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Synthesis and Structure Activity Relationship of 3-(Arylsulfonyl)-8-(piperidin-4-yl amino)quinoline Derivatives as 5-HT6 Receptor Antagonists

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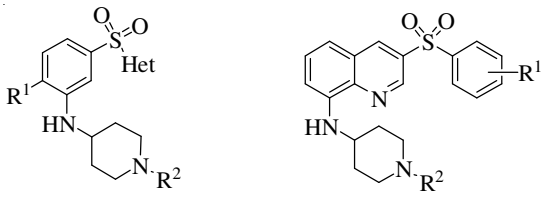
As part of our efforts to develop better therapies for the treatment of cognitive impairment associated with Alzheimer's disease and Schizophrenia, we have focused our research towards 5-HT_6 receptor (5-HT_6R) in order to identify potent and selective ligands for this purpose. Herein, we report the synthesis, structure activity relationship and biological evaluation of a novel series of 3-(arylsulfonyl)-8-(piperidin-4-yl amino)quinoline derivatives, as 5-HT_6 receptor (5-HT_6R) antagonists. In this work, we have shown that moving from aryl sulfonamide platform to biaryl sulfone platform retains the 5-HT_6R affinity when tested *in vitro* in cell based reporter gene functional assay.

Keywords: 5-HT_6R, Cognitive impairment, Alzheimer's disease, Structure Activity Relationship, Pharmacokinetic profile.

INTRODUCTION

The occurrence of decline in cognitive performances such as learning and memory are on a rise all over the world in elderly population and people with Alzheimer's disease[1]. The current medications, such as donepezil and memantine, used for the treatment of above neurological disorders have modest efficacy and lose their action over a period of time[2]. This poses a great challenge and requires continuing efforts to develop symptomatic treatments that have advantage over current therapies against cognitive impairment and Alzheimer's disease based on a novel mechanism of action. In recent years several experiments have shown that blockade of 5-HT_6R function improves cognition in a number of rodent behavioral models[3]. 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[4]. They are exclusively located in central nervous system (CNS), especially in the brain regions known to be associated with learning and memory[3]. The brain selective location, together with high affinity for therapeutically important antipsychotics and anti depressants, has stimulated significant interest for potential therapeutic utilities of 5-HT_6R in CNS diseases[5]. Thus, antagonism of the 5-HT_6R can potentially provide an effective treatment for cognitive impairment in Alzheimer's disease and Schizophrenia. Few of the reported 5-HT_6R antagonists *viz.* SB-742457[6] and Lu AE 58054[7] are in human phase 2 clinical trials whereas SUVN-502, which is our internally developed compound, completed human phase 1 clinical trials[8].

Our research group is engaged in developing better therapies for brain related disorders such as Alzheimer's disease, Schizophrenia and depression, *etc*. in a multi targeted approach and 5-HT_6R platform is one among them. Majority of the reported 5-HT_6R ligands have a positively ionizable basic amine moiety, two hydrophobic aryl functionalities and a hydrogen bond acceptor group, which are thought to be basic pharmacophoric requirements for 5-HT_6R binding[9]. We have recently reported a series of piperidin-4-ylamino aryl sulfonamides, that is, compound **I** (Fig. 1) which are potent, selective, orally active and brain penetrant 5-HT_6R antagonists[10]. In continuation to our research towards 5-HT_6R for developing better therapies for unmet medical needs, we then focused our attention to biaryl sulfones bearing cyclic amines such as piperidines as they were not much studied and evaluated. Herein we report the identification of a series of 3-sulfonyl quinoline derivatives, that is, Compound **II** (Fig. 1) obtained by migrating arylsulfonyl group from sulfonamidic position of Compound **I** to the 3-position of the quinoline core. The compound **II**, thus obtained, contain all the pharmacophoric requirements for 5-HT_6R binding as discussed above and hence we expect these compound to be potent 5-HT_6R antagonists.



Compound I **Compound II**

Fig. 1. Genesis of ligands

EXPERIMENTAL

All the reagents and chemicals used were of reagent grade. 8-Nitroquinoline was commercially procured. 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 Electrothermal (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 a 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 are expressed in parts per million (δ) and coupling constants are expressed in Hz. Analytical HPLC was routinely carried out using Agilant systems with auto sampler (Model-1100 series).

3-Bromo-8-nitro quinoline (2): N-Bromosuccinimide (0.84 g, 4.74 mmol) was added in portions to a stirred solution of 8-nitro quinoline (1 g, 3.95 mmol) in acetic acid (10 mL) at 25 °C. The mass was then stirred at 65-70 °C for 6 h under N_2 atmosphere. After completion of reaction (TLC), the mass was cooled to RT and poured onto cold water (25 mL) under stirring. The product was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain the crude mass. The resultant crude mass was chromatographed (silica gel, 1:9 ethyl acetate-hexane as eluent) to give 3-bromo-8-nitro quinoline (**2**) (1.09 g, 75 % yield). IR (KBr, ν_{max}, cm^{-1}): 3065, 1535, 1348, 792. ESI mass: m/e 253.1, 255.2 (M + H)$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65-7.69 (m, 1H), 7.97-7.99 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.06-8.08 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.44-8.44 (d, *J* = 2 Hz, 1H), 9.06-9.06 (d, *J* = 2.4 Hz, 1H).

