CHAPTER-3

SYNTHESES AND CHARACTERIZATION OF NOVEL
PIPERIDINYL AMINOARYLSULFONAMIDES AS 5-HT₆
RECEPTOR LIGANDS
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SYNTHESIS AND CHARACTERIZATION OF NOVEL PIPERIDINYL-AMINOARYLSULFONAMIDES AS 5-HT$_6$ RECEPTOR LIGANDS

3.1 Introduction

Synthesis of novel piperidinyl aminoarylsulfonamides was carried out by reacting differently substituted arylamines 21a-p (please see chapter-2) with substituted piperidones. The compounds were prepared using reductive amination and reductive alkylation methods. The details of the synthesis & characterization of these novel compounds as potential 5-HT$_6$ receptor ligands is described in this chapter.

3.2 Literature Background:

Filla et al. reported [79] the reaction of 5-benzyloxyindole (26) with 1-boc-4-piperidone under reductive amination condition, resulting in 4-(5-benzyloxy-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (27). The latter was N$^1$-alkylated to obtain 4-(5-benzyloxy-1-methyl-1H-indol-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid-tert-butylester (28). Debenzylation of 28 yielded 1-tert-butyloxy carbonyl-4-(5-hydroxy-1-methyl-1H-indol-3-yl)piperidine (29). 29 was reacted with 2,6-difluorobenzenesulfonyl chloride (30), which resulted in 1-tert-butoxycarbonyl-4-[5-(2,6-difluorobenzenesulfonyloxy)-1-methyl-1H-indol-3-yl]piperidine (31), which was deprotected and N-alkylated to obtain 5-(2,6-difluorobenzenesulfonyloxy)-1-methyl-3-(1-
methylpiperidin-4-yl)-1H-indole (32) (Scheme-3.1). The compound 32 was reported to be active as 5-HT₆ receptor antagonist.

\[ \text{Bromidge et al. reported [48] the reaction of 2-methoxy-5-nitroaniline (33) with bis-dichloroethylamine hydrochloride (34), which yielded 1-(2-methoxy-5-nitrophenyl)piperazine (35), which upon reaction with boc-anhydride afforded 1-\textit{tert}-butyloxy-carbonyl-4-(2-methoxy-5-nitrophenyl)piperazine (36). Reduction of nitro group of 36 followed by reaction with} \]
5-chloro-3-methyl benzo[b]thiophene-2-sulfonyl chloride (38) resulted in the formation of 1-tert-butyloxycarbonyl-4-[5-(5-chloro-3-methyl benzo[b]thiophene-2-sulfonylamino)-2-methoxy phenyl]piperazine (39). The latter was deprotected in acidic medium, which yielded 5-chloro-N-(4-methoxy-3-(piperazin-1-yl)phenyl)-3-methylbenzo[b]thiophene-2-sulfonamide (40) i.e. SB-271046 (Scheme-3.2). The compound 40 was reported to be active towards 5-HT$_6$ receptor.

Nirogi et al. reported [80] the reaction of 4-nitroindole (41) with benzenesulfonyl chloride (42) which yielded 1-benzenesulfonyl-4-nitro-
1H-indole (43). The latter was reduced with hydrogen in the presence of Pd/C resulting in the formation of 1-benzenesulfonyl-4-amino-1H-indole (44). Reductive amination reaction of 1-methyl-4-piperidone with 44 afforded 1-benzenesulfonyl-4-(1-methylpiperidin-4-ylamino)-1H-indole (45) (Scheme-3.3). The compound 45 was reported to be highly potent and selective 5-HT₆ receptor antagonist.

3.3 Present work:

A brief literature survey given above revealed about piperidinyl and piperizinyl aminoarylsulfonamides and their derivatives which are known as 5-HT₆ receptor ligands. However, not much work seems to have been reported around piperidinyl aminoarylsulfonamides. Based on this, it was thought appropriate to synthesize differently substituted piperidinyl
aminoarylsulfonamides and test their activities towards 5-HT₆ receptor. Hence, this chapter deals with preparations and characterization of substituted piperidinylaminoarylsulfonamides.

3.4. Results and Discussion:

The compounds were prepared using reductive amination and reductive alkylation methods. The details are discussed under following section:-

3.4.1 Preparation of N-aryl / N-aralkyl-4-substituted-3-[(1-methyl piperidin -4-yl)-amino]benzenesulfonamides (47):

21a (i.e. 21, R¹=CH₃, R²=2-bromophenyl) (please see, Chapter-2) was reacted with 1-methyl-4-piperidone (46) in the presence of reducing agent like sodium triacetoxyborohydride and acetic acid as a reaction medium. The mixture was processed and the isolated product was identified as N-(2-bromophenyl)-4-methyl-3-[(1-methylpiperidin-4-yl)amino]benzenesulfonamide (47a) (i.e. 47, R¹=CH₃, R²=2-bromophenyl) (Scheme-3.4) based on its spectral and analytical data. Thus, its IR (KBr) (Fig: 3.1) showed peaks at 3397 cm⁻¹ (sharp, strong, due to -NH) and an unequal, but strong doublet at 1330 & 1156 cm⁻¹ due to asymmetric and symmetric stretching vibrations of -SO₂ group. Its ¹H-NMR (CDCl₃/TMS) (Fig: 3.2) showed signals at δ 1.38 – 1.48 (m, 2H; piperidinyl-H), 1.88 – 1.91 (m, 2H; piperidinyl-H), 2.02 – 2.10 (m, 5H; Ar-CH₃ and piperidinyl-H), 2.32 (s, 3H; N-CH₃), 2.78 – 2.80 (m, 2H; piperidinyl-H), 3.21 – 3.22
(m, 1H; piperidinyl-H), 3.47 – 3.49 (m, 1H; NH), 6.79 (s, 1H; Ar-H), 6.95 (m, 1H; Ar-H), 7.05 – 7.06 (m, 2H; Ar-H & NH), 7.24 – 7.28 (m, 2H; Ar-H), 7.40 – 7.42 (dd, J = 1.35, 8.03 Hz, 1H; Ar-H), 7.69 – 7.72 (m, 1H; Ar-H). Its $^{13}$C-NMR (CDCl$_3$/TMS) (Fig: 3.3) showed characteristic signals at $\delta$ 18.24 (-CH$_3$), 31.16 (piperidinyl-C), 45.90 (-CH$_3$), 49.1 (piperidinyl-C), 54.53 (piperidinyl-C) and 107.21 – 145.89 (Ar-C). Its ESI-MS (Fig: 3.4) showed the twin molecular ion peaks at 440 [M$^+$+3] & 438 [M$^+$+1] corresponding to the molecular masses of 439 [M$^+$+2] & 437 [M$^+$] when recorded in the Q+1 mode.

![Scheme-3.4](image)

**Scheme-3.4** The above reaction of 21a with 46 was found to be a general one and has been extended to prepare derivatives 47a-p (where, R$^1$ = H, CH$_3$, C$_2$H$_5$, OCH$_3$ & R$^2$ = Substituted phenyls). The products were assigned their structures by analogy and on the basis of their spectral & analytical data. For details, please see the Experimental Section of this chapter.
General mechanism for reductive amination \[81\] is given as follows

\[
\text{Ar-NH}_2 + \text{O} = \text{N-R} \xrightleftharpoons{\text{Acid}} \text{HO-} \text{N-R} \xrightleftharpoons{\text{Reduction agent}} \text{Ar-} \text{N} = \text{N-R} + \text{H}_2\text{O}
\]

