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Rigidized 1-aryl sulfonyl tryptamines: Synthesis and pharmacological evaluation as 5-HT$_6$ receptor ligands

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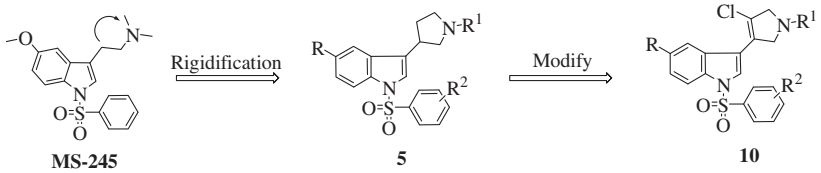
ABSTRACT

A series of N_1-arylsulfonyl-3-(pyrrolidin-3-yl)-1H-indole and N_1-arylsulfonyl-3-(4-chloro-2,5-dihydro-1H-pyrrol-3-yl)-1H-indole derivatives (tryptamine derivatives with rigidized side chain) have been prepared and tested for their binding affinity to 5-HT$_6$ receptor. Several compounds displayed potent binding affinity for the 5-HT$_6$ receptor when tested in in vitro binding assay. The primary SAR indicates that rigidification of dimethylamino alkyl chain at C_3 of indole carbon maintains the binding affinity to 5-HT$_6$R. The lead compound N_1-benzenesulfonyl-3-(4-chloro-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-1H-indole, **10a** (K_b = 0.1 nM) has shown excellent in vitro affinity and was active in animal models of cognition like NORT and water maze.

The 5-hydroxytryptamine6 receptor (5-HT$_6$R) which belongs to the family of 5-HT receptor (5-HT$_1$–5-HT$_7$) is mainly useful in the modulation of various disorders associated with learning, memory[1–3] and feeding behavior.[4,5] 5-HT$_6$R is a stimulatory G-protein coupled receptor which activates adenyl cyclase. Northern blot analysis has shown that the 5-HT$_6$R is expressed mainly in the brain, particularly high levels of 5-HT$_6$R mRNA present in the olfactory tubercle, cortex, nucleus accumbens, striatum, hippocampus, cerebellum and hypothalamus.[6,7] A through literature search reveals that several antipsychotic and antidepressant drugs have significant affinity for 5-HT$_6$R.[8,9] The specific localization of 5-HT$_6$ receptors in CNS and high affinity of antipsychotic and antidepressant drugs have promoted interest in this receptor as a promising target for schizophrenia, anxiety, impairment of learning, memory and obesity.[10–17] Since then, many 5-HT$_6$R ligands have been reported and some of the clinically advancing molecules include SB-742457,[18] SUVN-502,[19] Lu AE58054,[20] SAM-760[21] and SYN-114.[22] Indole nucleus is one of the most explored chemical class of 5-HT$_6$R ligands, which include the N_1-arylsulfonyl tryptamines, for example, MS-245[23] and 2-aryl tryptamines, for example, PMDT.[24] Mooradian et al. has published the 5-HT$_6$R binding activity for some carbazole derivatives, which are conformationally restricted tryptamines.[25]

N_1-Arylsulfonyl tryptamines, viz: MS-245, where the dimethylamino ethyl side chain at C-3 of indole is relatively flexible, is a known ligand at 5-HT$_6$R with high affinity (K_i = 2.1 nM). Our study was aimed at investigating the effect of rigidification of tryptamine side-chain, bearing terminal nitrogen. The side chain has been rigidized by incorporation into a five membered pyrrolidine ring. Based on the literature precedence, the minimum pharmacophore components of 5-HT$_6$R ligands are one protonizable nitrogen and two hydrophobic motifs.[26] The molecules of template **5** and **10** have all these features and hence we envisioned that these molecules would also have high affinity towards 5-HT$_6$ receptors. The results of these efforts are the subject matter of this paper.