3-Bromo-8-aminoquinoline (3): Concentrated hydrochloric acid (5.2 mL, 50 mmol) was added to a stirred suspension of 3-bromo-8-nitroquinoline (2.53 g, 10 mmol), iron powder (2.75 g, 50 mmol) and ethanol-water (40 mL: 20 mL) mixture. The mixture was refluxed for 3 h. After completion of the reaction (TLC), the mixture was cooled to room temperature and filtered to remove inorganics. The filtrate was concentrated under vacuum to obtain a residual mass. The residual mass was stirred with water (50 mL), basified with lye solution (pH-12) and the product was extracted with ethyl acetate (3 × 50 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 ethyl acetate-hexane as eluent) to afford the 3-bromo-8-quino quinoline (**3**) (1.4 g, 65 % yield). IR (KBr, ν_{max} cm^{-1}): 3472, 3361, 1613, 1369, 1126, 757. ESI mass: m/e 223.1, 225.1 (M + H)$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.91-6.92 (d, *J* = 7.56 Hz, 1H), 7.04-7.06 (d, *J* = 8.1 Hz, 1H), 7.32-7.36 (m, 1H), 8.21-8.21 (d, *J* = 2.2 Hz, 1H), 8.72-8.72 (d, *J* = 2.17 Hz, 1H).

8-Acetamino-3-bromoquinoline (4): Acetyl chloride (1.02 g, 13 mmol) was added to a stirred solution of 3-bromo-8-amino quinoline (2.23 g, 10 mmol) and triethylamine (2.52 g, 25 mmol) in dichloromethane (50 mL) under N_2 atmosphere at 0-5 °C. Then the mass was stirred at RT for 2 h. After completion of the reaction (TLC), the mixture was poured onto water (25 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain 8-acetamino-3-bromo quinoline (**4**) (2.2 g, 85 % yield). IR (KBr, ν_{max}, cm^{-1}): 3360, 1694, 1524, 1319, 1248, 887. ESI mass: *m/e* 265.1, 267.2 (M + H)$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 7.40-7.42 (m, 1H), 7.54-7.58 (m, 1H), 8.31-8.31 (d, *J* = 2.18 Hz, 1H), 8.76- 8.78 (m, 2H).

8-Acetamino-3-(4-chloro phenylsulfanyl)quinoline (5b, R^1 = 4-Cl): 4-Chloro thiophenol (2.16 g, 15 mmol) was added to a stirred suspension of 8-acetamino-3-bromo quinoline (2.65 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in DMF (25 mL) under N_2 atmosphere at RT. The mass was heated to 140 °C and maintained for 8 h. After completion of the reaction (TLC), the mixture was cooled to room temperature, poured onto cold water (25 mL) under stirring. The product was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to get dark residue. The resultant residual mass was chromatographed (silica gel, 3:7 ethyl acetate-hexane as eluent) to afford the title compound (2.26 g, 70 % yield). IR (KBr, $\nu_{max,}$ cm^{-1}): 3370, 1691, 1519, 1319, 760. ESI mass: m/e 329.2, 331.2 (M + H)$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 7.18-7.32 (m, 4H), 7.38-7.40 (d, *J* = 8.19 Hz, 1H), 7.51-7.55 (m, 1H), 8.05-8.06 (d, *J* = 2.14 Hz, 1H), 8.66-8.67 (d, *J* = 2.06 Hz, 1H), 8.73-8.75 (d, *J* = 7.69 Hz, 1H), 9.62 (1H, bs).

8-Acetamino-3-(4-chloro phenylsulfonyl)quinoline (6b, R^1 = 4-Cl): A solution of 8-acetamino-3-(4-chloro phenylsulfanyl)quinoline (1.64 g, 5 mmol) in dichloromethane (30 mL) was added to a solution of magnesium monoperoxyphthalate hexahydrate (9.8 g, 20 mmol) in methanol (20 mL) at 25-30 °C. Then the mixture was stirred overnight at RT, during which white solids precipitated. After completion of the reaction (TLC), the mixture was poured onto water (50 mL) and the product was extracted with dichloromethane (3 × 25 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain crude compound. The resultant residual mass was chromatographed (silica gel, 3:7 ethyl acetate-hexane as eluent) to afford the title compound (1.4 g, 78 % yield). ESI mass: m/e 361.4, 363.2 (M + H)$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.35 (s, 3H), 7.62-7.64 (m, 2H), 7.84-7.90 (m, 1H), 7.94-7.96 (d, *J* = 8.4 Hz,

2H), 8.07-8.09 (d, *J* = 8.8 Hz, 1H), 8.14-8.16 (d, *J* = 8.4 Hz, 1H), 8.78-8.78 (d, *J* = 2.4 Hz, 1H), 9.15-9.15 (d, *J* = 2.4 Hz, 1H).

