Synthesis, enzyme inhibition and molecular docking studies of 1-Arylsulfonyl-4-phenylpiperazine derivatives

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Abstract: Heterocyclic molecules have been frequently investigated to possess various biological activities during the last few decades. The present work elaborates the synthesis and enzymatic inhibition potentials of a series of sulfonamides. A series of 1-arylsulfonyl-4-Phenylpiperazine (3a-n) geared up by the reaction of 1-phenylpiperazine (1) and different (un)substituted alkyl/arylsulfonyl chlorides (2a-n), under defined pH control using water as a reaction medium. The synthesized molecules were characterized by ^{1}H-NMR, ^{13}C-NMR, IR and EI-MS spectral data. The enzyme inhibition study was carried on α-glucosidase, lipoxygenase (LOX), acetyl cholinesterase (AChE) and butyryl cholinesterase (BChE) enzymes supported by docking simulation studies and the IC_{50} values rendered a few of the synthesized molecules as moderate inhibitors of these enzymes where, the compound 3e exhibited comparatively better potency against α-glucosidase enzyme. The synthesized compounds showed weak or no inhibition against LOX, AChE and BChE enzymes.

Keywords: Phenylpiperazine, alkyl/arylsulfonyl chlorides, enzyme inhibition activity and spectral characterization.

INTRUDUCTION

Piperazine is an interesting heterocyclic moiety, a constituent of several biologically active molecules. The polar nitrogen atoms in the piperazine ring confer bioactivity to molecules and enhance favorable interaction with macromolecules (Todorovic *et al*., 2005). The substituted benzamide and substituted acetamide derivatives of piperazine have shown strong agonistic activity (Matulenko *et al*., 2004). Some piperazine sulfonamides were studied and found effective and selective beta (3)-AR agonists (Perrone *et al*., 2009). Moreover, Piperazine ring has been found to exhibit wide spectrum of biological activities and it is used in many drugs against different diseases. Some are known to exhibit anti-hypertensive, anti-inflammatory, anti-allergenic, anti-tussive, anti-bacterial, anti-serotonic, anti psychotic, anti-influenza, anti-cancer, anti-schizo-phernia, or central nervous system (CNS) depressant activity (Al-Samaraie *et al.,* 2005). Sulfonamides are known for their potent enzyme inhibition activities (Supuran *et al.*, 2003). On the basis of these facts, a number of researchers are attempting to inaugurate new drugs with improved pharmacokinetics with less inauspicious effects. AChE inhibitors are employed for the treatment of Alzheimer's disease (AD). AChE (EC 3.1.1.7) and BChE (EC 3.1.1.8) make part of the serine hydrolases. Variation in amino acid residues of the active sites of AChE and BChE determines the different specificities for the inhibitors and substrates for these enzymes. These enzymes are responsible for the extinction of acetylcholine at cholinergic synapses. These are major components of neuromuscular junctions and cholinergic brain synapses. Both these enzymes play major role in termination of the nerve impulse and to catalyze the hydrolysis of the neurotransmitter acetylcholine (CA) (Cygler *et al.*, 1993; Tougu, 2001). Thus, the search for novel CA inhibitors is a good approach to introduce new drug candidates for AD and related ailments (Gauthier, 2001; Bertaccini, 1982). LOX enzymes have iron in their structural framework and are involved in dioxygenation of lipids, consisting of polyunsaturated fatty acids. It performs a key role in the synthesis of leukotrienes, which are responsible for pathophysiology of different allergic diseases. LOX inhibitors are mainly used for the treatment of allergic and inflammatory diseases (Roussaki *et al.*, 2010; Jampilek *et al*., 2006; Pommery *et al*., 2004). Patients with type-2 *Diabetes mellitus* are treated with α-glucosidase inhibitors as oral anti-diabetic drugs. Liberation of D-glucose of oligosaccharides and disaccharides from dietary complex carbohydrates can be retarded by the inhibitors of enzyme, and resultant delay in glucose absorption causes reduction in postprandial hyperglycemia (Lebovitz, 1997). Therefore, inhibition of α-glucosidase is considered important in managing type-2 diabetes.

