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Synthesis and pharmacological evaluation of aryl aminosulfonamide derivatives as potent 5-HT$_6$ receptor antagonists

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ABSTRACT

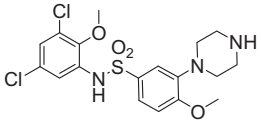
A series of novel aryl aminosulfonamides was designed and synthesized as 5-HT$_6$ receptor ligands. Many compounds screened in a functional reporter gene based assay displayed potent antagonistic activity with Kb values in the range of 0.02–10 nM. The lead compound **11m** exemplified in this series showed good ADME surrogate properties, acceptable pharmacokinetic profile and is active in animal models of cognition like novel object recognition test and Morris water maze. The compound was selected for detailed profiling.

Identification of ligands for the 5-hydroxytryptamine$_6$ receptor (5-HT$_6$R) has been the focus of several reports in the last decade.[1–9] Ligands for the 5-HT$_6$R may be useful in the treatment of CNS disorders such as schizophrenia, depression, Alzheimer's disease (AD)[10–14] and metabolic disorders like obesity. Research efforts from several groups, worldwide, have led to the discovery of several classes of serotonin 5-HT$_6$ receptor ligands[5,15–18] with high affinity and selectivity. Several lead molecules like SB-742457 and SUVN-502 for cognition, PRX-07034 for obesity and LY-483518 (SGS-518) for schizophrenia are in advanced stages of clinical studies. For all these compounds positive clinical study data have been reported in literature.[19–22] A common feature in many of these compound classes is the presence of basic amine functionality, which imparts potent binding site to the 5-HT$_6$ receptor and a second aryl moiety, which maintains the selectivity over other receptors.

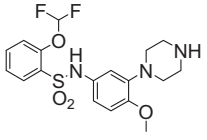
All the reported compounds by Glaxo Smithkline contain characteristic monocyclic aryl piperazine SB-399885 (compound **1**) or herteroaryl piperazine SB-742457 moiety as essential part of their structure. SB-399885 was active in animal model of cognition and SB-742457 is advanced into clinical studies.

Most recently[4] scientists at Abbott disclosed their various efforts to modulate the brain penetration by changing the overall lipophilicity of the molecule (compound **2**). There was an attempt to decrease the electron density around sulfonamide moiety by incorporating a difluoromethylene unit in aryl sulfonamide side chain. There was measurable impact on brain penetrations with these attempts. As can be seen in **2**, these analogues were closely related to SB-399885.

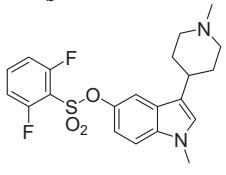
LY-483518, which was developed at Lilly for the treatment of cognitive impairment associated with schizophrenia, contains 3-piperadinyl indole as essential pharmacophore, confirming the importance of tertiary nitrogen on piperidine for receptor binding and affinity.



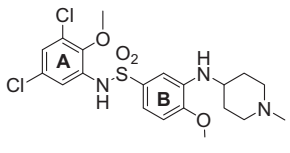
1 (SB-399885)
K_b = 0.25 nM



2 (Abbott)
Ki < 10 nM



3 LY-483518



11m K_b = 0.02 nM

Based on the above observations, we hypothesized that a basic amine function, like the terminal nitrogen of piperazine (as in

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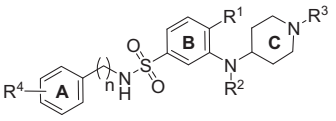
SB-399885), is essential for binding to the receptor and the nitrogen attached directly to the aromatic ring presumably help to impart the appropriate orientation for binding to 5-HT_6R. Based upon the structural features of Lilly and SKB compounds, we proposed that a 4-amino piperidine group could allow the appropriate spacing of the basic amine and the distal aryl group for binding to 5-HT_6R, as shown in **11m**. Thus, it is hypothesized that the NH group attached to ring B will impart the appropriate orientation for binding and the terminal nitrogen is expected to bind to the receptor. The results of these modifications constitute the subject matter of this report.

Synthesis of the proposed compounds was achieved as shown in Scheme 1. In general, sulfonamide compounds **2** were prepared by reacting appropriately substituted 3-nitrobenzene sulfonyl chlorides **1** with substituted amines. Compound **2** was reduced with Fe–HCl to obtain intermediate amines **3**. Reaction of these amines with appropriately substituted piperidones under reductive amination conditions afforded compound **4**. In situ deprotection and salt formation with IPA·HCl gave compounds **5a–5d** with good yields. Compound **7** was prepared from **4** using standard alkylation conditions. This intermediate **7** was further treated with isopropanolic hydrogen chloride to obtain compounds **8a–8c**. Further alkylation on piperidine nucleus yielded compound **9a**. The derivatives **11a–11p** were obtained from **3** by reductive amination of the appropriate sulfonamide with 1-methyl-4-piperidone. Few of the appropriately substituted 3-nitrobenzenesulfonyl chlorides were not readily available. Hence, the synthesis of compound **3** was achieved by reacting substituted 3-acetamido benzenesulfonyl chloride **10** with various substituted amines to obtain N-acetyl intermediate **6**, which on deacetylation with aqueous HCl yielded compound **3**.