8-Amino-3-(4-chloro phenylsulfonyl)quinoline (7b, R^1 = 4-Cl): A solution of 8-acetamino-3-(4-chloro phenylsulfonyl)quinoline (1.8 g, 5 mmol) in a mixture of ethanol-conc. hydrochloric acid (40 mL, 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 (25 mL), basified with aq. NaOH (pH-12) and extracted the product with chloroform (3 × 50 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 ethyl acetate-hexane as eluent) to afford the title compound (1.09 g, 69 % yield). IR (KBr, ν_{max}, cm^{-1}): 3386, 3296, 1498, 1149, 1086. ESI mass: m/e 319.5, 321.4 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.04-7.06 (m, 1H), 7.24-7.26 (m, 1H), 7.44-7.51 (m, 3H), 7.94-7.96 (d, *J* = 6.8 Hz, 2H), 8.68-8.68 (d, *J* = 2.4 Hz, 1H), 9.06-9.07 (d, *J* = 2.4 Hz, 1H).

3-(4-Chloro phenylsulfonyl)-8-(1-methyl piperidin-4-ylamino)quinoline (8b, R^1 = 4-Cl, R^2 = CH_3): Sodium triacetoxy borohydride (0.6 g, 2.83 mmol) was added in portions to a stirred suspension of 8-amino-3-(4-chloro phenylsulfonyl)quinoline (0.3 g, 0.94 mmol), 1-methyl-4-piperidone (0.31 g, 2.83 mmol) and sodium sulfate (1.33 g, 9.4 mmol) in glacial acetic acid (6 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 (15 mL), basified with aq. NaOH solution (pH-12) and extracted with chloroform (3 × 25 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 ethyl acetate-hexane and then 5:95 methanol-ethyl acetate) to afford the title product (0.2 g, 51 % yield). IR (KBr, ν_{max}, cm^{-1}): 3388, 2938, 1573, 1515, 1376, 1151. ESI mass: m/e 416.5 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.63-1.71 (m, 2H), 2.11-2.23 (m, 4H), 2.32 (s, 3H), 2.82-2.85 (m, 2H), 3.47-3.48 (m, 1H), 6.11-6.13 (d, *J* = 7.68 Hz, 1H), 6.78-6.80 (d, *J* = 7.76 Hz, 1H), 7.10-7.12 (d, *J* = 8.08 Hz, 1H), 7.48-7.52 (m, 3H), 7.92-7.94 (dd, *J* = 8.61, 1.71 Hz, 2H), 8.64-8.65 (d, *J* = 2.32 Hz, 1H), 9.01-9.02 (d, *J* = 2.22 Hz, 1H). HPLC purity: 98.0 %.

3-(3-Fluoro phenylsulfonyl)-8-(1-methyl piperidin-4-yl amino)quinoline (8a): The title compound (**8a**) was prepared using essentially the same procedure as described for the preparation of **8b**. IR (KBr, ν_{max}, cm^{-1}): 3411, 2934, 1570, 1516, 1371, 1150. ESI mass: m/e 400.5 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.62-1.72 (m, 2H), 2.11-2.23 (m, 4H), 2.32 (s, 3H), 2.83-2.85 (m, 2H), 3.46-3.49 (m, 1H), 6.12-6.14 (d, *J* = 7.76 Hz, 1H), 6.79-6.81 (d, *J* = 7.74 Hz, 1H), 7.11-7.13 (d, *J* = 8.08 Hz, 1H), 7.26-7.30 (m, 1H), 7.46-7.54 (m, 2H), 7.69-7.72 (m, 1H), 7.79-7.81 (d, *J* = 7.88 Hz, 1H), 8.67-8.67 (d, *J* = 2.22 Hz, 1H), 9.03-9.04 (d, *J* = 2.20 Hz, 1H). HPLC purity: 98.9 %.

8-(1-Methyl piperidin-4-yl amino)-3-(phenylsulfonyl)-quinoline (8c): The title compound was prepared using essentially the same procedure as described for the preparation of **8b**. IR (KBr, ν_{max}, cm^{-1}): 3402, 2932, 1572, 1517, 1318, 1155. ESI mass: m/e 382.5 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.64-1.71 (m, 2H), 2.11-2.21 (m, 4H), 2.32 (s, 3H), 2.82-2.85 (m, 2H), 3.46-3.47 (m, 1H), 6.11-6.13 (d, *J* = 7.80 Hz, 1H), 6.77-6.79 (d, *J* = 7.76 Hz, 1H), 7.10-7.12 (d, *J* = 8.09 Hz, 1H), 7.44-7.59 (m, 4H), 7.99-8.01 (m, 2H), 8.67-8.67 (d, *J* = 2.21 Hz, 1H), 9.01-9.01 (d, *J* = 2.22 Hz, 1H). HPLC purity: 98.3 %.