......Scheme-3.5

3.4.2 Preparation of N-aryl / N-aralkyl-4-substituted-3-[[piperidin-4-yl]amino] benzenesulfonamide (50):

21i (i.e. 21, \(R^1=\text{OCH}_3\), \(R^2=\text{benzyl}\)) (please see, chapter-2) was treated with 1-\text{tert}-butyloxy carbonyl-4-piperidone (48), catalytic amount of sodium sulfate and sodium triacetoxyborohydride in acetic acid as reaction medium. The mixture was processed and the isolated product was identified as N-benzyl-4-methoxy-3-[[1-\text{tert}-butyloxy carbonyl (piperidin-4-yl)amino]benzenesulfonamide (49a) (i.e. 49, \(R^1=\text{OCH}_3\), \(R^2=\text{benzyl}\)) (Scheme-3.6) based on its spectral and analytical data. Thus, its IR (KBr) (Fig: 3.5) showed the characteristic peaks at 3411 \& 3351 cm\(^{-1}\) (broad, short, due to -NH), 1683 cm\(^{-1}\) (strong, sharp, due to -CO-group) and 1318 \& 1151 cm\(^{-1}\) (strong, sharp, unequal doublet due to asymmetric and symmetric stretching vibrations of -SO\(_2\) group). Its \(^1\)H-NMR (CDCl\(_3\)/TMS) (Fig: 3.6) showed signals at \(\delta 1.44\) (m, 2H; piperidinyl-
\[ \text{H}, \text{1.47 \text{s, 9H; -(CH}_3\text{)}_3, \text{1.99 - 2.02 \text{m, 2H; piperidinyl-H}, 2.90 - 2.96 \text{m, 2H; piperidinyl-H}, 3.44 - 3.46 \text{m, 1H; piperidinyl-H}, 3.92 \text{s, 3H; -OCH}_3, 3.96 - 4.02 \text{m, 2H; piperidinyl-H}, 4.11 - 4.12 \text{d, 2H; PhCH}_2\text{NH}, 4.32 - 4.34 \text{d, 1H; -NH}, 4.71 - 4.74 \text{t, 1H; PhCH}_2\text{NH}, 6.80 - 6.82 \text{d, J} = 8.40 \text{Hz, 1H; Ar-H}, 7.02 \text{d, J} = 2.05 \text{Hz, 1H; Ar-H}, 7.20 - 7.31 \text{m, 6H; Ar-H}. \] Its ESI-MS showed (Fig: 3.7) the molecular ion peak at 474 [M\textsuperscript{+}-1] corresponding to the molecular mass of 475 [M] when recorded in the Q-1 mode.

![Scheme-3.6](image_url)

The above reaction of 21a with 48 was found to be a general one and has been extended to prepare different derivatives of 49 (where, R\textsuperscript{1} = H, CH\textsubscript{3}, C\textsubscript{2}H\textsubscript{5}, OCH\textsubscript{3} & R\textsuperscript{2} = Substituted phenyls). The products were assigned their structures by analogy and on the basis of their spectral & analytical data. For details, please see the Experimental Section of this chapter.

49a (i.e. 49, R\textsuperscript{1}=OCH\textsubscript{3}, R\textsuperscript{2}=benzyl) was treated with isopropanolic hydrochloric acid solution (IPA.HCl, 15-20% w/v) under heating conditions. The mixture was processed and the isolated product was
identified as N-benzyl-4-methoxy-3-[(piperidin-4-yl)amino]benzene sulfonamide hydrochloride (50a) (i.e. 50, $R^1=OCH_3$, $R^2=\text{benzyl}$) (Scheme-3.7) based on its spectral and analytical data. Thus, its IR (KBr) (Fig: 3.8) showed peaks at ~3430 cm$^{-1}$ (broad, medium, due to $\text{-NH}$), 1279 & 1151 cm$^{-1}$ (strong, sharp, twin peaks due to asymmetric and symmetric stretching vibrations of $\text{-SO}_2$ group). Its $^1\text{H-NMR}$ ($\text{CDCl}_3$/TMS) (Fig: 3.9) showed signals at $\delta$ 1.67 – 1.75 (m, 2H; piperidinyl-\text{H}), 2.00 – 2.03 (m, 2H; piperidinyl-\text{H}), 2.93 – 3.01 (m, 2H; piperidinyl-\text{H}), 3.25 – 3.28 (m, 2H; piperidinyl-\text{H}), 3.55 – 3.60 (m, 1H; piperidinyl-\text{H}), 3.86 (s, 3H; $\text{-OCH}_3$), 3.89 (s, 2H; $\text{ArCH}_2\text{NH}$), 6.97 – 6.99 (d, $J = 8.30$ Hz, 1H; $\text{Ar-H}$), 7.10 – 7.14 (m, 2H; $\text{Ar-H}$), 7.19 – 7.28 (m, 5H; $\text{Ar-H}$), 8.00 (s, 1H; $\text{-NH}$), 9.02 – 9.04 (s, 1H; $\text{-NH}$) and 9.19 (s, 1H; $\text{-HCl}$). Its $^{13}\text{C-NMR}$ (Fig: 3.10) showed signals at $\delta$ 32.64 (piperidinyl-\text{C}), 45.07 (piperidinyl-\text{C}), 46.51 (Ar$\text{CH}_2$) and 106.57 – 149.36 (Ar-\text{C}). Its ESI-MS (Fig: 3.11) showed the molecular ion peak at 376 $[M^+1]$ corresponding to the molecular mass of 375 $[M^+]$ when recorded in the Q+1 mode.

\[
\begin{array}{c}
\text{(49)} \\
\text{IPA.HCl, 2 hr} \\
\text{60 - 65 °C} \\
\text{60-75%} \\
\text{(50)}
\end{array}
\]

$R^1=OCH_3, C_2\text{H}_5$  
$R^2=\text{Benzyl; 2-Bromophenyl; 2-Chlorophenyl; 2-Bromophenyl; Phenyl}$  

......Scheme-3.7
The above reaction of 49a with IPA.HCl was found to be a general one and has been extended to prepare different derivatives of 50a-e (where, \( R^1 = H, CH_3, C_2H_5, OCH_3 \) & \( R^2 = \text{Substituted phenyls} \)). The products were assigned their structures by analogy and on the basis of their spectral & analytical data. For details, please see the Experimental Section of this chapter.

3.4.3 Preparation of N-aryl / N-aralkyl-4-substituted-3-[N-methyl-N-(piperidin-4-yl)amino]benzenesulfonamides (52):

49a (i.e. 49, \( R^1=OCH_3, R^2=\text{benzyl} \)) was reacted with formaldehyde in presence of sodium cyanoborohydride. The mixture was processed to obtain the reductively alkylated product N-benzyl-4-methoxy-3-[N-methyl-N-(1-t-butyloxycarbonylpiperidin-4-yl)-amino]benzenesulfonamide (51a) (i.e. 51, \( R^1=OCH_3, R^2=\text{benzyl} \)) (Scheme-3.8) whose structure was assigned based on its spectral and analytical data. Thus, its IR (KBr) (Fig: 3.12) showed the characteristic peaks at \( \sim 3270 \text{ cm}^{-1} \) (broad, medium, due to -NH), 1673 cm\(^{-1}\) (strong, sharp, due to –CO-group), 1329 & 1156 cm\(^{-1}\) (sharp, medium, unequal doublet due to asymmetric and symmetric stretching vibrations due to SO\(_2\) group). Its \(^1\)H-NMR (CDCl\(_3\)/TMS) (Fig: 3.13) showed signals at \( \delta 1.46 \text{ (s, 9H; (C}_3\text{H}_3)_3} \), 1.59 – 1.65 (m, 4H; piperidinyl-H), 2.66 (m, 2H; piperidinyl-H), 2.70 (s, 3H; N-C\(_3\)H\(_3\)), 3.31 – 3.34 (m, 1H; piperidinyl-H), 3.93 (s, 3H; -OCH\(_3\)), 4.12 – 4.18 (m, 4H; CH\(_2\)Ph & piperidinyl-H), 4.71 – 4.74 (t, 1H; PhCH\(_2\)NH), 6.90 – 6.92 (d, \( J = 8.40 \text{ Hz, 1H; Ar-H} \)), 7.16 – 7.26 (m, 5H; Ar-H), 7.40 (d,
J = 2.15 Hz, 1H; Ar-H, 7.51 – 7.54 (dd, J = 2.16, 8.40 Hz, 1H; Ar-H). Its ESI-MS (Fig: 3.14) showed the molecular ion peak at 490 [M⁺ +1] corresponding to the molecular mass of 489 [M⁺] when recorded in the Q+1 mode.

\[ \text{Scheme-3.8} \]

The above reaction of 49a with formaldehyde and sodium cyanoborohydride was found to be a general one and has been extended to prepare different derivatives of 51 (where, R¹=OCH₃ & R²=substituted phenyls). The products were assigned their structures by analogy and on the basis of spectral and analytical data. For details, please see the Experimental Section of this chapter.

