Asian Journal of Chemistry; Vol. 27, No. 6 (2015), 2117-2124

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.17783

Design, Synthesis and Biological Evaluation of Novel Benzopyran Sulfonamide Derivatives as 5-HT$_6$ Receptor Ligands

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Received: 8 April 2014; *Accepted*: 21 July 2014; *Published online*: 17 March 2015; AJC-16975

On the basis of a known pharmacophore model for 5-HT$_6$ receptor antagonists (5-HT$_6$R), we have designed and synthesized a novel series of benzopyran sulfonamide derivatives **9**(**a-d**), **20**(**a-d**) and **21**(**a-d**) and their structures were confirmed by ^{1}H NMR and mass spectral data. All the synthesized compounds were tested for their antagonistic activity towards 5-HT$_6$R in a cell based reporter gene *in vitro* functional assay. Most of the tested compounds showed moderate to potent binding affinities towards 5-HT$_6$R.

Keywords: 5-HT$_6$R, Benzopyran, Cognitive impairment, Alzheimer's disease, Structure activity relationship.

INTRODUCTION

Cognitive dysfunction is a characteristic feature of many neurological disorders like Alzheimer's disease (AD), Schizophrenia, Parkinson's disease (PD) and other neurodegenerative diseases[1]. Among these, Alzheimer's disease is the leading cause of dementia and affects 36 million people worldwide and this number is expected to increase with increased life expectancy around the world[2]. The current line of treatments, donepezil and memantine, lose their efficacy over a period of time[3]. The need of the moment is to develop new therapies for this debilitating disorder and 5-hydroxytryptamine 6 receptor (5-HT$_6$R) attracted a lot of focus for this purpose. It belongs to 5-hydroxytryptamine (5-HT, serotonin) super family of receptors which is subdivided into 14 subclasses[4]. 5-HT$_6$ receptors are exclusively located in brain regions such as olfactory tubercule, striatum and nucleus accumbens. These areas are known to be involved in cognitive processes[5]. 5-HT$_6$ receptors are positively coupled to adenylyl cyclase and receptor antagonism leads to elevation of cAMP and enhances neurotransmission at cholinergic and glutamatergic pathways[6]. Several atypical antipsychotics and tricyclic antidepressants bind with high affinity to 5-HT$_6$ receptor[7]. These facts suggest that antagonism of 5-HT$_6$ receptor could potentially provide better treatments for cognitive dysfunction associated with neurodegenerative disorders.

A number of selective 5-HT$_6$R antagonists were identified in the last decade[8] and a pharmacophoric model was constructed based on these structurally diverse 5-HT$_6$R antagonists[9]. In general, this model contains four different key elements, that is, a positively ionizable atom (PI, secondary or tertiary amine group), a hydrogen bond acceptor (HBA, a sulfone or a sulfonamide group), a hydrophobic site (HYD) and an aromatic ring hydrophobic site (AR) (Fig. 1). A few of the reported clinical stage 5-HT$_6$R antagonists *viz*. LuAE 58054[10] (phase II), SB-742457[11] (phase II) and SUVN-502[12] (phase I, our own internally discovered compound) align with above pharmacophoric model. Based on literature support and in continuation of our research[13] towards identifying potent 5-HT$_6$R antagonists, we have designed and synthesized compound **I**. It contains a benzopyran central core bearing piperazine and sulfonamide groups as pendant groups. The methylene group adjacent to oxygen of benzopyran central core could be a metabolic prone site by CYP enzymes. To minimize this metabolic issue, we introduced a cyclobutyl group adjacent to oxygen of compound **I** to obtain compound **II**. This modification could inhibit unforeseen metabolic issues, if any, associated with compound **I**. Compound **III** were obtained by interchanging the positions of piperazine and sulfonamide groups of Compounds **II**. Compounds **I**, compounds **II** and compounds **III** (Fig. 1) thus designed contains all the pharmacophoric requirements for 5-HT$_6$R binding as discussed above and we expect these compounds to show affinity towards 5-HT$_6$R.

EXPERIMENTAL

All the reagents and chemicals used were of reagent grade. 2-Bromophenol and 2'-hydroxyacetophenone were