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The literature survey and previous work by our group (Abbasi *et al*., 2014; Abbasi *et al*., 2014; Abbasi *et al*., 2014; Abbasi *et al*., 2013) have revealed that slight structural changes may have a great effect on the biological potentials of a molecule. Furthermore, molecular docking studies were performed for all the synthesized molecules. The docking method involves the prediction of ligand conformation and orientation with in a targeted binding site. In general, there are two aims of docking studies: precise structural modeling and accurate prediction of activity (Wadood *et al*., 2014). Molecular docking can be used to explain the mechanism of molecular recognition between the ligands and its receptor. Some theoretic docking methods have been used to study the interactions of molecular recognition. Among them one is MOE-Dock method which allows the ligands to be flexible during docking so that the ligands can adjust their different conformations in the binding pocket of the receptor. We have applied this method to find the best binding mode of the synthesized ligands with *α*-glucosidase, LOX, AChE and BChE enzymes.

MATERIALS AND METHODS

General

The chemical were purchased from Alfa Aesar, Merck and Sigma-Aldrich. The solvents were of analytical grade and used without further purification. Melting points were noted by open capillary tube on a Gallenkamp melting point apparatus and were uncorrected. Purity of the reactants and products was tested by thin layer chromatography (TLC) on pre-coated silica gel G-25-UV_{254} plates with ethyl acetate and *n*-hexane in various proportions as solvent system. KBr pellet method was used to record the IR spectra on a Jasco-320-A spectrometer and wave number on abscissa in cm^{-1}. ^{13}C-NMR/^{1}H-NMR spectra were taken on a Bruker spectrometer operating at frequency of 400 MHz and $CDCl_3$ was used as solvent. Chemical shifts (*δ)* are given in ppm. Mass spectra (EI-MS) were recorded on a JMS-HX-110 spectrometer, having a data system.

General procedure for the synthesis of 1-arylsulfonyl-4-phenylpiperazine (3a-n)

1-Phenylpiperazine 1 (1.0mmol) was dispersed in about 20mL distilled water in a 50mL round bottomed (RB) flask. Calculated equimolar amounts of aryl sulfonyl chlorides (2a-n) were added and stirred for 3-4 hours. The definite pH ranging 9-10 was maintained by the addition of solid sodium carbonate until completion of the reaction. Conc. HCl was added gradually on completion of reaction to adjust the pH about 4-5 to facilitate precipitation. The precipitated products were filtered, washed with distilled water and dried to obtain the desired products. All the compounds were re-crystallized from methanol.

1-(Phenylsulfonyl)-4-phenylpiperazine (3a)

White amorphous solid; Yield: 70.74%; m. p.: 128 ^{o}C; Mol. formula: $C_{16}H_{18}N_2O_2S$; Mol. mass: 302 $gmol^{-1}$;IR (KBr) v_{max}: 3050 (aromatic C-H stretching), 2900 (-CH_2 stretching), 1650 (aromatic C=C stretching), 1380 (S=O stretching);^{1}H-NMR (400MHz): *δ* 7.84 (t, *J*=7.2 Hz, 2H, H-2"& H-6"), 7.62 (d, *J*=7.2 Hz, 1H, H-4"), 7.51 (d, *J* =7.2 Hz, 2H, H-3" & H-5"), 7.29-7.24 (m, 5H, H-2' to H-6'), 3.31-3.19 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6); ^{13}C-NMR ($CDCl_3$,100MHz): *δ*151.2 (C-1'), 145.2 (C-1"), 133.4 (C-4"), 130.1 (C-3"& C-5"), 128.4 (C-3' & C-5'), 127.3 (C-2" & C-6"), 122.7 (C-4'), 116.1 (C-2' & C-6'), 53.3 (C-3 & C-5), 47.5 (C-2 & C-6); EIMS: *m/z* 302 $[M]^{\bullet+}$, 238 $[C_{16}H_{18}N_2]^{\bullet+}$, 161 $[C_{10}H_{13}N_2]^{+}$, 141 $[C_6H_5SO_2]^{+}$, 77 $[C_6H_5]^{+}$, 51 $[C_4H_3]^{+}$.

