Design, Synthesis and Pharmacological Evaluation of Piperidin-4- yl amino aryl sulfonamides: Novel, Potent, Selective, Orally Active and Brain Penetrant 5-HT6 Receptor Antagonists

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KEYWORDS: 5-HT_6R - 5-Hydroxytryptamine6 Receptor, CNS - Central Nervous System, SAR - Structure Activity Relationship, Cognition

Abstract

Our initial findings around aryl sulfonamide series led to N-(3,5-dichloro-2-methoxyphenyl)-3-(1-methylpiperidin-4-ylamino)-4-methoxy benzenesulfonamide as potent and selective 5-HT_6 receptor (5-HT_6R) antagonist with reasonable pharmacokinetic properties and activity in animal models of cognition. However lack of brain penetration and P-glycoprotein liability makes this scaffold unsuitable for further development. Our goal was to identify small molecule 5-HT_6R antagonist with adequate brain penetration, acceptable ADME properties, no P-glycoprotein and no hERG liability. Several structural modifications including bringing conformational constraint around sulfonamide –NH group and introduction of heteroatom to modulate the physicochemical properties were attempted. This effort culminated in the discovery of series of novel, potent, selective, orally bioavailable and adequately brain penetrant compounds with no hERG liability. These compounds showed activity in animal models of cognition like Object Recognition Task and Water maze and in brain microdialysis studies at lower doses.

INTRODUCTION

Alzheimer's Disease International[1] estimated that 36 million people worldwide are living with dementia and this number is expected to increase in future with the increased life expectancy around the globe. The worldwide costs of dementia (US$604 billion in 2010) amount to more than 1% of global GDP, according to the World Alzheimer Report 2010. Together, these reports clearly demonstrate that Alzheimer's disease (AD) is among the most significant social, health and economic crises of the 21st century. The current line of treatment of AD include cholinergic (Donepezil) and glutaminergic drugs (Memantine) that have modest efficacy and poor tolerability.[2-4] Hence there is a need to discover new and effective therapeutics based on novel mechanism of action with improved efficacy and tolerability for the treatment of dementia. The 5-hydroxytryptamine-6 receptor (5-HT_6R) is one such target. 5-HT_6R, a GPCR, is one of the most recently identified member of serotonin (5-HT) receptor super family which is positively coupled to adenylate cyclase.[5] 5-HT_6R have near exclusive expression in the central nervous system (CNS)[6]. Several psychiatric drugs have shown high affinities to this receptor.[7] Preclinical and clinical studies have shown that blockade of 5-HT_6R function improves cognition. In addition, *in vivo* microdialysis studies have shown that 5-HT_6R antagonism enhances neurotransmission at cholinergic and glutamatergic neurons, as well as in other pathways. Thus, antagonism of the 5-HT_6R can potentially provide an effective treatment for cognitive impairment in AD and schizophrenia. In the last decade, research effort in this area led to the discovery of several structurally diverse 5-HT_6R agonists and antagonists (**1**–**7**)[8-10] as depicted in Figure 1. These compounds have served as excellent tools to investigate the functional roles of the 5-HT_6R in great detail. 4-amino-*N*-[2,6-bis(methylamino) pyrimidin-4-yl]benzenesulfonamide (Ro 04-6790, **1**) and 4-amino-*N*-[2,6-bis(methylamino)pyridin-4-

yl]benzenesulfonamide (Ro 63-0563, **2**) were amongst the first reported 5-HT_6 antagonists from Roche. This was followed by the extensive work[11] of GSK scientists, which typically revolved around aryl/heteroaryl sulfonamide compounds bearing basic piperazine moiety, like 5-chloro-N-(4-methoxy-3-piperazin-1-ylphenyl)-3-methyl-1-benzothiophene-2-sulfonamide (SB-271046, **3**). This compound was found to be moderately brain penetrant (10 %) which could be the possible reason for its discontinuation from further development. Further SAR studies around SB-271046 has resulted in a highly potent and brain penetrant compound, 5-chloro-1-(3-chlorobenzenesulfonyl)-4-(piperazin-1-yl)-1*H*-indole (SB-699929, **4**)[12]. Currently two molecules from among several 5-HT_6R antagonists (for which the structure is disclosed) are believed to be in active clinical development. 3-phenylsulfonyl-8-(piperazin-1-yl)quinoline (SB-742457, **5**) from GSK is in Phase II clinical trials[13] for dementia as per their product development pipeline published in Feb. 2012. Recently Lundbeck has reported that 2-(6-fluoro-1*H*-indol-3-yl)-N-[[3-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]ethanamine (Lu AE58054, **6**) met its primary endpoint in large placebo-controlled clinical proof of concept study in people with AD.[14-15] The progress of these diverse compounds through various phases of clinical trials will further explore the potential utility of these ligands for the treatment of AD, schizophrenia and related cognitive disorders.

We have reported[16] our initial findings on N-(3,5-dichloro-2-methoxyphenyl)-4-methoxy-3-(1-methyl piperidin-4-yl amino) benzenesulfonamide, **7** (Figure 1) which is a highly potent and selective 5-HT_6R antagonist with moderate oral exposure and efficacy in animal models of cognition. However, the brain penetration of this lead compound **7** in male Wistar rat was found to be 0.08, indicating low brain penetration properties. This compound was also found to have P-glycoprotein liability. As we are targeting the CNS receptor, this combination of low brain penetration in rat and P-glycoprotein liability makes this scaffold unsuitable for further

development, as it carries high risk of not attaining adequate drug concentration in the brain in human clinical trials. Since our goal was to identify a small molecule 5-HT_6R antagonist with adequate brain to plasma ratio and acceptable ADME properties as a possible drug-candidate for the treatment of AD, it was decided to adopt a successful strategy for improving brain penetration that involved conformational constraint with concomitant reduction in hydrogen bond count.[17a-c] In compound 7, the 'N' of the sulfonamide group was attached to an aromatic ring by a single bond, across which free rotation is possible. Once it was brought inside a ring system, the C-N free rotation gets restricted resulting in rigidized conformation in that part of the structure. It was well documented in the literature[17b] that such a conformational constraint can increase brain penetration of the molecules. Thus, this modification around sulfonamide NH of compound **7** provided us various bicyclic structures like indole, azaindole, indazole, benzoxazine, tetrahydroquinoline, tetrahydroisoquinoline etc (Figure 2). The resultant bicyclic structures lacked the conformational freedom around sulfonamide NH as compared to compound **7**, thereby improving brain penetration. The results of these modifications covering *in vitro* binding affinity, pharmacokinetic, hERG affinity and *in vivo* efficacy profiling constitute the subject matter of this manuscript.

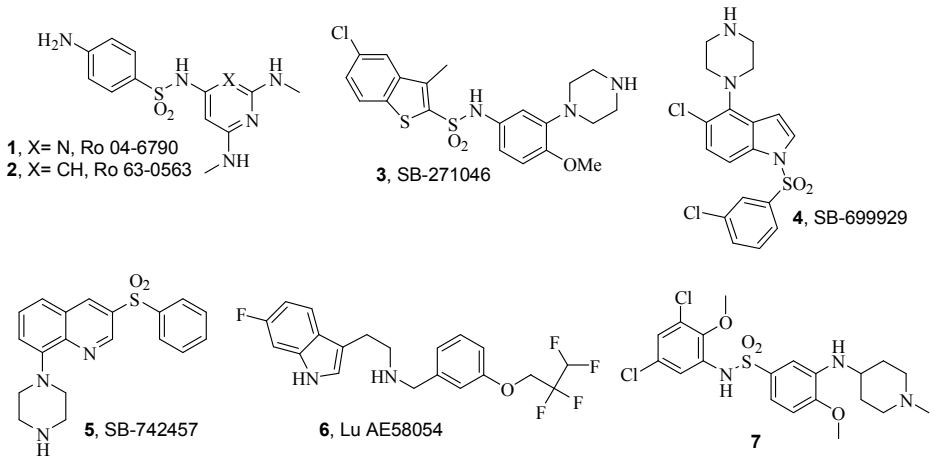


Figure 1. Reported 5-HT_6 ligands

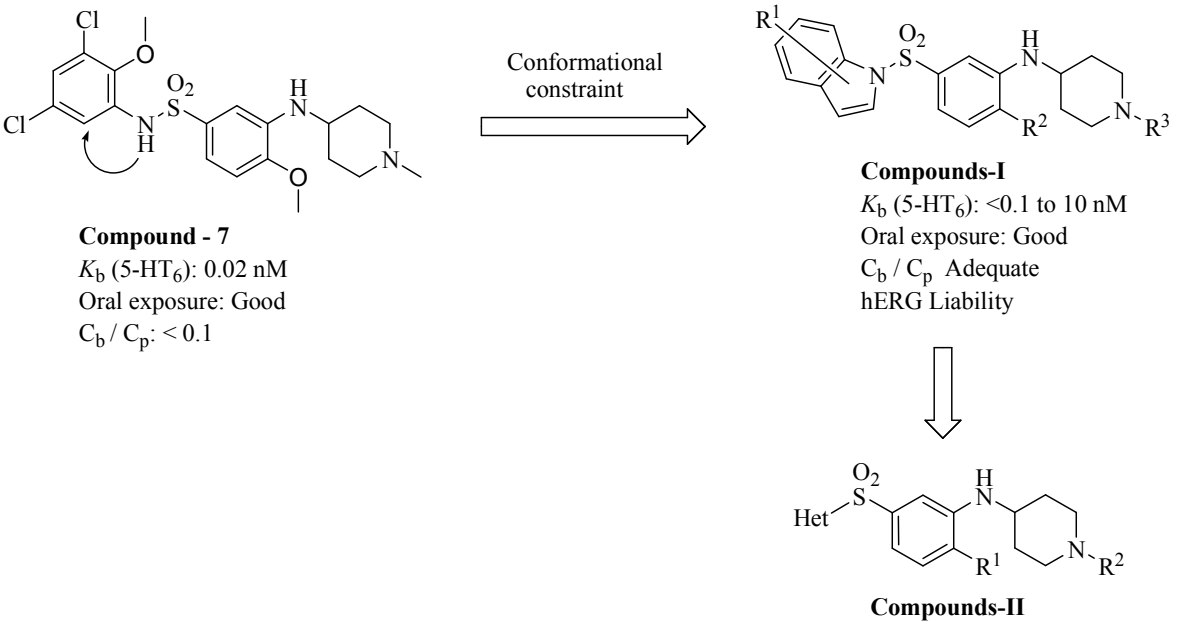
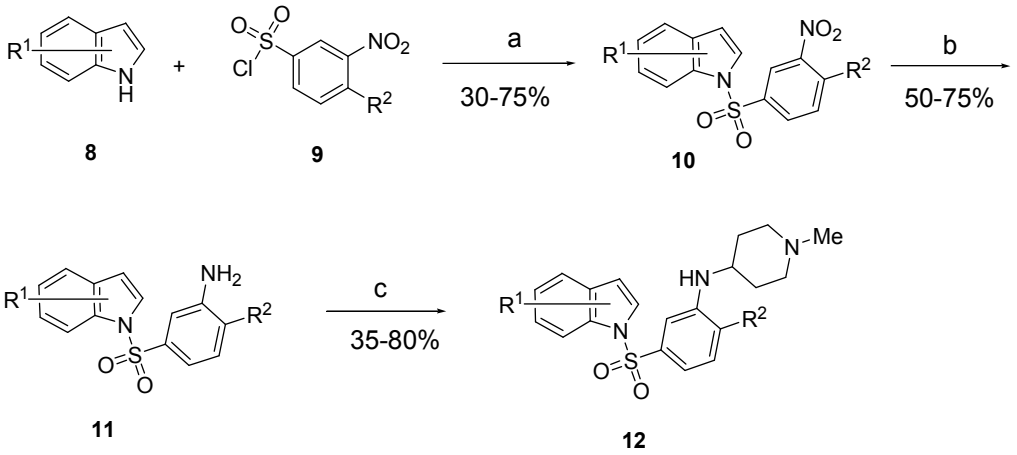


Figure 2. Genesis of Ligand

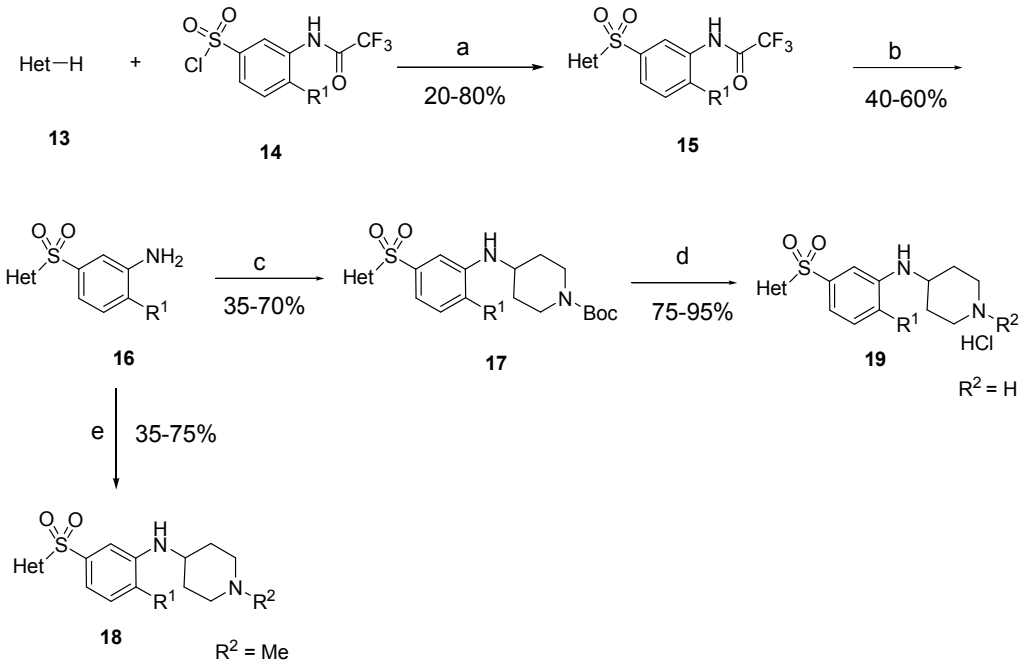
CHEMISTRY

Scheme 1.



Reagents and conditions: (a) Et_3N, DCM, 0-5 ^oC to RT, 24-48 h or DCM, Pyridine, RT, 24-48 h (b) HCl / Fe, ethanol, reflux, 2-10 h (c) 1-Methyl-4-piperidone, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25-30 ^oC, 6-24 h.

Scheme 2.



Reagents and conditions: (a) DMF / NaH, 0-25 ^oC, 12-24 h. or DCM, Et_3N, RT or Pyridine, RT (b) Ethanol, conc.HCl, reflux, 2-10 h (c) 1-Boc-4-piperidone, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25-30 ^oC, 6-24 h. (d) IPA.HCl, RT, 2-4 h. (e) 1-Methyl-4-piperidone, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25-30 ^oC, 6-24 h. For definition of Het, see Table 2.

Synthesis of the proposed **Compounds I** (e.g. compound **12**) and **Compounds II** (e.g. compounds **18** and **19**) was achieved as shown in Schemes 1 and 2 respectively. Substituted indoles **8** were treated with commercially available substituted 3-nitrobenzenesulfonyl chlorides **9** in presence of triethylamine or pyridine as base to afford (3-nitro-4-substituted phenylsulfonyl)-1*H*-indoles **10**. Reduction of **10** was carried out with Fe-HCl under reflux to obtain (3-amino-4-substituted phenylsulfonyl)-1*H*-indoles **11**. The latter compounds **11** were reacted with 1-methyl-4-piperidone in presence of acetic acid, sodium sulfate and sodium triacetoxyborohydride to afford targeted compounds **12**. Aromatic heterocycles **13** were reacted with 4-substituted-3-

trifluoroacetamido benzenesulfonyl chloride **14** in presence of sodium hydride as base yielding **15**. Hydrolysis of **15** with concentrated HCl in ethanol under reflux yielded compounds **16**. 1-Methyl-4-piperidone was reacted with **16** in presence of acetic acid, sodium sulfate and sodium triacetoxyborohydride to obtain the targeted compounds **18.** 1-Boc-4-piperidone was reacted with **16** under reductive amination conditions to obtain boc protected intermediates **17**. These on deprotection with IPA.HCl yielded targeted compounds **19** as HCl salts (Scheme 2).