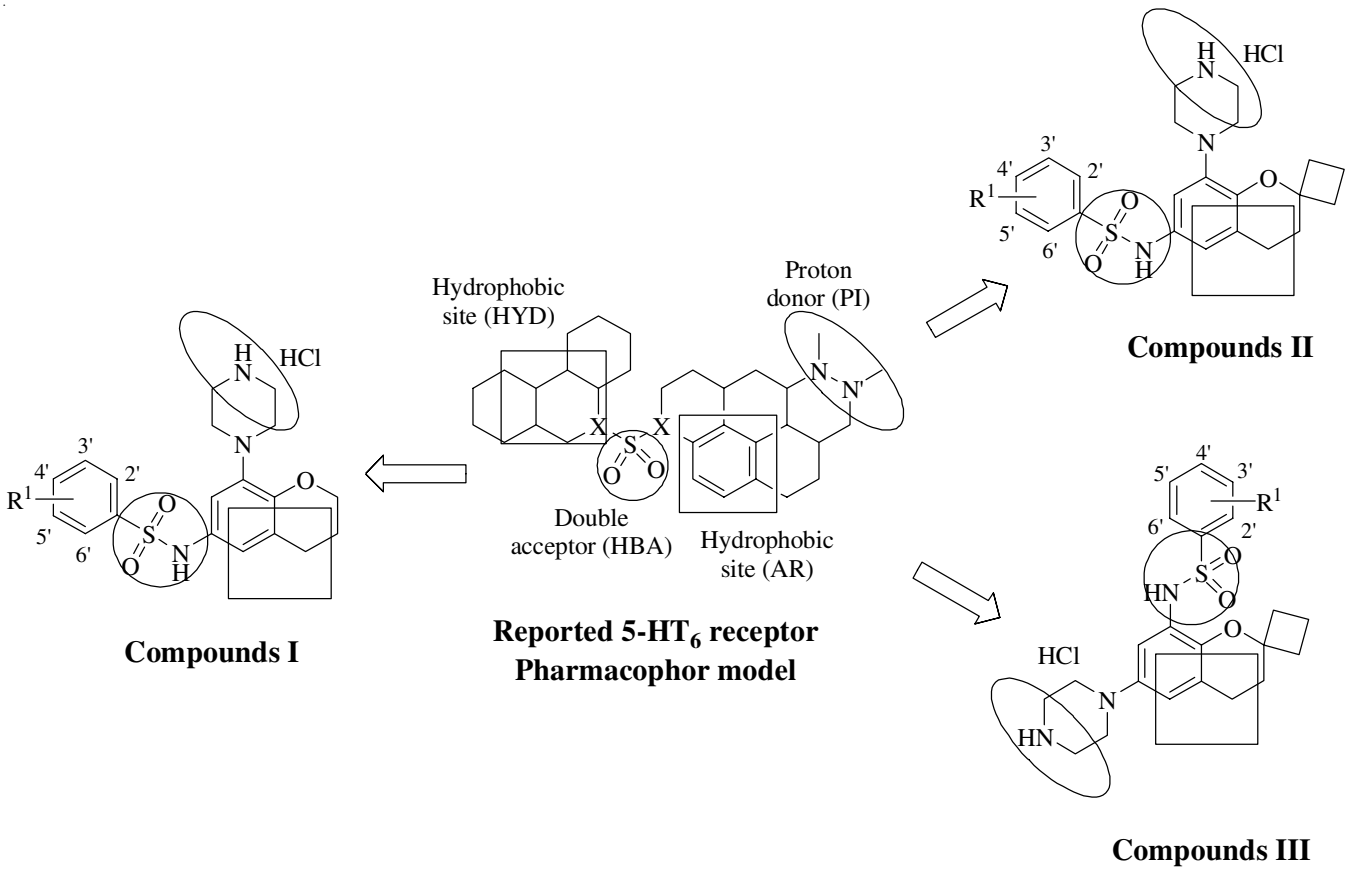


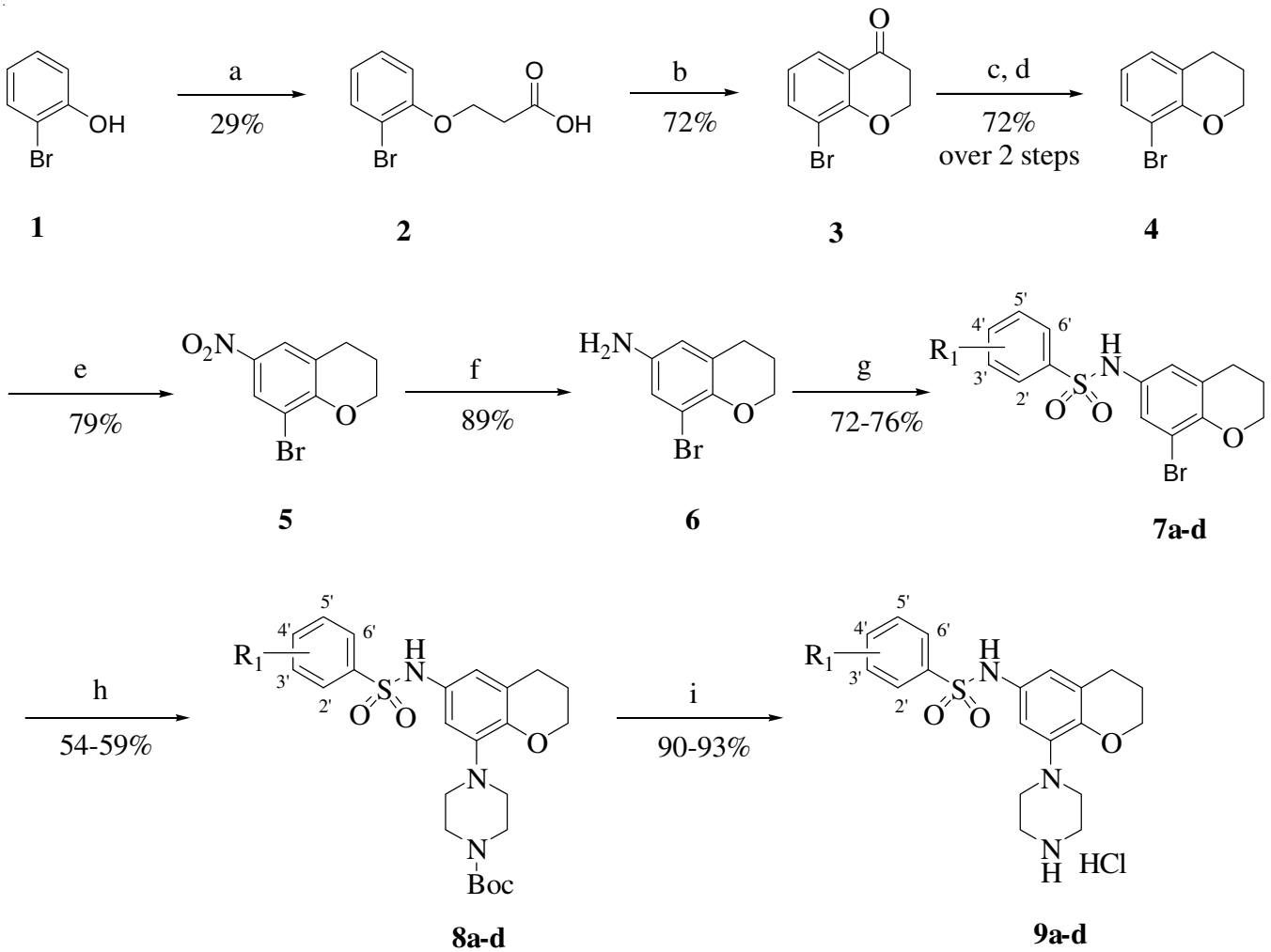
Fig. 1. Design of ligands

commercially procured and used as such without further purification. 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 iodine. 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. 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.

3-(2-Bromo phenoxy)propionic acid (2): Powdered KOH (6.16 g, 110 mmol) was added in portions to a stirred suspension of phenolic compound, **1** (8.65 g, 50 mmol) in water (250 mL) at 25-50 °C and stirred for 0.5 h, followed by the addition of 3-bromopropionic acid (8.41 g, 55 mmol) and then refluxed for 18 h. Then the reaction mixture was cooled to room temperature, acidified with conc. HCl (pH-2) and extracted with ethyl acetate (150 mL × 4). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated *in vacuo* to obtain a dark residue. The resultant residual mass was chromatographed (silica gel, 1:1 ethyl acetate-hexanes as eluent) to afford title compound (3.55 g, 29 % yield). ESI mass of a fragment: *m/e* 244.1, 245.3 (M-H$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.39 (1H, bs), 7.54-7.56 (1H, dd, *J* = 7.88, 1.48 Hz), 7.31-7.33 (1H, t, *J* = 7.16 Hz), 7.11-7.13 (1H, dd, *J* = 8.12, 0.76 Hz), 6.86-6.90 (1H, t, *J* = 7.76 Hz), 4.21-4.24 (2H, t, *J* = 5.97 Hz), 2.69-2.72 (2H, t, *J* = 6.95 Hz).

8-Bromo-3,4-dihydro-2*H*-1-benzopyran-4-one (3): Compound **2** (3.5 g, 14.28 mmol) was added in portions to a mechanically stirred mass of polyphosphoric acid (17.5 g) at 100-110 °C and stirred for 10-15 min (excessive heating decomposes the product). Then the reaction mixture was cooled to 50-60 °C and crushed ice (~150 g) was added to it under vigorous stirring during which solids precipitated out. The product was extracted with chloroform (100 mL × 3). Combined organic extracts were dried over anhydrous sodium sulfate, concentrated *in vacuo* to obtain a dark residue. The resultant residual mass was chromatographed (silica gel, 2:8 ethyl acetate-hexanes as eluent) to afford title compound (2.33 g, 72 % yield). ESI mass: *m/e* 227.3, 229.1 (M + H)$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86-7.88 (1H, dd, *J* = 7.84, 1.53 Hz), 7.72-7.75 (1H, dd, *J* = 7.76, 1.55 Hz), 6.90-6.94 (1H, t, *J* = 7.80 Hz), 4.64-4.68 (2H, t, *J* = 6.39 Hz), 2.84-2.88 (2H, t, *J* = 6.49 Hz).