The compounds were tested in a functional reporter gene based assay[23,24] for their functional effect on 5-HT_6R. In-short the assay uses a stable CHO cell line expressing recombinant human 5-HT_6R and pCRE-Luc reporter system which refers a non-radioactive based approach to determine binding of a compound to GPCRs. The K_b values of Aryl aminosulfonamides obtained from the cell-based assay of 5-HT_6R are given in Table 1.

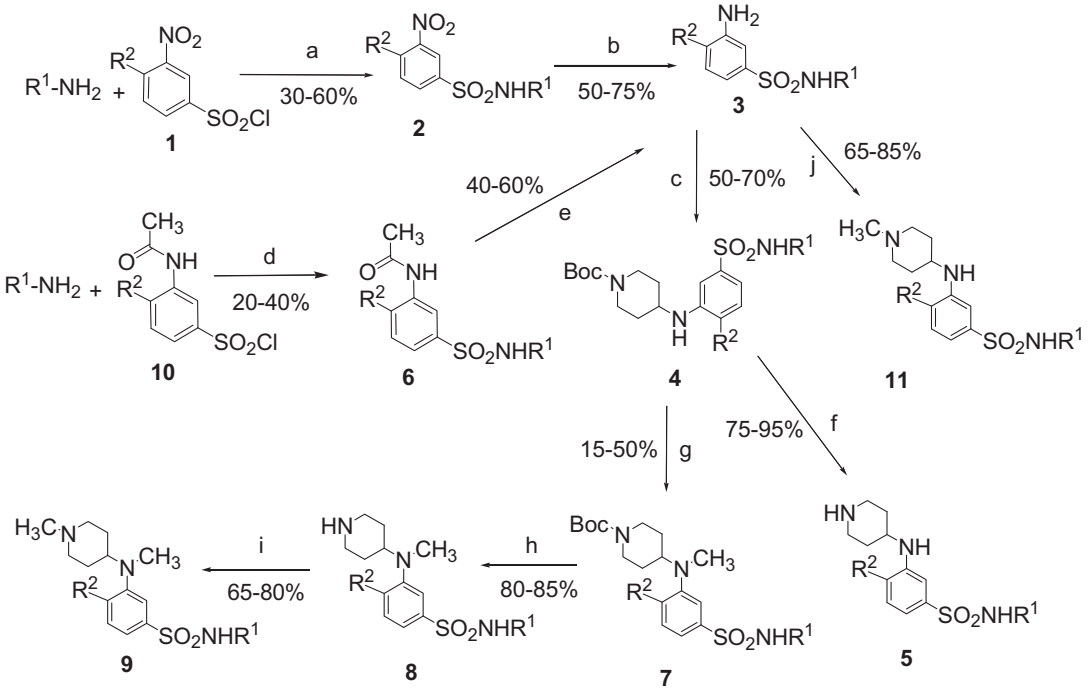
Table 1
5-HT_6R binding affinities[a]



Compound	R^1	R^2	R^3	R^4	n	K_b (nM)
5a	OCH_3	H	H	2-Br	0	0.6
5b	OCH_3	H	H	2-Cl	0	0.48
5c	OCH_3	H	H	H	1	4.26
5d	C_2H_5	H	H	2-Br	0	0.1
8a	OCH_3	CH_3	H	2-Br	0	0.2
8b	OCH_3	CH_3	H	2-Cl	0	0.86
8c	OCH_3	CH_3	H	H	1	2.65
9a	OCH_3	CH_3	CH_3	H	1	3.9
9b	OCH_3	C_2H_5	CH_3	H	0	18.6
11a	OCH_3	H	CH_3	H	1	3.36
11b	OCH_3	H	CH_3	H	0	1.23
11c	OCH_3	H	CH_3	2-Cl	0	0.584
11d	H	H	CH_3	2,4-Di-OCH_3	0	10.0
11e	H	H	CH_3	2,4-Di-CH_3	0	>10,000
11f	H	H	CH_3	2,5-Di-OCH_3	0	16.0
11g	H	H	CH_3	4-Br, 2-F	0	12.2
11h	H	H	CH_3	2-Br, 4,6-Di-F	0	>10,000
11i	OCH_3	H	CH_3	2-Br	0	0.296
11j	CH_3	H	CH_3	2-Br	0	1.31
11k	C_2H_5	H	CH_3	2-Br	0	0.19
11l	OCH_3	H	CH_3	2-OCH_3, 5-CH_3	0	0.02
11m	OCH_3	H	CH_3	3,5-Di-Cl, 2-OCH_3	0	0.02
11n	OCH_3	H	CH_3	2-Br	2	38.0
11o	OCH_3	H	CH_3	2-Cl	2	26.0
11p	C_2H_5	H	CH_3	3,5-Di-Cl, 2-OCH_3	0	1.65
SB399885						0.25

[a] The compounds were tested in vitro with non-radioactive based approach for determination of K_b values with cell-based assay for 5-HT_6R. The values reported here are a mean of two experiments. All the compounds were characterized by ^{1}H NMR and Mass and the purities were determined by HPLC.

