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N,N-Dimethyl-[9-(arylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]amines as novel, potent and selective 5-HT$_6$ receptor antagonists

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ABSTRACT

The design, synthesis and SAR of novel tetrahydrocarbazole derivatives having 5-HT$_6$ receptor antagonist activity is presented. The racemic compound **15e** was found to possess desirable pharmacokinetic properties, adequate brain penetration and activity in animal models of cognition.

The serotonin (5-hydroxytryptamine, 5-HT) neurotransmitter system in the brain plays a key role in a range of central functions which include cognitive, motor, sensory and affective functions as well as sleep and appetite. Hence it was in the focus with extensive drug-discovery efforts in the last decade.[1] 5-HT exerts its actions via seven plasma membrane receptor subtypes named 5-HT receptors 1–7 (5-HT$_1$–5-HT$_7$), all of which are G-protein coupled receptors (GPCR) except for 5-HT$_3$, which is a ligand-gated ion channel receptor.[2–5]

5-HT$_6$ receptors were first identified by molecular cloning in the rat, then in man and subsequently in mouse.[6,7] It's selective location in central nervous system (CNS), together with high affinity of therapeutically important atypical antipsychotic and tricyclic antidepressants at this receptor has stimulated significant interest in its pathophysiological function and potential therapeutic usefulness of this receptor in CNS disorders. The 5-HT$_6$ receptor has been implicated in a range of CNS disorders which include cognitive dysfunctions like Alzheimer's disease, schizophrenia, anxiety, depression, epilepsy, obesity and abnormal feeding behavior.[8–10] Research efforts in this area have led to the discovery of a number of potent and selective 5-HT$_6$ ligands including both agonists and antagonists.[11,12] The first selective 5-HT$_6$ antagonist Ro 04-6790 and Ro 63-0563 were reported by Roche.[13] Shortly after disclosure of these compounds a series of piperazinylbenzenesulfonamides, including SB-271046 and SB-357134 were revealed by Glaxo SmithKline-Beecham.[14,15] A number of 5-HT$_6$ antagonists have been advanced into clinical development, some of which are in phase I, while some others are in phase II clinical trials for cognitive impairment associated with Alzheimer's disease and schizophrenia. SB-742457 and Lu AE58054 are in phase II clinical trials.[16,17] SAM-760 and SYN-120 are in phase-I clinical trials.[18] Our internally discovered compound SUVN-502 has completed phase I clinical trials and is ready for phase-II.[19]

Tryptamine type scaffold is the most explored scaffold for the synthesis of 5-HT$_6$ receptor ligands, as they have the structural resemblance with 5-HT. Glennon et al. reported MS-245 (**1**, K_i = 2.3 nM) as 5-HT$_6$ receptor antagonist.[20] Several conformationally constrained derivatives of *N*,*N*-dimethyl tryptamine side chain are reported, covering rigidization of side chain along with indole ring or rigidization of the side chain alone (Fig. 1). Russell et al. have reported conformational constraint of the basic amine on the phenyl ring of the indole nucleus with flexible *N*-aryl sulfonyl motif leading to a compound with good binding affinity (**2**, K_i = 7.2 nM) towards 5-HT$_6$ receptor.[21] Structurally close analog was reported by cole et al. (**3**) with K_i of 1 nM.[22] Another close analog, compound **4** (K_i = 1.6 nM) was latter reported and the racemate displayed high affinity towards 5-HT$_6$ receptor.[23] Wyeth has described a series of azepinoindoles (**5**) as 5-HT$_6$ receptor ligands.[24] Glennon et al. have published the 5-HT$_6$ receptor binding activities for some tetrahydrocarbazole derivatives (**6**), which are in fact the conformationally restricted tryptamines.[25] Although,