8-Bromo-3,4-dihydro-2*H*-1-benzopyran (4): $NaBH_4$ (0.33 g, 8.817 mmol) was added in portions to a stirred suspension of **3** (2 g, 8.81 mmol) in methanol (10 mL) at 25-35 °C. The reaction mixture was stirred at room temperature for 0.5 h and then concentrated to obtain a thick residual mass. The resultant residual mass was diluted with water (25 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, concen-



1 **2** **3** **4** **5** **6** **7a-d** **8a-d** **9a-d**

Scheme-I: Reagents and conditions: (a) KOH, water, 3-bromopro-pionic acid, 100-110 °C, 18 h; (b) PPA, 100-110 °C, 15 min; (c) $NaBH_4$, MeOH, RT, 0.5 h; (d) Et_3SiH, CF_3CO_2H, 60-65 °C, 4 h; (e) KNO_3, H_2SO_4, 0-5 °C, 1 h; (f) Fe, NH_4Cl, H_2O:THF-:EtOH, reflux, 3 h; (g) substituted benzenesulfonyl chlorides, pyridine, DCM, RT, 4 h; (h) 1-Boc piperazine, pd_2dba_3, BINAP, NaOBut, toluene, reflux, 6 h; (i) MeOH.HCl, RT, 3 h

trated *in vacuo* to afford hydroxy derivative (1.83 g, 91 % yield). Et_3SiH (2 g, 17.29 mmol) was added to a solution of hydroxy derivative (1.8 g, 7.86 mmol) in trifluoroacetic acid (20 mL) at room temperature, then heated and maintained at 60-65 °C for 4 h. The reaction mixture was then poured on to water (25 mL), extracted with ethyl acetate (25 mL × 4). The combined organic extracts were washed with brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain a dark residual mass. The resultant residual mass was chromatographed (silica gel, 1:9 ethyl acetate-hexanes as eluent) to afford the title compound (1.2 g, 72 % yield). ESI mass: *m/e* 213.09, 215.01 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.35 (1H, d, *J* = 7.79 Hz), 6.98-7.00 (1H, d, *J* = 7.45 Hz), 6.69-6.73 (1H, t, *J* = 7.72 Hz), 4.29-4.32 (2H, t, *J* = 5.13 Hz), 2.80-2.83 (2H, t, *J* = 6.43 Hz), 2.00-2.06 (2H, m).

8-Bromo-6-nitro-3,4-dihydro-2*H*-1-benzopyran (5): KNO_3 (0.71 g, 7.04 mmol) was added to a stirred solution of **4** (1 g, 4.69 mmol) in conc. H_2SO_4 (10 mL) at 0-5 °C and then stirred at room temperature for 1 h. The reaction mixture was poured on to crushed ice (50 g) and extracted with chloroform (50 mL × 3). The combined organic extracts were washed with brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain a crude residual mass. The resultant residual mass was chromatographed (silica gel, 2:8 ethyl acetate-hexanes as eluent) to afford title compound (0.95 g, 79 % yield). ESI mass: *m/e* 258.14, 260.01 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.28-8.29 (1H, d, *J* = 2.45 Hz), 7.95-7.95 (1H, d, *J* = 2.29 Hz), 4.42-4.44 (2H, t, *J* = 5.32 Hz), 2.89-2.92 (2H, t, *J* = 6.41 Hz), 2.04-2.13 (2H, m).

6-Amino-8-bromo-3,4-dihydro-2*H*-1-benzopyran (6): A mixture of **5** (0.9 g, 3.48 mmol), Fe (0.87 g, 13.95 mmol) and NH_4Cl (1.1 g, 17.44 mmol) in EtOH:THF:water (1:1; 4, 20 mL) was refluxed for 3 h, cooled to room temperature, diluted with chloroform (50 mL) and filtered through celite. The organic layer was separated, dried over anhydrous sodium sulfate, concentrated *in vacuo* to afford the title compound (0.70 g, 89 %). ESI mass: *m/e* 228.30, 230.10 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.76-6.76 (1H, d, *J* = 2.38 Hz), 6.37-6.37 (1H, d, *J* = 2.27 Hz), 4.19-4.22 (2H, t, *J* = 5.28 Hz), 2.71-2.74 (2H, t, *J* = 6.35 Hz), 1.95-2.01 (2H, m).

6-(Benzenesulfonamido)-8-bromo-3,4-dihydro-2*H*-1-benzopyran (7a) (7, R^1 = H): Benzenesulfonyl chloride (0.18 g, 1.05 mmol) was added to a stirred solution of **6** (0.2 g, 0.87 mmol) and pyridine (0.20 g, 2.63 mmol) in dichloromethane (15 mL) and stirred at room temperature for 4 h. Then reaction

mixture was poured on to water (10 mL) and extracted with dichloromethane (15 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, concentrated *in vacuo* to obtain a dark residue. The resultant residual mass was chromatographed (silica gel, 3:7 ethyl acetate-hexanes as eluent) to afford title compound (0.24 g, 76 % yield). ESI mass: *m/e* 366.2, 368.3 $(M-H)^-$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.71-7.73 (2H, d, *J* = 7.45 Hz), 7.56-7.59 (1H, t, *J* = 7.30 Hz), 7.45-7.49 (2H, t, *J* = 7.84 Hz), 6.95-6.96 (1H, d, *J* = 2.34 Hz), 6.80-6.80 (1H, d, *J* = 2.09 Hz), 6.21 (1H, bs), 4.25-4.28 (2H, t, *J* = 5.09 Hz), 2.71-2.74 (2H, t, *J* = 6.40 Hz), 1.95-1.98 (2H, m).

6-(Benzenesulfonamido)-8-(1-*tert* butyloxycarbonyl-piperazin-4-yl)-3,4-dihydro-2*H*-1-benzopyran (8a) (8, R^1 = H): pd_2db_3 (14.9 mg, 0.016 mmol), BINAP (16.8 mg, 0.27 mmol) and NaOtBu (78 mg, 0.81 mmol) were added in sequence to a stirred solution of **7a** (0.2 g, 0.54 mmol) and 1-boc piperazine (0.12 g, 0.65 mmol) in dry toluene (15 mL) and refluxed for 6 h. Then the reaction mixture was cooled to room temperature, poured on to water (25 mL) and extracted with $CHCl_3$ (25 mL × 3). The combined organic extracts were washed with brine (25 mL), dried over anhydrous sodium sulfate, concentrated *in vacuo* to obtain a dark residue. The resultant residual mass was chromatographed (silica gel, 3:7 ethyl acetate-hexanes as eluent) to afford the title compound (0.15 g, 59 % yield). ESI mass: *m/e* 474.3 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.54-7.70 (2H, d, *J* = 7.43 Hz), 7.52-7.54 (1H, t, *J* = 7.54 Hz), 7.41-7.45 (2H, t, *J* = 7.88 Hz), 6.46-6.46 (1H, d, *J* = 2.06 Hz), 6.29-6.30 (1H, d, *J* = 2.32 Hz), 6.11 (1H, bs), 4.21-4.24 (2H, t, *J* = 5.02 Hz), 3.53-3.55 (4H, t, *J* = 4.78 Hz), 2.80-2.83 (4H, t, *J* = 4.94 Hz), 2.67-2.70 (2H, t, *J* = 6.38 Hz), 1.93-1.97 (2H, m), 1.48 (9H, s).