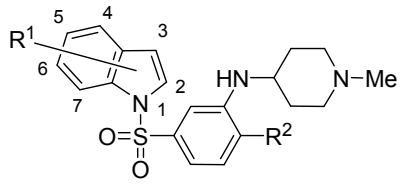
RESULTS AND DISCUSSION

We have synthesized a series of novel indole sulfonamides i.e. **Compounds-I** (**12a-12ad**, Table 1) and **Compounds-II** (**18a-18s** and **19a-19e**, Table 2). All the synthesized compounds were evaluated in a reporter gene based assay[18-19] for their functional activity at 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 the binding of a compound to GPCRs. The K_b and I_{max} (%) values of these compounds are given in Table 1 and Table 2.

We have initiated our initial SAR studies with commercially available unsubstituted indole. Several modifications (**12a-12d**) were attempted to arrive at the optimum substitution at R^2. All the synthesized compounds (**12a-12d**) were found to have potent *in vitro* affinity towards 5-HT_6R indicating that conformational constraint in compound **7** was well tolerated for binding affinity. With no clear preference to R^2 substitution in unsubstituted indole, we ran halo scan around indole nucleus by keeping R^2 as methoxy. Both 6-Cl and 5-Cl indole substituted compounds (**12e** and **12p**) were found to have potent 5-HT_6R affinity. However **12e** has clear preference over **12p** in terms of affinity with K_b of 0.14 nM. Replacement of methoxy group **(12e)** with ethyl (**12f**) and hydrogen (**12h**) at R^2 position gave less potent compounds as

compared to **12e**. Compounds **12n** and **12g** with 5-F and 6-F indole were also active. Compound **12i** (K_b = 1.91 nM) with 5-Br indole substitution was equipotent to **12n**.

Table 1. SAR of Compounds-I[a]



Compound	R^1	R^2	K_b (nM)	I_{max} (%)	CLogP
12a	H	OCH_3	1.22 ± 0.31	100	
12b	H	C_2H_5	1.39 ± 0.28	99	
12c	H	H	3.19 ± 0.27	92	
12d	H	F	1.6 ± 0.42	100	
12e	6-Cl	OCH_3	0.14 ± 0.02	100	
12f	6-Cl	C_2H_5	5.3 ± 1.59	98	
12g	6-F	OCH_3	0.2 ± 0.14	100	
12h	6-Cl	H	2.39 ± 0.55	98	
12i	5-Br	OCH_3	1.91 ± 0.43	97	
12j	5-Br	H	10.3 ± 2.05	98	
12k	5-Br	F	16.02 ± 4.94	94	
12l	5-F	CH_3	7.5 ± 1.41	97	
12m	5-F	C_2H_5	18.3 ± 4.03	95	
12n	5-F	OCH_3	1.80 ± 0.14	100	
12o	4-Cl	C_2H_5	12.80 ± 3.82	90	
12p	5-Cl	OCH_3	4.37 ± 0.82	98	
12q	5-OCH_3	OCH_3	3.80 ± 0.56	96	
12r	5-OCH_3	CH_3	51.30 ± 16.26	70	

12s	5-OCH_3	F	11.70 ± 2.50	95	
12t	5-OCH_3	H	12.50 ± 2.41	96	
12u	6-OCH_3	OCH_3	0.1 ± 0.07	100	
12v	6-OCH_3	CH_3	0.25 ± 0.07	98	
12w	6-OCH_3	Cl	3.30 ± 1.06	100	
12x	6-OCH_3	H	1.2 ± 0.28	100	
12y	5-$OCH(CH_3)_2$	OCH_3	2.2 ± 0.56	100	
12z	3-CH_3	F	0.52 ± 0.21	100	
12aa	5-F, 3-CH_3	OCH_3	0.52 ± 0.26	100	4.38
12ab	5-Cl, 3-CH_3	OCH_3	0.02 ± 0.01	100	4.95
12ac	6-Cl, 3-CH_3	OCH_3	0.1 ± 0.02	100	
12ad	6-OCH_3, 3-CH_3	OCH_3	0.1 ± 0.04	100	

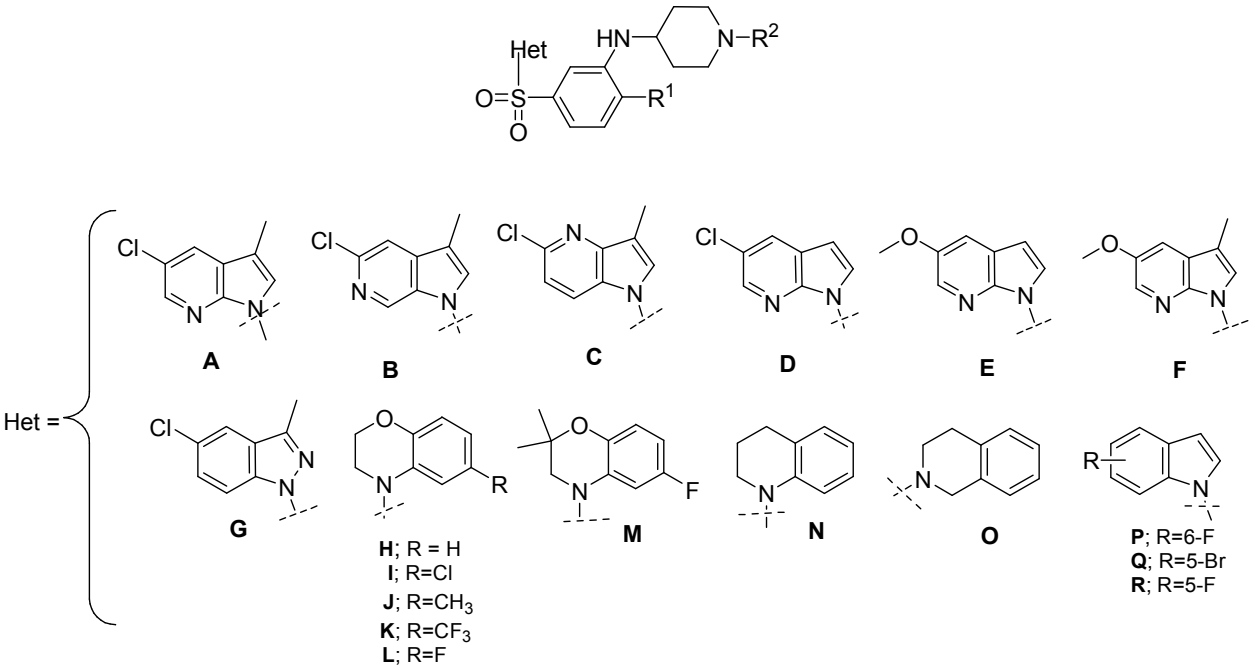
[a]The compounds were tested *in vitro* with non-radioactive based approach for determination of K_b values with cell-based assay for 5-HT_6R. Values are the average of at least two independent experiments. Compounds **12g**, **12h**, **12w** were tested as hydrochloride salts, while **12u**, **12v** and **12x** were tested as phosphate salts. Rests of the compounds were tested as free bases.

The other substitutions evaluated on indole ring include alkoxy groups (viz. OMe, OiPr) at 5 and 6 positions. Both 5-OMe and 6-OMe compounds were potent in terms of *in vitro* affinity. The most potent compound was **12u** (K_b = 0.1 nM) having 6-OMe indole and R^2 = OMe. It was observed that, there was considerable increase in potency after moving -OMe group from 5th position of indole (**12q**, K_b = 3.80 nM) to 6th position of indole (**12u**, K_b = 0.1 nM), indicating the preference for substitution at 6th position. Similar trend was observed with halo substitution as well (compare **12n** and **12g**). Generally, all 6-OMe indole analogues have shown potent 5-HT_6R affinities (**12u-12x**) with K_b in the range of 0.1 to 3.3 nM. In 5-OMe indole series, when R^2 was changed from -OMe **(12q,** K_b = 3.8 nM**)** to other substitutions like Me, F and H (**12r**, **12s** and **12t** with K_b = 51.3 nM, 11.7 nM, 12.5 nM respectively), there was nearly three to ten fold decrease in potency. Compound with 5-OiPr substitution on indole (**12y**, K_b = 2.2 nM) was also found to be

active like its analogue with 5-OMe substitution on indole (**12q**, K_b = 3.8 nM), indicating that higher alkoxy group was also well tolerated. 3-Me indole analogue **12z** was found to be three fold more potent (K_b = 0.52 nM) compared to compound **12d** (R^1=H, K_b = 1.6 nM). In 5-bromo indole compound (**12i**, K_b = 1.91 nM) replacement of methoxy at R^2 position with -H (**12j** with K_b = 10.3 nM) and -F (**12k** with K_b = 16.02 nM), gave less potent compounds. In 5-fluoro indole compound **12n** (K_b = 1.8 nM) when R^2 was replaced with lower alkyls viz. -Me (**12l,** K_b = 7.5 nM) and -Et (**12m,** K_b = 18.3 nM) gave compounds which were four to ten folds less potent than **12n**. In compounds **12f** and **12o**, where R^2 was –Et, the 6-chloro indole **12f** (K_b = 5.3 nM) was almost three fold more potent compared to 4-chloro indole **12o** (K_b = 12.8 nM). Most of the compounds, with diverse substitutions on indole were active towards 5-HT_6R, with few exceptions (viz. **12k, 12m, 12r** and **12t** with K_b values 16.02 nM, 18.3 nM, 51.3 nM and 12.5 nM respectively). Some di-substituted indoles, such as 5-halo-3-methyl, 6-halo-3-methyl and 6-alkoxy-3-methyl indoles **(12aa-12ad)** were also prepared for SAR studies. In general, all the synthesized compounds were found to have very potent binding affinities towards 5-HT_6R, with K_b < 4 nM. The 5-chloro-3-methyl indole analogue **12ab** (K_b < 0.02 nM) was found to be the most potent analog belonging to **Compounds-I**. The desmethyl analogues **19a-19c** (R^2 = H, Table 2) of **12g**, **12i** and **12n** respectively were found to have potent *in vitro* affinities with K_b values of 0.3 nM, 3.2 nM and 0.3 nM respectively. Since most of the modifications around indole nucleus gave us potent compounds, we did not make any further attempt to synthesize any additional analogs. As our main goal was to identify potent 5-HT_6R antagonist with adequate brain penetration, we have selected one of the most potent compounds each from mono (**12u**) and disubstituted (**12ab**) indoles for testing their brain penetration properties in the rat. The brain penetration ratio (C_{brain}/C_{plasma}) was found to be 0.6 ± 0.59 and 4.3 ± 0.9 for compound **12u** and **12ab** respectively, when dosed orally. Having achieved good brain penetration for **12ab,** we then

tested this compound for its target selectivity (serotonin subtypes, dopaminergic, transporters, α_{1B}, Histamine H_1 etc). The data, which is given in Table 5, indicate no major selectivity concerns over the tested receptors. Compound **12ab** had acceptable *in vitro* metabolic stability in both human (0 % metabolized) and rat (40 % metabolized) liver microsomes at 30 min. The IC_{50} values for CYP 2D6 and CYP 3A4 were found to be 14.7 μM and 6.46 μM respectively indicating less likely potential for drug-drug interactions in humans through the major metabolic enzymes tested (Table 3).

Table 2. SAR of Compounds-II[a]



Compound	Het	R^1	R^2	K_b (nM)	I_{max} (%)	CLogP
18a	A	H	CH_3	4 ± 0.71	99	
18b	A	CH_3	CH_3	3.9 ± 0.78	97	
18c	A	OCH_3	CH_3	0.04 ± 0.03	100	3.79

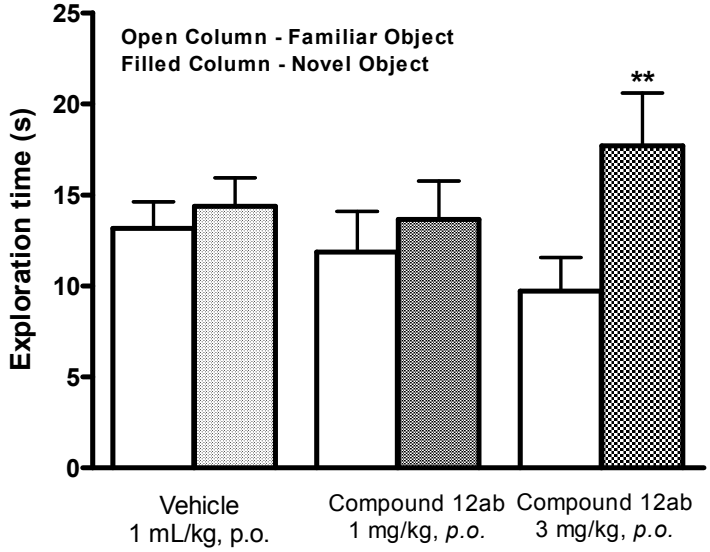
18d	B	OCH_3	CH_3	1.3 ± 0.42	85	
18e	C	OCH_3	CH_3	1.7 ± 0.56	98	
18f	D	OCH_3	CH_3	0.15 ± 0.07	98	
18g	E	OCH_3	CH_3	12 ± 2.82	90	
18h	F	OCH_3	CH_3	2.3 ± 0.69	95	
18i	G	OCH_3	CH_3	0.6 ± 0.14	100	2.36
18j	G	F	CH_3	10.1 ± 2.82	59	
18k	G	Cl	CH_3	28.6 ± 6.12	39	
18l	H	OCH_3	CH_3	0.2 ± 0.14	100	2.83
18m	I	OCH_3	CH_3	0.1 ± 0.014	100	
18n	L	OCH_3	CH_3	0.1 ± 0.015	100	
18o	J	OCH_3	CH_3	0.1 ± 0.013	100	
18p	K	OCH_3	CH_3	0.1 ± 0.014	100	
18q	M	OCH_3	CH_3	0.1 ± 0.014	100	
18r	N	OCH_3	CH_3	0.06 ± 0.04	100	
18s	O	OCH_3	CH_3	0.07 ± 0.01	98	
19a	P	OCH_3	H	0.3 ± 0.098	100	
19b	Q	OCH_3	H	3.2 ± 0.74	99	
19c	R	OCH_3	H	0.3 ± 0.07	100	
19d	A	OCH_3	H	0.1 ± 0.01	97	
19e	N	OCH_3	H	0.1 ± 0.014	100	

[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. Values are the average of at least two independent experiments. Compounds **18a**, **18b**, **18e**, **18f**, **18h**, **18i** and **18j** were tested as L-(+) tartarate salts. **19a**, **19b**, **19c**, **19d** and **19e** were tested as hydrochloride salts. Rest all were tested as free bases.

In rat pharmacokinetic experiment (Table 4) **12ab** showed acceptable pharmacokinetic properties (C_{max} = 296 ± 104 ng/mL, $t_{1/2}$ = 2.2 ± 0.8 h) and oral bioavailability (F = 75 ± 38 %).