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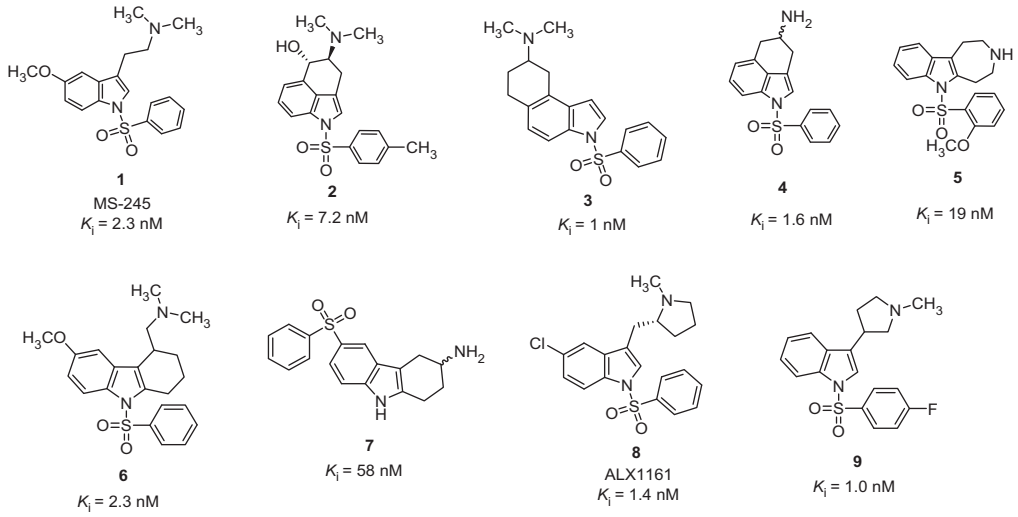


Figure 1. Structures of known 5-HT_6 receptor ligands.

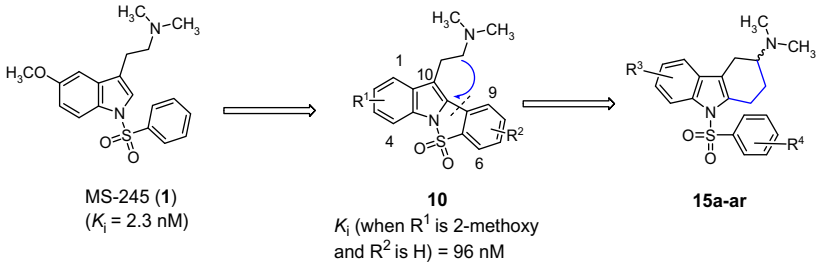


Figure 2. Design of ligands.

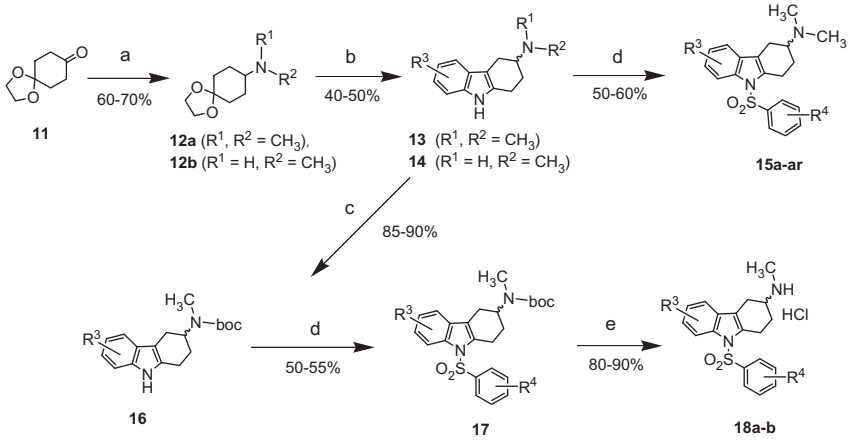
there was change in their spatial orientations, the compounds were active towards 5-HT_6 receptor. Similarly several other research groups attempted modifications of *N*,*N*-dimethylaminoethyl side chain at C3 of indole of MS-245 (**7**, **8** and **9**).[26–28]

Thus, most of the reported 5-HT_6 receptor antagonists are heterocyclic compounds bearing a sulfonyl or sulfonamide group and a basic group like piperazine or *N*,*N*-dimethylamine. On the basis of available structurally diverse 5-HT_6R antagonists, pharmacophoric models for 5-HT_6 receptor antagonists have been suggested.[29] In general the model entails the positive ionizable atom (PI, usually a secondary or tertiary amino group), a hydrogen bond acceptor group (HBA, usually a sulfone or sulfonamide group), a hydrophobic site (HYD) and π-electron donor aromatic or heterocyclic ring (AR).