51a (i.e., 51, R¹=OCH₃, R²=benzyl) was treated with isopropanolic hydrochloride solution (IPA.HCl, 15-20%, w/v). The mixture was processed and the isolated product was identified as N-benzyl-4-methoxy-3-[N-methyl-N-(piperidin-4-yl) amino]benzenesulfonamide (52a) (i.e., 52, R¹=OCH₃, R²=benzyl) (Scheme-3.9) based on its spectral and analytical data. Thus, its IR (CHCl₃) (Fig: 3.15) showed signals at ~3450 cm⁻¹ (broad, medium, due to -NH), 1329 & 1156 cm⁻¹ (short, sharp,
unequal doublet due to asymmetric and symmetric stretching vibrations of SO₂ group. Its ¹H-NMR (DMSO- d₆/TMS) (Fig: 3.16) showed signals at δ 1.52 (m, 4H; piperidinyl- H), 2.40 – 2.42 (m, 2H; piperidinyl- H), 2.60 (s, 3H; N-CH₃), 2.96 – 2.99 (m, 2H; piperidinyl- H), 3.20 (m, 1H; piperidinyl- H), 3.83 (s, 3H; -OCH₃), 3.91 (d, 2H; PhCH₂NH), 7.02 – 7.04 (d, J = 8.50 Hz, 1H; Ar- H), 7.19 – 7.27 (m, 6H; Ar- H), 7.33 – 7.35 (d, 1H; Ar- H), 7.93 (s, 1H; NH). Its ESI-MS (Fig: 3.17) showed the presence of molecular ion peak at 390 [M⁺]+1 corresponding to the molecular mass of 389 [M⁺] when recorded in the Q+1 mode.

![Reaction Diagram](image)

(51) → (52)

R¹=OCH₃  
R²=Benzyl; 2-Bromophenyl; 2-Chlorophenyl; Phenyl

![](image)

The above reaction of 51a with IPA.HCl was found to be a general one and has been extended to prepare different derivatives of 52 (where, R¹=OCH₃ & R²=substituted phenyls). The products were assigned their structures by analogy and on the basis of spectral and analytical data. For details, please see the Experimental Section of this chapter.
3.4.4 Preparation of N-aryl / N-aralkyl-4-substituted-3-[N-methyl-N-(1-methyl-piperidin-4-yl)amino]benzenesulfonamides (53):

52a (i.e., 52, \(R^1=\text{OCH}_3\), \(R^2=\text{benzyl}\)) was reacted with formaldehyde and sodium cyanoborohydride in methanol as solvent. The mixture was processed to obtain the reductively alkylated product N-benzyl-4-methoxy-3-[N-methyl-N-(1-methylpiperidin-4-yl)amino]-benzenesulfonamide (53a) (i.e. 53, \(R^1=\text{OCH}_3\), \(R^2=\text{benzyl}\)) (Scheme-3.10) whose structure was assigned based on its spectral and analytical data. Thus, its IR (CHCl\(_3\)) (Fig: 3.18) showed peaks at ~3450 cm\(^{-1}\) (broad, medium, due to -NH), 1325 & 1157 cm\(^{-1}\) (medium, sharp, unequal doublet due to asymmetric and symmetric stretching vibrations of -SO\(_2\) group). Its \(^1\)H-NMR (CDCl\(_3\)/TMS) (Fig: 3.19) showed signals at \(\delta\) 1.63 – 1.66 (m, 2H; piperidinyl-\(\text{H}\)), 1.80 – 1.84 (m, 2H; piperidinyl-\(\text{H}\)), 1.90 – 1.96 (m, 2H; piperidinyl-\(\text{H}\)), 2.26 (s, 3H; N-\(\text{CH}_3\)), 2.72 (s, 3H; N-\(\text{CH}_3\)), 2.88 – 2.91 (m, 2H; piperidinyl-\(\text{H}\)), 3.21 (m, 1H; piperidinyl-\(\text{H}\)), 3.92 (s, 3H; -\(\text{OCH}_3\)), 4.11 – 4.12 (d, 2H; ArCH\(_2\)NH), 4.62 (t, 1H; CH\(_2\)NH), 6.88 – 6.90 (d, J = 8.50 Hz, 1H; Ar-\(\text{H}\)), 7.15 – 7.26 (m, 5H; Ar-\(\text{H}\)), 7.38 – 7.39 (d, J = 2.3 Hz, 1H; Ar-\(\text{H}\)), 7.49 – 7.51 (dd, J = 2.3, 8.5 Hz, 1H; Ar-\(\text{H}\)). Its \(^{13}\)C-NMR (Fig: 3.20) showed characteristic signals at \(\delta\) 28.58 (piperidinyl-\(\text{C}\)), 46.48 (piperidinyl-\(\text{C}\)), 55.44 (CH\(_2\)Ar) and 112 – 157 (Ar-\(\text{C}\)). Its ESI-MS (Fig: 3.21) showed the molecular ion peak at 404 [M\(^+\)+1] corresponding to molecular mass of 403 [M\(^+\)] when recorded in the Q+1 mode.
The above reaction of 52a with formaldehyde in presence of sodium cyanoborohydride was found to be a general one and has been extended to prepare different derivatives of 53a-b (where, R¹=OCH₃ & R²=substituted phenyls). The products were assigned their structure by analogy and on the basis of spectral and analytical data. For details, please see the Experimental Section of this chapter.

All the above reactions are briefly summarized in Scheme-3.11 and Scheme-3.12.
3.5 Conclusion:

The compounds were prepared using reductive alkylation and reductive amination methods. All the compounds were fully characterized with spectral and analytical data, before testing for their in-vitro activities towards 5-HT₆ receptor.
3.6 Experimental Section:

Preparation of 47 (General procedure):

A mixture of 46 (0.113g, 1 mmol), sodium sulfate (1.42g, 10 mmol), acetic acid (8 mL), 21 (1 mmol) and sodium triacetoxyborohydride (0.633g, 3 mmol) was stirred for 15 hr at RT. After completion of the reaction (TLC), acetic acid was removed under reduced pressure. The residue was diluted with water (25 mL) and basified with 50% sodium hydroxide solution (pH~10). The mixture was extracted into ethyl acetate (25 mL x 2). The organic layers were combined, washed with brine solution (25 mL), dried over anhyd. sodium sulfate, filtered and concentrated under reduced pressure to obtain residue.

Purification: The products 47a-p were purified by flash column chromatography over silica gel, using ethyl acetate: n-Hexane as an eluent. The polarities were increased gradually from 5 to 50%.

47a (i.e. 47, R¹=CH₃, R²=2-Bromophenyl):
Yield = 0.29g (65%); M.R (0°C): 138.6 – 142.6; HPLC purity: 94.4%. For spectral details, please see under Results & Discussion section.

47b (i.e. 47, R¹=H, R²=2,5-Dimethoxyphenyl):
Yield = 0.25g (60%); Syrupy mass; IR (KBr): 3383 cm⁻¹ (-NH-), 1328 & 1158 cm⁻¹ (-SO₂⁻); ¹H-NMR (CDCl₃/TMS): δ 1.41 – 1.43 (m, 2H; piperidinyl-H), 1.88 – 1.92 (m, 2H; piperidinyl-H), 2.07 – 2.12 (m, 2H; piperidinyl-H), 2.30 (s, 3H; N-CH₃), 2.79 – 2.82 (m, 2H; piperidinyl-H),
3.10 – 3.20 (m, 1H; CH-NH), 3.48 (s, 3H; OCH₃), 3.54 (m, 1H; NH-CH), 3.75 (s, 3H; OCH₃), 6.28 – 6.29 (d, J = 2.60 Hz, 1H; Ar-H), 6.42 – 6.45 (m, 2H; Ar-H & NHSO₂), 6.65 (m, 1H; Ar-H), 6.73 – 6.74 (m, 1H; Ar-H), 6.99 – 7.00 (m, 1H; Ar-H), 7.11 – 7.15 (t, 1H; Ar-H), 7.44 – 7.46 (d, J = 8.72 Hz, 1H; Ar-H); ESI-MS (m/z): 406 [M⁺+1]; HPLC purity: 86.6%.