3-(4-Fluoro phenylsulfonyl)-8-(1-methyl piperidin-4-yl amino)quinoline (8d): The title compound was prepared using essentially the same procedure as described for the preparation of **8b**. IR (KBr, ν_{max}, cm^{-1}): 3391, 2935, 1582, 1518, 1374, 1152. ESI mass: m/e 400.1 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.69-1.72 (m, 2H), 2.11-2.23 (m, 4H), 2.32 (s, 3H), 2.82-2.85 (m, 2H), 3.46-3.48 (m, 1H), 6.11-6.13 (d, *J* = 7.79 Hz, 1H), 6.78-6.80 (d, *J* = 7.7 Hz, 1H), 7.10-7.12 (d, *J* = 7.76 Hz, 1H), 7.17-7.26 (m, 2H), 7.45-7.49 (m, 1H), 8.00-8.04 (m, 2H), 8.65 (d, *J* = 2.19 Hz, 1H), 9.02 (d, *J* = 2.21 Hz, 1H). HPLC purity: 96 %.

3-(3-Methyl phenylsulfonyl)-8-(1-methyl piperidin-4-yl amino)quinoline (8e): The title compound was prepared using essentially the same procedure as described for the preparation of **8b**. IR (KBr, ν_{max}, cm^{-1}): 3418, 2953, 1574, 1375, 1149, 1089. ESI mass: m/e 396.3 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.83-1.89 (m, 2H), 2.15-2.19 (m, 2H), 2.37 (s, 3H), 2.75 (s, 3H), 3.07-3.09 (m, 2H), 3.43-3.46 (m, 2H), 3.47-3.48 (m, 1H), 6.99-7.01 (d, *J* = 7.72 Hz,1H), 7.34-7.36 (d, *J* = 7.99 Hz, 1H), 7.51-7.56 (m, 3H), 7.84-7.88 (m, 2H), 8.95 (d, *J* = 1.98 Hz, 1H), 9.09-9.10 (d, *J* = 1.98 Hz, 1H). HPLC purity: 98.3 %.

3-(2-Bromo phenylsulfonyl)-8-(1-methyl piperidin-4-yl amino)quinoline (8f): The title compound was prepared using essentially the same procedure as described for the preparation of **8b**. IR (KBr, ν_{max}, cm^{-1}): 3383, 2931, 1570, 1518, 1373, 1157. ESI mass: m/e 460, 462 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.65-1.72 (m, 2H), 2.04-2.23 (m, 4H), 2.32 (s, 3H), 2.83-2.86 (m, 2H), 3.46-3.48 (m, 1H), 6.12-6.14 (d, J = 7.80 Hz, 1H), 6.80-6.82 (d, *J* = 7.66 Hz, 1H), 7.12-7.14 (d, *J* = 7.55 Hz, 1H), 7.43-7.48 (m, 2H), 7.57-7.61 (m, 1H), 7.64-7.66 (dd, *J* = 7.88, 1.02 Hz, 1H), 8.48-8.50 (dd, *J* = 7.95, 1.62 Hz, 1H), 8.74-8.75 (d, *J* = 2.25 Hz, 1H), 8.99-8.99 (d, *J* = 2.26 Hz, 1H). HPLC purity: 97.4 %.

3-(4-Chloro phenylsulfonyl)-8-(1-*tert* butoxycarbonyl piperidin-4-yl amino)quinoline (9b, R^1 = 4-Cl): Sodium triacetoxyborohydride (0.6 g, 2.83 mmol) was added in portions to a stirred suspension of 8-amino-3-(4-chloro phenylsulfonyl)quinoline (0.3 g, 0.94 mmol), 1-boc-4-piperidone (0.56 g, 2.83 mmol) and sodium sulfate (1.33 g, 9.4 mmol) in glacial acetic acid (6 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 (15 mL), basified with aq. NaOH solution (pH~12) and extracted with chloroform (3 × 25 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 ethyl acetate-hexane) to afford the title product (0.42 g, 90 % yield). ESI mass: m/e 502.7, 504.1 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.47 (s, 9H), 1.52-1.57 (m, 2H), 2.08-2.17 (m,

2H), 3.00-3.06 (m, 2H), 3.61-3.63 (m, 1H), 4.01-4.15 (m, 2H), 6.12-6.14 (d, *J* = 7.99 Hz, 1H), 6.80-6.82 (d, *J* = 7.74 Hz, 1H), 7.13-7.15 (d, *J* = 8.07 Hz, 1H), 7.46-7.52 (m, 3H), 7.93-7.95 (d, *J* = 9.27 Hz, 2H), 8.65-8.66 (d, *J* = 2.23 Hz, 1H), 9.01-9.01 (d, *J* = 2.21 Hz, 1H). HPLC purity: 97.8 %.