As part of an ongoing research program to develop 5-HT_6 receptor antagonists at Suven targeting cognitive disorders and obesity, we have previously reported tetracyclic compounds **10**,[30] which were in effect obtained from MS-245 by tethering the aryl sulfonyl groups to C2 of indole. These compounds have modest affinity (**10**, K_i = 96 nM) at 5-HT_6 receptor. While flexible MS-245 (**1**, K_i = 2.3 nM) has strong affinity towards 5-HT_6R, constraining the molecule by tethering the benzenesulfonyl group to the indole core resulted in a dramatic reduction in affinity. In order to improve upon the potency of compound **10**, we aimed at investigating the effect of cyclization of the side-chain bearing terminal nitrogen with C2 of indole nucleus resulting in tetrahydrocarbazole derivatives **15a**–**ar** (Fig. 2). This modification gave us a novel series of potent 5-HT_6 receptor antagonists with reasonably good PK properties and efficacy in animal model of cognition. The results of these efforts are the subject matter of this communication.

The general synthetic strategy used for the preparation of compounds **15a**–**ar** and **18a**–**b** have been summarized in Scheme 1. Reductive amination of 1,4-dioxaspiro[4.5]decan-8-one (**11**) with mono- or dimethylamine in methanol in the presence of sodium cyanoborohydride yielded protected mono- or dimethylamino ketones **12a** or **12b**. These compounds were reacted, as per literature methods,[31,32] with appropriately substituted phenyl hydrazines in 10% aqueous sulfuric acid at reflux, to obtain variously substituted 3-mono- or dimethylamino-2,3,4,9-tetrahydro-1*H*-carbazoles (**13** or **14**). The monomethyl tetrahydrocarbazole derivatives **14** were further reacted with di-*tert*-butyl dicarbonate to obtain *tert*-butyl 2,3,4,9-tetrahydro-1*H*-carbazol-3-yl-carbamate derivatives **16**. The tetrahydrocarbazoles **13**, thus obtained, were reacted with substituted benzenesulfonyl chlorides in presence of a base in tetrahydrofuran to obtain compounds **15a**–**ar**. The tetrahydrocarbazoles **16** were reacted with substituted benzenesulfonyl chlorides in a similar fashion to obtain compounds **17** which on deprotection with IPA HCl gave compounds **18a**–**b**.

The synthetic strategy used to prepare compounds **24a**–**b** was summarized in Scheme 2. Cyclohexane-1,4-dioxaspiro[4.5]decan-8-one (**11**) was reacted with hydroxylamine hydrochloride in the presence of pyridine to obtain the ketoxime **19**. The latter compound was reduced with LAH to obtain the intermediate 1,4-dioxaspiro[4.5]dec-8-yl-amine **20**. The compound **20** was further treated with para substituted phenylhydrazines in 10% aqueous sulfuric acid at reflux, to obtain variously substituted 2,3,4,9-tetrahydro-1*H*-carbazol-3-yl-amines **21**. The tetrahydrocarbazole derivatives **21**, thus obtained, were reacted with di-*tert*-butyl dicarbonate to obtain intermediates **22**. Intermediates **22** were further reacted with 3-trifluoromethyl benzenesulfonyl chloride in the presence



Scheme 1. Reagents and conditions: (a) NHR^1R^2, methanol, acetic acid, $NaCNBH_3$; (b) substituted phenylhydrazines, 10% aq H_2SO_4; (c) di-*tert*-butyl dicarbonate, DCM, TEA; (d) substituted benzenesulfonyl chlorides, KH, THF; (e) DCM, IPA HCl.

of a base in tetrahydrofuran solvent to obtain key intermediates **23**. The latter intermediates were reacted with alcoholic HCl to afford the targeted compounds **24a**–**b**.