Compound **12ab** was evaluated for its procognitive potential using a rat model of cognition i.e. object recognition task[20]. Compound **12ab** reversed the time delay induced memory deficit and the effect reached statistical significance at 3 mg/kg (Figure 3). This compound was further tested in 7 day repeated dose oral toxicity in rats to determine its safety. The compound exhibited phospholipidosis type of changes in multiple organs. The possible reason could be the high lipophilic nature[21] of the compound **12ab** (CLogP = 4.95, Cambridge Chemoffice software) which drive high tissue distribution inducting phospolipidosis. Later **12ab** was found to have hERG liability (K_i = 800 nM). The Phospholipidosis type of changes in multiple organs and hERG data makes this compound in particular and the scaffold in general less suitable for further development.

Figure 3. Episodic memory in adult rats for **12ab**



Data represents Mean ± SEM of exploration time (Students paired 't' test, **P<0.01).

Hence the next set of modifications were then targeted around compound **12ab** so as to get rid of the toxicity and hERG liability of this series while maintaining adequate levels of brain

penetration. To achieve this goal we thought of replacing indole with several other bicyclic heterocycles like azaindole, indazole, benzoxazine, tetrahydroquinoline, tetrahydroisoquinoline **(Compounds-II)**. Several analogs were synthesized (Table 2). Initially three analogs prepared with 5-Chloro-3-methyl-7-azaindole as Het (**18a-18c**) were found to maintain the potent binding affinity. However, amongst them, as expected **18c** (K_b = 0.04 nM) which is an azaindole analog of **12ab** was found to maintain a similar potency as that of **12ab**. Other regioisomers of **18c** were also prepared. Compound **18d** and **18e** with Het = 5-Chloro-3-methyl-6-azaindole and 5-Chloro-3-methyl-4-azaindole respectively as central core were found to be > 30 fold less potent compared to **18c**. Compound **18h** with Het = 5-methoxy-3-methyl-7-azaindole was found to be ~60 fold less potent compared to **18c**. It's close analog **18g** with Het = 5-methoxy-7-azaindole was found to be ~ 6 fold less potent as compared to **18h**. Compound **18f,** where Het is 5-Chloro-7-azaindole, was found to have almost equipotent activity as that of **18c**. We then next turned our attention to indazole type of compounds. Three analogs were prepared (**18i-18k**) where changes were made at R^1. Out of these compounds, **18i** was found to posses good *in vitro* potency for 5-HT_6R with K_b of 0.6 nM. We then introduced Het=variously substituted 2,3-dihydro-benzo[1,4]oxazine ring system and synthesized compounds **18l-18q.** All these compounds were found to have potent *in vitro* activity with K_b in the range of 0.1-0.2 nM. Compounds with tetrahydroquinoline (**18r**) and tetrahydroisoquinoline (**18s**) moieties were also found to maintain the *in vitro* potency with K_b < 0.1 nM. Compounds **19d**, K_b = 0.1 nM and **19e**, K_b = 0.1 nM which might be the possible metabolites of compounds **18c** and **18r** respectively maintained the functional activity towards 5-HT_6R, indicating secondary amines were also well tolerated.

Compounds **18c**, **18i**, **18m, 18r** and **18s** which are the most potent compounds and represent major changes brought about in **Compounds-II** were selected for brain penetration study to confirm that these structural modifications maintain the brain penetration. **18r** and **18s** were

found to have C_b/C_p ratio of 0.02 and 0.24 respectively and thus were not profiled further. Based on the adequate brain penetration ratio of **18c** (C_b/C_p = 0.9), **18i** (C_b/C_p = 0.5) and **18m** (C_b/C_p = 0.6), these three compounds were subjected to ADME surrogate assay (Table 3) and preclinical pharmacokinetic profiling (Table 4). All these compounds were moderately metabolized in human and rat liver microsomes and the CYP 3A4 and 2D6 inhibition values were found to be >10 μM except for **18m**. The pharmacokinetic studies conducted in rats for compound **18c** (Table 4) showed acceptable oral exposure (C_{max} = 156 ± 61 ng/mL), *i. v.* half life of 1.7 ± 0.1 h with oral bioavailability of 29 ± 5 %. Good oral bioavailability was observed in Beagle dogs as well (92 ± 25%) for compound **18c** with adequate oral exposure (C_{max} = 549 ± 69 ng/mL) and *i. v.* half life of 2.3 ± 0.8 h. The total clearance, after intravenous administration, was high in rats and low in dog for **18c**. The brain penetration of **18c** in rat was on a lower side (C_b/C_p = 0.9 ± 0.3) compared to that of compound **12ab** (C_b/C_p = 3.8 ± 0.2), possibly because of the polar nature of **18c** compared to **12ab**. We did not profile **18i** further because of its low oral exposure (C_{max} = 57 ± 19 ng/mL), high clearance (143 ± 41 mL/min/kg) and **18m** because of its poor bioavailability.

Table 3. CYP P450 inhibition and microsomal metabolic stability data for selected compounds

Compound	IC_{50} (μM)		Surrogate % Metabolism @ 30 min	
	2D6	3A4	Human	Wister Rat
12ab	14.70	6.46	0	40
18c	>45	10	72	76
18i	14.5	10	60	69
18m	27	2.8	70	85

The CYP P450 inhibitory potential was determined using isoform-selective assays using human liver microsomes. These values are the mean of duplicate determinations. Microsomal metabolic stability was performed at 30 min incubations in Wistar rat and Human (2.5 μM).

Table 4. Pharmacokinetic and brain penetration profile of selected compounds in rat and dog

Species		**Rat[a]**				**Dog[b]**
Compound		**12ab**	**18i**	**18m**	**18c**	**18c**
Intravenous	**Dose (mg/kg)**	10	5	5	5	1
	AUC_{0-24} (ng.hr/mL)	2756 ± 375	600 ± 164	1448 ± 175	1311 ± 249	1402 ± 479
	$t_{1/2}$ (h)	2.2 ± 0.8	1.7 ± 0.2	0.7 ± 0.1	1.7 ± 0.1	2.3 ± 0.8
	Vz (L/kg)	11 ± 2	16 ± 5	2.5 ± 0.6	10 ± 1	2.1 ± 0.2
	CL (mL/min/kg)	59 ± 8	143 ± 41	58 ± 7	64 ± 13	12 ± 3
Oral	**Dose (mg/kg)**	10	10	10	5	3
	C_{max} (ng/mL)	296 ± 104	57 ± 19	197 ± 240	156 ± 61	549 ± 69
	T_{max} (h)	1.67 ± 0.58	2.0 ± 0	0.50 ± 0	1.0 ± 0	1.7 ± 0.6
	AUC_{0-24} (ng.hr/mL)	2091 ± 1266	300 ± 90	384 ± 425	389 ± 143	3631 ± 203
	F (%)	75 ± 38	25 ± 2	12 ± 12	29 ± 5	92 ± 25
	$^{\#}C_b/C_p$	3.8 ± 0.2	0.5 ± 0.2	0.6 ± 0.5	0.9 ± 0.3	NA

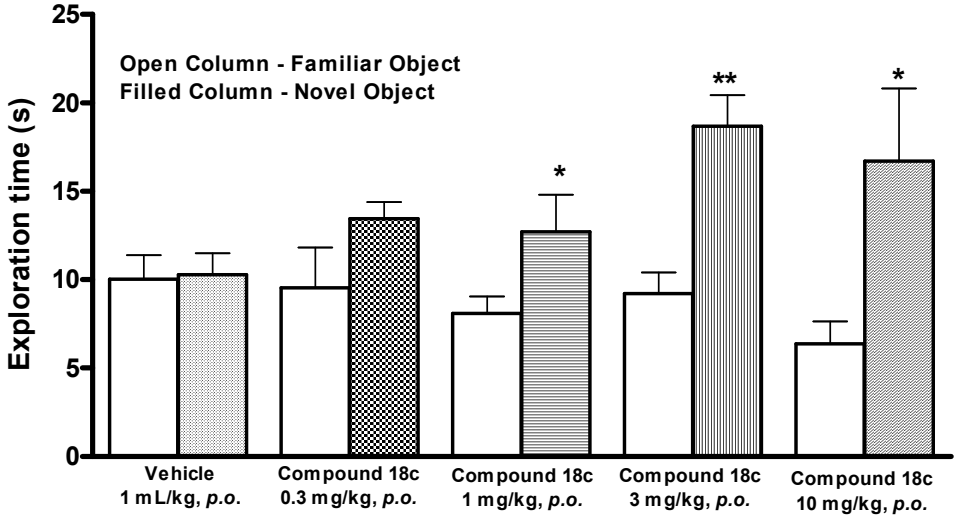
[a]Fasted male Wistar rats, water was used as a vehicle for dose formulation preparation. 10 mL/kg for oral and 2 mL/kg for intravenous was used as dosing volume. [b] Fasted male Beagle dogs, water was used as a vehicle for dose formulation preparation. 1 mL/kg was used as a dosing volume. Values are mean ± SD; N=3 animals/route. NA - Not applicable. # Discrete brain penetration was performed in rats at 10 mg/kg at 1 hour after oral administration

Table 5. Selectivity data[a]

Compound	12ab	18c
5-HT_6 K_b (nM)	2.7	0.04
5-HT_{2A} K_i (nM)	536	2374
5-HT_{2C} K_i (nM)	3124	2243
5-HT_7 K_i (nM)	6371	1956
D_2 K_i (nM)	302.6	1812
H_1 K_i (nM)	681.8	586
α_{1b} K_i (nM)	955.4	3791
SERT K_i (nM)	1942	>10000
DOPT K_i (nM)	2899	3221
NORT K_i (nM)	2006	2129
5-HT_4 EC_{50} (nM)	>10000	>10000
5-HT_3 IC_{50} (nM)	>10000	>10000
5-HT_{1A} EC_{50} (nM)	>1000	>10000

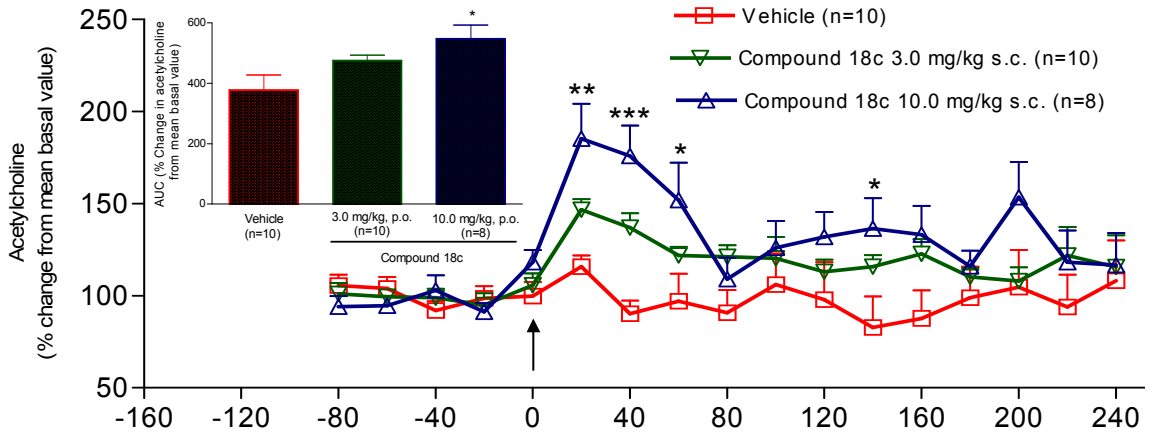
[a]Values are the average of at least two independent experiments.

Figure 4. Episodic memory in adult rats for **18c**



Data represents Mean ± SEM of exploration time (Students paired 't' test, *P<0.05, **P<0.01).

Figure 5. Effect of compound **18c** on acetylcholine modulation in medial prefrontal cortex.



Data expressed mean±SEM. *p<0.05, **p<0.01,***p<0.001 Vs vehicle

Given the hERG concern with **Compounds-I**, we have tested highly potent and selective **Compounds-II** for their hERG affinity by radioligand binding assay. In both series I and II compounds, we have observed a good correlation between hERG K_i value and the theoretical CLogP value. More the lipophilic nature of a compound, the stronger is its hERG inhibitory activity.[22] Lipophilic compounds **12aa** and **12ab** with ClogP of 4.38 and 4.95 respectively showed potent hERG inhibitory value of 950 nM and 800 nM. More polar compounds **18c** (Clog P = 3.79), **18i** (Clog P = 2.36) and **18l** (Clog P = 2.83) showed significantly lower inhibitory activities at the hERG channel with K_i >10 µM. The adequate C_b/C_p ratio, good pharmacokinetic profile in rat and dog and no hERG concern for **18c** has prompted us to subject this compound for detailed pharmacological profiling. In the rats object recognition task[20], Compound **18c** reversed the time delay induced memory deficit and the effect reached statistical significance at doses ranging from 1 - 10 mg/kg (Figure 4). Acetylcholine (ACh) modulation in medial prefrontal cortex was evaluated after subcutaneous administration of compound **18c** in Wistar rats using brain microdialysis.[23-24] Acute administration of compound **18c** (3 and 10 mg/kg)

increased extracellular ACh in medial prefrontal cortex in a dose dependent manner (Figure 5), the significant increase ($p > 0.05$) was observed at 10 mg/kg compare to vehicle treated animals. Pro-cognitive properties of **18c** are mediated through increase in cortical ACh levels in pre-clinical species.

CONCLUSION

Thus, starting from low brain penetrant compound **7**, through an iterative cycle we have identified novel series of **Compounds-I and II** which are highly potent, selective, brain penetrant and active in animal models of cognition. The correlation between the lipophilicity and hERG is reported for both the series of compounds. Based on its overall profile, compound **18c** was selected for further development.

EXPERIMENTAL SECTION

Chemistry All the reagents and chemicals used were of 'reagent grade'. Substituted indoles **8** (substituted indoles were either commercially procured or synthesized according to literature methods)[25], Aromatic heterocycles **13 (**5-chloroindazole, 5-chloro-7-aza-indole, tetrahydroquinoline and tetrahydroisoquinoline were commercially procured, whereas 5-chloro-4-azaindole, 5-chloro-6-azaindole and benzo[1,4]oxazine derivatives were synthesized according to literature methods).[26] Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates and spots visualization was accomplished with UV light (254 nm) and / or iodometry. Chromatography refers to column chromatography performed using 60-120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions. All the mentioned yields refer to isolated pure products. Melting points of synthesized compounds were determined using Electro thermal (Model-IA 9300 series) open capillary apparatus and are uncorrected. Infrared spectra were recorded on KBr disc and in solid state using Perkin-Elmer model 1600 FT-IR spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). Electrospray ionization mass spectra

were recorded on API 4000 triple quadrupole instrument (MDS-SCIEX, Concord, Ontario, Canada). ^{1}H-NMR spectra were obtained on a Bruker NMR spectrometer (Fallanden, Switzerland) at 400 MHz. Deuterated reagents were used as solvents and were commercially procured. Tetramethylsilane (TMS) was used as an internal standard. Chemical shift values were expressed in parts per million (δ) and coupling constants were expressed in Hz. Purity of the final compounds (>95%) was established using Agilent 1100 high-performance liquid chromatography (HPLC) system equipped with (i). XBridge column, 150 x 4.6 mm, S-5 µm with detection at 220 nm, using a UV-visible detector; flow rate = 1 mL/min; column temperature 30 ^{o}C, gradient elution over a run time of 35 min, using buffer : acetonitrile (buffer: 50mM $HCOONH_4$, adjusted to pH 9.0 with aqueous NH_3) and compounds **18a, 18d, 18e, 18l, 18m, 18n, 18p** and **18q** were tested using this method. (ii). YMC-pack-ODS-AM column, 250 x 4.6 mm, S-5 µm with detection at 220 nm, using a UV-visible detector; flow rate = 1 mL/min; column temperature 30 ^{o}C, gradient elution over a run time of 35 min, using buffer : acetonitrile (buffer: 0.05 % Et_3N in water, adjusted to pH 2.5 with CF_3COOH) and compounds **12a-12ad**, **18r, 18s, 19a-19c** and **19e** were tested using this method. (iii).YMC-pack-ODS-AM column, 250 x 4.6 mm, S-5 µm with detection at 220 nm, using a UV-visible detector; flow rate = 1 mL/min; column temperature 30 ^{o}C, gradient elution over a run time of 35 min, using buffer : acetonitrile (buffer: 5 mM CH_3COONH_4 in water, adjusted pH to 3.0 with HCOOH) and compounds **18b, 18c, 18f, 18g, 18h, 18i, 18j, 18k, 18o** and **19d** were tested using this method.