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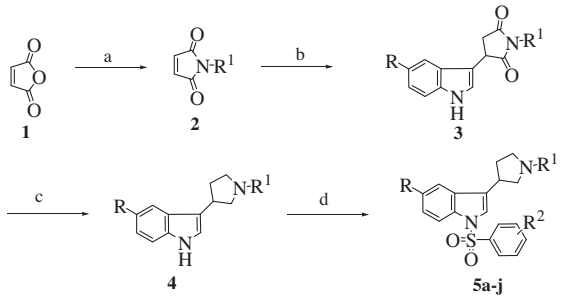
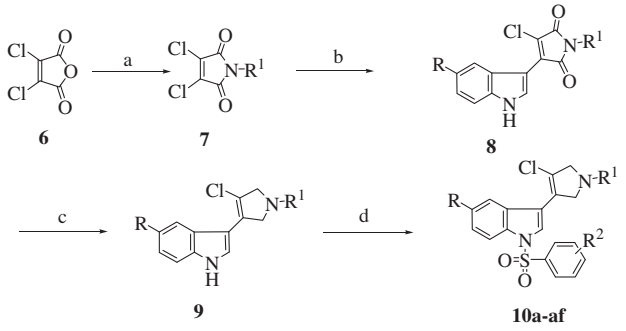
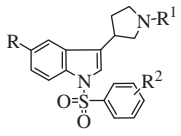


Scheme 1. Reagents and conditions: (a) CH_3COOK, AcOH, $R^1NH_2{\cdot}HCl$, 110 °C, 4 h, 30–35%; (b) Mg, MeI, substituted indoles, THF/toluene, 70 °C, 3–4 h, 65–70%; (c) LAH, THF, reflux, 2–3 h, 70–75%; (d) substituted arylsulfonyl chlorides, NaH, DMF, RT, 3–4 h, 65–75%.



Scheme 2. Reagents and conditions: (a) CH_3COOK, AcOH, $R^1NH_2{\cdot}HCl$, 110 °C, 4 h, 70–75%; (b) Mg, MeI, substituted indoles, THF/toluene, 70 °C, 3–4 h, 70–75%; (c) LAH, THF, reflux, 2–3 h, 25–30%; (d) substituted arylsulfonyl chlorides, NaH, DMF, RT, 3-4 hrs, 65-75%.

Table 1
5-HT_6R binding affinities of N_1-arylsulfonyl-3-(pyrrolidin-3-yl)-1H-indole derivatives[a]

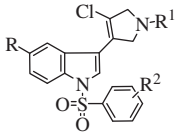


Compound	R	R^1	R^2	K_b (nM)
MS-245	–	–	–	5.8 ± 0.25
5a	H	CH_3	H	1.52 ± 0.15
5b	H	CH_3	4-F	1.00 ± 0.30
5c	H	CH_3	2-Br	0.13 ± 0.07
5d	H	C_2H_5	2-Br	0.10 ± 0.03
5e	OCH_3	CH_3	H	0.89 ± 0.11
5f	OCH_3	CH_3	2-Br	0.13 ± 0.02
5g	OCH_3	CH_3	4-$CH(CH_3)_2$	0.10 ± 0.04
5h	OCH_3	C_2H_5	2-Br	1.30 ± 0.20
5i	OC_2H_5	CH_3	2-Br	0.10 ± 0.02
5j	$OCH(CH_3)_2$	CH_3	2-Br	4.15 ± 0.50

The compounds were tested in vitro using nonradioactive cell-based assay for determination of K_b values at 5-HT_6R.
The reported K_b values are mean of three experiments.
[a] All compounds were characterized and purity was assessed using 1H NMR, MS and HPLC.