Analytically (IR, ^{1}H NMR and ESI-MS) well characterized *N*,*N*-dimethyl-[(9-arylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-yl]amine derivatives were tested for their *in vitro* affinity towards the human 5-HT_6 receptor, using radioligand binding assays and the values determined were reported in Table 1.[33] All the synthesized compounds were tested as racemates.

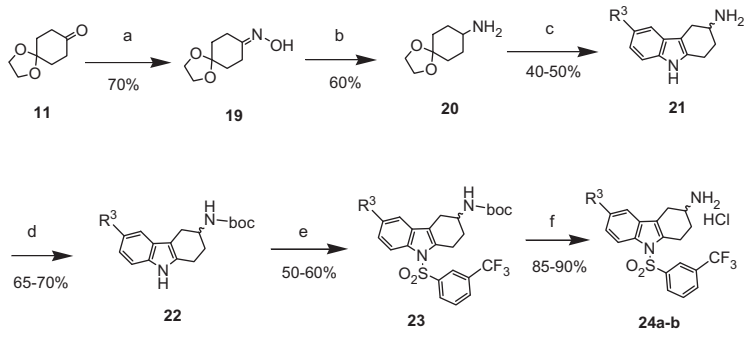
Many of the compounds synthesized exhibited high affinity towards 5-HT_6 receptor with K_i values in the range of 1.8 to 20 nM. The compounds with varied substitutions like halogens (Br, Cl and F), methoxy and methyl mercapto groups at position 6 of the tetrahydrocarbazole moiety were the most explored. Among all these substituents explored, the order of preference in terms of in vitro affinity was found to be Br > alkoxy > H > Cl, F in ring A, when the ring B is unsubstituted as can be seen from the K_i values of compounds **15a**–**g**. The difluoro substitution in ring A was also well tolerated and the compound was found to be two fold more potent compared to the monofluoro derivative (**15g** vs **15d**).

As compounds with Br and OCH_3 substituents at position 6 in ring A have shown good in vitro affinity when ring B was unsubstituted (**15b**, K_i = 1.83 ± 0.15 nM and **15e**, K_i = 5.44 ± 0.30 nM), we thought of investigating the impact of substituents in ring B, keeping Br, OCH_3 groups as substituents at position 6 in ring A. The compounds with 6-OCH_3 substitution in ring A retained their in vitro affinity when ring B was substituted with m-CF_3, p-methyl and halogens at o-position (see, **15v**, **15z**, **15ab**, **15ad** and **15ai**), while drop in potency was observed for compounds which are substituted with halogens and OCH_3 at the para position in ring B (see **15k**, **15n** and **15an**). But in the case of 6-bromo substitution in ring A, slight drop in vitro potency was observed when ring B was bearing a substituents as can be seen by comparing the K_i values of **15b** and **15t**, **15aj**, **15am**. These results confirm the importance of the 6-OCH_3 substitution in ring A for 5-HT_6 activity.

Several substituents were tried on ring B, which include alkyl, alkoxy, halo, haloalkyl and multisubstitutions. The most preferred positions for substitution in ring B were found to be ortho and meta positions, while the para substituted compounds were found less potent. The halo substitutions (Br, F) at para position were detrimental to affinity (see **15h**–**o**). When moving these substituents from para to ortho and meta positions in ring B, a significant improvement was seen in terms of in vitro affinity (see, **15h**–**k** vs **15w**–**z** and **15n** vs **15ad**). The fluoroalkyl substitution, like CF_3, at meta position in ring B showed better affinity towards 5-HT_6 receptor, indicating that electron withdrawing groups are very well tolerated at this position (**15s**–**v**). Noteworthy, multiple substitutions in ring B (**15ap**–**ar**) exhibit 20 to 30-fold lower affinity towards 5-HT_6 receptor compared to the corresponding mono substituted compounds.

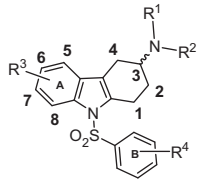
Removal of the dimethyl substitution on the side-chain amino functionality, resulting in the primary amine, led to a 10 to 35-fold decrease in affinity (see, **15s**, **15v** vs **24a**, **24b**). Interestingly, replacement of the primary amine functionality with secondary amine (monomethylamine) led to three- to fivefold improvement in terms of in vitro affinity, as can be seen from the K_i values of the compounds (**24a**, **24b** vs **18a**, **18b**). These results show that tertiary amine function was preferred over primary and secondary amine functions.