6-(Benzenesulfonamido)-8-(piperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran hydrochloride (9a) (9, R^1 = H): Compound **8a** (0.15 g, 0.31 mmol) was stirred in methanolic HCl (20 % w/v solution, 5 mL) for 3 h and then solvent was removed *in vacuo* to obtain the title compound (0.12 g, 93 % yield). ESI mass: *m/e* 374.4 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.84 (1H, s), 8.86 (2H, bs), 7.69-7.71 (2H, d, *J* = 7.45 Hz), 7.58-7.62 (1H, t, *J* = 7.24 Hz), 7.51-7.55 (2H, t, *J* = 7.65 Hz), 6.43 (1H, d, *J* = 2.01 Hz), 6.42 (1H, d, *J* = 1.97 Hz), 4.05-4.08 (2H, t, *J* = 4.60 Hz), 3.31 (4H, bs), 3.15 (4H, bs), 2.56-2.59 (2H, t, *J* = 5.98 Hz), 1.80-1.82 (2H, m).

6-(3-Fluoro-1-benzenesulfonamido)-8-(piperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran hydrochloride (9b) (9, R^1 = 3-F): The title compound was prepared using essentially the same procedure as described for the preparation of **9a**. ESI mass: *m/e* 392.4 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 7.47-7.49 (2H, m), 7.29-7.35 (2H, m), 6.59-6.60 (1H, d, *J* = 1.98 Hz), 6.47-6.47 (1H, d, *J* = 1.97 Hz), 3.95-3.99 (2H, t, *J* = 6.37 Hz), 3.35-3.39 (4H, m), 3.19-3.21 (4H, m), 2.41-2.43 (2H, m), 1.71-1.74 (2H, m).

6-(1-Naphthalenesulfonamido)-8-(piperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran hydrochloride (9c) (9, R^1 together with benzene ring is 1-naphthyl): The title compound was prepared using essentially the same procedure as described for the preparation of **9a**. ESI mass: *m/e* 424.3 $(M + H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ:10.28 (1H, s), 8.78-8.79 (2H, bs), 8.66-8.68 (1H, d, *J* = 8.36 Hz), 8.19-8.21 (1H, d, *J* = 8.2 Hz), 8.11-8.13 (1H, d, *J* = 7.2 Hz), 8.06-8.08 (1H, d, *J* = 7.9 Hz), 7.57-7.72 (3H, m), 6.32-6.35 (2H, d, *J* = 12.24 Hz), 3.99-4.02 (2H, m), 3.12-3.14 (4H, m), 2.88-2.91 (4H, m), 2.47-2.49 (2H, m), 1.74-1.76 (2H, m).

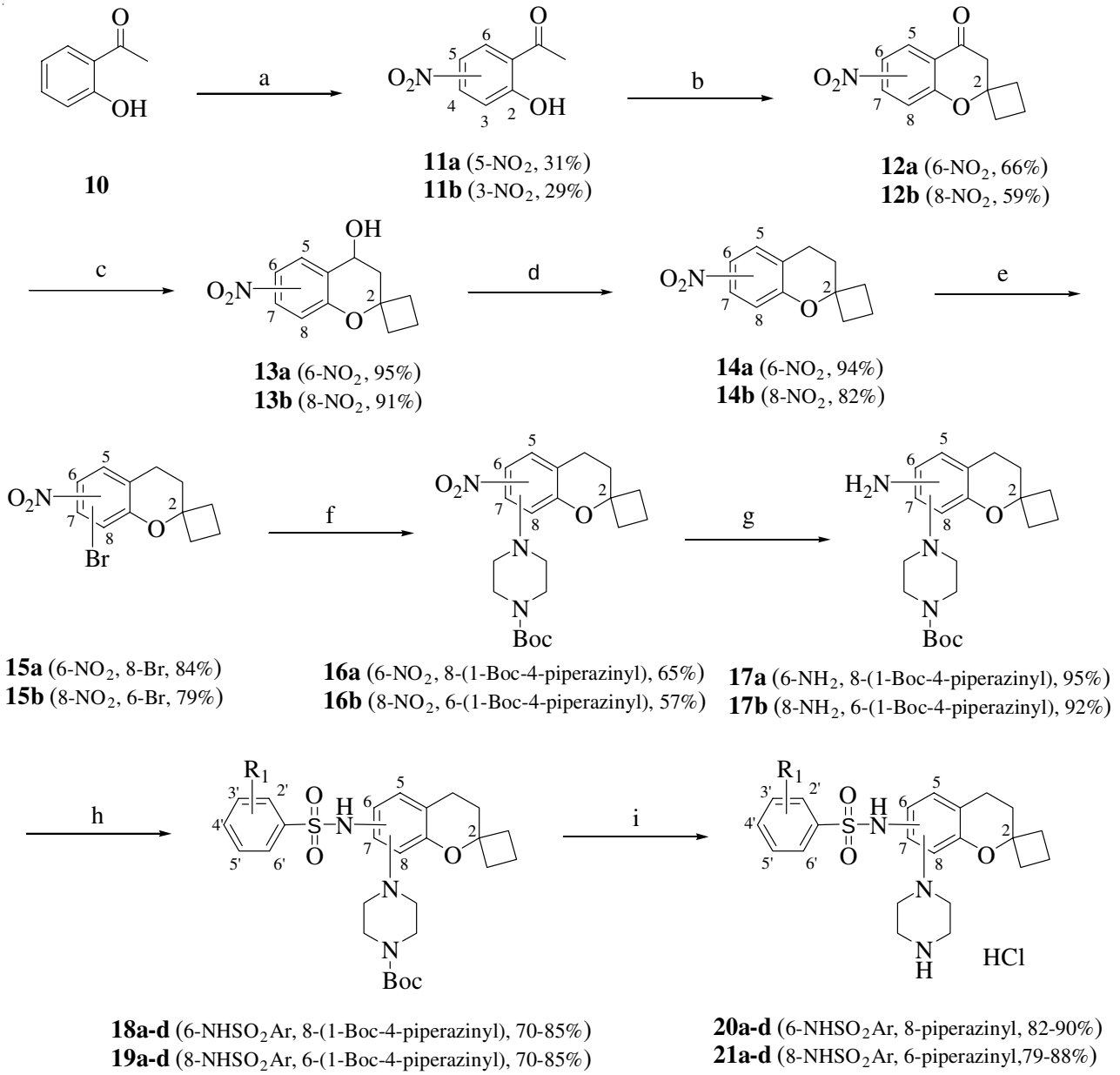
6-(2-Fluoro-1-benzenesulfonamido)-8-(piperazin-1-yl)-3,4-dihydro-2*H*-1-benzopyran hydrochloride (9d) (9, R^1 = 2-F): The title compound was prepared using essentially the same procedure as described for the preparation of **9a**. ESI mass: *m/e* 392.4 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 7.64-7.67 (1H, m), 7.25-7.32 (3H, m), 6.49-6.50 (1H, d, *J* = 1.95 Hz), 6.41-6.41 (1H, d, *J* = 1.96 Hz), 3.91-3.95 (2H, t, *J* = 6.37 Hz), 3.31-3.34 (4H, m), 3.15-3.17 (4H, m), 2.39-2.42 (2H, m), 1.71-1.74 (2H, m).