47c (i.e. 47, R¹=H, R²=2,4-Dimethylphenyl):

Yield = 0.25g (65%); Syrupy mass; IR (KBr): 3385 cm⁻¹ (-NH-), 1323 & 1157 cm⁻¹ (-SO₂-); ¹H-NMR (CDCl₃/TMS): δ 1.41 – 1.47 (m, 2H; piperidinyl-H), 1.86 – 1.90 (m, 2H; piperidinyl-H), 1.93 (s, 3H; ArCH₃), 2.04 – 2.11 (m, 2H; piperidinyl-H), 2.26 (s, 3H; ArCH₃), 2.31 (s, 3H; N-CH₃), 2.79 – 2.82 (m, 2H; piperidinyl-H), 3.15 (bs, 1H; piperidinyl-H), 3.70 – 3.80 (bs, 1H; NH-CH), 6.30 (s, 1H; NHSO₂), 6.68 – 6.70 (dd, J = 1.70, 7.90 Hz, 1H; Ar-H), 6.74 – 6.75 (t, 1H; Ar-H), 6.90 (bs, 1H; Ar-H), 6.92 – 6.95 (m, 1H; Ar-H), 7.01 – 7.03 (m, 1H; Ar-H), 7.16 – 7.20 (m, 2H; Ar-H); ¹³C-NMR (DMSO-d₆/TMS) δ: 17.79, 20.81, 31.59, 46.28, 48.84, 54.41, 109.35, 113.19, 116.85, 127.05, 129.77, 131.46, 132.83, 134.44, 135.78, 141.46, 148.41; ESI-MS (m/z): 374 [M⁺+1]; HPLC purity: 98.73%.

47d (i.e. 47, R¹=H, R²=2,4-Dimethoxyphenyl):

Yield = 0.28g (70%); Syrupy mass; IR (KBr): 3354 cm⁻¹ (-NH-), 1323 & 1125 cm⁻¹ (-SO₂-); ¹H-NMR (CDCl₃/TMS): δ 1.44 – 1.48 (m, 2H; piperidinyl-H), 1.90 – 1.99 (m, 2H; piperidinyl-H), 2.10 – 2.15 (m, 2H; piperidinyl-H), 2.30 (s, 3H; N-CH₃), 2.75 – 2.78 (m, 2H; piperidinyl-H), 3.20 (bs, 1H; piperidinyl-H), 3.59 (s, 3H; -OCH₃), 3.73 (s, 4H; OCH₃ and
NH), 6.52 – 6.56 (dd, J = 2.0, 8.10 Hz, 1H; Ar-H), 6.65 – 6.69 (m, 3H; Ar-H & NHSO₂), 6.88 – 6.90 (m, 1H; Ar-H), 7.06 – 7.19 (m, 3H; Ar-H); ¹³C-NMR (DMSO-d₆/TMS) δ: 31.59, 34.56, 46.11, 46.29, 48.76, 53.39, 54.42, 55.60, 56.63, 109.44, 109.69, 109.91, 113.16, 113.40, 116.84, 127.39, 129.62, 141.30, 145.95, 148.40, 153.25; ESI-MS (m/z): 406 [M⁺+1];

HPLC purity: 95.53%.

47e (i.e. 47, R¹=H, R²=4-Br, 2-F phenyl):

Yield = 0.30g (75%); Syrupy mass; IR (KBr): 3357 cm⁻¹ (-NH-), 1325 & 1122 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): δ 1.38 – 1.42 (m, 2H; piperidinyl-H), 1.75 – 1.78 (m, 2H; piperidinyl-H), 2.04 – 2.09 (m, 2H; piperidinyl-H), 2.21 (s, 3H; N-CH3), 2.75 – 2.78 (m, 2H; piperidinyl-H), 3.03 – 3.07 (m, 1H; piperidinyl-H), 3.46 – 3.48 (bs, 1H; NH), 5.95 – 5.96 (d, J = 7.75 Hz, 1H; Ar-H), 6.70 – 6.82 (m, 4H; Ar-H & NHSO₂), 7.12 – 7.25 (m, 3H; NH & Ar-H), 7.39 – 7.42 (m, 1H; Ar-H); ¹³C-NMR (DMSO-d₆/TMS) δ: 14.43, 21.11, 21.68, 31.21, 33.61, 45.17, 45.78, 48.43, 52.67, 54.12, 60.11, 109.36, 113.31, 115.36, 115.45, 116.49, 119.15, 119.38, 126.58, 127.76, 127.88, 128.01, 129.73, 142.13, 148.32, 154.26, 156.75; ESI-MS (m/z): 442 [M⁺+1]; HPLC purity: 97.96%.

47f (i.e. 47, R¹=H, R²=2-Br 4,6-difluoro phenyl):

Yield = 0.25g (55%); Syrupy mass; IR (KBr): 3366 cm⁻¹ (-NH-), 1325 & 1122 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): 1.32 – 1.41 (m, 2H; piperidinyl-H), 1.81 – 1.83 (m, 2H; piperidinyl-H), 2.02 – 2.07 (m, 2H; piperidinyl-H), 2.19 (s, 3H; N-CH3), 2.74 – 2.77 (m, 2H; piperidinyl-H),
3.11 – 3.13 (m, 1H; piperidinyl-H), 5.92 – 5.94 (d, 1H; -NH), 6.74 – 6.82 (m, 4H; Ar-H & NHSO₂), 7.15 – 7.19 (m, 1H; Ar-H), 7.31 – 7.37 (m, 1H; Ar-H), 7.47 – 7.49 (m, 1H; Ar-H); ¹³C-NMR (DMSO-d₆/TMS) δ: 31.37, 45.91, 48.55, 54.16, 104.57, 104.82, 105.08, 109.89, 113.48, 116.40, 122.84, 123.0, 125.86, 125.98, 129.66, 143.06, 148.38, 158.36, 158.50, 158.79, 158.91, 161.02, 161.27; ESI-MS (m/z): 462 [M⁺+3], 460 [M⁺+1]; HPLC purity: 99.11%.

47g (i.e. 47, R¹=C₂H₅; R²=2-Bromophenyl):
Yield = 0.27g (60%); M.R (°C): 168.2 – 169.5; IR (KBr): 3407 cm⁻¹ (-NH-), 1330 & 1135 cm⁻¹ (-SO₂-); ¹H-NMR (CDCl₃/TMS): δ 1.19 – 1.26 (t, 3H; CH₂CH₃), 1.42 – 1.44 (m, 2H; piperidinyl-H), 1.88 – 1.91 (m, 2H; piperidinyl-H), 2.04 – 2.18 (m, 2H; piperidinyl-H), 2.30 (s, 3H; N-CH₃), 2.38 – 2.44 (q, 2H; CH₂CH₃), 2.74 – 2.77 (bs, 2H; piperidinyl-H), 3.22 (bs, 1H; piperidinyl-H), 3.56 – 3.58 (d, 1H; -NH), 6.81 (m, 2H; NH & Ar-H), 6.93 – 6.97 (m, 1H; Ar-H), 7.06 – 7.11 (m, 2H; Ar-H), 7.23 – 7.28 (m, 1H; Ar-H), 7.40 – 7.42 (dd, J = 1.36, 8.03 Hz, 1H; Ar-H), 7.69 – 7.72 (dd, J = 1.36, 8.03 Hz, 1H; Ar-H); ESI-MS (m/z): 454, 452 [M⁺+1]; HPLC purity: 98.66%.

47h (i.e. 47, R¹=C₂H₅; R²=3,5-di-Cl, 2-OMe phenyl):
Yield = 0.30g (70%); Syrupy mass; IR (KBr): 3224 cm⁻¹ (-NH-), 1336 & 1162 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): δ 1.06 – 1.10 (t, 2H; CH₂CH₃), 1.46 – 1.54 (m, 2H; piperidinyl-H), 1.75 – 1.78 (m, 2H; piperidinyl-H), 2.21 - 2.27 (m, 2H; piperidinyl-H), 2.30 (s, 3H; N-CH₃),
2.43 – 2.47 (q, 3H; CH₂CH₃), 2.86 – 2.89 (m, 2H; piperidinyl-H), 3.15 (m, 1H; CH-NH), 3.45 (s, 3H; -OCH₃), 4.90 – 4.92 (m, 1H; -NH), 6.80 (d, 1H; Ar-H), 6.95 – 6.97 (d, J = 7.87 Hz, 1H; Ar-H), 7.08 – 7.10 (d, J = 7.79 Hz, 1H; Ar-H), 7.20 (s, 1H; Ar-H), 7.32 (d, J = 2.2 Hz, 1H; Ar-H), 9.84 (bs, 1H; NH₂SO₂); ¹³C-NMR (DMSO-d₆/TMS) δ: 12.88, 23.52, 30.78, 45.47, 48.82, 54.29, 60.56, 107.28, 114.10, 120.01, 128.08, 128.31, 132.57, 139.60, 145.10, 146.47; ESI-MS (m/z): 471 [M⁺ -1]; HPLC purity: 98.61%.

