S.; Ellingboe, J. W.; Bernotas, R. C.; Tawa, G. J.; Mazandarani, H.; Smith, D. L.; Zhang, G.; Coupet, J.; Schechter, L. E. *J. Med. Chem.* **2005**, *48*, 353.
15. Kaumann, A. J.; Levy, F. O. *Pharmacol. Ther.* **2006**, *111*, 674.
16. Porter, R. H. P.; Benwell, K. R.; Lamb, H.; Malcolm, C. S.; Allen, N. H.; Revell, D. F.; Adams, D. R.; Sheardown, M. J. *Br. J. Pharmacol.* **1999**, *128*, 13.
17. Winters, B. D.; Saksida, L. M.; Bussey, T. *J. Neurosci. Biobehav. Rev.* **2008**, *32*, 1055.
18. Di, L.; Kerns, E.; Li, S.; Petusky, S. *Int. J. Pharm.* **2006**, *317*, 54.
19. Di, L.; Kerns, E.; McConnell, O.; Carter, G. *Eur. J. Med. Chem.* **2003**, *38*, 223.