General procedures (10, 11, 12a-12ad)

The substituted indoles (**8,** 1 mmol) were reacted with commercially procured 4-substituted-3-nitrobenzenesulfonyl chlorides (**9**, 2 mmol) in presence of triethylamine (3 mmol) and dichloromethane. The reaction mass was stirred at rt for 24-48 hr. After completion of the reaction (TLC), the reaction mass was diluted with water and extracted with dichloromethane.

The organic layer was washed with brine solution, dried over sodium sulfate and concentrated under reduced pressure to obtain nitro intermediates **10** as residual mass which were used as such in the next step without purification.

The nitro intermediate (**10,** 1 mmol**),** thus obtained, was added to a stirred mixture of iron powder (10 mmol), ethanol : water (8:2) and conc.HCl (5 mmol). The reaction mass was heated at reflux for 2-10 h. After completion of the reaction (TLC), the reaction mass was filtered through celite bed and solvent was removed under reduced pressure to obtain a thick syrupy mass. The mass was diluted with excess of water, basified with aqueous sodium carbonate and extracted the product with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a syrupy mass, which was purified by flash column chromatography using ethylacetate : hexane (1:1) as eluent to obtain amine intermediates **11**. These amine intermediates **11** (1 mmol) were treated with 1-methyl-4-piperidone (3 mmol), sodium triacetoxyborohydride (3 mmol) and sodium sulfate (10 mmol) in acetic acid. The reaction mass was stirred for 6-24 h. After completion of the reaction (TLC), the reaction mass was poured onto water, neutralized with 40 % sodium hydroxide solution (pH~12) and extracted with dichloromethane. The organic layer was washed with brine solution, dried over sodium sulfate and concentrated under reduced pressure to obtain a syrupy mass, which was purified by flash column chromatography using ethylacetate : hexanes (8:2) as eluent to obtain the targeted compounds **12**.

1-(3-Nitro-4-methoxybenzenesulfonyl)-5-chloro-3-methyl-1*H*-indole (10, R^1=5-Cl, 3-CH_3, R^2=OCH_3): 3-Nitro-4-methoxybenzenesulfonyl chloride (15.2 g, 60.6 mmol) was added to a stirred solution of 5-chloro-3-methyl indole (5 g, 30.3 mmol), DCM (100 mL) and triethylamine (12.6 mL, 90.9 mmol) and the mass was further stirred for 24 h at room temperature. After completion of the reaction (TLC), the mixture was poured onto water (100 mL), separated the

organic layer, dried over sodium sulfate and concentrated under vacuum to obtain residual oil (crude). ESI Mass: m/e 381 $(M+H)^+$.

1-(3-Amino-4-methoxybenzenesulfonyl)-5-chloro-3-methyl-1*H*-indole (11, R^1=5-Cl, 3-CH_3, R^2=OCH_3): Concentrated hydrochloric acid (6.7 mL, 65.8 mmol) was added to a stirred solution of 1-(3-nitro-4-methoxybenzenesulfonyl)-5-chloro-3-methyl-1*H*-indole (**10**, 5 g, 13 mmol), iron powder (3.7 g, 65.8 mmol) and ethanol : water (40 mL : 10 mL) mixture. The mixture was refluxed for 3 h. After completion of the reaction (TLC), the mixture was cooled to room temperature and removed solvent under vacuum. The residual mass was stirred with water (100 mL) and ethyl acetate (100 mL) for 15 min. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo. The resultant residual mass was chromatographed (silica gel, 2:8 to 1:1 ethylacetate-hexanes as eluent) to obtain the title compound, as brown solid (2.5 g, 54% yield). IR (cm^{-1}): 3480, 3384, 1286, 1167; ESI Mass: m/e 351 $(M+H)^+$; M.R (^OC): 139-141; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.20 (s, 3H), 3.83 (s, 3H), 4.01 (bs, 2H), 6.73-6.70 (d, *J* = 8.50 Hz, 1H), 7.06 (d, *J* = 2.27 Hz, 1H), 7.23-7.29 (m, 3H), 7.40-7.41 (d, *J* = 1.96 Hz, 1H), 7.87-7.89 (d, *J* = 8.78 Hz, 1H), 7.50-7.53 (m, 2H), 8.01-8.03 (d, *J* = 8.20 Hz, 1H); HPLC purity: 98.9 %.

General procedure for the preparation of phosphate salt: The compounds **12** (1 mmol) were treated with ortho phosphoric acid (2 mmol) in dichloromethane : IPA (2 : 8) and stirred for 2 h at 25-30 ^oC. The solids that separated were filtered and dried under reduced pressure to obtain the phosphate salt.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-indole (12ab, R^1=5-Cl,3-CH_3, R^2=OCH_3). Sodium triacetoxyborohydride (4.33 g, 20.55 mmol) was added in portions to a stirred suspension of 1-(3-amino-4-methoxy benzenesulfonyl)-1H-5-chloro-3-methyl indole (2.4 g, 6.85 mmol), 1-methyl-4-piperidone (2.3 g, 20.55 mmol), sodium

sulfate (9.7 g, 68.5 mmol) in glacial acetic acid (30 mL) at room temperature under N_2 atmosphere. The mass was stirred overnight at room temperature. After completion of the reaction (TLC), the mixture was poured onto cold water, neutralized with aq.NaOH solution and extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain an oily residue. The mass was chromatographed (neutral silica gel, 80:20 ethylacetate-hexanes, and then ethylacetate) to afford the title product as pale yellow solid (1.8 g, 60 % yield). IR (cm^{-1}): 3427, 2935, 1359, 1165, 1126; ESI Mass: m/e 448 $(M+H)^+$; M.R (^OC): 141-144; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36-1.45 (m, 2H), 1.84-1.87 (m, 2H), 2.08-2.13 (m, 2H), 2.19 (s, 3H), 2.32 (s, 3H), 2.77-2.80 (m, 2H), 3.13-3.15 (m, 1H), 3.82 (s, 3H), 4.21-4.23 (d, 1H), 6.65-6.67 (d, *J* = 8.44 Hz, 1H), 6.78-6.79 (d, *J* = 2.20 Hz, 1H), 7.13-7.16 (dd, *J* = 8.40, 2.28 Hz, 1H), 7.23-7.28 (m, 2H), 7.40 (d, *J* = 1.92 Hz, 1H), 7.93-7.95 (d, *J* = 8.80 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 9.47, 31.85, 46.16, 54.34, 55.58, 106.15, 108.43, 114.79, 115.57, 117.64, 119.0, 124.39, 124.70, 128.61, 130.05, 132.94, 133.85, 137.12, 150.40; HPLC purity: 99 %.

Compounds **12a-12aa** and **12ac-12ad** were prepared analogously.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-1*H*-indole (12a). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3412, 2937, 1267, 1165; ESI Mass: m/e 400 $(M+H)^+$; M.R (^OC): 140-142; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.35-1.44 (m, 2H), 1.85-1.89 (m, 2H), 2.08-2.14 (m, 2H), 2.31 (s, 3H), 2.75-2.78 (m, 2H), 3.15-3.20 (m, 1H), 3.80 (s, 3H), 4.20-4.22 (d, 1H), 6..61-6.62 (d, *J* = 3.60 Hz, 1H), 6.65-6.67 (d, *J* = 8.48 Hz, 1H), 6.86-6.87 (d, *J* = 2.24 Hz, 1H), 7.18-7.28 (m, 3H), 7.50-7.53 (m, 2H), 8.01-8.03 (d, *J* = 8.20 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-ethylbenzenesulfonyl]-1*H*-indole (12b). The title compound was prepared using essentially the same procedure as described for the preparation of

12ab. IR (cm^{-1}): 3429, 2939, 2783, 1519, 1440, 1367, 1267, 1166, 1132; M.R (^{O}C): 144-145; ESI Mass: m/e 398 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.15-1.18 (t, 3H), 1.36-1.44 (m, 2H), 1.88-1.92 (m, 2H), 2.10-2.16 (m, 2H), 2.32 (s, 3H), 2.33-2.38 (q, 2H), 2.74-2.77 (m, 2H), 3.23-3.25 (m, 1H), 3.57-3.59 (d, 1H), 6.63 (d, *J* = 3.68 Hz, 1H), 6.92-6.93 (d, *J* = 1.72 Hz, 1H), 7.05-7.07 (d, *J* = 7.96 Hz, 1H), 7.13-7.54 (m, 5H), 8.02-8.04 (d, *J* = 8.28 Hz, 1H); HPLC purity: 98 %.

1-[3-(1-Methylpiperidin-4-yl amino)benzenesulfonyl]-1*H*-indole (12c). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3244, 2934, 2800, 1599, 1352, 1167, 1133; ESI Mass: m/e 370 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36-1.45 (m, 2H), 1.89-1.96 (m, 2H), 2.04-2.30 (m, 2H), 2.30 (s, 3H), 2.76-2.79 (m, 2H), 3.17-3.19 (m, 1H), 3.77-3.79 (d, 1H), 6.64-6.65 (m, 2H), 6.95-6.96 (t, 1H), 7.12-7.30 (m, 4H), 7.52-7.54 (m, 2H), 7.99-8.01 (d, *J* = 8.28 Hz, 1H); HPLC purity: 97 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-fluorobenzenesulfonyl]-1*H*-indole (12d). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3404, 2939, 1522, 1375, 1130; ESI Mass: m/e 388 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.40-1.47 (m, 2H), 1.85-1.90 (m, 2H), 2.10-2.15 (m, 2H), 2.32 (s, 3H), 2.77-2.79 (m, 2H), 3.13-3.22 (m, 1H), 3.92-3.95 (m, 1H), 6.65-6.66 (m, 1H), 6.92-6.94 (d, *J* = 8.4 Hz, 1H), 6.95-6.97 (d, *J* = 8.44 Hz, 1H), 7.00-7.30 (m, 4H), 7.50-7.52 (m, 1H), 7.99 (m, 1H); HPLC purity: 97 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-chloro-1*H*-indole (12e). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3423, 2937, 1520, 1268, 1135; M.R (^{O}C): 147-149; ESI Mass: m/e 434 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.40-1.49 (m, 2H), 1.91-1.95 (m, 2H), 2.14-2.19 (m, 2H), 2.32 (s, 3H), 2.78-2.81 (m, 2H), 3.17-3.21 (m, 1H), 3.83 (s, 3H), 4.25-4.27 (d, 1H), 6.58-6.59 (d, *J* = 3.56 Hz, 1H), 6.66-6.71 (d, *J* = 8.52 Hz, 1H), 6.90-6.90 (d, *J* = 2.28 Hz, 1H),

7.17-7.2 (m, 2H), 7.41-7.43 (d, *J* = 8.36 Hz, 1H), 7.51-7.52 (d, *J* = 3.64 Hz, 1H), 8.05-8.06 (d, *J* = 1.56 Hz, 1H); HPLC purity: 98 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-ethylbenzenesulfonyl]-6-chloro-1*H*-indole (12f). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3424, 2935, 1598, 1355, 1268, 1165, 1136; M.R (^{O}C): 143-147. ESI Mass: m/e 432 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.16-1.20 (t, 3H), 1.43-1.45 (m, 2H), 1.94-2.01 (m, 2H), 2.16-2.21 (m, 2H), 2.32 (s, 3H), 2.35-2.40 (q, 2H), 2.77-2.80 (d, 2H), 3.27-3.29 (m, 1H), 3.62-3.64 (m, 1H), 6.59-6.60 (d, *J* = 3.56 Hz, 1H), 6.97-6.98 (d, *J* = 1.49 Hz, 1H), 7.07-7.14 (m, 2H), 7.18-7.20 (dd, *J* = 8.36, 1.77 Hz, 1H), 7.42-7.44 (d, *J* = 8.38 Hz, 1H), 7.52-7.53 (d, *J* = 3.60 Hz, 1H), 8.06 (bs, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-fluoro-1*H*-indole hydrochloride (12g). The free base of title compound was prepared using essentially the same procedure as described for the preparation of 12ab. This was converted to its hydrochloride salt (**12g)** by treating with IPA.HCl. IR (cm^{-1}): 3408, 2944, 2669, 1611, 1521, 1166; ESI Mass: m/e 418 $(M+H)^+$; M.R (^{O}C): 150-152; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.69-1.75 (m, 2H), 1.83-1.836 (m, 2H), 2.72 (s, 3H), 3.10-3.15 (m, 2H), 3.38-3.41 (m, 2H), 3.60 (m, 1H), 3.78 (s, 3H), 3.82 (bs, 1H), 6.78-6.79 (m, 1H), 6.91-7.23 (m, 4H), 7.59-7.62 (m, 1H), 7.76-7.78 (m, 2H), 10.60 (s, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)benzenesulfonyl]-6-chloro-1*H*-indole hydrochloride (12h). The free base of title compound was prepared using essentially the same procedure as described for the preparation of 12ab. This was converted to its hydrochloride salt (**12h)** by treating with IPA.HCl. IR (cm^{-1}): 3403, 2939, 2797, 1601, 1374, 1174, 1139. ESI Mass: m/e 404 $(M+H)^+$; M.R (^{O}C): 126-128; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.43-1.48 (m, 2H), 1.92-1.97 (m, 2H), 2.10-2.16 (m, 2H), 2.31 (s, 3H), 2.78-2.81 (m, 2H), 3.19-3.26 (m, 1H), 3.81-3.83 (d, 1H),

6.60-6.61 (d, *J* = 3.99 Hz, 1H), 6.66-6.69 (m, 1H), 6.97-6.98 (m, 1H), 7.09-7.11 (m, 1H), 7.16-7.18 (d, *J* = 7.97 Hz, 1H), 7.19-7.21 (m, 1H), 7.42-7.45 (d, *J* = 8.37 Hz, 1H), 7.51-7.52 (d, *J* = 3.73 Hz, 1H), 8.03 (bs, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-bromo-1*H*-indole (12i). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3404, 2931, 2783, 1440, 1354, 1259, 1145; M.R (^0C): 115-116; ESI Mass: m/e 478, 480 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.37-1.46 (m, 2H), 1.85-1.88 (m, 2H), 2.08-2.16 (m, 2H), 2.32 (s, 3H), 2.78-2.81 (m, 2H), 3.11-3.18 (m, 1H), 3.83 (s, 3H), 4.23-4.25 (d, 1H), 6.55-6.56 (d, *J* = 3.64 Hz, 1H), 6.67-6.69 (d, *J* = 8.44 Hz, 1H), 6.79-6.80 (d, *J* = 2.24 Hz, 1H), 7.16-7.19 (dd, *J* = 8.44, 2.28 Hz, 1H), 7.37-7.39 (dd, *J* = 8.80, 1.88 Hz, 1H), 7.52-7.53 (d, *J* = 3.64 Hz, 1H), 7.65 (d, *J* = 1.84 Hz, 1H), 7.89-7.91 (d, *J* = 8.80 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)benzenesulfonyl]-5-bromo-1*H*-indole (12j). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3406, 1601, 1368, 1439, 1368, 1170, 1129; ESI Mass: m/e 448, 450 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.42-1.47 (m, 2H), 1.89-1.93 (m, 2H), 2.08-2.17 (m, 2H), 2.32 (s, 3H), 2.79-2.82 (m, 2H), 3.17-3.19 (m, 1H), 3.79-3.81 (d, 1H), 6.58-6.59 (d, *J* = 3.64 Hz, 1H), 6.66-6.68 (m, 1H), 6.89-6.90 (m, 1H), 7.09-7.18 (m, 2H), 7.38-7.41 (dd, *J* = 7.92, 1.8 Hz, 1H), 7.52-7.53 (d, *J* = 3.68 Hz, 1H), 7.66-7.67 (d, *J* = 1.88 Hz, 1H), 7.87-7.89 (d, *J* = 8.80 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-fluorobenzenesulfonyl]-5-bromo-1*H*-indole (12k). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3396, 2931, 2789, 1616, 1521, 1367, 1165, 1118. ESI Mass: m/e 466, 468 $(M+H)^+$; M.R (^OC): 85-87; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.39-1.48 (m, 2H), 1.85-