Some of the selected compounds were evaluated for their 5-HT_6 functional activity by measuring their ability to produce cyclic AMP (cAMP) through modulation of 5-HT_6 receptor function in a



Scheme 2. Reagents and conditions: (a) $NH_2OH.HCl$, pyridine, ethanol; (b) LAH, THF; (c) para substituted phenylhydrazines, 10% aq H_2SO_4 (d) di-*tert*-butyl dicarbonate, DCM, TEA; (e) 3-triflurometyhl benzenesulfonyl chloride, KH, THF; (f) DCM, IPA HCl.

Table 1
5-HT_6 Receptor radioligand binding data of substituted *N*,*N*-Dimethyl-[9-(arylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl] amines[a]



Compound	R^1	R^2	R^3	R^4	K_i (nM)
15a	CH_3	CH_3	H	H	8.82 ± 0.20
15b	CH_3	CH_3	6-Br	H	1.83 ± 0.15
15c	CH_3	CH_3	6-Cl	H	16.10 ± 0.50
15d	CH_3	CH_3	6-F	H	15.70 ± 0.45
15e	CH_3	CH_3	6-OCH_3	H	5.44 ± 0.30
15f	CH_3	CH_3	6-SCH_3	H	4.57 ± 0.28
15g	CH_3	CH_3	6,8-difluoro	H	7.95 ± 0.32
15h	CH_3	CH_3	H	4-Br	15.50 ± 0.31
15i	CH_3	CH_3	6-Cl	4-Br	41.10 ± 0.33
15j	CH_3	CH_3	6-F	4-Br	43.50 ± 0.29
15k	CH_3	CH_3	6-OCH_3	4-Br	15.10 ± 0.25
15l	CH_3	CH_3	H	4-F	12.50 ± 0.22
15m	CH_3	CH_3	6-F	4-F	32.80 ± 0.33
15n	CH_3	CH_3	6-OCH_3	4-F	24.30 ± 0.25
15o	CH_3	CH_3	6-SCH_3	4-F	24.90 ± 0.18
15p	CH_3	CH_3	H	3-Cl	4.21 ± 0.14
15q	CH_3	CH_3	6-F	3-Cl	5.01 ± 0.29
15r	CH_3	CH_3	6-SCH_3	3-Cl	2.68 ± 0.12
15s	CH_3	CH_3	H	3-CF_3	1.92 ± 0.11
15t	CH_3	CH_3	6-Br	3-CF_3	5.50 ± 0.33
15u	CH_3	CH_3	6-Cl	3-CF_3	12.20 ± 0.42
15v	CH_3	CH_3	6-OCH_3	3-CF_3	3.71 ± 0.11
15w	CH_3	CH_3	H	2-Br	2.85 ± 0.12
15x	CH_3	CH_3	6-Cl	2-Br	8.13 ± 0.42
15y	CH_3	CH_3	6-F	2-Br	5.02 ± 0.12
15z	CH_3	CH_3	6-OCH_3	2-Br	4.30 ± 0.22
15aa	CH_3	CH_3	H	2-Cl	9.15 ± 0.52
15ab	CH_3	CH_3	6-OCH_3	2-Cl	4.68 ± 0.12
15ac	CH_3	CH_3	H	2-F	10.40 ± 0.49
15ad	CH_3	CH_3	6-OCH_3	2-F	3.63 ± 0.16
15ae	CH_3	CH_3	H	4-CH_3	8.28 ± 0.33
15af	CH_3	CH_3	6-Cl	4-CH_3	18.09 ± 0.50
15ag	CH_3	CH_3	6-F	4-CH_3	32.40 ± 0.62
15ah	CH_3	CH_3	6-SCH_3	4-CH_3	13.80 ± 0.35
15ai	CH_3	CH_3	6-OCH_3	4-CH_3	5.89 ± 0.26
15aj	CH_3	CH_3	6-Br	4-$CH(CH_3)_2$	7.50 ± 0.39
15ak	CH_3	CH_3	6-F	4-$CH(CH_3)_2$	15.50 ± 0.28
15al	CH_3	CH_3	H	4-OCH_3	20.40 ± 0.43
15am	CH_3	CH_3	6-Br	4-OCH_3	28.99 ± 0.52
15an	CH_3	CH_3	6-OCH_3	4-OCH_3	19.80 ± 0.31
15ao	CH_3	CH_3	6-SCH_3	4-OCH_3	6.89 ± 0.12
15ap	CH_3	CH_3	6-Br	2-Cl,5-CF_3	70.60 ± 0.64
15aq	CH_3	CH_3	6-Br	2,3,4-trifluoro	61.21 ± 0.52
15ar	CH_3	CH_3	6-Br	3,4-difluoro	29.01 ± 0.26
18a	H	CH_3	H	3-CF_3	17.12 ± 0.19
18b	H	CH_3	6-OCH_3	3-CF_3	13.10 ± 0.21
24a	H	H	H	3-CF_3	73.40 ± 0.58
24b	H	H	6-OCH_3	3-CF_3	39.10 ± 0.27