₄₇i (i.e. ₄₇, R¹=OCH₃; R²=Benzyl):
Yield = 0.29g (75%); M.R (ºC): 175.3 – 176.7; IR (KBr): 3418 cm⁻¹ (-NH-), 1315 & 1140 cm⁻¹ (-SO₂-); ¹H-NMR (CDCl₃/TMS): 1.41 – 1.49 (m, 2H; piperidinyl-H), 1.83 – 1.86 (m, 2H; piperidinyl-H), 1.96 – 2.01 (m, 2H; piperidinyl-H), 2.15 (s, 3H; N-CH₃), 2.69 – 2.72 (m, 2H; piperidinyl-H), 3.15 – 3.17 (m, 1H; piperidinyl-H), 3.84 (s, 3H; -OCH₃), 3.87 (s, 2H; CH₂Ph), 4.84 – 4.86 (d, 1H; -NH₂SO₂), 6.87 – 6.92 (m, 3H; Ar-H & NH₂SO₂), 7.00 – 7.02 (d, J = 2 Hz, 1H; Ar-H), 7.21 – 7.28 (m, 4H; Ar-H), 7.85 (s, 1H; Ar-H). ¹³C-NMR (DMSO-d₆/TMS) δ: 31.68, 46.37, 46.52, 48.90, 54.65, 56.08, 106.55, 109.31, 115.14, 127.42, 127.89, 128.53, 132.83, 137.51, 138.19, 149.40; ESI-MS (m/z): 390 [M⁺+1]; HPLC purity: 99.90%.

₄₇j (i.e. ₄₇, R¹=OCH₃; R²=phenyl):
Yield = 0.26g (70%); M.R (ºC): 221.9 – 223.9; IR (KBr): 3425 cm⁻¹ (-NH-), 1340 & 1159 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): 1.35 – 1.40 (m, 2H; piperidinyl-H), 1.68 – 1.71 (m, 2H; piperidinyl-H), 1.91 – 1.97 (m, 2H; piperidinyl-H), 2.15 (s, 3H; N-CH₃), 2.49 – 2.71(d, 2H; piperidinyl-H),
3.01 – 3.03 (m, 1H; piperidinyl-H), 3.78 (s, 3H; -OCH₃), 4.80 – 4.82 (d, 1H; NH), 6.72 – 6.73 (d, J = 2.13 Hz, 1H; Ar-H), 6.83 – 6.85 (d, J = 8.42 Hz, 1H; Ar-H), 6.94 – 6.98 (m, 2H; Ar-H), 7.06 – 7.09 (m, 2H; Ar-H), 7.17 – 7.21 (m, 2H; Ar-H), 9.96 (s, 1H; NHSO₂); ¹³C-NMR (DMSO-d₆/TMS) δ: 31.49, 46.34, 49.05, 54.69, 55.99, 106.63, 109.26, 115.32, 120.24, 124.05, 129.32, 131.91, 137.26, 138.73, 149.65; ESI-MS (m/z): 376 [M⁺+1]; HPLC purity: 99.86%.

47k (i.e. 47, R¹=OCH₃; R²=2-Chlorophenyl):

Yield = 0.30g (75%); M.R (°C): 60.2 – 63.6; IR (KBr): 3418 & 3397 cm⁻¹ (-NH-), 1332 & 1156 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): 1.38 – 1.41 (m, 2H; piperidinyl-H), 1.69 – 1.72 (m, 2H; piperidinyl-H), 1.94 – 1.99 (m, 2H; piperidinyl-H), 2.18 (s, 3H; N-CH₃), 2.70 – 2.73 (m, 2H; piperidinyl-H), 3.00 – 3.02 (m, 1H; piperidinyl-H), 3.81 (s, 3H; -OCH₃), 4.84 – 4.86 (d, 1H; NH), 6.68 – 6.69 (d, J = 2.07 Hz, 1H; Ar-H), 6.85 – 6.87 (d, J = 8.42 Hz, 1H; Ar-H), 6.92 – 6.95 (dd, J = 2.07, 8.42 Hz, 1H; Ar-H), 7.10 – 7.11 (m, 1H; Ar-H), 7.20 – 7.24 (m, 1H; Ar-H), 7.27 – 7.29 (dd, 1H; Ar-H), 7.30 – 7.35 (dd, 1H; Ar-H), 9.90 (s, 1H; NH); ¹³C-NMR (DMSO-d₆/TMS) δ: 31.35, 46.11, 54.56, 56.03, 106.77, 109.25, 115.18, 126.39, 126.64, 127.84, 128.46, 130.07, 132.97, 135.31, 137.21, 149.64; ESI-MS (m/z): 410 [M²⁺+1]; HPLC purity: 99.42%.

47l (i.e. 47, R¹=OCH₃; R²=2-Bromophenyl):

Yield = 0.34g (75%); M.R (°C): 136 – 137; IR (KBr): 3374 cm⁻¹ (-NH-), 1332 & 1151 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): δ 1.38 – 1.42 (m,
2H; piperidinyl-H), 1.75 – 1.78 (m, 2H; piperidinyl-H), 2.04 – 2.09 (m, 2H; piperidinyl-H), 2.21 (s, 3H; N-CH₃), 2.75 – 2.78 (m, 2H; piperidinyl-H), 3.03 – 3.07 (m, 1H; piperidinyl-H), 3.46 – 3.48 (bs, 1H; NH), 3.83 (s, 3H; -OCH₃), 6.68 – 6.69 (d, J = 2.06 Hz, 1H; Ar-H), 6.86 – 6.88 (d, J = 8.0 Hz, 1H; Ar-H), 7.00 – 7.04 (m, 1H; Ar-H), 7.20 – 7.27 (m, 2H; Ar-H), 7.50 – 7.53 (m, 1H; Ar-H), 9.90 (s, 1H; NH); ¹³C-NMR (DMSO-d₆/TMS) δ: 31.28, 45.97, 48.77, 54.47, 56.04, 106.90, 109.28, 115.24, 119.62, 126.61, 126.87, 128.40, 132.29, 137.0, 137.19, 149.60; ESI-MS (m/z): 456, 454 [M⁺+1]; HPLC purity: 98.47%.

47m (i.e. 47, R¹=OCH₃; R²=2-OCH₃,5-CH₃ phenyl):

Yield = 0.27g (65%); M.R (0°C): 134.8 – 136.9; IR (KBr): 3425 cm⁻¹ (-NH-), 1328 & 1163 cm⁻¹ (-SO₂-); ¹H-NMR (CDCl₃/TMS): δ 1.32 – 1.47 (m, 2H; piperidinyl-H), 1.88 – 1.91 (m, 2H; piperidinyl-H), 2.03 – 2.12 (m, 2H; piperidinyl-H), 2.26 (s, 3H; ArCH₃), 2.31 (s, 3H; N-CH₃), 2.77 – 2.79 (m, 2H; piperidinyl-H), 3.15 (bs, 1H; CH-NH), 3.60 (s, 3H; OCH₃), 3.84 (s, 3H; OCH₃), 4.17 – 4.19 (d, 1H; NH-CH), 6.60 – 6.63 (d, J = 8.24 Hz, 1H; Ar-H), 6.67 – 6.69 (d, J = 8.38 Hz, 1H; Ar-H), 6.78 – 6.80 (m, 2H; Ar-H), 6.90 (bs, 1H; Ar-H), 7.11 – 7.12 (m, 1H; Ar-H); ESI-MS (m/z): 420 [M⁺+1]; HPLC purity: 98.74%.