The target compounds **20a-d** and **21a-d** were synthesized according to **Scheme-II**.

2'-Hydroxy-5'-nitro acetophenone (11a) and 2'-hydroxy-3'-nitro acetophenone (11b): Nitrating mixture, prepared from conc. HNO_3 (60 mmol) and conc. H_2SO_4 (60 mmol), was added drop wise to a stirred mixture of 2'-hydroxyacetophenone (**10**) (5.44 g, 40 mmol) in conc. H_2SO_4 (16.5 mL) at -5 to 0 °C under stirring and maintained at 0 °C for 2 h. The reaction mixture was then poured on to cold water (100 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain crude yellow residue. The resultant residual mass was chromatographed (silica gel, 2:8 to 4:6 ethyl acetate-hexane as eluent) to afford title compounds **11a** (2.30 g, 31 % yield) and **11b** (2.12 g, 29 % yield). The ESI mass for both compounds **11a** and **11b** was observed at *m/e* 180.1 $(M-H^+)$. ^1H NMR of **11a** (400 MHz, $CDCl_3$) δ: 8.79-8.79 (1H, d, *J* = 2.6 Hz), 8.36-8.39 (1H, dd, *J* = 9.09, 2.48 Hz), 7.11-7.13 (1H, d, *J* = 9.13 Hz), 2.75 (3H, s). ^1H NMR of **11b** (400 MHz, CD_3OD) δ: 8.17-8.20 (1H, dd, *J* = 7.08, 1.05 Hz), 8.04-8.06 (1H, dd, *J* = 7.58, 1.27 Hz), 7.02-7.06 (1H, t, *J* = 7.97 Hz), 2.70 (3H, s).

6-Nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane]-4-one (12a): Cyclobutanone (0.91 g, 13 mmol) was added to a solution of **11a** (1.81 g, 10 mmol) in benzene (35 mL) and pyrrolidine (0.71 g, 10 mmol) at room temperature and the resulting mixture was refluxed for 3 h. Then the reaction mixture was concentrated *in vacuo* to obtain a dark residue. The resultant residual mass was chromatographed (silica gel, 1:9 ethyl acetate-hexanes as eluent) to afford title compound (1.54 g, 66 % yield). ESI mass: *m/e* 234.1 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.74-8.75 (1H, d, *J* = 2.6 Hz), 8.32-8.34 (1H, dd, *J* = 9.0, 2.6 Hz), 7.09-7.12 (1H, d, *J* = 9.12 Hz), 2.98 (2H, s), 2.35-2.41 (2H, m), 2.19-2.25 (2H, m), 1.97-2.00 (1H, m), 1.74-1.80 (1H, m).

6-Nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane]-4-ol (13a): $NaBH_4$ (0.15 g, 4.07 mmol) was added in portions to a stirred suspension of **12a** (0.95 g, 4.07 mmol) in methanol (10 mL) at 25-35 °C. The reaction mixture was stirred at room temperature for 0.5 h and then concentrated to obtain a thick residual mass. Then the reaction mixture was concentrated to get a thick residual mass. The resultant residual mass was diluted with water (25 mL), extracted with ethyl acetate (25 mL × 3) and the combined organic extracts were dried over anhydrous sodium sulfate, concentrated *in vacuo* to afford the title compound (0.91 g, 95 % yield). ESI mass:



Scheme-II: Reagents and conditions: (a) HNO_3:H_2SO_4, 0-5 °C, 2 h; (b) cyclobutanone, pyrrolidine, benzene, reflux, 3 h; (c) $NaBH_4$, MeOH, RT, 0.5 h; (d) Et_3SiH, TFA, 60-65 °C, 4 h; (e) Br_2, CH_3CO_2H, RT, 4 h; (f) 1-Boc piperazine, pd_2dba_3, BINAP, NaOBut, toluene, reflux, 6 h; (g) 10 % Pd-C, H_2 (g), RT, 2 h; (h) Substituted benzenesulfonyl chlorides, pyridine, RT, 4 h; (i) MeOH.HCl, RT, 3 h

m/e 236.1 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.37-8.38 (1H, d, *J* = 2.51 Hz), 8.05-8.08 (1H, dd, *J* = 8.99, 2.70 Hz), 6.87-6.89 (1H, d, *J* = 9.02 Hz), 4.87-4.91 (1H, m), 2.30-2.45 (4H, m), 2.14-2.15 (1H, m), 1.94-2.07 (3H, m), 1.75-1.77 (1H, m).

6-Nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (14a): Et_3SiH (0.97 g, 8.4 mmol) was added to a solution of **13a** (0.9 g, 3.8 mmol) in trifluoroacetic acid (9 mL) at room temperature and then heated and maintained at 60-65 °C for 4 h. Then the reaction mixture was poured on to water (25 mL), extracted with ethyl acetate (25 mL × 4). The combined organic extracts were washed with brine (25 mL), dried over anhydrous sodium sulfate, concentrated *in vacuo* to obtain dark residual mass. The resultant residual mass was chromatographed (silica gel, 1:9 ethyl acetate-hexane as eluent) to afford the title compound (0.79 g, 94 % yield). ESI mass: *m/e* 220.1 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.96-7.99 (2H, d, *J* = 9.23 Hz), 6.82-6.84 (1H, dd, *J* = 6.77, 3.04 Hz), 2.82-2.86 (2H, t, *J* = 6.47 Hz), 2.30-2.38 (2H, m), 2.07-2.13 (2H, m), 1.99-2.02 (2H, t, *J* = 6.46 Hz), 1.68-1.73 (1H, m), 1.54-1.57 (1H, m).

8-Bromo-6-nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (15a): Bromine (0.82 g, 5.1 mmol) was added at room temperature to a stirred solution of **14a** (0.75 g, 3.4 mmol) in acetic acid and maintained for 4 h. The reaction mixture was poured on to saturated Na_2SO_3 solution (10 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic extracts were washed with brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford title compound (0.86 g, 84 % yield). ESI mass: *m/e* 298.9, 300.6 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.28-8.28 (1H, d, *J* = 2.43 Hz), 7.94-7.94 (1H, d, *J* = 2.17 Hz), 2.86-2.89 (2H, t, *J* = 6.48 Hz), 2.41-2.44 (2H, m), 2.12-2.16 (2H, m), 2.02-2.05 (2H, t, *J* = 6.52 Hz), 1.96-1.99 (1H, m), 1.70-1.75 (1H, m).