1.88 (m, 2H), 2.09-2.17 (m, 2H), 2.33 (s, 3H), 2.78-2.81 (m, 2H), 3.16-3.17 (m, 1H), 3.96-3.97 (d, 1H), 6.59-6.60 (d, *J* = 3.56 Hz, 1H), 6.94-6.97 (m, 1H), 6.98-6.99 (d, *J* = 3.67 Hz, 1H), 7.07-7.11 (m, 1H), 7.39-7.42 (dd, *J* = 8.8, 1.84 Hz, 1H), 7.50-7.52 (d, *J* = 3.64 Hz, 1H), 7.67 (d, *J* = 1.80 Hz, 1H), 7.88-7.90 (d, *J* = 8.80 Hz, 1H); HPLC purity: 99.8 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methylbenzenesulfonyl]-5-fluoro-1*H*-indole (12l). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3422, 2940, 1459, 1367, 1170, 1138; M.R (^{O}C): 129-131; ESI Mass: m/e 402 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.39-1.46 (m, 2H), 1.88-1.91 (m, 2H), 2.05 (s, 3H), 2.11-2.16 (m, 2H), 2.33 (s, 3H), 2.78-2.80 (m, 2H), 3.17-3.28 (m, 1H), 3.51-3.52 (m, 1H), 6.58-6.59 (d, *J* = 3.68 Hz, 1H), 6.83-6.87 (m, 1H), 6.98-7.10 (m, 3H), 7.15-7.18 (dd, *J* = 8.77, 2.5 Hz, 1H), 7.56-7.56 (d, *J* = 3.61 Hz, 1H), 7.94-7.98 (dd, *J* = 9.06, 4.65 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-ethylbenzenesulfonyl]-5-fluoro-1*H*-indole (12m). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3428, 2933, 1359, 1271, 1165, 1133; ESI Mass: m/e 416 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.18-1.21 (t, 3H), 1.43-1.46 (m, 2H), 1.98-2.01 (m, 2H), 2.18-2.24 (m, 2H), 2.35 (s, 3H), 2.38-2.42 (q, 2H), 2.75-2.78 (d, 2H), 3.30 (m, 1H), 3.61-3.63 (m, 1H), 6.60-6.98 (m, 2H), 7.11-7.15 (m, 2H), 7.18-7.19 (m, 1H), 7.49-7.51 (d, 1H), 7.59-7.60 (d, *J* = 3.64 Hz, 1H), 8.1 (bs, 1H); HPLC purity: 95 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-fluoro-1*H*-indole (12n). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3424, 2939, 1519, 1367, 1160, 1139; ESI Mass: m/e 418 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38-1.48 (m, 2H), 1.86-1.90 (m, 2H), 2.11-2.16 (m, 2H), 2.33 (s, 3H), 2.79-2.82 (m, 2H), 3.16-3.18 (m, 1H), 3.82 (s, 3H), 4.23-4.25 (d, 1H), 6.58 (d, *J* = 3.60 Hz,

1H), 6.67-6.69 (d, *J* = 8.48 Hz, 1H), 6.82 (d, *J* = 2.28 Hz, 1H), 7.01-7.02 (d, *J* = 2.52 Hz, 1H), 7.15-7.19 (m, 2H), 7.55-7.56 (d, *J* = 3.6 Hz, 1H), 7.94-7.97 (m, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-ethylbenzenesulfonyl]-4-chloro-1*H*-indole (12o). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3427, 3124, 2927, 1587, 1512, 1359, 1274, 1166, 1139; ESI Mass: m/e 432, 434 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.16-1.19 (t, 3H), 1.41-1.46 (m, 2H), 1.89-1.93 (m, 2H), 2.12-2.17 (m, 2H), 2.33 (s, 3H), 2.34-2.39 (q, 2H), 2.77-2.79 (m, 2H), 3.24-3.25 (m, 1H), 3.61-3.63 (d, 1H), 6.75-6.76 (d, *J* = 3.72 Hz, 1H), 6.88-6.89 (d, *J* = 1.76 Hz, 1H), 7.07-7.09 (d, *J* = 7.96 Hz, 1H), 7.13-7.23 (m, 3H), 7.58-7.59 (d, *J* = 3.68 Hz, 1H), 7.92-7.94 (m, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-1*H*-indole (12p). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3418, 2940, 1519, 1166, 1129; ESI Mass: m/e 434, 436 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38-1.44 (2H, m), 1.85-1.89 (m, 2H), 2.09-2.15 (m, 2H), 2.33 (s, 3H), 2.79-2.81 (m, 2H), 3.09-3.20 (m, 1H), 3.82 (s, 3H), 4.23-4.25 (m, 1H), 6.55-6.56 (m, 1H), 6.67-6.69 (d, *J* = 8.48 Hz, 1H), 6.80-6.81 (d, *J* = 2.28 Hz, 1H), 7.16-7.19 (dd, *J* = 8.48, 2.4, 2.32 Hz, 1H), 7.23-7.26 (m, 1H), 7.48-7.49 (d, *J* = 2.04 Hz, 1H), 7.54 (d, *J* = 3.6 Hz, 1H), 7.94-7.96 (d, *J* = 8.92 Hz, 1H); HPLC purity: 98 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-methoxy-1*H*-indole (12q). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3400, 2941, 1521, 1169, 1148; M.R (^OC): 118-120; ESI Mass: m/e 430 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.37-1.46 (m, 2H), 1.86-1.90 (m, 2H), 2.10-2.16 (m, 2H), 2.33 (s, 3H), 2.78-2.81 (m, 2H), 3.15-3.17 (m, 1H), 3.80-3.81 (d, 6H), 4.20-4.22 (d, *J* = 7.91 Hz, 1H), 6.54–6.55 (d, *J* = 3.62 Hz, 1H), 6.65-6.67 (d, *J* = 8.47 Hz, 1H), 6.82-6.83

(d, *J* = 2.22 Hz, 1H), 6.88-6.91 (dd, *J* = 9.02, 2.48 Hz, 1H), 6.95-6.96 (d, *J* = 2.25 Hz, 1H), 7.15-7.18 (dd, *J* = 8.42, 2.25 Hz, 1H), 7.47-7.48 (d, *J* = 3.59 Hz, 1H), 7.90-7.92 (d, *J* = 8.96 Hz, 1H); HPLC purity: 98 **%.**

1-[3-(1-Methylpiperidin-4-yl amino)-4-methylbenzenesulfonyl]-5-methoxy-1*H*-indole (12r). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3412, 1928, 1467, 1364, 1147; ESI Mass: m/e 414 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.42-1.48 (m, 2H), 1.88-1.92 (m, 2H), 2.04 (s, 3H), 2.10-2.17 (m, 2H), 2.35 (s, 3H), 2.81-2.84 (m, 2H), 3.19-3.28 (m, 2H), 3.47-3.52 (m, 1H), 3.81 (s, 3H), 6.55-6.56 (d, *J* = 3.56 Hz, 1H), 6.86 (d, *J* = 1.52 Hz, 1H), 6.88-6.91 (dd, *J* = 9.02, 2.52 Hz, 1H), 6.96 (d, *J* = 2.48 Hz, 1H), 7.03-7.05 (d, *J* = 7.88 Hz, 1H), 7.06-7.09 (dd, *J* = 7.82, 1.72 Hz, 1H), 7.47-7.48 (d, *J* = 3.6 Hz, 1H), 7.90-7.92 (d, *J* = 8.96 Hz, 1H); HPLC purity: 98 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-fluorobenzenesulfonyl]-5-methoxy-1*H*-indole (12s). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3400, 3138, 2943, 1610, 1525, 169, 1224, 1145; M.R (^OC): 157-160; ESI Mass: m/e 418 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.44-1.49 (m, 2H), 1.87-1.90 (m, 2H), 2.12-2.17 (m, 2H), 2.34 (s, 3H), 2.81-2.83 (m, 2H), 3.18 (m, 1H), 3.81 (s, 3H), 3.93-3.94 (m, 1H), 6.58 (d, *J* = 3.56 Hz, 1H), 6.90-6.99 (m, 4H), 7.07-7.09 (m, 1H), 7.45-7.46 (d, 1H), 7.88-7.90 (d, 1H); HPLC purity: 98.5 %.

1-[3-(1-Methylpiperidin-4-yl amino)benzenesulfonyl]-5-methoxy-1*H*-indole (12t). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3410, 3255, 1600, 1366, 1225, 1148; ESI Mass: m/e 400 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38-1.48 (m, 2H), 1.90-2.00 (m, 2H), 2.10-2.15 (m, 2H), 2.32 (s, 3H), 2.80-2.82 (m, 2H), 3.18-3.20 (m, 1H), 3.76-3.78 (d, 1H), 3.81 (s, 3H), 6.57-6.58 (d, *J* = 3.56 Hz, 1H),

6.64-6.66 (m, 1H), 6.90-6.93 (m, 2H), 6.97 (d, *J* = 2.26 Hz, 1H), 7.09-7.14 (m, 2H), 7.48-7.49 (d, *J* = 3.59 Hz, 1H), 7.88-7.90 (d, *J* = 9.07 Hz, 1H); HPLC purity: 95 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-methoxy-1*H*-indole phosphate (12u). The free base of title compound was prepared using essentially the same procedure as described for the preparation of 12ab. This was converted to its phosphate salt (**12u)** by treating with o-phosphoric acid. IR (cm^{-1}): 3391, 2951, 1614, 1522, 1285, 1215, 1166, 1115, 1013; ESI Mass: m/e 430 $(M+H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.51-1.56 (m, 2H), 1.74-1.77 (m, 2H), 2.52-2.54 (m, 2H), 3.02-3.07 (m, 2H), 3.15 (s, 3H), 3.37 (m, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 5.18-5.20 (d, 1H), 6.68-6.69 (d, *J* = 3.67 Hz, 1H), 6.83-6.92 (m, 3H), 7.16-7.19 (dd, *J* = 8.48, 2.25 Hz, 1H), 7.42-7.46 (m, 2H), 7.59-7.60 (d, *J* = 3.70 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methylbenzenesulfonyl]-6-methoxy-1*H*-indole diphosphate (12v). The free base of title compound was prepared using essentially the same procedure as described for the preparation of 12ab. This was converted to its phosphate salt (**12v)** by treating with o-phosphoric acid. IR (cm^{-1}): 3416, 2946, 1362, 1214, 1168; M.R (^0C): 182-186; ESI Mass: m/e 414 $(M+H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.60 (bs, 2H), 1.85-1.89 (m, 2H), 2.05 (s, 3H), 2.49-2.52 (m, 2H), 2.65 (m, 2H), 3.10 (m, 3H), 3.80 (s, 3H), 5.10 (bs, 1H), 6.69-6.70 (d, *J* = 3.54 Hz, 1H), 6.82 (s, 1H), 6.87-6.90 (dd, *J* = 8.60, 2.18 Hz, 1H), 7.04-7.06 (dd, *J* = 7.78, 1.46 Hz, 1H), 7.12-7.14 (d, *J* = 7.83 Hz, 1H), 7.40-7.41 (d, *J* = 1.9 Hz, 1H), 7.45-7.47 (d, *J* = 8.62 Hz, 1H), 7.58-7.59 (d, *J* = 3.59 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-chlorobenzenesulfonyl]-6-methoxy-1*H*-indole hydrochloride (12w). The free base of title compound was prepared using essentially the same procedure as described for the preparation of 12ab. This was converted to its hydrochloride salt (**12w)** by treating with IPA.HCl. IR (cm^{-1}): 3421, 3092, 2944, 1614, 1370, 1166, 1118; ESI Mass: m/e 434 $(M+H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.70-1.76 (m, 2H), 1.82-1.85 (m,

2H), 2.76 (s, 3H), 3.09-3.11 (m, 2H), 3.22 (m, 2H), 3.65 (m, 1H), 3.81 (s, 3H), 5.80-5.82 (d, 1H), 6.74-6.75 (d, *J* = 3.32 Hz, 1H), 6.90-6.92 (m, 1H), 7.09-7.12 (m, 2H), 7.41-7.49 (m, 3H), 7.63-7.64 (d, *J* = 3.42 Hz, 1H), 10.03 (bs, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)benzenesulfonyl]-6-methoxy-1*H*-indole phosphate (12x). The free base of title compound was prepared using essentially the same procedure as described for the preparation of 12ab. This was converted to its phosphate salt (**12x)** by treating with o-phosphoric acid. IR (cm-1): 3379, 2719, 1601, 1213, 1174, 1116; M.R (^{O}C): 145-148; ESI Mass: m/e 400 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.44-1.76 (m, 2H), 1.83-1.86 (m, 2H), 2.54-2.57 (m, 2H), 3.02 (s, 3H), 3.30 (m, 2H), 3.80 (s, 3H), 4.07 (m, 1H), 6.72-6.73 (d, J = 3.76 Hz, 1H), 6.79-6.81 (m, 1H), 6.88-6.90 (dd, J = 8.65, 2.23 Hz, 1H), 7.00-7.02 (m, 2H), 7.20-7.24 (m, 1H), 7.38 (bs, 1H), 7.47-7.49 (d, J = 8.62 Hz, 1H), 7.56-7.57 (d, J = 3.66 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-isopropoxy-1*H*-indole (12y). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3403, 2937, 1519, 1454, 1147; ESI Mass: m/e 458 $(M+H)^+$; M.R (^{O}C): 116-118; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31-1.32 (d, *J* = 6.08 Hz, 6H), 1.39-1.44 (m, 2H), 1.86-1.89 (m, 2H), 2.08-2.14 (m, 2H), 2.31 (s, 3H), 2.76-2.79 (m, 2H), 3.15-3.17 (m, 1H), 3.81 (s, 3H), 4.20-4.22 (d, *J* = 7.84 Hz, 1H), 4.47-4.53 (q, 1H), 6.52-6.53 (d, *J* = 3.6 Hz, 1H), 6.65-6.67 (d, *J* = 8.52 Hz, 1H), 6.83-6.84 (d, *J* = 2.2 Hz, 1H), 6.86-6.89 (dd, *J* = 8.98, 2.44 Hz, 1H), 6.95-6.96 (d, *J* = 2.4 Hz, 1H), 7.16-7.18 (dd, *J* = 8.40, 2.24 Hz), 7.46-7.47 (d, *J* = 3.6 Hz, 1H), 7.88-7.90 (d, *J* = 9.0 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-fluorobenzenesulfonyl]-3-methyl-1*H*-indole (12z). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3398, 2939, 1365, 1168, 1128; ESI Mass: m/e 402 $(M+H)^+$; M.R

(^{O}C): 136-138; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38-1.47 (m, 2H), 1.85-1.88 (m, 2H), 2.10-2.15 (m, 2H), 2.23 (s, 3H), 2.33 (s, 3H), 2.77-2.80 (m, 2H), 3.17-3.19 (m, 1H), 3.91-3.92 (d, 1H), 6.91-6.95 (m, 1H), 6.98-7.01 (dd, *J* = 8.46, 2.20 Hz, 1H), 7.07-7.11 (m, 1H), 7.23-7.32 (m, 3H), 7.45-7.47 (d, *J* = 7.57 Hz, 1H), 7.98-8.01 (d, *J* = 8.16 Hz, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-fluoro-3-methyl-1*H*-indole (12aa). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3417, 2931, 2773, 1593, 1363, 1159, 1103; ESI Mass: m/e 432 $(M+H)^+$; M.R (^{O}C): 172-174; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36–1.45 (m, 2H), 1.85-1.88 (m, 2H), 2.08-2.13 (m, 2H), 2.18 (s, 3H), 2.32 (s, 3H), 2.77-2.80 (m, 2H), 3.14-3.16 (m, 1H), 3.81 (s, 3H), 4.20-4.22 (d, 1H), 6.65-6.67 (d, *J* = 8.44 Hz, 1H), 6.80 (d, *J* = 2.24 Hz, 1H), 7.00-7.09 (m, 2H), 7.13-7.16 (m, 1H), 7.30 (m, 1H), 7.93-7.96 (m, 1H); HPLC purity: 99 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-chloro-3-methyl-1*H*-indole (12ac). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. IR (cm^{-1}): 3400, 2937, 2779, 1518, 1363, 1169, 1136; M.R (^{0}C): 179-181; ESI Mass: m/e 448 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40-1.47 (m, 2H), 1.62 (m, 2H), 1.90-1.93 (m, 2H), 2.20 (s, 3H), 2.32 (s, 3H), 2.78-2.81 (m, 2H), 3.19 (m, 1H), 3.83 (s, 3H), 4.23-4.25 (d, 1H), 6.68-6.70 (d, *J* = 8.38 Hz, 1H), 6.88 (bs, 1H), 7.15-7.35 (m, 4H), 8.04 (bs, 1H); HPLC purity: 98 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-methoxy-3-methyl-1*H*-indole (12ad). The title compound was prepared using essentially the same procedure as described for the preparation of 12ab. ESI Mass: m/e 444 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.71-1.83 (m, 2H), 1.99-2.02 (m, 2H), 2.18 (s, 3H), 2.87 (s, 3H), 3.08-3.17 (m, 2H), 3.44-3.51

(m, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 6.85-6.90 (m, 3H), 7.20 (m, 2H), 7.34-7.36 (d, *J* = 8.62 Hz, 1H), 7.53 (s, 1H); HPLC purity: 99.54 %.