1-[(4-Methylphenyl)sulfonyl]-4-phenylpiperazine (3b)

Off white amorphous solid; Yield: 65.45%; m.p.:180-182^{o}C; Mol. formula: $C_{17}H_{20}N_2O_2S$; Mol. mass: 316$gmol^{-1}$; IR (KBr) v_{max}: 3040 (aromatic C-H stretching), 2895 (-CH_2 stretching), 1660 (aromatic C=C stretching), 1370 (S=O stretching); ^{1}H-NMR (400MHz): *δ*7.66 (d, *J*=8.4 Hz, 2H, H-2" & H-6"), 7.45 (br. t, *J* =7.2 Hz, 2H, H-2' & H-6'), 7.35 (d, *J*=8.0 Hz, 2H, H-3" & H-5"), 7.02-6.97 (m, 3H, H-3' to H-5'), 3.68-3.10 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6), 2.43 (s, 3H, CH_3-7"); ^{13}C-NMR ($CDCl_3$, 100 MHz): *δ*150.9 (C-1'), 142.6 (C-1"), 133.2 (C-4"), 131.3 (C-3" & C-5"), 129.7 (C-3' & C-5'), 126.2 (C-2" & C-6"), 123.1 (C-4'), 116.2 (C-2' & C-6'), 52.8 (C-3 & C-5), 48.6 (C-2 & C-6), 21.2 (C-7"); EIMS: *m/z* 316 $[M]^{\bullet+}$, 252 $[C_{17}H_{20}N_2]^{\bullet+}$, 161 $[C_{10}H_{13}N_2]^{+}$, 155 $[CH_3C_6H_5SO_2]^{+}$, 91 $[CH_3C_6H_5]^{+}$, 77 $[C_6H_5]^{+}$, 51 $[C_4H_3]^{+}$.

1-{[4-(tert-Butyl)phenyl]sulfonyl}-4-phenylpiperazine (3c)

Off white amorphous solid; Yield: 59.36%; m.p.: 143 ^{o}C; Mol. formula: $C_{20}H_{26}N_2O_2S$; Mol. mass: 358 $gmol^{-1}$; IR (KBr) v_{max}: 3040 (aromatic C-H stretching), 2918 (-CH_2 stretching), 1645 (aromatic C=C stretching), 1385 (S=O stretching); ^{1}H-NMR (400MHz): *δ*7.70 (d, *J* = 8.8Hz, 2H, H-2" & H-6"), 7.55 (d, *J*=8.4 Hz, 2H, H-3" & H-5"), 7.40-6.95 (m, 5H, H-2' to H-6'), 3.46-3.11 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6), 1.34 (s, 9H, CH_3-8", CH_3-9", CH_3-10"); ^{13}C-NMR ($CDCl_3$, 100MHz): *δ*155.3 (C-4"), 151.7 (C-1'), 141.3 (C-1"), 130.2 (C-3', C-5'), 129.0 (C-3" & C-5"), 126.9 (C-2" & C-6"), 121.4 (C-4'), 116.4 (C-2' & C-6'), 50.5 (C-3 & C-5), 49.0 (C-2 & C-6), 34.2 (C-7"), 31.5 (CH_3-8", CH_3-9", CH_3-10"); EIMS: *m/z* 358 $[M]^{\bullet+}$, 294 $[C_{20}H_{26}N_2]^{\bullet+}$, 197 $[C_{10}H_{13}O_2S]$, 161 $[C_{10}H_{13}N_2]^{+}$, 133 $[C_{10}H_{13}]^{+}$, 84 $[C_4H_8N_2]^{\bullet+}$, 77 $[C_6H_5]^{+}$, 51 $[C_4H_3]^{+}$.