8-(1-*tert* butyloxycarbonyl piperazin-4-yl)-6-nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (16a): pd_2db_3 (78.2 mg, 0.085 mmol), BINAP (88.7 mg, 0.14 mmol) and NaOtBu (0.41 g, 4.27 mmol) were added in sequence to a stirred solution of **15a** (0.85 g, 2.85 mmol) and 1-boc piperazine (0.58 g, 3.13 mmol) in dry toluene (50 mL) and refluxed for 6 h. Then the reaction mixture was cooled to room temperature, poured on to water (50 mL) and extracted with $CHCl_3$ (50 mL × 3). The combined organic extracts were washed with brine (25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to get a dark residue. The resultant residual mass was chromatographed (silica gel, 2:8 ethyl acetate-hexane as eluent) to afford the title compound (0.75 g, 65 % yield). ESI mass: *m/e* 404.2 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.71-7.71 (1H, d, *J* = 2.17 Hz), 7.58-7.59 (1H, d, *J* = 2.53 Hz), 3.62-3.64 (4H, t, *J* = 4.81 Hz), 3.04-3.06 (4H, t, *J* = 4.64 Hz), 2.83-2.86 (2H, t, *J* = 6.45 Hz), 2.30-2.35 (2H, m), 2.11-2.18 (2H, m), 2.00-2.04 (2H, t, *J* = 6.49 Hz), 1.92-1.94 (1H, m), 1.72-1.75 (1H, m), 1.49 (9H, s).

6-Amino-8-(1-*tert* butyloxycarbonyl piperazin-4-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (17a): 10 % Pd-C (21 mg) was added to a stirred solution of **16a** (0.7 g, 1.73 mmol) in methanol (15 mL) and maintained at room temperature under H_2 (g) balloon pressure for 2 h. Then the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to afford title compound (0.61 g, 95 % yield). ESI mass: *m/e* 374.3 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.13 (1H, d, *J* = 2.12 Hz), 6.10 (1H, d, *J* = 1.98 Hz), 3.60-3.61 (4H, m), 3.32-3.38 (2H, bs), 2.97-2.99 (4H, m), 2.68-2.71 (2H, t, *J* = 6.51 Hz), 2.19-2.24 (2H, m), 2.04-2.10 (2H, m), 1.91-1.95 (2H, t, *J* = 6.50 Hz), 1.65-1.68 (1H, m), 1.51-1.56 (1H, m), 1.48 (9H, s).

6-(Benzenesulfonamido)-8-(1-*tert* butyloxycarbonyl piperazin-4-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (18a): Benzenesulfonyl chloride (0.1 g, 0.59 mmol) was added to a stirred solution of **17a** (0.2 g, 0.53 mmol) and pyridine (0.13 g, 1.6 mmol) in dichloromethane (15 mL) and stirred at room temperature for 4 h. Then the reaction mixture was poured on to water (10 mL) and extracted with dichloromethane (15 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo* to obtain a dark residue. The resultant residual mass was chromatographed (silica gel, 3:7 ethyl acetate-hexane as eluent) to afford the title compound (0.2 g, 72 % yield). ESI mass: *m/e* 514.5 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66-7.68 (2H, d, *J* = 8.00 Hz), 7.51-7.55 (1H, t, *J* = 7.09 Hz), 7.40-7.44 (2H, t, *J* = 7.64 Hz), 6.44 (1H, s), 6.26-6.26 (1H, d, *J* = 2.05 Hz), 3.54-3.61 (4H, t, *J* = 4.56 Hz), 2.84-2.86 (4H, t, *J* = 4.85 Hz), 2.66-2.69 (2H, t, *J* = 6.42 Hz), 2.20-2.25 (2H, m), 2.04-2.09 (2H, m), 1.87-1.94 (3H, m), 1.66-1.71 (1H, m), 1.48 (9H, s).

6-(Benzenesulfonamido)-8-(piperazin-1-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane]-hydrochloride (20a): Compound **18a** (0.2 g, 0.37 mmol) was stirred in methanolic HCl (20 % w/v solution, 5 mL) for 3 h and then solvent was removed *in vacuo* to obtain the title compound (0.15 g, 85 % yield). ESI mass: *m/e* 414. $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 7.69-7.71 (2H, d, *J* = 7.60 Hz), 7.56-7.60 (1H, t, *J* = 7.33 Hz), 7.46-7.50 (2H, t, *J* = 7.74 Hz), 6.65-6.65 (1H, d, *J* = 1.81 Hz), 6.47-6.47 (1H, d, *J* = 1.75 Hz), 3.40-3.42 (4H, m), 3.28-3.31 (4H, m), 2.65-2.68 (2H, t, *J* = 6.48 Hz), 2.23-2.30 (2H, m), 2.06-2.12 (2H, m), 1.90-1.93 (2H, t, *J* = 6.33 Hz), 1.84-1.88 (1H, m), 1.69-1.76 (1H, m).

6-(3-Fluoro-1-benzenesulfonamido)-8-(piperazin-1-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] hydrochloride (20b): The title compound was prepared using essentially the same procedure as described for the preparation of **20a**. ESI mass: *m/e* 432.4 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 7.50-7.53 (2H, m), 7.31-7.40 (2H, m), 6.61-6.61 (1H, d, *J* = 2.02 Hz), 6.43-6.43 (1H, d, *J* = 1.63 Hz), 3.37-3.39 (4H, m), 3.22-3.27 (4H, m), 2.66-2.69 (2H, t, *J* = 6.44 Hz), 2.21-2.29 (2H, m), 2.07-2.13 (2H, m), 1.91-1.94 (2H, t, *J* = 6.43 Hz), 1.87-1.88 (1H, m), 1.69-1.76 (1H, m).

6-(1-Naphthalenesulfonamido)-8-(piperazin-1-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] hydrochloride (20c): The title compound was prepared using essentially the same procedure as described for the preparation of **20a**. ESI mass: *m/e* 464.4 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 8.63-8.65 (1H, d, *J* = 7.88 Hz), 8.10-8.13 (2H, m), 7.98-8.00 (1H, m), 7.59-7.66 (2H, m), 7.48-7.52 (1H, t, *J* = 7.83 Hz), 6.43-6.44 (1H, d, *J* = 2.05 Hz), 6.32-6.33 (1H, d, *J* = 1.87 Hz), 3.31-3.35 (4H, m), 3.08-3.13 (4H, m), 2.52-2.56 (2H, t, *J* = 6.44 Hz), 2.16-2.24 (2H, m), 2.01-2.07 (2H, m), 1.83-1.85 (2H, t, *J* = 6.39 Hz), 1.86-1.89 (1H, m), 1.67-1.72 (1H, m).

6-(2-Fluoro-1-benzenesulfonamido)-8-(piperazin-1-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] hydrochloride (20d): The title compound was prepared using essentially the same procedure as described for the preparation of **20a**. ESI mass: *m/e* 432.4 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 7.49-7.51 (1H, m), 7.32-7.39 (3H, m), 6.58-6.59 (1H, d, *J* = 2.00 Hz), 6.39-6.40 (1H, d, *J* = 1.79 Hz), 3.39-3.41 (4H, m), 3.26-3.31 (4H, m), 2.69-2.71 (2H, t, *J* = 6.49 Hz), 2.19-2.23 (2H, m), 2.04-2.09 (2H, m), 1.89-1.91 (2H, t, *J* = 6.49 Hz), 1.89-1.91 (1H, m), 1.65-1.71 (1H, m).