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors stably expressed in HEK293 cells. K_i Values were determined in triplicate.

reporter gene based assay.[34,35,38] All the tested compounds have shown antagonistic activity by inhibiting the 5-HT stimulated accumulation. The IC_{50} and K_b values are summarized in Table 2. The compound **15e** was found to be a potent 5-HT_6 antagonist.

As our aim was to discover a potent and selective 5-HT_6 antagonist, few of the selected potent 5-HT_6 antagonist compounds were profiled in in-house selectivity panel of closely related receptors and transporters at two concentrations 1 μM and 10 μM. The values are summarized in Table 3. These results indicate that all the tested compounds are selective over the tested receptors.

Table 2
Functional activity data at 5-HT_6R[a]

Compound	K_b (nM)	IC_{50} (nM)
15b	21.50 ± 0.20	2056 ± 4
15e	4.70 ± 0.12	457 ± 2
15s	20.40 ± 0.30	1951 ± 3

[a] Antagonism of 5-HT stimulated cAMP formation using non-radioactive cell-based assay. IC_{50} and K_b values were determined in duplicate.

Table 3
Selectivity profile of selected compounds[a]

% Inhibition					
	Concentration (μM)	**15b**	**15e**	**15s**	**15p**
$Alpha_{1B}$	1	4.22	5.21	5.26	4.24
	10	16.19	5.26	8.72	7.92
5-HT_{1A}	1	22.32	28.28	44.53	29.90
	10	43.88	43.12	57.53	50.27
5-HT_{2A}	1	15.15	8.15	5.60	7.37
	10	51.37	46.71	19.61	35.19
D_2	1	16.45	10.96	16.26	15.31
	10	67.39	51.32	60.40	32.10
SERT	1	0	2.52	9.14	2.69
	10	2.77	3.35	20.72	1.49
DAT	1	0	1.48	18.36	0
	10	7.70	6.23	24.75	7.21
H_3	1	23.42	22.75	26.80	11.04
	10	24.77	32.66	49.10	39.86
H_4	1	0	0	4.14	4.90
	10	3.85	13.94	17.96	10.32

[a] Percent inhibition values were determined in duplicate and the mean of the two values was reported here.

The most promising compounds from this series were profiled for their CYP450 inhibitory potential using isoform selective assays [33] and heterologously expressed human CYP1A2, CYP2A6, CYP2C19, CYP2C9, CYP2D6 and CYP3A4, in order to assess the potential likelihood of drug-drug interactions. The CYP450 inhibition data highlighted that the compounds (**15e, 15b, 15s**) tested at 3 μM concentration, generally have the propensity to inhibit CYP2C19, CYP2D6 (50–60%) whereas a very low level of inhibition was observed for the tested compounds against CYP3A4 (10–15%) isoform. The compounds **15e** and **15s** were tested for in vitro metabolic stability study in rat and human liver microsomes.[36] The percent metabolism in human liver microsomes was found to be 49% and 17% for **15e** and **15s** respectively. The percent metabolism in rat liver microsomes was found to be 74% and 72% for **15e** and **15s** respectively.