47n (i.e. 47, R¹=OCH₃; R²=3,5-di-Cl, 2-OMe phenyl) (HCl salt):

Yield = 0.31g (65%); M.R (0°C): 145 – 148.3 oC; IR (KBr): 3374 cm⁻¹ (-NH-), 1338 & 1160 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): δ 1.59 – 1.66 (m, 2H; piperidinyl-H), 1.93 – 1.96 (m, 2H; piperidinyl-H), 2.40 – 2.44 (m, 2H; piperidinyl-H), 2.46 – 2.50 (m, 2H; piperidinyl-H), 3.46 – 3.48 (bs, 1H; NH), 3.83 (s, 3H; -OCH₃), 6.67 – 6.69 (d, J = 8.38 Hz, 1H; Ar-H), 6.78 – 6.80 (m, 2H; Ar-H), 6.90 (bs, 1H; Ar-H), 7.11 – 7.12 (m, 1H; Ar-H); ESI-MS (m/z): 420 [M⁺+1]; HPLC purity: 98.74%.
N-CH₃), 3.01 – 3.07 (m, 2H; piperidinyl-H), 3.13 (m, 2H; piperidinyl-H),
3.47 (s, 3H; -OCH₃), 3.81 (s, 3H; -OCH₃), 5.50 (m, 1H; piperidinyl-H),
6.87 (d, J = 2.0 Hz, 1H; Ar-H), 6.93 – 6.95 (d, J = 8.4 Hz, 1H; Ar-H), 7.04 –
7.07 (dd, J = 2.2, 8.3 Hz, 1H; Ar-H), 7.35 – 7.36 (d, J = 2.40 Hz, 1H; Ar-
H), 7.37 (d, J = 2.4 Hz, 1H; Ar-H), 9.95 – 9.96 (d, 1H; NH), 10.24 – 10.34
(d, 1H; HCl); ¹³C-NMR (DMSO-d₆/TMS) δ: 28.82, 42.80, 46.90, 52.95,
56.14, 61.27, 106.81, 109.79, 115.80, 120.49, 125.14, 128.44, 128.51,
131.73, 134.09, 136.90, 146.53, 150.24; ESI-MS (m/z): 476 [M⁺+3], 474
[M⁺+1]; HPLC purity: 98.51%.

47o (i.e. 47, R¹=OCH₃; R²=2-Bromophenethyl):

Yield = 0.36g (75%); Syrupy mass; IR (KBr): 3375 cm⁻¹ (-NH-), 1338 &
1160 cm⁻¹ (-SO₂-); ¹H-NMR (CDCl₃/TMS): δ 1.89 – 1.90 (m, 2H; piperidinyl-H), 2.03 – 2.05 (m, 2H; piperidinyl-H), 2.11 – 2.12 (m, 2H; piperidinyl-H), 2.15 (s, 3H; N-CH₃), 2.46 – 2.49 (m, 2H; Ar-CH₂), 2.70 –
2.73 (m, 2H; ArCH₂CH₂NH), 2.90 – 2.93 (m, 2H; piperidinyl-H), 3.90 (s, 3H; -OCH₃), 4.30 – 4.32 (m, 1H; piperidinyl-H), 4.39 (d, 1H; NH), 6.75 –
6.77 (m, 2H; Ar-H), 6.93 – 6.94 (d, 1H; Ar-H), 7.06 – 7.24 (m, 4H; Ar-H),
7.49 – 7.51 (d, 1H; -NHSO₂); ESI-MS (m/z): 484, 482 [M⁺+1]; HPLC
purity: 96%.

47p (i.e. 47, R¹=OCH₃; R²=2-Chlorophenethyl):

Yield = 0.33g (75%); Syrupy mass; IR (KBr): 3374 cm⁻¹ (-NH-), 1338 &
1160 cm⁻¹ (-SO₂-); ¹H-NMR (ppm, CD₃OD): δ 1.71 – 1.74 (m, 2H; piperidinyl-H), 2.18 – 2.21 (m, 2H; piperidinyl-H), 2.71 (s, 3H; N-CH₃),
2.83 – 2.89 (m, 4H; piperidinyl-H), 3.04 – 3.08 (t, 2H; CH$_2$Ar), 3.17 – 3.23 (t, 2H; NHCH$_2$), 3.56 – 3.57 (m, 1H; piperidinyl-H), 3.92 (s, 3H; -OCH$_3$), 6.93 – 6.98 (m, 2H; Ar-H), 7.13 – 7.21 (m, 4H; Ar-H), 7.30 – 7.32 (m, 1H; Ar-H); ESI-MS (m/z): 440 [M$^+3$], 438 [M$^+1$]; HPLC purity: 96.98%.

**Compounds 50a-e:**

**Preparation of 49 (General procedure):**

A mixture of 48 (0.597g, 3 mmol), sodium sulfate (1.42g, 10 mmol), acetic acid (10 mL), 21 (1 mmol) and sodium triacetoxyborohydride (0.64g, 3 mmol) was stirred for 12 hr at RT. After completion of the reaction (TLC), the acetic acid was removed under reduced pressure. The residual oil was diluted with water (25 mL) and basified with 50% NaOH (pH~ 9). The product was extracted into ethyl acetate (25 mL x 2). The organic layers were combined, washed with brine solution (20 mL), dried over anhyd. sodium sulfate, filtered and concentrated under reduced pressure to obtain crude product.

Purification: The products 50a-e were purified by flash column chromatography over silica gel, using ethyl acetate: n- Hexane as an eluent. The polarities were increased gradually from 5 to 20%.

49a (i.e. 49, R$^1$=OCH$_3$, R$^2$=Benzyl):

Yield = 0.28g (60%); M. R ($^{0}$C): 100 – 103.3; HPLC purity: 99.46%. For spectral details, please see under Results & Discussion section.
49b (i.e. 49, R₁=OCH₃, R₂=2-bromophenyl):

Yield = 0.31g (65%); Syrupy mass; ¹H-NMR (CDCl₃/TMS): 1.31 (m, 4H; piperidinyl-H), 1.45 (s, 9H; (CH₃)₃OCO), 1.81 (m, 2H; piperidinyl-H), 2.86 (m, 2H; piperidinyl-H), 3.30 (m, 1H; piperidinyl-H), 3.86 (s, 3H; OCH₃), 4.20 – 4.22 (d, 1H; NH), 6.69 – 7.72 (m, 8H; Ar-H & NH); ESI-MS (m/z): 486, 484 [M⁺-56]; HPLC purity: 95.30%.

49c (i.e. 49, R₁=OCH₃, R₂=2-Chlorophenyl):

Yield = 0.27g (55%); Syrupy mass; ¹H-NMR (CDCl₃/TMS): 1.40 (s, 9H; (CH₃)₃OCO), 1.77 (m, 4H; piperidinyl-H), 2.10 (m, 2H; piperidinyl-H), 3.30 (m, 1H; piperidinyl-H), 3.76 (m, 2H; piperidinyl-H), 3.80 (s, 3H; OCH₃), 4.01 (s, 1H; NH), 6.65 – 7.63 (m, 8H; Ar-H & NH); ESI-MS (m/z): 496 [M⁺+1], 440 [M⁺-56].

49d (i.e. 49, R₁=C₂H₅, R₂=2-Bromophenyl):

Yield = 0.32g (60%); M. R (°C): 129 – 130.7; IR (KBr): 1159 & 1367 cm⁻¹ (-SO₂-); ¹H-NMR (CDCl₃/TMS): δ 1.19 – 1.27 (m, 5H; piperidinyl-H & CH₃CH₂), 1.46 (s, 9H; (CH₃)₃OCO), 1.83 – 1.85 (m, 2H; piperidinyl-H), 2.38 – 2.44 (q, 2H; CH₃CH₂), 2.87 (m, 2H; piperidinyl-H), 3.35 (m, 1H; piperidinyl-H), 3.55 (s, 1H; NH), 3.99 (m, 2H; piperidinyl-H), 6.79 – 7.72 (m, 8H; Ar-H & NH); HPLC purity: 97.05%.

49e (i.e. 49, R₁=OCH₃, R₂=phenyl):

Yield = 0.23g (50%); Syrupy mass; ¹H-NMR (CDCl₃/TMS): 1.45 (s, 9H; (CH₃)₃OCO), 1.24 (m, 2H; piperidinyl-H), 1.78 – 1.84 (m, 2H; piperidinyl-H), 2.82 (m, 2H; piperidinyl-H), 3.20 (m, 1H; piperidinyl-H), 3.83 (s, 3H;
OCH₃), 4.0 (m, 2H; piperidinyl-H), 4.19 – 4.21 (s, 1H; NH), 6.61 – 7.23 (m, 9H; Ar-H & NH); ESI-MS (m/z): 462 [M+1], 406 [M-56].

**Preparation of 50 (General procedure):**

A mixture of 49 (1.51 mmol), isopropyl alcohol (5 mL) and IPA.HCl solution (15.1 mmol, ~15% w/v) was heated to 60 – 65 °C for 2 hr. The solids separated was cooled to RT & filtered at suction under nitrogen blanket. The product was washed with isopropyl alcohol (3 mL) and sucked dried under nitrogen blanket. The solid was transferred to single neck flask and kept under high vacuum (< 1 mbar) at 50 °C for 1 hr.