8-Nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane]-4-one (12b): The title compound was prepared using essentially the same procedure as described for the preparation of **12a**. ESI mass: *m/e* 234.3 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.07-8.13 (2H, m), 7.08-7.12 (1H, t, *J* = 7.92 Hz), 3.07 (2H, s), 2.40-2.50 (2H, m), 2.19-2.24 (2H, m), 1.97-2.00 (1H, m), 1.72-1.77 (1H, m).

8-Nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane]-4-ol (13b): The title compound was prepared using essentially the same procedure as described for the preparation of **13a**. ESI mass: *m/e* 236.3 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.73-7.76 (1H, dd, *J* = 8.02, 0.92 Hz), 7.64 - 7.66 (1H, d, *J* = 7.46 Hz), 6.93-6.97 (1H, d, *J* = 8.36 Hz), 4.87-4.90 (1H, m), 2.33-2.57 (4H, m), 2.09-2.16 (2H, m), 1.95-1.96 (1H, m), 1.71-1.78 (2H, m).

8-Nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (14b): The title compound was prepared using essentially the same procedure as described for the preparation of **14a**. ESI mass: *m/e* 220.1 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.62-7.64 (1H, d, *J* = 8.04 Hz), 7.22-7.24 (1H, d, *J* = 7.41 Hz), 6.82-6.86 (1H, t, *J* = 7.77, 7.83 Hz), 2.83-2.86 (2H, t, *J* = 6.52 Hz), 2.35-2.40 (2H, m), 2.07-2.12 (2H, m), 2.02-2.06 (2H, t, *J* = 6.71 Hz), 1.91-1.94 (1H, m), 1.60-1.69 (1H, m).

6-Bromo-8-nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (15b): The title compound was prepared using essentially the same procedure as described for the preparation of **15a**. ESI mass: *m/e* 298.0, 300.1 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.77 (1H, d, *J* = 2.15 Hz), 7.36 (1H, d, *J* = 2.27 Hz), 2.82-2.85 (2H, m), 2.34-2.42 (2H, m), 2.02-2.10 (4H, m), 1.89-1.94 (1H, m), 1.64-1.71 (1H, m).

6-(1-*tert* butyloxycarbonyl piperazin-4-yl)-8-nitro-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (16b): The title compound was prepared using essentially the same procedure as described for the preparation of **16a**. ESI mass: *m/e* 404.4 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22-7.22 (1H, d, *J* = 2.72 Hz), 6.87-6.87 (1H, d, *J* = 2.52 Hz), 3.55-3.57 (4H, m), 3.01-3.03 (4H, m), 2.80-2.83 (2H, t, *J* = 6.47 Hz), 2.33-2.36 (2H, m), 2.01-2.10 (4H, m), 1.89-1.92 (1H, m), 1.65-1.70 (1H, m).

8-Amino-6-(1-*tert* butyloxycarbonyl piperazin-4-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (17b): The title compound was prepared using essentially the same procedure as described for the preparation of **17a**. ESI mass: *m/e* 374.4 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.29 (1H, d, *J* = 2.31 Hz), 6.16 (1H, d, *J* = 2.23 Hz), 3.47-3.48 (4H, m), 2.82-2.84 (4H, m), 2.58-2.61 (2H, m), 1.97-2.14 (4H, m), 1.81-1.85 (2H, m), 1.62-1.78 (2H, m), 1.39 (9H, s).

8-(Benzenesulfonamido)-6-(1-*tert* butyloxycarbonyl piperazin-4-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] (19a): The title compound was prepared using essentially the same procedure as described for the preparation of **18a**. ESI mass: *m/e* 514.4 $(M + H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.73-7.75 (2H, d, *J* = 7.58 Hz), 7.47-7.51 (1H, t, *J* = 8.03 Hz), 7.37-7.40 (1H, t, *J* = 7.50 Hz), 7.04 (1H, bs), 6.90 (1H, bs), 6.35 (1H, bs), 3.55 (4H, m), 2.97 (4H, m), 2.57-2.60 (2H, m), 1.85-1.88 (4H, m), 1.72-1.75 (2H, m), 1.55-1.60 (2H, m), 1.48 (9H, s).

8-(Benzenesulfonamido)-6-(piperazin-1-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] hydrochloride (21a): Compound **19a** (0.2 g, 0.38 mmol) was stirred in methanolic HCl (20 % w/v solution, 5 mL) for 3 h. After completion of the reaction (TLC), the solvent was removed *in vacuo* to obtain the title compound (0.15 g, 85 % yield). ESI mass: *m/e* 414.1 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 7.71-7.72 (2H, d, *J* = 7.76 Hz), 7.55-7.58 (1H, t, *J* = 7.40 Hz), 7.43-7.47 (2H, t, *J* = 7.69 Hz), 7.09-7.09 (1H, d, *J* = 2.19 Hz), 6.66-6.66 (1H, d, *J* = 1.86 Hz), 3.48-3.54 (4H, m), 3.41-3.42 (4H, m), 2.62-2.65 (2H, t, *J* = 6.31 Hz), 1.81-1.85 (4H, m), 1.69-1.75 (3H, m), 1.53-1.62 (1H, m).

8-(3-Fluoro-1-benzenesulfonamido)-6-(piperazin-1-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] hydrochloride (21b): The title compound was prepared using essentially the same procedure as described for the preparation of **21a**. ESI mass: *m/e* 431.7 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 7.41-7.43 (2H, m), 7.29-7.31 (2H, m), 6.57-6.58 (1H, d, *J* = 2.02 Hz), 6.41-6.41 (1H, d, *J* = 1.63 Hz), 3.34-3.37 (4H, m), 3.26-3.29 (4H, m), 2.56-2.59 (2H, t, *J* = 6.44 Hz), 2.18-2.25 (2H, m), 2.01-2.08 (2H, m), 1.87-1.91 (2H, t, *J* = 6.43 Hz), 1.82-1.86 (1H, m), 1.69-1.76 (1H, m).

8-(1-Naphthalenesulfonamido)-6-(piperazin-1-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] hydrochloride (21c): The title compound was prepared using essentially the same procedure as described for the preparation of **21a**. ESI mass: *m/e* 464.2 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 8.79-8.82 (1H, d, *J* = 8.57 Hz), 8.09-8.11 (1H, d, *J* = 8.18 Hz), 7.99-8.01 (2H, m), 7.68-7.72 (1H, t, *J* = 7.29 Hz), 7.62-7.65 (1H, t, *J* = 7.61 Hz), 7.41-7.45 (1H, t, *J* = 7.75 Hz), 7.10-7.11 (1H, d, *J* = 1.98 Hz), 6.53-6.53 (1H, d, *J* = 1.97 Hz), 3.31-3.40 (8H, m), 2.47-2.50 (2H, t, *J* = 6.34 Hz), 1.51-1.54 (2H, t, *J* = 6.40 Hz), 1.47-1.48 (2H, m), 1.26-1.32 (2H, m), 1.05-1.13 (2H, m).