3-(4-Chloro phenylsulfonyl)-8-(piperidin-4-yl amino)-quinoline dihydrochloride (10b, R^1 = 4-Cl, R^2 = H): 3-(4-Chloro phenylsulfonyl)-8-(1-*tert* butoxycarbonyl piperidin-4-yl amino)quinoline (0.42 g, 0.83 mmol) was stirred in isopropanolic HCl (20 % w/v solution, 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 (0.36 g, 93% yield). IR (KBr, ν_{max} cm^{-1}): 3366, 2957, 1582, 1323, 1156, 1066. ESI mass: m/e 402.4 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 1.77-1.85 (m, 2H), 2.32-2.35 (m, 2H), 3.16-3.22 (m, 2H), 3.43-3.46 (m, 2H), 3.87-3.92 (m, 1H), 7.08-7.10 (d, *J* = 7.69 Hz,1H), 7.35-7.37 (d, *J* = 8.1 Hz, 1H), 7.54-7.58 (m, 1H), 7.61-7.64 (d, *J* = 8.41 Hz, 2H), 8.04-8.06 (d, *J* = 8.36 Hz, 2H), 8.86 (s, 1H), 9.09 (s, 1H). HPLC purity: 99.5 %. M.R = 295.2-297.0 °C.

3-(3-Fluoro phenylsulfonyl)-8-(piperidin-4-yl amino)-quinoline dihydrochloride (10a): The title compound was prepared using essentially the same procedure as described for the preparation of **10b**. IR (KBr, ν_{max}, cm^{-1}): 3389, 2954, 1590, 1373, 1152, 701. ESI mass: m/e 386.4 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.70-1.78 (m, 2H), 2.10-2.13 (m, 2H), 2.97-3.05 (m, 2H), 3.28-3.31 (m, 2H), 3.79-3.81 (m, 1H), 7.02-7.04 (d, *J* = 7.71 Hz, 1H), 7.33-7.35 (d, *J* = 8.02 Hz, 1H), 7.52-7.61 (m, 2H), 7.67-7.72 (m, 1H), 7.90-7.97 (m, 2H), 8.89-8.91 (m, 1H), 9.01-9.14 (m, 3H). HPLC purity: 98.4 %. M.R = 250.2-252.5 °C.

3-(Phenylsulfonyl)-8-(piperidin-4-yl amino)quinoline dihydrochloride (10c): The title compound was prepared using essentially the same procedure as described for the preparation of **10b**. IR (KBr, ν_{max} cm^{-1}): 3380, 2958, 1585, 1317, 1155, 1028. ESI mass: m/e 368.5 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.70-1.72 (m, 2H), 2.10-2.17 (m, 2H), 2.87-3.02 (m, 2H), 3.27-3.36 (m, 2H), 3.73-3.81 (m, 1H), 7.01-7.03 (d, *J* = 7.74 Hz, 1H), 7.34-7.36 (d, *J* = 8.04 Hz, 1H), 7.51-7.55 (m, 1H), 7.61-7.65 (m, 2H), 7.69-7.72 (m, 1H), 8.05-8.07 (d, *J* = 7.44 Hz, 2H), 8.90-8.92 (m, 1H), 8.97 (d, *J* = 2.02 Hz, 1H), 9.09-9.10 (d, *J* = 2.08 Hz, 1H), 9.13-9.15 (m, 1H). HPLC purity: 95.3 %. M.R = 159.6-161.9 °C.

3-(4-Fluoro phenylsulfonyl)-8-(piperidin-4-yl amino)quinoline dihydrochloride (10d): The title compound was prepared using essentially the same procedure as described for the preparation of **10b**. IR (KBr, ν_{max}, cm^{-1}): 3408, 2958, 1585, 1326, 1155, 1105. ESI mass: m/e 386.4 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 1.79-1.87 (m, 2H), 2.31-2.34 (m, 2H), 3.12-3.21 (m, 2H), 3.49-3.50 (m, 2H), 4.08-4.09 (m, 1H), 7.12-7.14 (d, *J* = 7.62 Hz, 1H), 7.32-7.40 (m, 3H), 7.55-7.59 (m, 1H), 8.11-8.15 (m, 2H), 8.86-8.87 (d, *J* = 1.90 Hz, 1H), 9.10 (m, 1H). HPLC purity: 96.2 %. M.R = 245.4-250.9 °C.