General procedures (Compounds 13, 14, 15, 16, 17, 18a-18s and 19a-19e)

2-(Substituted/unsubstituted) anilines (1 mmol) were reacted with trifluoroacetic anhydride (1.2 mmol) in presence of pyridine (1.5 mmol) in dichloromethane at 0-5 ^{o}C. After completion of the reaction (TLC), the reaction mass was poured onto water and the product was extracted with ethylacetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain N-(2-substituted/unsubstituted phenyl)-2,2,2-trifluoro acetamide. This was treated with chlorosulfonic acid (1.5 mmol) in dichloromethane at 0-5 ^{o}C. The mixture was stirred for 2 h. After completion of the reaction (TLC), the reaction mass was carefully poured onto ice-water and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain 4-(substituted/unsubstituted)-3-(2,2,2-trifluoroacetamido) benzenesulfonyl chloride intermediates **14**. The substituted aromatic heterocycles **13 (**1 mmol) were reacted with **14 (**1.5 mmol) in presence of sodium hydride (3 mmol) in DMF at 0-5 ^{o}C and stirred at room temperature for 12-24 h. After completion of the reaction (TLC), the reaction mass was poured onto water and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain crude mass**,** which was purified by flash column chromatography using ethylacetate : hexanes (8:2) as eluent to obtain intermediates **15.** These intermediates **15** were refluxed in Ethanol: conc. HCl mixture for 2-10 h. After completion of the reaction (TLC), the solvent was removed in vacuo. The oil was poured onto water, neutralized with 10 % sodium hydroxide solution and extracted with dichloromethane. The organic layer was separated, dried over sodium sulfate and concentrated in vacuo to obtain intermediates **16.** These amine intermediates **16 (**1 mmol) were treated with 1-

methyl-4-piperidone (3 mmol) or 1-Boc-4-piperidone (3 mmol) in presence of sodium triacetoxyborohydride (3 mmol), acetic acid and sodium sulfate (10 mmol) as discussed in general procedure for Scheme 1 to obtain the targeted compounds **18** and Boc protected intermediates **17** respectively. The deprotection of intermediates **17** (1 mmol) with isopropanolic HCl (20 % w/v solution, 2.5 mL) gave targeted compounds **19** as their corresponding HCl salts.

5-Chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (13, Het=A)

Phosphorous oxy chloride (10 g, 65.8 mmol) was added to a stirred solution of 5-chloro-1*H*-pyrrolo[2,3-b]pyridine (5 g, 32.9 mmol) in DMF (25 mL) at 0-5 ^{o}C. The stirred mixture was heated at 60 ^{o}C for 6 h, cooled to room temperature and poured onto cold water (50 mL). The pH of the reaction mass was adjusted to ~ 12 with cold, aq.NaOH solution and extracted the product with chloroform (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The resultant residual mass was chromatographed (silica gel, 3:7 to 1:1 ethylacetate-hexanes as eluent) to obtain 5-chloro-1*H*-pyrrolo[2,3-b]pyridine-3-carboxaldehyde as off white solid, 2.07 g (35% yield). ESI Mass: m/e 179 ($M-H^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.37-8.39 (m, 2H), 8.55 (s, 1H), 9.91 (s, 1H), 12.92 (bs, 1H); HPLC purity: 99.5 %. Hydrazine hydrate (4.2 g, 83.3 mmol) was added to a stirred suspension of 5-chloro-1*H*-pyrrolo[2,3-b]pyridine-3-carboxaldehyde (5 g, 27.7 mmol), KOH powder (4.7 g, 83.3 mmol) in ethylene glycol (50 mL) at room temperature. The mixture was heated at 180 ^{o}C for 5 h. After completion of the reaction (TLC), the reaction mass was cooled to room temperature and poured onto cold water (100 mL). The solids that separated were filtered, dissolved in ethylacetate (100 mL), separated the aqueous layer and the organic layer was concentrated in vacuo to obtain the title compound **13,** Het=A as off white solid (3.78 g, 82% yield). ESI Mass: m/e 167 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.23 (s, 3H), 7.33 (s, 1H), 8.02-8.03 (d, J = 2.20 Hz, 1H), 8.16 (d, J = 2.24 Hz, 1H), 11.54 (bs, 1H).

4-Methoxy-3-(2,2,2-trifluoroacetamido)benzenesulfonyl chloride (14, R^1=OCH_3)

Trifluoroacetic anhydride (12.6 g, 60 mmol) was added to a stirred solution of o-anisidine (6.15 g, 50 mmol) and pyridine (5.9 g, 75 mmol) in dichloromethane (60 mL) at 0-5 ^oC. Then the reaction mixture was warmed to room temperature and stirred for 2 h. After completion of the reaction (TLC), the reaction mass was poured onto water and the product was extracted with ethylacetate (3 x 100 mL). Combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain 9.2 g of N-(2-methoxy phenyl)-2,2,2-trifluoroacetamide (84% yield). ESI Mass: m/e 218 ($M-H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.92 (s, 3H), 6.92-6.94 (d, *J* = 8.19 Hz, 1H), 6.99-7.02 (m, 1H), 7.15-7.19 (m, 1H), 8.29-8.31 (d, *J* = 8.03 Hz, 1H), 8.58-8.61 (bs, 1H).

Chlorosulfonic acid (7.2 g, 61 mmol) was added to a solution of N-(2-methoxy phenyl)-2,2,2-trifluoroacetamide (9 g, 41 mmol) in dichloromethane (100 mL) at 0-5 ^oC. The reaction mass was warmed to room temperature, stirred for 2 h and then carefully poured onto water (50 mL). The mass was extracted with ethylacetate (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain 11.4 g of (**14, R^1=OCH_3)** as solids (88% yield). ESI Mass: m/e 316 ($M-H^+$); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.09 (s, 3H), 7.10-7.12 (d, *J* = 8.81 Hz, 1H), 7.89-7.92 (m, 1H), 8.59 (bs, 1H), 9.05-9.06 (d, *J* = 2.22 Hz, 1H).

1-[3-(2,2,2-trifluoroacetamido)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (15, Het=A, R^1=OCH_3)

A solution of 5-chloro-3-methyl-1*H*-pyrrolo[2,3-b]pyridine (**13, Het=A**, 5 g, 30.1 mmol) in DMF (10 mL) was added to a stirred suspension of NaH (3.6 g, 90.3 mmol, 60% w/v oil suspension) in DMF (25 mL) below 10 ^oC under N_2 atmosphere. The mixture was further stirred for 30 min at 5-10 ^oC. A solution of 4-methoxy-3-(2,2,2-trifluoroacetamido)benzenesulfonyl chloride (**14, R^1=OCH_3**, 14.3 g, 45.1 mmol) in DMF (25 mL) was added to the above mass and stirred

overnight. After completion of the reaction (TLC), the reaction mass was poured onto cold water (100 mL) and the product was extracted with chloroform (4 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The resultant residual mass was chromatographed (silica gel, 2:8 to 1:1 ethylacetate-hexanes as eluent) to obtain the title compound, as pale yellow solid (10.5 g, 78% yield). ESI Mass: m/e 448, 450 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.24 (s, 3H), 3.99 (s, 3H), 7.01-7.03 (d, J = 8.80 Hz, 1H), 7.55 (s, 1H), 7.76-7.77 (d, J = 2.09 Hz, 1H), 8.17-8.19 (dd, J = 8.77, 2.32 Hz, 1H), 8.36 (d, J = 2.27 Hz, 1H), 8.48 (bs, 1H), 8.97-8.98 (d, J = 2.29 Hz, 1H).

1-(3-amino-4-methoxybenzenesulfonyl)-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (16, Het=A, R^1=OCH_3)

A solution of 1-[3-(2,2,2-trifluoroacetamido)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (10 g, 22.3 mmol) in a mixture of ethanol:water:conc.hydrochloric acid (300 mL, 1:1:1) was refluxed for 6 h. After completion of the reaction (TLC), the mass was cooled and concentrated in vacuo. The residual mass was diluted with cold water (50 mL), neutralized with aq.NaOH and extracted the product with chloroform (3 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The resultant residual mass was chromatographed (silica gel, 1:1 to 1:0 ethylacetate-hexanes as eluent) to obtain the title product as white solid (3.7 g, 48% yield). ESI Mass: m/e 352, 354 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.59 (bs, 2H), 2.24 (s, 3H), 3.87 (s, 3H), 6.77-6.80 (d, J = 8.56 Hz, 1H), 7.40 (d, J = 2.28 Hz, 1H), 7.49 (s, 1H), 7.52-7.55 (dd, J = 8.54, 2.29 Hz, 1H), 7.75-7.76 (d, J = 2.25 Hz, 1H), 8.36-8.37 (d, J = 2.21 Hz, 1H); HPLC purity: 99.5 %.

1-[3-(1-tert-Butyloxycarbonyl piperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (17, Het=A, R^1=OCH_3)

Sodium triacetoxyborohydride (1.8 g, 8.4 mmol) was added in portions to a stirred suspension of 1-(3-amino-4-methoxybenzenesulfonyl)-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**16, Het=A, R^1=OCH_3**, 1 g, 2.8 mmol), 1-boc-4-piperidone (1.7 g, 8.4 mmol), sodium sulfate (3.4 g, 24 mmol) in glacial acetic acid (20 mL) at room temperature under N_2 atmosphere. The mass was stirred overnight at room temperature. After completion of the reaction (TLC), the mixture was poured onto cold water, neutralized with aq.NaOH solution and extracted with chloroform (3 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain an oily residue. The mass was chromatographed (neutral silica gel, 20:80 ethylacetate-hexanes) to afford the title product as an oily mass (0.6 g, 40 % yield). ESI Mass: m/e 535, 537 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40-1.43 (m, 2H), 1.46 (s, 9H), 1.85-1.88 (m, 2H), 2.22 (s, 3H), 2.97-3.04 (m, 4H), 3.43-3.45 (m, 1H), 3.85 (s, 3H), 4.04-4.07 (bs, 1H), 6.78-6.80 (d, *J* = 8.6 Hz, 1H), 7.44-7.47 (m, 3H), 7.73-7.74 (d, *J* = 2.0 Hz, 1H), 8.32 (d, *J* = 2.07 Hz, 1H); HPLC purity: 98.9 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (18, Het=A, R^1=OCH_3, R^2=CH_3)

Sodium triacetoxyborohydride (21.2 g, 99.9 mmol) was added in portions to a stirred suspension of 1-(3-amino-4-methoxybenzenesulfonyl)-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (11.7 g, 33.3 mmol), 1-methyl-4-piperidone (11.3 g, 99.9 mmol), sodium sulfate (47.3 g, 333.3 mmol) in glacial acetic acid (110 mL) at room temperature under N_2 atmosphere. The mass was stirred overnight at room temperature. After completion of the reaction (TLC), the mixture was poured onto cold water, neutralized with aq.NaOH solution and extracted with chloroform (3 x 150 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to obtain an oily residue. The mass was chromatographed (neutral silica gel, 80:20 ethylacetate-hexanes, and then 5:95 methanol-ethylacetate) to afford the title product as an oily

mass (5.56 g, 37% yield). ESI Mass: m/e 449, 451 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.34-1.40 (m, 2H), 1.68-1.71 (m, 2H), 1.99-2.05 (m, 2H), 2.18 (s, 3H), 2.19 (s, 3H), 2.69-2.71 (m, 2H), 3.08-3.16 (m, 1H), 3.80 (s, 3H), 4.99-5.01 (d, J = 8.13 Hz, 1H), 6.91-6.93 (d, J = 8.52 Hz, 1H), 7.06 (d, J = 2.20 Hz, 1H), 7.21-7.24 (dd, J = 8.42, 2.22 Hz, 1H), 7.72 (s, 1H), 8.17-8.18 (d, J = 2.30 Hz, 1H), 8.35-8.36 (d, J = 2.30 Hz, 1H); HPLC purity: 98.8 %.

General procedure for the preparation of L-(+)-tartarate salt: Compounds **18** (1 mmol) were treated with L(+)-tartaric acid (1 mmol) in methanol under N_2 atmosphere for 2 h and then concentrated under reduced pressure to obtain respective L-(+)-tartarate salts.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine L(+)-tartarate (18c)

L(+)Tartaric acid (1.84 g, 12.3 mmol) was added to a stirred solution of 1-[3-(1-methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (18, Het=A, R^1=OCH_3, R^2=CH_3, 5.5 g, 12.3 mmol) in methanol (50 mL) under N_2 atmosphere. The resulting solution was stirred at room temperature for 2 h and concentrated in vacuo to obtain 7.3 g (100 % yield) of the title compound as off white solid. ESI Mass: m/e 449, 451 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.59-1.65 (m, 2H), 1.81-1.84 (m, 2H), 2.19 (s, 3H), 2.57 (s, 3H), 2.76-2.82 (m, 2H), 3.16-3.18 (m, 2H), 3.39-3.42 (m, 1H), 3.80 (s, 3H), 4.07 (s, 2H), 5.23-5.25 (d, J = 8.00 Hz, 1H), 6.91-6.94 (d, J = 8.54 Hz, 1H), 7.11 (d, J = 1.89 Hz, 1H), 7.22-7.24 (dd, J = 8.41, 1.96 Hz, 1H), 7.71 (s, 1H), 8.17 (d, J = 2.19 Hz, 1H), 8.37 (d, J = 2.16 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 9.54, 29.43, 43.91, 47.22, 53.07, 56.23, 72.11, 106.75, 109.81, 114.89, 116.33, 125.0, 126.0, 126.39, 128.37, 129.69, 137.28, 142.79, 145.54, 151.17, 174.31; HPLC purity: 99.1 %.