**50a** (i.e. 50, R¹=OCH₃, R²=Benzyl) (HCl salt):

Yield = 0.22g (70%); M.R (°C): 187 – 190; HPLC purity: 99.43%. For spectral details, please see under Results & Discussion section of this chapter.

**50b** (i.e. 50, R¹=OCH₃, R²=2-Bromophenyl) (HCl salt):

Yield = 0.29g (65%); M.R (°C): 199.3 – 201.6 (decomposed); IR (KBr): 3340 cm⁻¹ (-NH-), 1340 & 1162 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): δ 1.53 – 1.61 (m, 2H; piperidinyl-H), 1.85 – 1.88 (m, 2H; piperidinyl-H), 2.87 – 2.95 (m, 2H; piperidinyl-H), 3.23 – 3.26 (m, 2H; piperidinyl-H), 3.37 – 3.42 (m, 1H; piperidinyl-H), 3.83 (s, 3H; -OCH₃), 6.75 (d, J = 1.52 Hz, 1H; Ar-H), 6.91 – 6.93 (d, J = 8.44 Hz, 1H; Ar-H), 6.98 – 7.01 (dd, J = 1.74, 8.43 Hz, 1H; Ar-H), 7.07 – 7.11 (m, 1H; Ar-H), 7.19 – 7.21 (m, 1H; Ar-H), 7.27 – 7.30 (m, 1H; Ar-H), 7.54 – 7.56 (d, J = 7.24 Hz, 1H; Ar-H),
8.64 – 8.66 (s, 1H; -NH), 8.81 (s, 1H; HCl), 9.5 (s, 1H; NH); ESI-MS (m/z): 442 [M⁺+3], 440 [M⁺+1]; HPLC purity: 98.58%.

50c (i.e. 50, R¹=OCH₃, R²=2-Chlorophenyl) (HCl salt):

Yield = 0.30g (75%); Syrupy mass; IR (KBr): 3418 cm⁻¹ (-NH-), 1333 & 1163 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): 1.56 – 1.59 (m, 2H; piperidinyl-H), 1.85 – 1.97 (m, 2H; piperidinyl-H), 2.89 – 2.92 (m, 2H; piperidinyl-H), 3.23 – 3.26 (m, 2H; piperidinyl-H), 3.37 (m, 1H; piperidinyl-H), 3.82 (s, 3H; -OCH₃), 6.76 – 6.77 (d, J = 2.06 Hz, 1H; Ar-H), 6.90 – 6.92 (d, J = 8.46 Hz, 1H; Ar-H), 6.97 – 7.00 (dd, J = 2.06, 8.44 Hz, 1H; Ar-H), 7.13 – 7.17 (m, 1H; Ar-H), 7.22 – 7.29 (m, 2H; Ar-H), 7.36 – 7.38 (m, 1H; Ar-H), 8.67 – 8.70 (s, 1H; NH), 8.84 (s, 1H; HCl), 9.63 (s, 1H; NH). ¹³C-NMR (DMSO-d₆/TMS) δ: 28.18, 37.68, 42.44, 47.18, 56.14, 107.75, 109.7, 116.36, 126.87, 127.37, 127.96, 128.82, 130.18, 132.54, 134.47, 136.23, 150.24; ESI-MS (m/z): 398 [M⁺+3], 396 [M⁺+1]; HPLC purity: 97.4%.

50d (i.e. 50, R¹=C₂H₅, R²=2-Bromophenyl) (HCl salt):

Yield = 0.26g (60%); M.R (⁰C): 192.3 – 194.6; IR (KBr): 3424 cm⁻¹ (-NH-), 1323 & 1160 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): δ 1.08 – 1.12 (t, 3H; CH₂CH₃), 1.55 – 1.63 (m, 2H; piperidinyl-H), 1.83 – 1.86 (m, 2H; piperidinyl-H), 2.47 – 2.53 (m, 4H; CH₂ of piperidine and CH₂CH₃), 2.86 – 2.95 (m, 2H; piperidinyl-H), 3.14 (m, 1H; CH-NH), 3.23 – 3.26 (m, 1H; NH-CH), 6.75 (s, 1H; Ar-H), 6.94 – 6.96 (d, J = 7.72 Hz, 1H; Ar-H), 7.06 – 7.29 (m, 4H; Ar-H), 7.54 – 7.56 (d, J = 7.90 Hz, 1H; Ar-H), 8.58 (s, 1H;
NH), 8.73 (s, 1H; HCl), 9.58 (s, 1H; NH); ESI-MS (m/z): 440 [M\(^{+3}\)], 438 [M\(^{+1}\)]; HPLC purity: 98.63%.

\textbf{50e} (i.e. 50, R\(^{1}=\)OCH\(_{3}\), R\(^{2}=\) Phenyl) (HCl salt):

Yield = 0.24g (65%); Syrupy mass; IR (KBr): 3418 cm\(^{-1}\) (-NH-), 1342 & 1157 cm\(^{-1}\) (-SO\(_{2}\)-); \(^{1}\)H-NMR (DMSO-d\(_{6}\)/TMS): 1.56 – 1.61 (m, 2H; piperidinyl-H), 1.84 – 1.87 (m, 2H; piperidinyl-H), 2.91 – 3.00 (m, 2H; piperidinyl-H), 3.24 – 3.27 (m, 2H; piperidinyl-H), 3.40 – 3.43 (m, 1H; piperidinyl-H), 3.79 (s, 3H; -OCH\(_{3}\)), 6.85 – 6.89 (m, 2H; Ar-H), 6.96 – 7.01 (m, 2H; Ar-H), 7.10 – 7.21 (m, 4H; Ar-H), 8.83 – 8.86 (bs, 1H; NH), 9.02 (bs, 1H; HCl), 10.03 (s, 1H; NH); ESI-MS (m/z): 362 [M\(^{+1}\)]; HPLC purity: 95.56%.

**Compounds 52a-d:**

**Preparation of 51 (General procedure):**

A mixture of sodium cyanoborohydride (0.077, 1.2 mmol), formic acid (catalytic), 49 (1 mmol) and methanol (5 mL) was stirred and cooled to 0 – 5 °C. Aqueous formaldehyde solution (0.2 mL, 2 mmole, 30 - 35% w/v) was added below 5 °C. The reaction mixture was brought to RT and stirred for 12 hr. After completion of the reaction (TLC), the mixture was diluted with excess of water (20 mL) and extracted into ethyl acetate (20 mL x 2). The organic layer was washed with brine solution (20 mL), dried over anhyd. sodium sulfate, filtered and concentrated under reduced pressure to obtain the product.
Purification: The products were purified by flash column chromatography over silica gel, using ethyl acetate: n-Hexane (1:1) as an eluent.

51a (i.e. 51, R₁=OCH₃, R₂=Benzyl):
Yield = 0.15g (30%); Syrupy mass; HPLC purity: 98.36%. For spectral details, please see under Results & Discussion section of this chapter.

51b (i.e. 51, R₁=OCH₃, R₂=2-Bromophenyl):
Yield = 0.14g (25%); Syrupy mass; ¹H-NMR (CDCl₃/TMS): 1.42 (s, 9H; (CH₃)₃CO), 1.94 (m, 4H; piperidinyl-H), 2.59 (s, 3H; NCH₃), 2.60 (m, 2H; piperidinyl-H), 3.11 (m, 2H; piperidinyl-H), 3.72 (s, 3H; OCH₃), 4.12 (m, 1H; piperidinyl-H), 6.56 – 7.51 (m, 8H; Ar-H & NH); ESI-MS (m/z): 556 [M⁺+3], 554 [M⁺+1]; HPLC purity: 93.91%.

51c (i.e. 51, R₁=OCH₃, R₂=2-Chlorophenyl):
Yield = 0.15g (30%); Syrupy mass; ¹H-NMR (CDCl₃/TMS): 1.45 (s, 9H; (CH₃)₃CO), 1.48 (m, 2H; piperidinyl-H), 1.81 (m, 2H; piperidinyl-H), 2.48 (s, 3H; CH₃N), 2.49 (m, 2H; piperidinyl-H), 2.96 (m, 2H; piperidinyl-H), 3.10 (m, 1H; piperidine-H), 3.79 (s, 3H; OCH₃), 6.65 – 7.45 (m, 8H; Ar-H & NH); ESI-MS (m/z): 512 [M⁺+3], 510 [M⁺+1].