3-(3-Methyl phenylsulfonyl)-8-(piperidin-4-yl amino)quinoline dihydrochloride (10e): The title compound was prepared using essentially the same procedure as described for the preparation of **10b**. IR (KBr, ν_{max}, cm^{-1}): 3409, 2958, 1588, 1374, 1150, 1105. ESI mass: m/e 382.4 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.68-1.72 (m, 2H), 2.10-2.13 (m, 2H), 2.37 (s, 3H), 2.97-3.06 (m, 2H), 3.29-3.32 (m, 2H), 3.75-3.78 (m, 1H), 6.99-7.01 (d, *J* = 7.72 Hz,1H), 7.33-7.35 (d, *J* = 8.00 Hz, 1H), 7.51-7.55 (m, 3H), 7.84-7.92 (m, 2H), 8.65-8.67 (m, 1H), 8.87-8.88 (m, 1H), 8.94-8.95 (d, *J* = 2.10 Hz, 1H), 9.09-9.10 (d, *J* = 2.13 Hz, 1H). HPLC purity: 95 %. M.R = 129.5-135.3 °C.

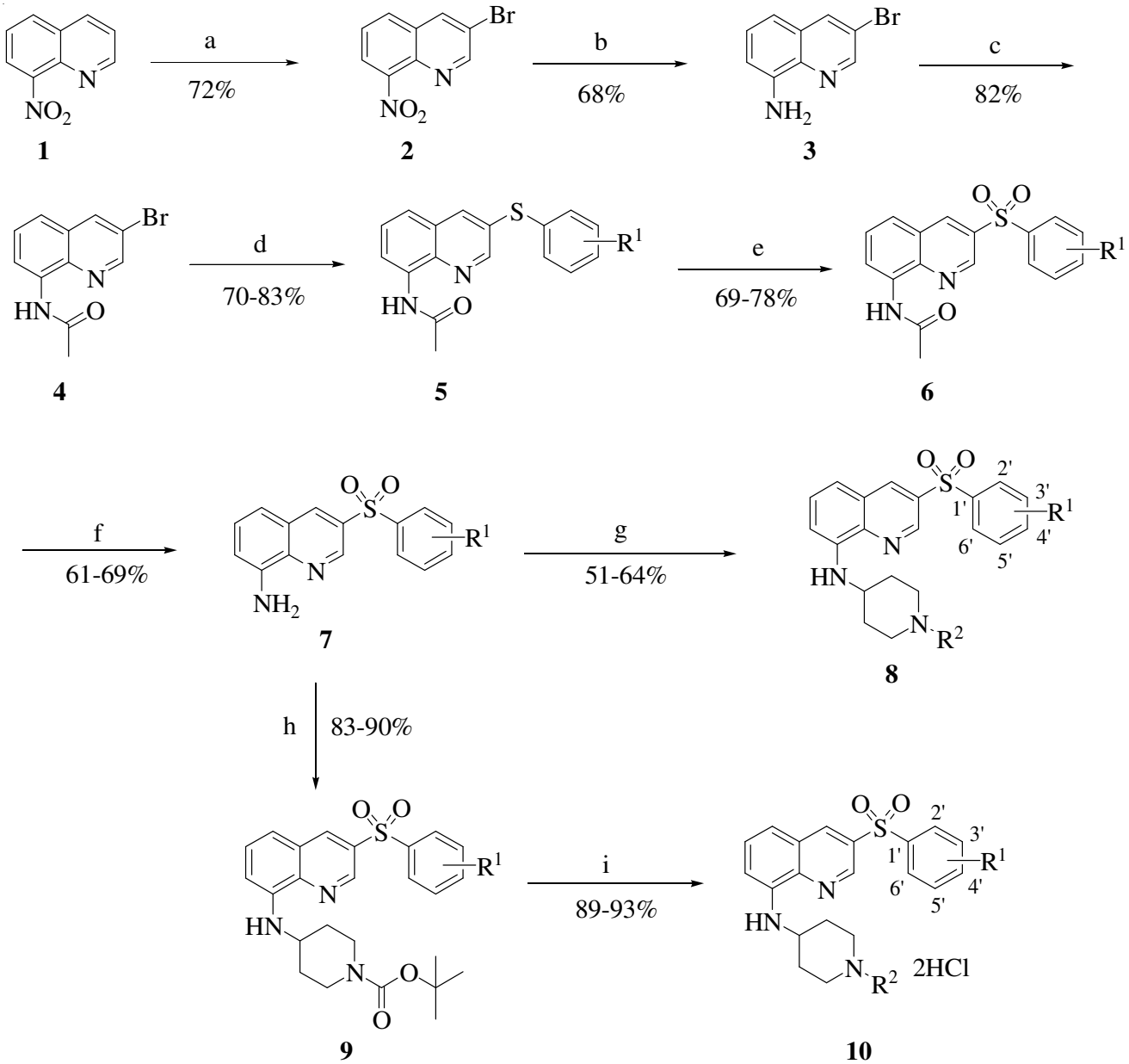
3-(2-Bromo phenylsulfonyl)-8-(piperidin-4-yl amino)-quinoline dihydrochloride (10f): The title compound was prepared using essentially the same procedure as described for the preparation of **10b**. IR (KBr, ν_{max}, cm^{-1}): 3383, 2935, 1571, 1517, 1374, 1157. ESI mass: m/e 446.4, 448 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.69-1.77 (m, 2H), 2.11-2.14 (m, 2H), 3.01-3.06 (m, 2H), 3.30-3.33 (m, 2H), 3.76-3.79 (m, 1H), 7.02-7.04 (m,1H), 7.34-7.36 (d, *J* = 8.03 Hz, 1H), 7.52-7.56 (m, 1H), 7.64-7.67 (m, 1H), 7.74-7.78 (m, 1H), 7.81-7.83 (d, *J* = 7.74 Hz, 1H), 8.41-8.43 (d, *J* = 7.70 Hz, 1H), 8.66-8.68 (m, 1H), 8.86-8.88 (m, 1H), 8.93-8.94 (d, *J* = 1.57 Hz, 1H), 9.03-9.03 (d, *J* = 1.49 Hz, 1H). HPLC purity: 98.47 %. M.R = 130.2-133.1 °C.