Compounds **18a-18b** and **18d-18s** were prepared analogously.

1-[3-(1-Methylpiperidin-4-yl amino)benzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine L(+)-tartarate (18a). The title compound was prepared using essentially the same procedure as described for the preparation of **18c**. ESI Mass: m/e 419, 421 $(M+H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.68-1.77 (m, 2H), 2.14-2.17 (m, 2H), 2.25 (s, 3H), 2.87 (s, 3H), 3.14-3.17 (m, 2H), 3.35-3.48 (m, 2H), 3.59-3.62 (m, 1H), 4.43 (s, 2H), 6.85-6.87 (d, *J* = 7.14 Hz, 1H), 7.19-7.25 (m, 2H), 7.31 (s, 1H), 7.60 (s, 1H), 8.00-8.01 (s, *J* = 2.13 Hz, 1H), 8.28 (s, *J* = 2.10 Hz, 1H); HPLC purity: 97.0 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methylbenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine L(+)-tartarate (18b). The title compound was prepared using essentially the same procedure as described for the preparation of **18c**. ESI Mass: m/e 433, 435 $(M+H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.79-1.87 (m, 2H), 2.13 (s, 3H), 2.19-2.29 (m, 2H), 2.24 (s, 3H), 2.91 (s, 3H), 3.21-3.24 (m, 2H), 3.48-3.53 (m, 2H), 3.67-3.71 (m, 1H), 4.43 (s, 2H), 7.12-7.19 (m, 2H), 7.32 (s, 1H), 7.60 (s, 1H), 8.00-8.01 (d, *J* = 2.15 Hz, 1H), 8.28 (s, *J* = 2.11 Hz, 1H).

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*c*]pyridine (18d). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). ESI Mass: m/e 449, 451$(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.84-1.88 (m, 4H), 2.21 (s, 3H), 2.39-2.52 (m, 5H), 3.08-3.10 (m, 2H), 3.22-3.26 (m, 1H), 3.85 (s, 3H), 4.30-4.32 (d, *J* = 8.04 Hz, 1H), 6.70-6.72 (d, *J* = 8.48 Hz, 1H), 6.84-6.85 (d, *J* = 2.14 Hz, 1H), 7.19-7.22 (dd, *J* = 8.37, 2.13 Hz, 1H), 7.40-7.41 (m, 2H), 9.08 (s, 1H); HPLC purity: 96.8 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[3,2-*b*]pyridine L(+)-tartarate (18e). The title compound was prepared using essentially the same procedure as described for the preparation of **18c**. ESI Mass: m/e 449, 451 $(M+H)^+$; ^{1}H

NMR (400 MHz, DMSO-d_6) δ: 1.53-1.55 (m, 2H), 1.75-1.77 (m, 2H), 1.98 (s, 3H), 2.56 (s, 3H), 2.72-2.75 (m, 2H), 3.11-3.15 (m, 2H), 3.34-3.58 (m, 1H), 3.79 (s, 3H), 4.11 (s, 2H), 5.29-5.32 (d, J = 8.16 Hz, 1H), 6.85 (s, 1H), 6.90-6.93 (d, J = 8.47 Hz, 1H), 7.17-7.19 (m, 1H), 7.38-7.41 (d, J = 8.62 Hz, 1H), 8.00 (s, 1H), 8.33-8.36 (d, J = 8.63 Hz, 1H); HPLC purity: 96.3 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-1*H*-pyrrolo[2,3-*b*]pyridine L(+)-tartarate (18f). The title compound was prepared using essentially the same procedure as described for the preparation of **18c**. ESI Mass: m/e 435, 437 $(M+H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.71-1.76 (m, 2H), 2.16-2.21 (m, 2H), 2.91 (s, 3H), 3.13-3.24 (m, 2H), 3.48-3.52 (m, 2H), 3.63-3.68 (m, 1H), 3.88 (s, 3H), 4.45 (s, 2H), 6.68-6.69 (d, J = 3.79 Hz, 1H), 6.92-6.94 (d, J = 8.23 Hz, 1H), 7.36-7.38 (m, 2H), 7.84-7.85 (d, J = 3.72 Hz, 1H), 8.04 (s, 1H), 8.29 (s, 1H); HPLC purity: 97.4 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-methoxy-1*H*-pyrrolo [2,3-*b*]pyridine (18g). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). ESI Mass: m/e 431 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.66-1.68 (m, 2H), 2.06-2.12 (m, 2H), 2.49-2.55 (m, 5H), 3.08-3.12 (m, 2H), 3.47-3.49 (m, 1H), 3.85 (s, 6H), 4.28-4.30 (d, J = 6.96 Hz, 1H), 6.49-6.50 (d, J = 3.82 Hz, 1H), 6.72-6.74 (d, J = 8.29 Hz, 1H), 7.31-7.31 (d, J = 2.35 Hz, 1H), 7.37-7.39 (d, J = 7.79 Hz, 2H), 7.65-7.66 (d, J = 3.80 Hz, 1H), 8.11 (d, J = 1.99 Hz, 1H); HPLC purity: 99.8 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-methoxy-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine L(+)-tartarate (18h). The title compound was prepared using essentially the same procedure as described for the preparation of **18c**. ESI Mass: m/e 445 $(M+H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.69-1.76 (m, 2H), 2.12-2.15 (m, 2H), 2.23 (s, 3H), 2.84 (s, 3H), 3.13-3.27 (m, 2H), 3.48-3.52 (m, 2H), 3.59-3.63 (m, 1H), 3.85 (s, 3H), 3.88 (s, 3H),

4.46 (s, 2H), 6.86-6.88 (d, *J* = 8.94 Hz, 1H), 7.26-7.27 (m, 2H), 7.47-7.49 (m, 2H), 8.01-8.02 (d, *J* = 2.32 Hz, 1H); HPLC purity: 95.8 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-indazole L(+)-tartarate (18i). The title compound was prepared using essentially the same procedure as described for the preparation of **18c**. ESI Mass: m/e 449, 451 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.46-1.49 (m, 2H), 1.72-1.89 (m, 2H), 2.07 (s, 3H), 2.45 (s, 3H), 2.88-3.25 (m, 4H), 3.31-3.33 (m, 1H), 3.79 (s, 3H), 4.19 (s, 2H), 5.20-5.22 (d, *J* = 7.19 Hz, 1H), 6.74-6.74 (d, *J* = 1.66 Hz, 1H), 6.89-6.91 (d, *J* = 8.50 Hz, 1H), 7.10-7.13 (dd, *J* = 8.42, 2.1 Hz, 1H), 7.63-7.66 (dd, *J* = 8.89, 1.90 Hz, 1H), 7.95 (d, *J* = 1.79 Hz, 1H), 8.07-8.09 (d, *J* = 8.89 Hz, 1H); HPLC purity: 98.5 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-fluorobenzenesulfonyl]-5-chloro-3-methyl-1*H*-indazole L(+)-tartarate (18j). The title compound was prepared using essentially the same procedure as described for the preparation of **18c**. ESI Mass: m/e 437, 439 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.49-1.57 (m, 2H), 1.71-1.74 (m, 2H), 1.88 (s, 3H), 2.46 (s, 3H), 2.57-2.61 (m, 2H), 3.07-3.09 (m, 2H), 3.33-3.35 (m, 1H), 4.01-4.09 (s, 2H), 6.01-6.03 (d, *J* = 7.58 Hz, 1H), 6.98-7.00 (d, *J* = 7.69 Hz, 1H), 7.05-7.07 (m, 1H), 7.17-7.22 (m, 1H), 7.65-7.68 (dd, *J* = 8.89, 1.74 Hz, 1H), 7.98 (d, *J* = 1.50 Hz, 1H), 8.07-8.09 (d, *J* = 8.88 Hz, 1H); HPLC purity: 99.5 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-chlorobenzenesulfonyl]-5-chloro-3-methyl-1*H*-indazole (18k). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). ESI Mass: m/e 453, 455 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41-1.53 (m, 2H), 2.10-2.18 (m, 5H), 2.49 (s, 3H), 2.66-2.72 (m, 2H), 3.55-3.57 (m, 3H), 4.53 (bs, 1H), 7.04-7.12 (m, 2H), 7.28-7.30 (m, 1H), 7.50-7.52 (d, *J* = 8.72 Hz, 1H), 7.73 (s, 1H), 8.07-8.10 (d, *J* = 8.84 Hz, 1H); HPLC purity: 94.7 %.

4-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-2,3-dihydro benzo[1,4] oxazine (18l). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). IR (cm^{-1}): 3393, 2935, 1518, 1159. ESI Mass: m/e 418 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.22-1.33 (m, 2H), 1.43-1.45 (m, 2H), 1.82-1.89 (m, 2H), 2.16 (s, 3H), 2.63-2.66 (m, 2H), 2.73-2.75 (m, 1H), 3.51-3.53 (t, *J* = 4.52 Hz, 2H), 3.75-3.77 (t, *J* = 4.52 Hz, 2H), 3.82 (s, 3H), 4.95-4.97 (d, *J* = 7.88 Hz, 1H), 6.23 (d, *J* = 1.53 Hz, 1H), 6.77-6.79 (dd, *J* = 8.15, 1.12 Hz, 1H), 6.91-6.98 (m, 3H), 7.06-7.10 (m, 1H), 7.73-7.75 (dd, *J* = 8.28, 1.26 Hz, 1H); HPLC purity: 99.6 %.

4-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-chloro-2,3-dihydro benzo[1,4]oxazine (18m). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). IR (cm^{-1}): 3397, 2787, 1519, 1159; ESI Mass: m/e 452, 454 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.29-1.39 (m, 2H), 1.48-1.51 (m, 2H), 1.91-1.96 (m, 2H), 2.20 (s, 3H), 2.69-2.72 (m, 2H), 2.81-2.82 (m, 1H), 3.53-3.55 (t, *J* = 4.52 Hz, 2H), 3.78-3.80 (t, *J* = 4.52 Hz, 2H), 3.85 (s, 3H), 5.07-5.09 (d, *J* = 7.79 Hz, 1H), 6.28 (d, *J* = 1.84 Hz , 1H), 6.84-6.87 (dd, *J* = 6.58, 2.22 Hz, 1H), 6.96-7.02 (m, 2H), 7.14-7.17 (dd, *J* = 8.79, 2.53 Hz, 1H), 7.77-7.78 (d, *J* = 2.52 Hz, 1H); HPLC purity: 99.2 %.

4-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-fluoro-2,3-dihydro benzo[1,4]oxazine (18n). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). IR (cm^{-1}): 3393, 2935, 1495, 1160; ESI Mass: m/e 436 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.28-1.37 (m, 2H), 1.47-1.50 (m, 2H), 1.85-1.91 (m, 2H), 2.18 (s, 3H), 2.67-2.69 (m, 2H), 2.83-2.85 (m, 1H), 3.53-3.55 (t, *J* = 4.51 Hz, 2H), 3.78-3.80 (t, *J* = 4.46 Hz, 2H), 3.85 (s, 3H), 5.02-5.04 (d, *J* = 7.91 Hz, 1H),

6.33 (d, *J* = 1.98 Hz, 1H), 6.82-6.86 (m, 1H), 6.96-7.02 (m, 3H), 7.55-7.58 (dd, *J* = 10.78, 3.04 Hz, 1H); HPLC purity: 97.3 %.

4-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-methyl-2,3-dihydro benzo[1,4]oxazine (18o). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). ESI Mass: m/e 432 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.57-1.65 (m, 2H), 1.82-1.87 (m, 2H), 2.32 (s, 6H), 2.62 (m, 2H), 3.15-3.24 (m, 2H), 3.54-3.56 (t, *J* = 4.77 Hz, 2H), 3.77-3.79 (t, *J* = 4.82 Hz, 2H), 3.89 (s, 3H), 4.27-4.29 (m, 1H), 6.43 (d, *J* = 1.95 Hz, 1H), 6.66-6.68 (d, *J* = 8.29 Hz, 1H), 6.75-6.77 (d, *J* = 8.38 Hz, 1H), 6.85-6.87 (d, *J* = 8.18 Hz, 1H), 7.07-7.10 (m, 1H), 7.73 (s, 1H); HPLC purity: 99.1 %.

4-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-trifluoromethyl-2,3-dihydro benzo[1,4]oxazine (18p). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). ESI Mass: m/e 486 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76-1.78 (m, 4H), 2.31-2.33 (m, 2H), 2.50 (s, 3H), 3.06-3.12 (m, 3H), 3.69-3.71 (t, *J* = 4.76 Hz, 2H), 3.84-3.87 (t, *J* = 4.82 Hz, 2H), 3.89 (s, 3H), 4.29-4.32 (m, 1H), 6.42 (d, *J* = 1.95 Hz, 1H), 6.76-6.78 (d, *J* = 8.38 Hz, 1H), 6.88-6.90 (d, *J* = 8.56 Hz, 1H), 7.07-7.10 (dd, *J* = 8.32, 2.03 Hz, 1H), 7.28-7.31 (dd, *J* = 8.66, 1.76 Hz, 1H), 8.26 (s, 1H); HPLC purity: 89.9 %.

4-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-fluoro-2,2-dimethyl-2,3-dihydro benzo[1,4]oxazine (18q). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). IR (cm^{-1}): 3420, 2932, 1496, 1160; ESI Mass: m/e 464 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.21 (s, 6H), 1.40-1.48 (m, 2H), 1.72-1.75 (m, 2H), 2.05-2.08 (m, 2H), 2.21 (s, 3H), 2.73-2.75 (m, 2H), 3.16-3.21 (m, 1H), 3.66 (s, 2H), 3.84 (s, 3H), 5.05-5.07 (d, *J* = 7.98 Hz, 1H), 6.78-6.83 (m, 3H), 6.97-

6.99 (d, *J* = 8.44 Hz, 1H), 7.13-7.15 (dd, *J* = 8.36, 1.85 Hz, 1H), 7.44-7.46 (dd, *J* = 11.13, 1.58, Hz, 1H); HPLC purity: 97 %.

1-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-1,2,3,4-tetrahydroquinoline (18r). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). IR (cm^{-1}): 3423, 2940, 1518, 1157; ESI Mass: m/e 416 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36-1.39 (m, 2H), 1.54-1.57 (m, 2H), 1.72-1.75 (m, 2H), 2.00-2.01 (m, 2H), 2.30 (s, 3H), 2.41-2.44 (m, 2H), 2.76-2.79 (m, 2H), 3.0 (bs, 1H), 3.75-3.78 (m, 2H), 3.86 (s, 3H), 4.3 (bs, 1H), 6.41-6.42 (d, *J* = 2.0 Hz, 1H), 6.69-6.71 (d, *J* = 8.30 Hz, 1H), 6.96-7.00 (d, *J* = 7.3 Hz, 1H), 7.03-7.07 (m, 2H), 7.17-7.21 (m, 1H), 7.86-7.88 (d, *J* = 8.10 Hz, 1H); HPLC purity: 99.2 %.

2-[3-(1-Methylpiperidin-4-yl amino)-4-methoxybenzenesulfonyl]-1,2,3,4-tetrahydroisoquinoline (18s). The title compound was prepared using essentially the same procedure as described for the preparation of **18** (Het=A, R^1=OCH_3, R^2=CH_3). IR (cm^{-1}): 3425, 3020, 1597, 1216; ESI Mass: m/e 416 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60-1.65 (m, 2H), 2.01-2.07 (m, 2H), 2.17-2.31 (m, 4H), 2.39 (s, 3H), 2.89-2.91 (t, 3H), 3.34 -3.37 (t, 2H), 3.89 (s, 3H), 4.27 (s, 2H), 4.30-4.32 (bs, 1H), 6.79-6.81 (d, *J* = 8.30 Hz, 1H), 6.91-6.92 (d, *J* = 1.90 Hz, 1H), 7.01-7.03 (m, 1H), 7.06-7.08 (m, 1H), 7.12 -7.16 (m, 3H); HPLC purity: 96.2 %.