N_1-Arylsulfonyl-3-(pyrrolidin-3-yl)-1H-indole (**5a–j**) and N_1-arylsulfonyl-3-(4-chloro-2,5-dihydro-1H-pyrrol-3-yl)-1H-indole (**10a–af**) compounds were prepared by a sequence of reactions shown in Schemes 1 and 2. Intermediates **2** and **7** were prepared

Table 2
5-HT_6R binding affinities of N_1-arylsulfonyl-3-(4-chloro-2,5-dihydro-1H-pyrrol-3-yl)-1H-indole derivatives[a]



Compound	R	R^1	R^2	K_b (nM)
10a	H	CH_3	H	0.10 ± 0.03
10b	H	CH_3	4-Br	0.35 ± 0.05
10c	H	CH_3	4-F	0.60 ± 0.20
10d	H	CH_3	4-OCH_3	10.00 ± 1.00
10e	H	C_2H_5	2-Br	1.10 ± 0.30
10f	H	C_2H_5	4-Br	3.90 ± 0.50
10g	H	C_2H_5	4-F	5.80 ± 0.50
10h	H	C_2H_5	3-Cl	12.52 ± 0.70
10i	OCH_3	CH_3	H	0.10 ± 0.02
10j	OCH_3	CH_3	2-Br	0.30 ± 0.10
10k	OCH_3	CH_3	4-Br	1.78 ± 0.30
10l	OCH_3	CH_3	4-F	0.63 ± 0.20
10m	OCH_3	CH_3	3-Cl	0.84 ± 0.16
10n	OCH_3	CH_3	4-OCH_3	1.65 ± 0.25
10o	OCH_3	CH_3	4-$CH(CH_3)_2$	0.25 ± 0.15
10p	OCH_3	CH_3	2, 4, 5-Cl	18.45 ± 0.95
10q	OCH_3	C_2H_5	H	0.70 ± 0.20
10r	OCH_3	C_2H_5	2-Br	6.15 ± 0.95
10s	OCH_3	C_2H_5	4-Br	4.75 ± 0.25
10t	OCH_3	C_2H_5	4-F	8.70 ± 0.80
10u	OCH_3	C_2H_5	3-Cl	2.40 ± 0.02
10v	OCH_3	C_2H_5	4-OCH_3	14.5 ± 1.20
10w	OC_2H_5	CH_3	H	1.00 ± 0.30
10x	OC_2H_5	CH_3	2-Br	0.40 ± 0.10
10y	OC_2H_5	CH_3	4-Br	4.45 ± 0.50
10z	OC_2H_5	CH_3	4-F	6.16 ± 0.70
10aa	OC_2H_5	C_2H_5	2-Br	0.45 ± 0.15
10ab	$OCH(CH_3)_2$	CH_3	H	0.70 ± 0.25
10ac	$OCH(CH_3)_2$	CH_3	F	7.27 ± 1.05
10ad	F	CH_3	H	0.10 ± 0.04
10ae	F	CH_3	2-Br	0.25 ± 0.10
10af	F	C_2H_5	3-Cl	6.15 ± 1.10

The compounds were tested in vitro using nonradioactive cell-based assay for determination of K_b values at 5-HT_6R.
The reported K_b values are mean of three experiments.
[a] All compounds were characterized and purity was assessed using ^{1}H NMR, MS and HPLC.

by reaction of appropriately substituted maleic anhydride with alkyl amines in presence of acetic acid and potassium acetate.[27] The latter were reacted with appropriately substituted indoles[28–30] under Grignard conditions to obtain 3-substituted pyrrolidine diones (intermediates **3** and **8**).[31,32] These dione intermediates were reduced with lithium aluminum hydride to obtain intermediates **4** and **9**, which were further reacted with substituted aryl sulfonyl chlorides to obtain the targeted compounds (**5a–j** and **10a–af**).

In vitro binding affinities were determined for all the synthesized compounds using functional reporter gene based assay.[33,34] This assay uses a stable CHO cell line expressing recombinant human 5-HT_6R and pCRE-Luc reporter system which refers a nonradioactive based approach to determine binding of a compound to GPCRs. By using this specific assay, the level of intracellular cyclic AMP which is modulated by activation or inhibition of the receptor is measured.