RESULTS AND DISCUSSION

The target compounds **8** and **10** were prepared as according to **Scheme-I**.

The general synthetic strategy for the proposed targets **8** and **10** was achieved as shown in **Scheme-I**. Electrophilic bromination of 8-nitroquinoline (**1**) with N-bromosuccinimide (NBS) provided intermediate **2**. Reduction of nitro functional group of intermediate **2** with Fe/HCl followed by acetylation under basic conditions afforded intermediate **4**. The intermediate 4 was further reacted with substituted thiophenols to get the biarylsulfide intermediates **5**. Oxidation of intermediates **5** using appropriate oxidizing reagents provided intermediates **6**. Hydrolysis of intermediates **6** with conc. HCl in ethanol under reflux yielded intermediates **7**. The intermediates **7** were reacted with 1-methyl-4-piperidone in the presence of acetic acid, sodium sulfate and sodium triacetoxyborohydride to afford targeted compound **8**. 1-Boc-4-piperidone was reacted with **7** under reductive amination conditions to obtain Boc protected intermediates **9**. These on deprotection with IPA·HCl yielded targeted compound **10** as HCl salts.

Structure activity relationship (SAR): We used various substituents at R^1 and R^2 positions of compound **II** and explored their antagonistic activity at 5-HT_6R at 1 μM concentration (Table-1). We initially tested compound **8c** where R^1 = H, R^2 = CH_3 and inhibition at 5-HT_6R was found to be 43 %. Later, we introduced various substituents like halogen, alkyl and alkoxy at R^1 position and H, CH_3 at R^2 position of compound **II**. Among these derivatives, compound **8f** (R^1 = 2'-Br, R^2 = CH_3) with an inhibition of 89 % was found to be most potent. Other derivatives from the series, like compound **8a** (R^1 = 3'-F, R^2 = CH_3) has shown 62 % inhibition whereas compound **8d** (R^1 = 4'-F, R^2 = CH_3) and compound **8b** (R^1 = 4'-Cl, R^2 = CH_3) have shown an inhibition 7 and 9 %, respectively. These compounds, **8b** and **8d** are almost 7- to 9- fold less potent compared to compound **8a**. Compound **8e** (R^1 = 3'-CH_3, R^2 = CH_3) with 76 % inhibition is found to be equipotent compared to **8f**. From the above structure activity relationship, it can be observed that the presence of halo and alkyl derivatives at 2', 3' position of compound **II** are more preferable compared to those substituted at 4' position. Later, we made compounds



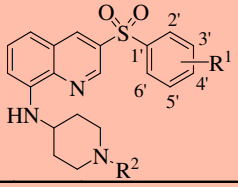
Scheme-I[a]: [a]Reagents and conditions: (a) NBS, CH_3CO_2H, 65-70 °C; (b) Fe/HCl, H_2O:EtOH, reflux; (c) CH_3COCl, Et_3N, DCM; (d) substituted thiophenols, K_2CO_3, DMF, 140 °C; (e) Magnesium monoperoxyphthalate hexahydrate, MeOH:DCM, RT; (f) Conc.HCl, Ethanol, reflux; (g) 1-methyl-4-piperidone, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25-30 °C; (h) 1-Boc-4-piperidone, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25-30 °C; (i) IPA·HCl, RT, 2-4 h

10a-**10f** with R^2 = H. These compound could be the possible metabolites of compounds **8a**-**8f**, respectively. Among these, compound **10f** (R^1 = 2'-Br, R^2 = H), compound **10a** (R^1 = 3'-F, R^2 = H), compound **10e** (R^1 = 3'-CH_3, R^2 = H) and compound **10c** (R^1 = H, R^2 = H) have shown an inhibition of 66, 51, 64 and 49 % towards 5-HT_6R. The activities of these compounds follow a similar trend when compared with their parent compounds, that is, **8f**, **8a**, **8e** and **8c,** respectively. In general, all the tested compounds **8a**-**8f** and **10a**-**10f** were showing moderate to potent inhibitory affinity towards 5-HT_6R. This proves the concept that moving from aryl sulfonamides (compound **I**) to biaryl sulfones (compound **II**) retains binding affinities towards 5-HT_6R.