1-[3-(Piperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine hydrochloride (19d)

1-[3-(1-tert-Butyloxycarbonyl piperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-chloro-3-methyl-1*H*-pyrrolo[2,3-b]pyridine (**17**, Het=A, R^1=OCH_3, 0.5 g, 0.94 mmol) was stirred in isopropanolic HCl (20 % w/v solution, 2.5 mL) for 2 h. After completion of the reaction (TLC), the solvent was removed in vacuo to obtain the title compound as white solids (0.35 g, 85 % yield). ESI Mass: m/e 435, 437 $(M+H)^+$; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.66-1.70 (m, 2H),

2.14-2.18 (m, 2H), 2.24 (s, 3H), 3.19-3.24 (m, 2H), 3.46-3.49 (m, 2H), 3.63-3.69 (m, 1H), 3.88 (s, 3H), 6.93-6.95 (d, *J* = 8.14 Hz, 1H), 7.37 (m, 2H), 7.61 (s, 1H), 8.01-8.02 (d, *J* = 2.08 Hz, 1H), 8.27-8.28 (d, *J* = 2.00 Hz, 1H); HPLC purity: 98.8 %.

Compounds **19a-19c** and **19e** were prepared analogously.

1-[3-(Piperidin-4-yl amino)-4-methoxybenzenesulfonyl]-6-fluoro-1*H*-indole hydrochloride (19a). The title compound was prepared using essentially the same procedure as described for the preparation of **19d**. IR (cm^{-1}): 3428, 2952, 1602, 1433, 1284, 1168, 1179; ESI Mass: m/e 404 $(M+H)^+$; M.R (^OC): 203-205; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.57-1.63 (m, 2H), 1.80-1.83 (m, 2H), 3.01-3.07 (m, 2H), 3.21-3.24 (m, 2H), 3.63-3.67 (m, 1H), 3.78 (s, 3H), 3.79 (s, 1H), 6.77-6.78 (d, *J* = 3.52 Hz, 1H), 6.91-6.93 (d, *J* = 8.50 Hz, 1H), 7.02-7.03 (d, *J* = 2.16 Hz, 1H), 7.08-7.13 (m, 1H), 7.21-7.23 (dd, *J* = 8.45, 2.19 Hz, 1H), 7.57-7.61 (m, 1H), 7.75-7.79 (m, 2H), 8.49 (bs, 1H), 9.24 (bs, 1H); HPLC purity: 99 %.

1-[3-(Piperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-bromo-1*H*-indole hydrochloride (19b). The title compound was prepared using essentially the same procedure as described for the preparation of **19d**. IR (cm^{-1}): 3422, 2955, 1600, 1433, 1374, 1168, 1179; ESI Mass: m/e 464, 466 $(M+H)^+$; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.53-1.54 (m, 2H), 1.79-1.82 (m, 2H), 3.02-3.04 (m, 2H), 3.12-3.15 (m, 2H), 3.24-3.27 (m, 1H), 3.77 (s, 3H), 6.75-6.76 (d, *J* = 3.62 Hz, 1H), 6.90-6.92 (m, 2H), 7.17-7.20 (dd, *J* = 8.50, 2.24 Hz, 1H), 7.42-7.45 (dd, *J* = 8.46, 1.93 Hz, 1H), 7.80-7.84 (m, 2H), 7.93-7.95 (d, *J* = 8.84 Hz, 1H), 8.60 (bs, 1H), 8.90 (bs, 1H), 9.3 (bs, 1H); HPLC purity: 95 %.

1-[3-(Piperidin-4-yl amino)-4-methoxybenzenesulfonyl]-5-fluoro-1*H*-indole hydrochloride (19c). The title compound was prepared using essentially the same procedure as described for the preparation of **19d**. IR (cm^{-1}): 3429, 2945, 1604, 1510, 1456, 1375, 1139; ESI Mass: m/e 404 $(M+H)^+$; M.R (^OC): 155-157; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.52-1.58 (m, 2H), 1.80-1.83

(m, 2H), 3.02-3.07 (m, 2H), 3.25-3.28 (m, 2H), 3.56-3.61 (m, 1H), 3.77 (s, 3H), 6.76-6.77 (m, 1H), 6.90-6.92 (d, J = 8.57 Hz, 1H), 6.93 (d, J = 2.28 Hz, 1H), 7.14-7.19 (m, 2H), 7.38-7.41 (dd, J = 9.10, 2.60 Hz, 1H), 7.85-7.86 (d, J = 3.65 Hz, 1H), 7.96-7.97 (m, 1H), 8.57 (s, 1H), 8.90 (s, 1H); HPLC purity: 98 %.

1-[3-(Piperidin-4-yl amino)-4-methoxybenzenesulfonyl]-1,2,3,4-tetrahydroquinoline hydrochloride (19e). The title compound was prepared using essentially the same procedure as described for the preparation of **19d**. IR (cm^{-1}): 3426, 1504, 1352, 1158; ESI Mass: m/e 402 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.45-1.51 (m, 4H), 1.62 (m, 2H), 2.36-2.39 (t, 2H), 2.80-2.82 (m, 2H), 3.18-3.20 (d, 3H), 3.67- 3.70 (m, 2H), 3.81 (s, 3H), 6.33-6.34 (d, J = 1.78 Hz, 1H), 6.91-6.97 (m, 2H), 7.03-7.09 (m, 2H), 7.14-7.19 (m, 1H), 7.67-7.69 (d, J = 8.0 Hz, 1H), 8.75-8.77 (bs, 1H), 8.90 (bs, 1H); HPLC purity: 99.8 %.

SUPPORTING INFORMATION AVAILABLE: Experimental protocols for the determination of K_b values for 5-HT_6 receptor, dofetilide binding hERG assay, microsomal metabolic and CYP 3A4 and 2D6 inhibition protocol, pharmacokinetic study in rats and dogs, rodent brain penetration study, *in-vivo* brain microdialysis and object recognition task are available free of charge via the internet at http://pubs.acs.org.

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Abbreviations List: SAR, Structure-Activity Relationships; **CNS,** Central Nervous System; **5-HT_6R,** 5-Hydroxytryptamine 6 Receptor**; ORT,** Object Recognition Test; **GPCR**, G-protein coupled receptors; **AD,** Alzheimer's disease.

REFERENCES

1. http://www.alz.co.uk visited on 11-Jun -2012

2. Doody, R. S.; Ferris, S. H.; Salloway, S.; Sun, Y.; Goldman, R.; Watkins, W. E.; Xu, Y.; Murthy, A. K. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. *Neurology* **2009**, *72*, 1555-1561.

3. Farlow, M. R.; Cummings, J. L. Effective Pharmacologic Management of Alzheimer's disease. *The Am. J. Med.* **2007**, *120*, 388-397.

4. Van Marum, R. J.; Update on the use of memantine in Alzheimer's disease. *Neuropsychiatr Dis. Treat.* **2009**, *5*, 237-247.

5. Sebben, M.; Ansanay, H.; Bockaert, J.; Dumuis, A. 5-HT_6 receptors positively coupled to adenylyl cyclase in striatal neurones in culture. *Neuroreport* **1994**, *5*, 2553-2557.

6. Woolley, M. L.; Marsden, C. A.; Fone, K. C. F. 5-HT_6 receptors. *Curr. Drug Targets*: *CNS Neurol. Disord.* **2004**, *3*, 59-79.

7. Monsma, F. J. Jr.; Shen, Y.; Ward, R. P.; Hamblin, M. W.; Sibley, D. R. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.* **1993**, *43*, 320-327.

8. Liu, K. G.; Robichaud, A. J. 5-HT_6 antagonists as potential treatment for cognitive dysfunction. *Drug Dev. Res.* **2009**, *70*, 145-168.

9. Witty, D.; Ahmed, M.; Chuang, T. T. Advances in the design of 5-HT_6 receptor ligands with therapeutic potential. *Prog. Med. Chem.* **2009**, *48*, 163-224.

10. Glennon, R. A.; Siripurapu, U.; Roth, B. L.; Kolanos, R.; Bondarev, M. L.; Sikazwe, D.; Lee, M.; Dukat, M. The Medicinal Chemistry of 5-HT_6 Receptor Ligands with a Focus on Arylsulfonyltryptamine Analogs. *Curr. Top. Med. Chem.* **2010**, *10*, 579-595.

11. Bromidge, S. M.; Brown, A. M.; Clarke, S. E.; Dodgson, K.; Gager, T.; Grassam, H. L.; Jeffrey, P. M.; Joiner, G. F.; King, F. D.; Middlemiss, D. N.; Moss, S. F.; Newman, H.; Riley, G.; Routledge, C.; Wyman, P. 5-Chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfon- amide (SB-271046): A Potent, Selective, and Orally Bioavailable 5-HT_6 Receptor Antagonist *J. Med. Chem.* **1999**, *42*, 202-205.

12. (a)Ahmed, M.; Briggs, M. A.; Bromidge, S. M.; Buck, T.; Campbell, L.; Deeks, N. J.; Garner, A.; Gordon, L.; Hamprecht, D. W.; Holland, V.; Johnson, C. N.; Medhurst, A. D.; Mitchell, D. J.; Moss, S. F.; Powles, J.; Seal, J. T.; Stean, T.O.; Stemp, G.; Thompson, M.; Trail, B.; Upton, N.; Winbornc, K.; Witty. D. R. Bicyclic heteroarylpiperazines as selective brain penetrant 5-HT_6 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4867-4871. (b). Brmoidge, S. M. Indolesulfonyl compounds useful in the treatment of CNS disorders , **2002**, WO2002041889.

13. http://www.gsk.com visited on 11-Jun -2012.

14. http://www.lundbeck.com/global visited on 01-Jun-2012.

15. Jorn, A., Benny, B., Ben, G., Franklin, P. B., Michael, P. C., Neil, W. D., Bruno, G., Mads, K., David, L. M., Joanna, C. N., David, L. N., Soren, M. N., Mette, N. P., John, M. S. Louise, M. W. Lu AE58054, a 5-HT_6 antagonist, reverses cognitive impairment induced by subchronic phencyclidine in a novel object recognition test in rats *Int J Neuropsychopharmacol*. **2010**, *13,* 1021-1033.

16. Nirogi, R. V. S.; Daulatabad, A. V.; Parandhama, G.; Mohammad, S.; Sastri, K. R.; Shinde, A. K.; Dubey, P. K. Synthesis and pharmacological evaluation of aryl aminosulfonamide derivatives as potent 5-HT_6 receptor antagonists *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4440-4443.

17. (a) Zhao, S. H.; Berger, J.; Clark, R. D.; Sethofer, S. G.; Krauss, N. E.; Brothers, J. M.; Martin, R. S.; Misner, D. L.; Schwab, D.; Alexandrova, L. 3,4-Dihydro-2*H*-benzo[1,4]oxazine derivatives as 5-HT_6 receptor antagonists *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3504-3507. (b) Trani, G.; Baddeley, S. M.; Briggs, M. A.; Chuang, T. T.; Deeks, N. J.; Johnson, C. N.; Khazragi, A. A.; Mead, T. L.; Medhurst, A. D.; Milner, P. H.; Quinn, L. P.; Ray, A. M.; Rivers, D. A.; Stean, T. O.; Stemp, G.; Trail, B. K.; Witty, D. R. Tricyclic azepine derivatives as selective brain penetrant 5-HT6 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5698-5700. (c) Bromidge, S. M.; Clarke, S. E.; Gager, T.; Griffith, K.; Jeffrey, P.; Jennings, A. J.; Joiner, G. F.; King, F. D.; Lovell, P. J.; Moss, S. F.; Newman, H.; Riley, G.; Rogers, D.; Routledge, C.; Serafinowska, H.; Smith, D. R. Phenyl benzenesulfonamides are novel and selective 5-HT6 antagonists: identification of N-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide (SB-357134). *Bioorg. Med. Chem. Lett.* **2001**, *11*, 55-58.

18. Ruth, K.; Lucy, A. F.; Doris, E. A. H.; Chris, R. G.; Mark, W. H. Cloning of the mouse 5-HT_6 serotonin receptor and mutagenesis studies of the third cytoplasmic loop. *Mol. Brain. Res*. **2001**, *90*, 110-117.

19. Gonzalo, R.; Elisabeth, S.; Marta, P.; Pilar, P.; Xavier, C.; Jorg, H.; Helmut, B.; Petrus, J. P. Efficacy of selective 5-HT6 receptor ligands determined by monitoring 5-HT6 receptor-mediated cAMP signaling pathways. *Br. J. Pharmacol*. **2006**, *148*, 1133-1143.

20. Anglade, V. B.; Enjuanes, E.; Morillon. D.; Drieu la Rochelle, C. The object recognition task in rats and mice: A simple and rapid model in safety pharmacology to detect amnesic properties of a new chemical entity *J. Pharmacol. Toxicol. Methods* **2006**, *54*, 99-105.

21. Takashi, N.; Ryo, F. Drug induced Phospholipidosis - Pathological Aspects and its Prediction *J Toxicol. Pathol.* **2008**, *21*, 9-24.

22. Jamieson, C.; Moir, E. M.; Rankovic, Z.; Wishart, G. Medicinal Chemistry of hERG Optimizations: Highlights and Hang-Ups. *J. Med. Chem.* **2006**, *49*, 5029-5046.

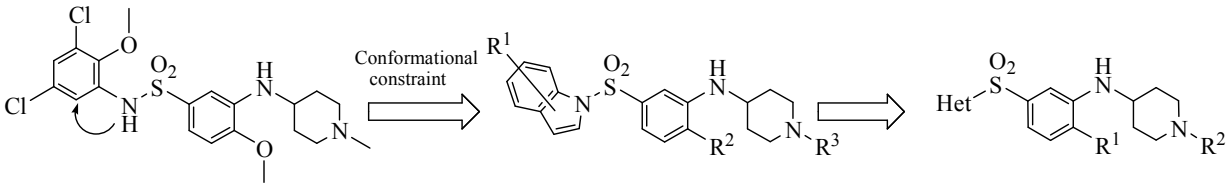
23. Nirogi, R.; Bhyrapuneni, G.; Kandikere, V.; Benade, V.; Muddana, N.; Saralaya, R.; Irappanavar, S.; Ponnamaneni, R.; Mukkanti, K. Concurrent administration of atypical antipsychotics and donepezil: drug interaction study in rats. *Eur J. Drug Metab Pharmacokinet.*[online early access].DOI: 10.1007/s13318-012-0081-1. Published online February 03, 2012.

24. Paxinos, G.; Watson, C. In *Rat brain in stereotaxic coordinates*, 3rd ed.; Academic Press: New York, 2004.

25. Batcho, A. D.; Leimgruber, W. *Org. Synth*. **1985**, *63*, 214-220.

26. a). Zhu, J.; Wong, H.; Zhang, Z.; Yin, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. An effective procedure for the preparation of 3-substituted-4- or 6-azaindoles from *ortho*-methyl nitro pyridines. *Tetrahedron Lett.* **2006**, *47*, 5653-5656. b). Bonhaus, D. W.; Martin, R. S.; Sethofer, S.; Zhang, L.; Zhao, S. Benzoxazine and quinoxaline derivatives and uses. **2006**, WO 2006037481 A1.

Table of Contents Graphic (TOC)



K_b (5-HT$_6$): 0.02 nM
Oral exposure: Good
C_b / C_p: < 0.1

K_b (5-HT$_6$): <0.1 to 10 nM
Oral exposure: Good
C_b / C_p Adequate
hERG Liability

Het represents aromatic heterocycles
K_b (5-HT$_6$): <0.1 to 10 nM
Oral exposure: Good
C_b / C_p Adequate and No hERG Liability Active in cognition models