1-(Mesitylsulfonyl)-4-phenylpiperazine (3d)

Cream colored amorphous solid; Yield: 60.31%; m.p: 124-126^{o}C; Mol. formula: $C_{19}H_{24}N_2O_2S$; Mol. mass: 344 $gmol^{-1}$; IR (KBr) v_{max}: 3096 (aromatic C-H stretching), 2905 (-CH_2 stretching), 1680 (aromatic C=C stretching), 1400 (S=O stretching); ^{1}H-NMR (400MHz): *δ*7.44 (br.t , *J* = 6.4 Hz, 2H, H-2' & H-6'), 7.01-6.92 (m, 3H, H-3' to

H-5'), 6.83 (s, 2H, H-3" & H-5"), 3.85-3.05 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6), 2.64 (s, 6H, CH_3-7" & CH_3-9"), 2.23 (s, 3H, CH_3-8"); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ152.6 (C-1'), 150.7 (C-1"), 148.3 (C-2" & C-6"), 142.1 (C-3" & C-5"), 140.9 (C-4"), 133.2 (C-3' & C-5'), 122.3 (C-4'), 115.6 (C-2' & C-6'), 51.7 (C-3 & C-5), 48.6 (C-2 & C-6), 24.4 (C-7" & C-9"), 21.1 (C-8"); EIMS: *m/z* 344 $[M]^{\bullet+}$, 280 $[C_{19}H_{24}N_2]^{\bullet+}$, 183 $[C_9H_{11}SO_2]^+$, 161 $[C_{10}H_{13}N_2]^+$, 119 $[C_9H_{11}]^+$, 84 $[C_4H_8N_2]^{\bullet+}$, 77 $[C_6H_5]^+$, 56 $[C_2H_4N_2]^{\bullet}$, 51 $[C_4H_3]^+$.

1-[(4-Acetylphenyl)sulfonyl]-4-phenylpiperazine (3e)

Yellowish amorphous solid; Yield: 60.00%; m.p: 152-153 ^oC; Mol. formula: $C_{18}H_{20}N_2O_3S$; Mol. mass: 344 $gmol^{-1}$; IR (KBr) ν_{max}: 3070 (aromatic C-H stretching), 2885 (-CH_2 stretching), 1710 (C=O ketone stretching), 1655 (aromatic C=C stretching), 1380 (S=O stretching); ^{1}H-NMR (400 MHz): δ 8.15-8.10 (m, 3H, H-3' to H-5'), 7.88 (d, *J* = 8.0 Hz, 2H, H-2" & H-6"), 7.78 (d, *J*=7.6 Hz, 2H, H-3" & H-5"), 7.52 (d, *J* = 8.4 Hz, 2H, H-2' & H-6'), 3.88-3.60 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6), 2.65 (s, 3H, CH_3-8"); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ198.3 (C-7"), 152.4 (C-1'), 148.3 (C-1"), 142.2 (C-4"), 131.4 (C-3' & C-5'), 128.3 (C-3" & C-5"), 125.3 (C-2" & C-6"), 121.1 (C-4'), 117.3 (C-2' & C-6'), 52.4 (C-3 & C-5), 46.8 (C-2 & C-6), 27.1 (C-8"); EIMS: *m/z* 344 $[M]^{\bullet+}$, 280 $[C_{18}H_{20}N_2O]^{\bullet+}$, 183 $[C_8H_7SO_3]^+$, 161 $[C_{10}H_{13}N_2]^+$, 119 $[C_8H_7O]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

1-[(4-Acetamidophenyl)sulfonyl]-4-phenylpiperazine (3f)