8-(2-Fluoro-1-benzenesulfonamido)-6-(piperazin-1-yl)-3,4-dihydro spiro[2*H*-1-benzopyran-2,1'-cyclobutane] hydrochloride (21d): The title compound was prepared using essentially the same procedure as described for the preparation of **21a**. ESI mass: *m/e* 432.2 $(M + H)^+$. ^1H NMR (400 MHz, CD_3OD) δ: 7.53-7.55 (1H, m), 7.31-7.36 (3H, m), 6.59-6.598 (1H, d, *J* = 2.07 Hz), 6.45-6.46 (1H, d, *J* = 1.71 Hz), 3.30-3.32 (4H, m), 3.21-3.26 (4H, m), 2.51-2.56 (2H, t, *J* = 6.44 Hz), 2.15-2.19 (2H, m), 1.97-1.98 (2H, m), 1.81-1.84 (2H, t, *J* = 6.43 Hz), 1.79-1.82 (1H, m), 1.65-1.71 (1H, m).

RESULTS AND DISCUSSION

The synthesis of target compounds **9a-d**, **20a-d** and **21a-d** was achieved as given in **Schemes-I** and **II**. Condensation of 2-bromophenol (**1**) with 3-bromopropionic acid gave intermediate **2** which upon treatment with polyphosphoric acid underwent cyclization and yielded intermediate **3**. Reduction of **3** followed by dehydroxylation gave intermediate **4**. Nitration of **4** with nitrating mixture gave intermediate **5**. The reduction of intermediate **5** with Fe/NH_4Cl yielded intermediate **6** which upon treatment with various substituted benzenesulfonyl chlorides gave intermediates **7a-d**. The intermediates **7a-d** were treated with 1-Boc-piperazine under Buchwald coupling conditions and obtained intermediates **8a-d** which upon deprotection with methanolic HCl gave targeted compounds **9a-d** (**Scheme-I**). Nitration of 2′-hydroxyaceto-phenone (**10**) with nitrating mixture gave the isomeric compounds **11a** and **11b**. Condensation of **11a** with cyclobutanone gave intermediate **12a**. The intermediate **12a** upon reduction gave intermediate **13a** which was subjected to dehydroxylation to obtain intermediate **14a**. Bromination of intermediate **14a** gave intermediate **15a** which upon reaction with 1-Boc piperazine under Buchwald coupling conditions yielded intermediate **16a**. The reduction of nitro group with 10 % Pd-C in methanol yielded intermediate **17a**. The intermediate **17a** was treated with substituted benzenesulfonyl chlorides in presence of an appropriate base and obtained intermediates **18a-d**. The deprotection of **18a-d** with methanolic HCl gave targeted compounds **20a-d** as HCl salts. A similar strategy was followed for the synthesis of targeted compounds **21a-d** starting from intermediate **11b** with some non-critical variations.

Structure activity relationship (SAR): All the synthesized compounds, belonging to compounds **I**, **II** and **III**, were tested for their antagonistic activity towards $5\text{-}HT_6R$ at 1 μM concentration (Table-1). For the exploration of SAR, we introduced selective substitutions at R^1 position of compounds **I**, **II** and **III**. We initially tested compound **9a** where R^1 = H and its inhibition at $5\text{-}HT_6R$ was found to be 73 %. Among compounds **I**, compound **9c** bearing 1-naphthylsulfonamide group was found to be most potent with an inhibition of 89 %.

TABLE-1
5-HT_6 RECEPTOR BINDING DATA OF COMPOUNDS **I**, **II** AND **III**

Compound	R^1	% Inhibition at 1 μM concentration[a]
9a	H	73
9b	3-F	39
9c	R^1 together with benzene ring is 1-naphthyl	89
9d	2-F	18
20a	H	69
20b	3-F	42
20c	R^1 together with benzene ring is 1-naphthyl	92
20d	2-F	11
21a	H	9
21b	3-F	8
21c	R^1 together with benzene ring is 1-naphthyl	13
21d	2-F	6

[a]%inhibition towards 5-HT_6R was measured using cell based reporter gene functional assay. Values are mean of two experiments

The other compounds from the series *i.e*. compound **9b** (R^1 = 3-F) and compound **9d** (R^1 = 2-F) have shown 39 and 18 % of inhibition, respectively towards 5-HT_6R. These compounds were almost 3 to 4 fold less potent compared **9a** and **9c**. Among compound **II**, compound **20a** (R^1 = H) has shown an inhibition of 69 % whereas compound **20c** with a 1-naphthylsulfon-amide group was found to be most potent among all compounds with an inhibition of 92 % towards 5-HT_6R. The compound **20b** (R^1 = 3-F) has shown moderate antagonistic activity with an inhibition of 42 % towards 5-HT_6R. compound **20d** (R^1 = 2-F) was inactive which showed an inhibition of 11 %. Compounds **21a-d** which represent compound **III** were all inactive towards 5-HT_6R with poor antagonistic activity. More over these compounds were 8-9 folds less potent compared to the most potent compounds **9c** and **20c**. In general, all the tested compounds belonging to compound **I** and compound **II** have shown moderate to potent antagonistic activities where as derivatives belonging to compound **III** were inactive.

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 potent compounds of the series, that is, compound **9c** and **20c** were further evaluated for their CYP liabilities, microsomal metabolic stability (Table-2). Both the compounds **9c** and **20c** were found to be metabolically stable *in vitro* in rat (less than 40 %) and human (less than 35 %) in liver microsomes at 0.5 h. The IC_{50} values for CYP3A4 and CYP2D6 were found to 1.5 and > 10 μM, respectively for compound **9c** whereas the IC_{50} value for compound **20c** were found to be 3.2 and > 10 μM. These results show that the compounds from this series have lower potential for drug-drug interaction, thereby maximizing the safety.

TABLE-2
HUMAN CYP450[14] INHIBITORY DATA AND MICROSOMAL METABOLIC STABILITY[a]

Compound	IC_{50} (μM)		% Metabolism in liver microsomes	
	CYP 3A4	CYP 2D6	Human	Rat
9c	1.5	7.5	30.16	33.42
20c	3.2	>10	35.14	40.09

[a]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, con. 2.5 μM

Conclusion

We have reported a set of new compounds belonging to three different platforms obtained by rational medicinal chemistry approach. These compounds have shown moderate to potent *in vitro* binding affinities towards 5-HT_6R. Both the compounds **9c** and **20c** were found to be metabolically stable when tested in liver microsomes. Compound **20c** was shown more resistance to metabolism by CYP3A4 enzyme compared to **9c**, proving the fact that the insertion of cyclobutyl group, in general, could improve metabolic stability of the compound **II**, in addition to maintaining the potency. Based on these findings, the novel series of compounds **I** and II, could be further optimized to obtain potent 5-HT_6R antagonists with a balanced biological profile, for the treatment of neurological disorders.

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