As part of SAR studies, several analogues of N_1-arylsulfonyl-3-pyrrolidinyl indole **(5a–j)** were synthesized and their K_b values are given in Table 1. All the compounds were tested as racemates. In this series all the reported compounds were found to be high affinity ligands with K_b values <5 nM. This high affinity shows that the rigidification of dimethylamino alkyl chain at C-3 carbon of MS-245 is tolerated in terms of 5-HT_6 receptor binding. Substitu-

Table 3
Pharmacokinetic profile of compound **10a**[a]

			Compound **10a**					
Route	*n*	Dose (mg/kg)	C_{max} (ng/mL)	AUC_t (ng h/mL)	$t_{1/2}$ (h)	V_z (mL/kg)	Cl (mL/min/kg)	*F* (%)
Oral	3	10	105 ± 27	268 ± 61	3.75 ± 1.32	19,6287	584.8	12 ± 4
i.v.	3	10	2694 ± 656	2319 ± 404	5.48 ± 0.81	34,868	72.53	

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

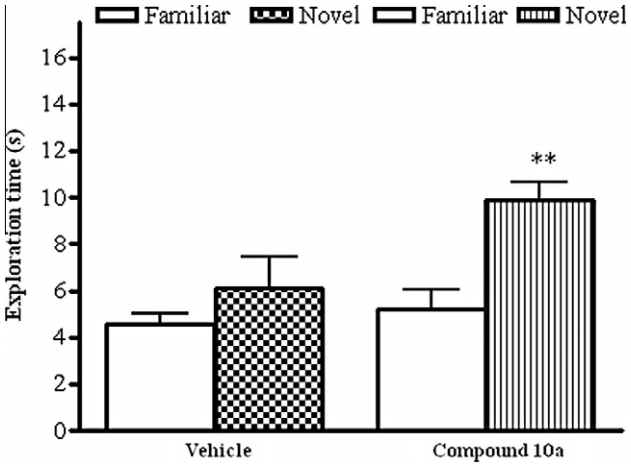


Figure 1. Novel object recognition test data for compound **10a** in rats. $^{**}p$ <0.01 versus vehicle (paired *t* test), *n* = 8–12/group, *p.o.*, dosing; 60 min prior to test. Vehicle – PEG 400 50% v/v; 1 mL/kg, *p.o.*

tion at C-5 carbon of indole ring, with electron donating groups like methoxy (**5f**), ethoxy (**5i**) and isopropoxy (**5j**) groups was well tolerated. The compounds with halo and alkyl substitutions on phenyl sulfonyl ring as well as unsubstituted phenyl sulfonyl group were tolerated.

Encouraged by the above in vitro results, we explored the modifications around pyrrolidine ring. Several analogues of N_1-arylsulfonyl-3-(4-chloro-2,5-dihydro-1H-pyrrol-3-yl)-1H-indole **(10a–af)** were synthesized and their K_b values are given in Table 2. Introduction of double bond (unsaturation) and chloro substitution in the pyrrolidine ring did have a favorable effect on the binding affinities. Most of the compounds have shown high 5-HT_6R binding affinities, in sub-nanomolar concentration range. Substitution on the phenyl portion of indole C-5 with electron donating groups like methoxy (**10i**, **10j**), ethoxy (**10w**, **10x**) and isopropoxy (**10ab**), electron withdrawing group like fluoro (**10ad**, **10ae**) have resulted in compounds with excellent affinities at 5-HT_6R.

In general, unsubstituted phenyl sulfonyl analogs have shown excellent affinity compared to substituted phenyl sulfonyl analogs. Small liphophilic substituents like fluoro, chloro, bromo or methoxy substitution on the phenyl sulfonyl ring were well tolerated and it seems there is a slight preference for ortho substitution. Replacing the methyl substituent on the amine with ethyl has retained the 5-HT_6R binding affinities (**10i** and **10q**).

Selected compounds that showed excellent potency in in vitro binding assay were further profiled for their selectivity for a panel of receptors including serotonin subtypes, transporters, adrenergic and muscarnic receptors. The compounds (**10a, 10b, 10c, 10i, 10j** and **10n**) have excellent selectivity over a range of closely related receptors like 5-HT_{2A}, 5-HT_{2C}, 5-HT_4, 5-HT_7, histamine H_1, dopamine D_2, adrenergic α_{1b}, muscarinic acetylcholine receptor M_1 and the transporters like SERT, DAT and NET. All the tested compounds produced <50% inhibition at a concentration of 0.5 μM (data not shown).