Yellowish amorphous solid; Yield: 55.90%; m.p: 145-146 ^oC; Mol. formula: $C_{18}H_{21}N_3O_3S$; Mol. mass: 359 $gmol^{-1}$; IR (KBr) ν_{max}: 3105 (aromatic C-H stretching), 2910 (-CH_2 stretching), 1680 (aromatic C=C stretching), 1670 (C=O stretching of amide), 1377 (S=O stretching); ^{1}H-NMR (400 MHz): δ 8.12 (d, *J* = 8.4 Hz, 2H, H-2" & H-6"), 7.88 (d, *J* = 7.6 Hz, 2H, H-3" & H-5"), 7.50-7.44 (m, 5H, H-2' to H-6'), 3.89-3.58 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6), 2.64 (s, 3H, CH_3-8"); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ167.8 (C-7"), 152.3 (C-1'), 143.4 (C-4"), 141.1 (C-1"), 135.3 (C-3' & C-5'), 127.5 (C-2" & C-6"), 122.4 (C-4'), 118.3 (C-2' & C-6'), 113.6 (C-3" & C-5"), 53.2 (C-3 & C-5), 49.3 (C-2 & C-6), 30.4 (C-8"); EIMS: *m/z* 359 $[M]^{\bullet+}$, 295 $[C_{18}H_{21}N_3O]^{\bullet+}$, 198 $[C_8H_8NO_3S]$, 161 $[C_{10}H_{13}N_2]^+$, 134 $[C_8H_8NO]^+$, 84 $[C_4H_8N_2]^{\bullet+}$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

1-[(4-Methoxyphenyl)sulfonyl]-4-phenylpiperazine (3g)

Off white amorphous solid; Yield: 55.57%; m.p: 154-156 ^oC; Mol. formula: $C_{17}H_{20}N_2O_3S$; Mol. mass: 332 $gmol^{-1}$; IR (KBr) ν_{max}: 3070 (aromatic C-H stretching), 2885 (-CH_2 stretching), 1655 (aromatic C=C stretching), 1380 (S=O stretching); ^{1}H-NMR (400 MHz): δ 7.72 (d, *J* = 8.8 Hz, 2H, H-2" & H-6"), 7.33-7.26 (m, 5H, H-2' to H-6'), 7.01 (d, *J* =8.4 Hz, 2H, H-3" & H-5"), 3.86 (s, 3H, CH_3-7"), 3.53-3.15 (m, 8H, CH_2-2 , CH_2-3, CH_2-5, CH_2-6); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ161.8 (C-4"), 152.2 (C-1'), 137.1 (C-1"), 132.4 (C-3' & C-5'), 128.9 (C-2" & C-6"), 123.2 (C-4'), 119.5 (C-2' & C-6'), 58.6 (C-7"), 50.9 (C-3 & C-5), 48.3 (C-2 & C-6); EIMS: *m/z* 332 $[M]^{\bullet+}$, 268 $[C_{17}H_{20}N_2O]^{\bullet+}$, 171 $[CH_3OC_6H_5SO_2]^+$, 161 $[C_{10}H_{13}N_2]^+$, 107 $[CH_3OC_6H_5]^+$, 84 $[C_4H_8N_2]^{\bullet+}$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

1-[(4-Bromophenyl)sulfonyl]-4-phenylpiperazine (3h)

Cream colored amorphous solid; Yield: 57.26%; m.p: 172.58^oC; Mol. formula: $C_{16}H_{17}BrN_2O_2S$; Mol. mass: 380 $gmol^{-1}$; IR (KBr) ν_{max}: 3090 (aromatic C-H stretching), 2915 (-CH_2 stretching), 1640 (aromatic C=C stretching), 1365 (S=O stretching), 550 (C-Br); ^{1}H-NMR (400 MHz): δ 7.72 (d, *J* = 8.4 Hz, 2H, H-2" & H-6"), 7.64 (d, *J* = 8.4 Hz, 2H, H-3" & H-5"), 7.51-7.48 (m, 5H, H-2' to H-6'), 3.81-3.12 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ153.1 (C-1'), 143.0 (C-1"), 135.2 (C-3" & C-5"), 130.7 (C-3' & C-5'), 129.1 (C-4"), 128.8 (C-2" & C-6"), 121.3 (C-4'), 116.5 (C-2' & C-6'), 51.6 (C-3 & C-5), 47.9 (C-2 & C-6); EIMS: *m/z* 382 $[M+2]^{\bullet+}$, 380 $[M]^{\bullet+}$, 316 $[C_{16}H_{17}BrN_2]^{\bullet+}$, 219 $[C_6H_4BrSO_2]$, 161 $[C_{10}H_{13}N_2]^+$, 155 $[C_6H_4Br]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