A number of compounds that displayed satisfactory inhibitory potential towards 5-HT_6R in functional assay were profiled for their selectivity against a panel of closely related receptors and transporters. In general, these compounds have shown excellent selectivity over all the receptors examined (data not shown). The most potent compound of the series, that is, compound **8f** was further evaluated for its CYP liabilities, microsomal metabolic stability (Table-2) and pharmacokinetic profile (Table-3). Compound **8f** was moderately metabolized in both rat liver microsomes (54.5 %) and human liver microsomes (56.9 %). The IC_{50} value for compound **8f** at CYP 3A4 was found to be 33.88 µM whereas the IC_{50} value at CYP 2D6 enzymes were found to be 17.46 µM. These results show that the compounds from this series have lower potential for drug-drug interaction, thereby maximizing the safety.

The pharmacokinetic profile of compound **8f** was assessed in male Wister rats (Table-3). Compound **8f** at an oral dose of 3 mg/kg was rapidly absorbed in rats with a half-life of 1.9 ± 0.1 h with an oral bioavailability of 20 ± 5 %. The observed

TABLE-1
5-HT$_6$ RECEPTOR BINDING DATA OF COMPOUNDS



Compound	R^1	R^2	% inhibition at 1 µM concentration[a]
8a	3'-F	CH_3	62
8b	4'-Cl	CH_3	9
8c	H	CH_3	43
8d	4'-F	CH_3	7
8e	3'-CH_3	CH_3	76
8f	2'-Br	CH_3	89
10a	3'-F	H	51
10b	4'-Cl	H	10
10c	H	H	49
10d	4'-F	H	12
10e	3'-CH_3	H	64
10f	2'-Br	H	66

[a]% Inhibition towards 5-HT$_6$R was measured using cell based reporter gene functional assay. Values are mean of two experiments

TABLE-2
HUMAN CYP450[11] INHIBITORY DATA AND MICROSOMAL METABOLIC STABILITY[(a)]

Compound	IC_{50} (µM)		% Metabolism in liver microsomes	
	CYP 3A4	CYP 2D6	Human	Rat
8f	33.88	17.46	56.9	54.5

[a]The cytochrome P450 inhibitory potential was determined using isoform-selective assays and heterologously expressed human CYP 2D6 and CYP 3A4. These values are the mean of duplicate determinations. Microsomal metabolic stability in wistar rat and human at 0.5 h, conc. 2.5 µM.

TABLE-3
PHARMACOKINETIC PROFILE OF COMPOUND **8f** IN MALE WISTER RATS[a]

Compound	**8f**
i.v.	
Dose	1 mg/kg
$t_{1/2}$ (h)	1.9 ± 0.1
Vz (L/kg)	20.0 ± 5.4
CL (mL/min/kg)	120 ± 27
p.o.	
Dose	3 mg/kg
C_{max} (ng/mL)	36 ± 12
T_{max} (h)	1.00 ± 0.00
AUC_t (ng h/mL)	104 ± 19
F (%)	20 ± 5

[a]Fasted male wistar rats, Vehicle used: water for injection for both oral and intravenous routes. Dosing Volumes: 10 mL/kg p.o. and 2 mL/kg for i.v.

oral C_{max} was 36 ± 12 ng/mL and occurred at 1 h. The compound displayed an oral exposure of 104 ± 19 ng h/mL. It had a clearance of 120 ± 27 mL/min/kg and a volume of distribution of 20 ± 5.4 L/kg for i.v. dose. Importantly, compound **8f** was selectively partitioned in brain with a Cb/Cp value of 8.18, which would be one of the requirements for achieving *in vivo* activity against neuropsychiatric indications.

Conclusion

We have disclosed a new series of compound **II**, *i.e.*, 3-(arylsulfonyl)-8-(piperidin-4-yl amino)quinoline derivatives, obtained by moving arylsulfonyl group from 'N' in compound **I** to 'C' in compound **II** (using C/N functional group flip strategy)[12] .The new series of compound **II**, thus disclosed herein, have moderate to potent *in vitro* binding affinities towards 5-HT$_6$R. The lead compound **8f** from this series has shown excellent inhibitory affinity with adequate pharmacokinetic profile, acceptable selectivity over other closely related receptors. Based on the above findings, the novel series of compound **II**, in general, could be used for further optimization to obtain potent 5-HT$_6$R antagonists.

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