As part of SAR various substitutions were tried on ring **B**, like alkoxy, alkyl and halo. All of these substitutions gave potent



Scheme 1. Synthesis of aryl aminosulfonamide derivatives. Reagents and conditions: (a) TEA, DCM, 0–5 °C, 2–4 h or KOH/THF, rt, 24–48 h; (b) Fe/HCl, ethanol, reflux, 2–4 h; (c) $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25–30 °C, 5–10 h, 1-boc-4-piperidone; (d) DCM, TEA; (e) ethanol, concd HCl, reflux; (f) IPA·HCl, IPA, heat; (g) HCHO, $NaBH_3CN$, MeOH; (h) IPA·HCl, IPA, heat; (i) HCHO, $NaBH_3CN$, MeOH; (j) 1-methyl-4-piperidone, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25–30 °C, 5–10 h.

Table 2
Pharmacokinetic profile of compound **11m** in male Wister rats[a]

			Compound **11m**					
Route	*n*	Dose (mg/kg)	C_{max} (ng/mL)	AUC_t (ng h/mL)	$t_{1/2}$ (h)	V_z (mL/kg)	Cl (mL/hr/kg)	*F* (%)
Oral	3	10	536 ± 416	941 ± 533	1.72 ± 1.22	34,332	12,399	38 ± 22
iv	3	10	1915 ± 130	2533 ± 129	2.96 ± 2.38	16,935	3929	

[a] Fasted male Wistar rats, vehicle used: water for injection for both oral and iv routes. Dosing volumes: 10 mL/kg for oral and 2 mL/kg for iv.

Table 3
Human cytochrome P450 inhibitory data and %surrogate metabolism for compounds **11k** and **11m**

Compound	IC_{50} (μM)		Surrogate% metabolism	
	2D6	3A4	Human	Wister rat
11k	>45	9.62	26	99
11m	41.75	8.44	21	77

The cytochrome P450 inhibitory potential was determined using isoform-selective assays and heterologously expressed human CYP2D6 and CYP3A4. These values are the mean of duplicate determinations. Microsomal metabolic stability in Wistar Rat and Human at 0.5 h, Concn 2.5 μM.

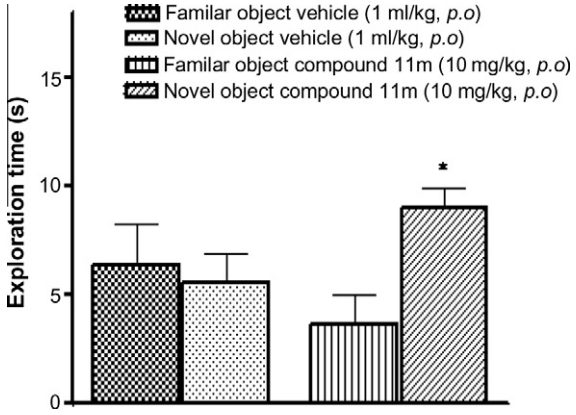


Figure 1. Data represents mean ± SEM of exploration time (Paired '*t*' test), $^*p < 0.05$). Vehicle-PEG 400 50% v/v; 1 mL/kg, po $n = 6–9$ /group, po, dosing vehicle/drug:60 min prior to test (po).

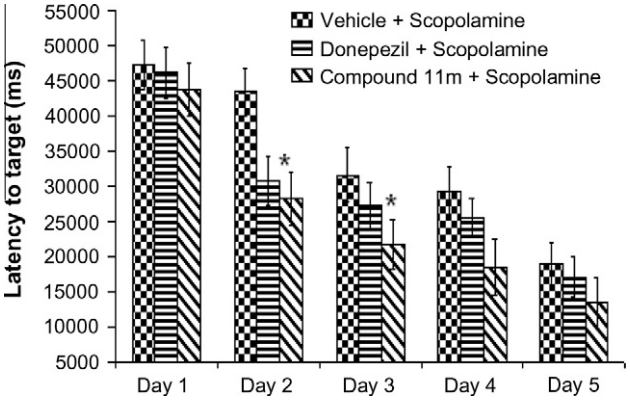


Figure 2. Effect of acute treatment of compound **11m** in Morris water maze for latency to target in rats. Data represents mean ± SEM of latency to target, $^*p < 0.05$, (one way ANOVA, Dunnett's post hoc analysis).