1-[(4-Chlorophenyl)sulfonyl]-4-phenylpiperazine (3i)

Off white amorphous solid; Yield: 59.36%; m.p: 143 ^oC; Mol. formula: $C_{16}H_{17}ClN_2O_2S$; Mol. mass: 336 $gmol^{-1}$; IR (KBr) ν_{max}: 3105 (aromatic C-H stretching), 2910 (-CH_2 stretching), 1680 (aromatic C=C stretching), 1670 (C=O stretching of amide), 1377 (S=O stretching), 700 (C-Cl stretching); ^{1}H-NMR (400 MHz): δ 7.73 (d, *J* = 8.4 Hz, 2H, H-2" & H-6"), 7.54 (d, *J* = 8.4 Hz, 2H, H-3" & H-5"), 7.41-7.32 (m, 5H, H-2' to H-6'), 3.89-3.31 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6); ^{13}C-NMR ($CDCl_3$,100 MHz): δ153.1 (C-1'), 142.1 (C-1"), 140.5 (C-4"), 132.7 (C-3" & C-5"), 128.4 (C-3' & C-5'), 126.3 (C-2" & C-6"), 115.4 (C-2' & C-6'), 113.6 (C-3" & C-5"), 53.6 (C-3 & C-5), 47.3 (C-2 & C-6); EIMS: *m/z* 338 $[M+2]^{\bullet+}$, 336 $[M]^{\bullet+}$, 272 $[C_{16}H_{17}ClN_2]^{\bullet+}$, 175$[C_6H_4ClO_2S]^+$, 161 $[C_{10}H_{13}N_2]^+$, 111 $[C_6H_4Cl]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

1-[(2,3-Dichlorophenyl)sulfonyl]-4-phenylpiperazine (3j)

Off white amorphous solid; Yield: 78.11%; m.p: 111-112 ^oC; Mol. formula: $C_{16}H_{16}Cl_2N_2O_2S$; Mol. mass: 370 $gmol^{-1}$; IR (KBr) ν_{max}: 3095 (aromatic C-H stretching), 2905 (-CH_2 stretching), 1655 (aromatic C=C stretching), 1377 (S=O stretching), 710 (C-Cl stretching); ^{1}H-NMR (400 MHz): δ 8.00 (dd, *J* = 8.0, 1.2 Hz, 1H, H-6"), 7.69 (dd, *J* =8.0, 0.8 Hz, 1H, H-4"), 7.37 (t, *J* = 8.4 Hz, 1H, H-5"), 7.36-7.31 (m, 2H, H-2', H-6'), 7.15-6.99 (m, 3H, H-3' to H-5'), 3.72-3.07 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6); ^{13}C-NMR ($CDCl_3$,100 MHz): δ151.8 (C-1'), 141.2 (C-1"), 136.1 (C-4"), 133.2 (C-2"), 131.5 (C-3"), 130.3 (C-3' & C-5'), 127.8 (C-5"), 123.5 (C-6"), 119.3 (C-4"), 114.8 (C-2' & C-6'), 52.3 (C-3 & C-5), 47.4 (C-2 & C-6); EIMS: *m/z* 374 $[M+4]^+$, 372 $[M+2]^{\bullet+}$, 370 $[M]^{\bullet+}$, 306 $[C_{16}H_{16}Cl_2N_2]^{\bullet+}$, 161 $[C_{10}H_{13}N_2]^+$, 145 $[C_6H_3Cl_2]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

Table 1: Enzyme inhibition activities of 1-arylsulfonyl-4-phenylpiperazine derivatives (3a-n)