Due to the overall favorable attributes, compound **15e** was advanced to rat pharmacokinetic profiling.[38] The pharmacokinetic profile of **15e** was assessed in male Wistar rats (Table 4). Following iv administration at a dose of 10 mg/kg, compound **15e** had the mean half life of 3.86 h and average clearance of 73.78 ml/min/kg. Upon an oral administration of compound **15e** at a dose of 10 mg/kg, **15e** was found to have an oral exposure 90 ng/mL and the oral bioavailability was found to be 26%. Also compound **15e** had excellent brain to plasma ratio (C_b/C_p) of 7.6 ± 1.42. Based on its overall rat PK profile, compound **15e** was progressed for further evaluation.

In order to examine the potential utility of our compounds in the treatment of cognitive impairment, compound **15e** was tested in the Novel Object Recognition Test (NORT) paradigm,[37,38] using a 24-h delay procedure. Animals treated with compound **15e** at a dose of 1, 3 and 10 mg/kg spend significantly more time with the novel object compared to familiar object, thereby demonstrating the efficacy of the compound (Fig. 3). These results confirmed the

Table 4
The pharmacokinetic profile of **15e** in male wistar rats [a]

			Compound **15e**					
Route	*n*	Dose (mg/kg)	C_{max} (ng/mL)	AUC (ng.hr/mL)	$t_{1/2}$ (hr)	V_d (L/kg)	Cl (mL/min/kg)	F (%)
p.o.	3	10	90 ± 35	544 ± 236	7.67 ± 2.8	21.95 ± 12.52	331.35 ± 179.75	26
i.v.	3	10	928 ± 378	2116 ± 135	3.86 ± 1.05	24.26 ± 6.25	73.78 ± 12.21	

[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.

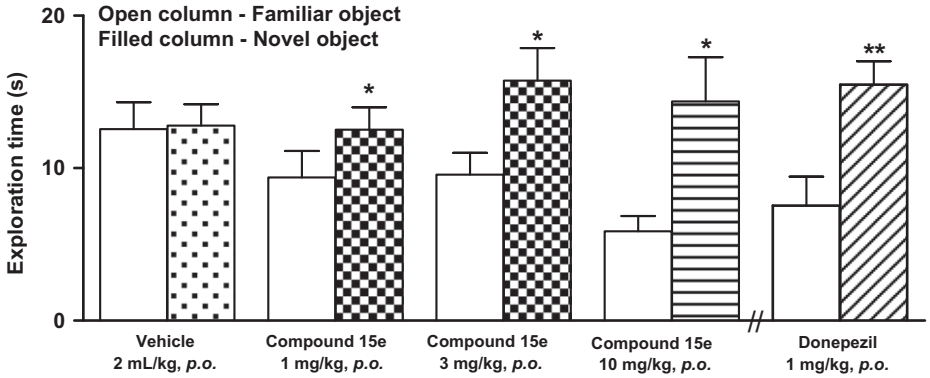


Figure 3. Novel object recognition test data for compound **15e** in rats. $^{**}p < 0.01$, $^{*}p < 0.05$ versus familiar object (Paired *t* test), *n* = 8–10/group, *p.o.*, dosing; 60 min prior to test. Vehicle-Water for injection 2 mL/kg, *p.o.*

procognitive potential of selective CNS penetrant 5-HT_6 antagonists.

In summary, we have disclosed a series of novel *N*,*N*-dimethyl-[9-(arylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl] amines as potent and selective 5-HT_6 receptor antagonists. From the results discussed above, it is evident that cyclization of the side-chain bearing terminal nitrogen with C2 of indole nucleus was very well tolerated. Selected lead compound, **15e** was efficacious in animal models like NORT confirming the memory enhancing properties. These data further support the potential utility of 5-HT_6 receptor antagonists for the treatment of psychiatric and neurological disorders associated with cognitive dysfunction.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.06.002.

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