51d (i.e. 51, R₁=OCH₃, R₂=phenyl):
Yield = 0.14g (30%); Syrupy mass; ¹H-NMR (CDCl₃/TMS): 1.48 (s, 9H; (CH₃)₃CO), 1.51 – 1.54 (m, 4H; piperidinyl-H), 2.52 (s, 3H; CH₃N), 2.80 (m, 2H; piperidinyl-H), 3.87 (s, 3H; OCH₃), 4.14 (m, 2H; piperidinyl-H), 6.78 – 7.46 (m, 9H; Ar-H & NH); ESI-MS (m/z): 476 [M⁺+3], 474 [M⁺+1].
Preparation of (52) (General procedure):

A mixture of 51 (1 mmol), isopropyl alcohol (10 mL) and isopropanolic hydrochloride solution (5 mmol) was heated to reflux for 2 hr. The separated solid was cooled to RT & filtered at suction under nitrogen blanket. The solid was washed with isopropyl alcohol (10 mL) and suck dried under nitrogen blanket.

Free base liberation: The product was stirred over ammonia solution (30%, pH~8) & simultaneously extracted into ethyl acetate (20 mL x 2). The organic layers were combined, dried over anhyd. sodium sulfate, filtered & concentrated under reduced pressure to obtain the free base. The product was kept under high vacuum (< 0.5 mbar) at 50 °C for 1 hr.

52a (i.e. 52, R¹=OCH₃ and R²=Benzyi):
Yield = 0.31g (80%); Syrupy mass; ¹³C-NMR (DMSO-d₆/TMS) δ: 25.07, 30.69, 40.74, 42.43, 46.45, 57.05, 62.93, 127.42, 127.95, 128.54, 133.18, 137.96, 155.76; HPLC purity: 99.18%. For other spectral details, please see under Results & Discussion section of this chapter.

52b (i.e. 52, R¹=OCH₃, R²=2-Bromophenyl) (HCl salt):
Yield = 0.36g (80%); IR (KBr): 3432 cm⁻¹ (-NH-), 1337 & 1163 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d₆/TMS): 1.65 – 1.67 (m, 2H; piperidinyl-H), 1.85 – 1.89 (m, 2H; piperidinyl-H), 2.52 (s, 3H; N-CH₃), 2.79 – 2.84 (m, 2H; piperidinyl-H), 3.21 – 3.24 (m, 2H; piperidinyl-H), 3.54 (m, 1H; CH-NCH₃), 3.84 (s, 3H; -OCH₃), 7.06 – 7.20 (m, 4H; Ar-H), 7.28 – 7.33 (m,
2H; Ar-H), 7.54 – 7.56 (dd, J = 1.34, 7.99 Hz, 1H; Ar-H), 9.02 (s, 1H; NH), 9.15 (s, 1H; HCl), 9.69 (s, 1H; NH); 13C-NMR (DMSO-d6/TMS) δ: 25.34, 42.72, 56.57, 120.66, 128.19, 128.38, 128.64, 132.15, 133.50, 135.48, 156.35; ESI-MS (m/z): 454 [M+3], 456 [M+1]; HPLC purity: 96.1%.

52c (i.e. 52, R1=OCH3, R2=2-Chlorophenyl) (HCl salt):
Yield = 0.33g (80%); Syrupy mass; IR (KBr): 3431 cm⁻¹ (-NH-), 1334 & 1159 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d6/TMS): 1.54 – 1.57 (m, 2H; piperidinyl-H), 1.81 – 1.86 (m, 2H; piperidinyl-H), 2.49 (s, 3H; N-CH₃), 2.86 – 2.88 (m, 2H; piperidinyl-H), 3.10 – 3.14 (m, 2H; piperidinyl-H), 3.46 (m, 1H; CH-NCH₃), 3.84 (s, 3H; -OCH₃), 7.16 - 7.20 (m, 2H; Ar-H), 7.25 – 7.28 (m, 3H; Ar-H), 7.37 – 7.39 (m, 2H; Ar-H), 8.87 (s, 1H; NH), 9.05 (s, 1H; HCl), 9.81 (s, 1H; NH); 13C-NMR (DMSO-d6/TMS) δ: 25.07, 30.60, 42.42, 57.04, 62.91, 128.21, 129.80, 130.26, 132.18, 133.79, 156.25; ESI-MS (m/z): 412 [M+3], 410 [M+1]; HPLC purity: 92.16%.

52d (i.e. 52, R1=OCH3, R2=Phenyl) (HCl salt):
Yield = 0.32g (85%); M.R (⁰C): 189.8 – 193.1 (clear); IR (KBr): 3422 cm⁻¹ (-NH-), 1349 & 1163 cm⁻¹ (-SO₂-); ¹H-NMR (DMSO-d6/TMS): 1.60 – 1.63 (m, 2H; piperidinyl-H), 1.72 – 1.81 (m, 2H; piperidinyl-H), 2.54 (s, 3H; N-CH₃), 2.76 – 2.85 (m, 2H; piperidinyl-H), 3.23 – 3.26 (m, 2H; piperidinyl-H), 3.35 (m, 1H; CH-NCH₃), 3.80 (s, 3H; -OCH₃), 6.98 – 7.08 (m, 5H; Ar-H), 7.18 – 7.24 (m, 2H; Ar-H), 7.35 – 7.37 (m, 1H; Ar-H), 8.49 – 8.51 (bs, 1H; NH), 8.73 (bs, 1H; HCl), 10.04 (s, 1H; NH); ESI-MS (m/z): 376 [M+1]; HPLC purity: 99.57%.
Compounds (53a-b):

Preparation of (53) (General procedure):

A mixture of sodium cyanoborohydride (0.064g, 1.2 mmol), formic acid (catalytic), 52 (1 mmol) and methanol (5 v/w) was stirred & cooled at 0 – 5 °C. Aqueous formaldehyde (0.2 mL, 2 mmole, 30% w/v) solution was added below 5 °C. The reaction mixture was brought to RT and stirred for 12 hr. After completion of the reaction (TLC), the mixture was diluted with water (25 mL) and extracted into ethyl acetate (20 mL x 2). The combined the organic layer was washed with brine solution, dried over anhyd. sodium sulfate, filtered and concentrated under reduced pressure to obtain product.

Purification: The products 53a-b were purified by flash column chromatography over silica gel, using ethyl acetate: n- Hexane as an eluent. The polarities were increased gradually from 10 to 70%.

53a (i.e. 53, R¹=OCH₃, R²=Benzyl):

Yield = 0.35g (87%); HPLC purity: 96.68%. For spectral details, please see under Results & Discussion section of this chapter.

53b (i.e. 53, R¹=OCH₃, R²=2-Bromophenyl):

Yield = 0.37g (80%); M.R (⁰C): 164.2 – 166.8 (clear); IR (KBr): 1323 & 1165 cm⁻¹ (-SO₂⁻); ¹H-NMR (CDCl₃/TMS): 1.45 – 1.47 (m, 2H; piperidinyl-H), 1.58 – 1.62 (m, 2H; piperidinyl-H), 1.87 – 1.92 (m, 2H; piperidinyl-H), 2.07 (s, 3H; N-CH₃), 2.17 (s, 3H; N-CH₃), 2.79 – 2.82 (m, 2H; piperidinyl-
H), 3.13 (m, 1H; CH-NH), 3.78 (s, 3H; -OCH₃), 6.98 – 7.06 (m, 3H; Ar-H), 7.20 – 7.27 (m, 3H; Ar-H), 7.49 – 7.51 (m, 2H; Ar-H & NH); ESI-MS (m/z): 470 [M+3], 468 [M+1]; HPLC purity: 95.64%.

3.7 Biological studies:

The well-characterized compounds obtained from chemistry efforts described under Chapter-2 and Chapter-3 were evaluated in a functional reporter gene based assay for their functional activity at 5-HT₆ receptor. Few of the compounds were tested over other panel of closely related CNS receptors and transporters in radioligand binding assays. All the compounds found to be very potent and selective 5-HT₆ receptor antagonists. Few of the selected compounds were evaluated in pharmacokinetic assays, CYP liability assay, metabolic stability assays and finally in animal models of cognition (pharmacological studies). The results are discussed and summarized in Chapter-6.