The in vitro metabolic stability of compounds **10a** and **10i** in rat and human liver microsomes was carried out for 30 min. Compound **10i** has extensively metabolized (96% and 97%) compared to compound **10a** (70% and 43%) in rat and human, respectively. The IC_{50} values for compound **10a** was found to be 21.1 μM for CYP $2D_6$ and 14.7 μM for CYP $3A_4$. Brain penetration is an important property for agents targeting CNS disorders. Brain and plasma levels were calculated in male Wister rats after 6 h *i.v.* continuous infusion of compound **10a** at 1 mg/kg/h dose. This compound has shown adequate brain to plasma ratio of 1.79. The pharmacokinetic profile of **10a** was assessed in Wister rats (Table 3). Following *i.v.* administration of 10 mg/kg, the mean half-life was 5.48 ± 0.81 h and the average

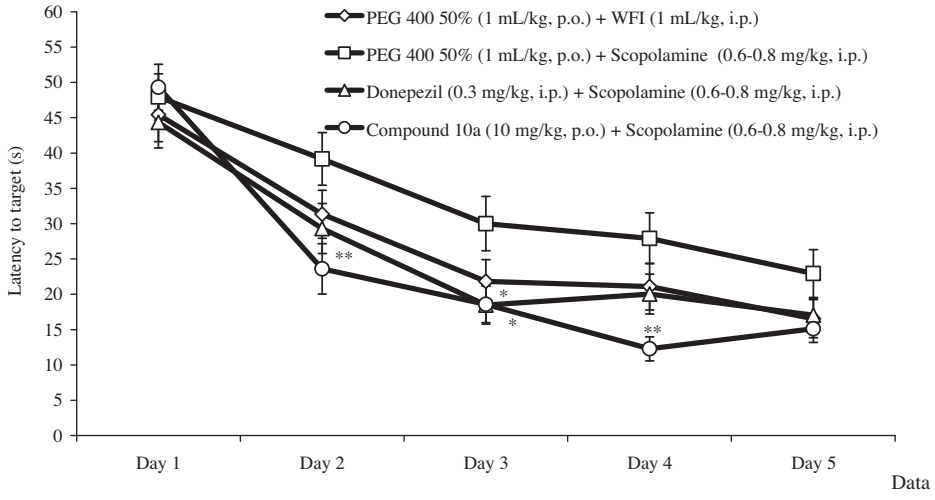


Figure 2. Latency to target in Morris water maze test data for compound **10a** in rats. Data represents Mean ± SEM of latency to target, $^{*}p$ <0.05, $^{**}p$ <0.01 (One Way ANOVA, Dunnett's post hoc analysis).

clearance was 72.53 mL/min/kg. Following oral administration at 3 mg/kg, mean plasma concentration was found to be 105 ± 27 ng/mL, the average half-life was 3.75 ± 1.32 h. The mean oral bioavailability was 12 ± 4%. The low oral bioavailability may be because of its poor metabolic stability in rat liver microsomes.

Compound **10a** was selected for further profiling in animal models of cognition. Oral administration of compound **10a** (10 mg/kg) has significantly improved performance of rats in novel object recognition test (NORT, Fig. 1). In Morris water maze test the compound significantly reversed the scopolamine induced memory deficit which was apparent from lesser target latency (Fig. 2).

In summary, starting from MS-245, by rigidizing the tryptamine side chain into a pyrrolidine ring, we were able to retain 5-HT_6 affinity and very high selectivity over other receptors. The lead compound showed activity in cogition models like NORT and Water maze. High intravenous clearance and metabolic instability could be the reason for suboptimal pharmacokinetic profile. Efforts are underway towards identifying the metabolic sites and blocking them with appropriate substitutions so as to maintain the desired 5-HT_6 affinity and improving upon the metabolic stability of these compounds.

Acknowledgments

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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.2011.05.106.

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