in vitro compounds. There was sevenfold increase in potency when we introduced ethyl group instead of methyl group in ring **B** (**11j**, K_b = 1.31 nM; **11k**, K_b = 0.19 nM). *N*-Alkylation on the spacer NH group between ring **B** and **C** is tolerated and maintains the potent binding affinity as that of its unalkylated analogues (**5b**, K_b = 0.48 nM and **8b**, K_b = 0.86 nM). However, moving from methyl to ethyl on this spacer nitrogen generally reduces affinity by more than 10-fold compared to unsubstituted or methyl analogues (**11b**, K_b = 1.23 nM and **9b**, K_b = 18.6 nM). With the optimum substitution in ring **B**, we focused our SAR effort on ring **A**. In ring **A**, halogen and alkoxy are among the most tolerated groups (**11c**, K_b = 0.584 nM; **11i**, K_b = 0.296 nM and **11m**, K_b = 0.02 nM). Multiple halo substitutions on ring **A** were found to deteriorate the activities when the ring **B** was not substituted (**11h**, K_b = >10,000 nM), while these multiple substitutions were tolerated when the alkoxy was present in ring **B** (**11m**, K_b = 0.02 nM) confirming the importance of alkoxy group on ring **B** for activity. The compound **11p**, where in R^1 is ethyl has a K_b value of 1.65 nM. It was found that **5d** (R^1 is ethyl) was sixfold more potent than **5a** (R^1 is methoxy), where as in the case of **11p** (R^1 is ethyl) the molecule was almost eighty fold less potent compared to **11m** (R^1 is methoxy). Obviously the substitution pattern on ring **A** was playing a role in the in vitro potency of the compound, in addition to the substitution pattern on ring **B**. The compound with 2,4-dimethoxy substitution in ring **A** was very potent (**11d**, K_b = 10 nM) compared to its 2,4-dimethyl analogue (**11e**, K_b = >10,000 nM). Introduction of spacer between sulfonamide NH and ring **A** was not tolerated (**11n**, K_b = 38 nM and **11o**, K_b = 26 nM).

Furthermore, majority of these compounds were profiled for their selectivity against a panel of receptors including several 5-HT receptor subtypes like 5-HT_4, 5-HT_{2A} and 5-HT_{2C}, Adrenergic α_{1b}, Dopamine D_2, Histamine H_1, and the transporters like SERT, NET and DAT. The compounds were found to have >100-fold selectivity over these panel of CNS receptors (data not shown).

The most potent and selective 5-HT_6R antagonist **11m** was further evaluated for its pharmacokinetic profile (Table 2), CYP liability and metabolic stability (Table 3). The effect of **11m** on cytochrome P450 (CYP) enzyme was determined in human liver microsomes. The IC_{50} values were found to be >40 μM and 8.44 μM for CYP2D6 and CYP3A4, respectively. The pharmacokinetics profile of compound **11m** was investigated in rats. The compound **11m** was found to be rapidly metabolized in rat (77% metabolized) and minimally metabolized (22% metabolized) in human liver microsomes. The low oral bioavailability of **11m** in rats was in consistence with its high metabolic instability in rat liver microsomes. The dose of 10 mg/kg was rapidly absorbed in rats with $t_{1/2}$ of 1.72 ± 1.22 h, when it was administered orally. The percent bioavailability (%*F*) was found to be 38 ± 22. The observed C_{max} value was 536 ± 416 ng/mL and occurred at 0.33 ± 0.14 h. The clearance (12,399 ml/h/kg) value was found to be very high. The volume of distribution (V_z) was found to be 34,332 mL/kg for 10 mg/kg, po dose and 16,935 mL/kg for 10 mg/kg, iv dose. In steady state brain penetration study in Male Wistar Rat (water for injection) Cb/Cp was found to be 0.08 indicating low brain penetration properties of the lead compound.

Compound **11m** was further profiled in animal models of cognition like novel object recognition test (NORT) and Morris water maze.[25,26] Oral administration of compound **11m** has shown improvement in cognitive performance of rats in NORT (Fig. 1)

and significantly reversed scopolamine induced special memory deficits (Fig. 2) in Morris water maze test indicating cognitive improvement potential of the compound.

In summary, a novel series of 5-HT_6 receptor antagonists have been identified. In vitro functional data confirms the antagonistic nature of this series. This series also confirms our hypothesis about the importance of terminal nitrogen for binding to 5-HT_6R. Compound **11m** was active in animal models of cognition like NORT and Water maze confirming the cognitive enhancing properties of the series. Further development and SAR modifications to improve the brain penetration and overall pharmacokinetics behavior are in progress and will the subject matter of subsequent publication.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.060.

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