Comp	α-Glucosidase		LOX		AChE		BChE	
	%age Inhibition	IC_{50} (μM)	%age Inhibition	IC_{50} (μM)	%age Inhibition	IC_{50} (μM)	%age Inhibition	IC_{50} (μM)
3a	8.75±0.12	-	35.85±1.21	-	15.28±0.16	-	62.03±0.67	355.61±0.37
3b	6.31±0.75	-	4.65±0.99	-	12.18±0.08	-	45.69±0.31	>500
3c	83.51±0.35	133.67±0.81	36.54±1.05	-	99.08±1.19	290.81±0.76	76.59±0.75	316.31±0.38
3d	43.30±0.55	>500	21.95±1.31	-	51.13±0.43	493.78±0.26	52.64±0.46	498.63±0.22
3e	99.42±1.22	68.13±0.27	98.43±1.33	221.91±1.21	63.38±0.45	442.04±0.28	46.92±0.41	>500
3f	98.54±1.75	147.34±0.54	94.43±1.23	239.61±1.29	34.79±0.36	>500	45.76±0.39	>500
3g	12.82±0.35	-	26.01±1.02	-	49.86±0.22	>500	48.59±0.36	>500
3h	12.51±0.21	-	29.43±1.12	-	49.86±0.22	>500	48.59±0.36	>500
3i	8.16±0.98	-	13.31±1.47	-	54.93±0.45	467.89±0.35	74.13±0.78	323.09±0.39
3j	17.09±0.12	-	28.94±1.13	-	67.32±0.56	355.24±0.27	52.28±0.32	493.99±0.19
3k	85.44±1.55	98.12±0.39	4.71±1.35	-	22.61±0.19	-	47.79±0.39	>500
3l	5.83±0.25	-	32.40±1.21	-	46.69±0.32	>500	56.21±0.47	456.12±0.28
3m	23.69±1.45	-	30.28±1.17	-	41.27±0.38	>500	57.36±0.63	193.18±0.29
3n	90.32±0.21	162.31±0.14	86.52±1.16	187.41±1.01	75.07±0.71	413.21±0.43	71.88±0.72	358.05±0.29
Control	92.23±0.14[a]	38.25±0.12[a]	93.79±1.27[b]	22.4±1.3[b]	91.27±1.17[c]	0.04±0.0001[c]	82.82±1.09[c]	0.85±0.0001[c]

NOTE: IC_{50} values (concentration at which there is 50% in enzyme catalyzed reaction) compounds were calculated using EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA). a = Acarbose, b = Baicalein, c = Eserine

1-[(3,4-Dichlorophenyl)sulfonyl]-4-phenylpiperazine (3k)

Off white amorphous solid; Yield: 70.31%; m.p: 170-171 ^oC; Mol. formula: $C_{16}H_{16}Cl_2N_2O_2S$; Mol. mass: 370 $gmol^{-1}$; IR (KBr) ν_{max}: 3092 (aromatic C-H stretching), 2908 (-CH_2 stretching), 1656 (aromatic C=C stretching), 1373 (S=O stretching), 707(C-Cl stretching); ^{1}H-NMR (400 MHz): δ 7.86 (d, J = 1.6 Hz, 1H, H-2"), 7.65 (d, J = 8.4 Hz, 1H, H-5"), 7.59 (dd, J = 8.4, 1.6 Hz, 1H, H-6"), 7.39-7.37 (m, 2H, H-2' & H-6'), 7.01-6.90 (m, 3H, H-3' to H-5'), 3.55-3.12 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6); ^{13}C-NMR ($CDCl_3$,100 MHz): δ151.9 (C-1'), 139.0 (C-1"), 135.1 (C-4"), 131.6 (C-5"), 130.9 (C-3"), 130.2 (C-3' & C-5'), 126.7 (C-2"), 124.3 (C-6"), 121.8 (C-4'), 115.7 (C-2' & C-6'), 53.2 (C-3 & C-5), 49.5 (C-2 & C-6); EIMS: *m/z* 374 $[M+4]^+$, 372 $[M+2]^{\bullet+}$, 370 $[M]^{\bullet+}$, 306 $[C_{16}H_{16}Cl_2N_2]^{\bullet+}$, 161 $[C_{10}H_{13}N_2]^+$, 145 $[C_6H_3Cl_2]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

1-[(2,4-Dinitrophenyl)sulfonyl]-4-phenylpiperazine (3l)

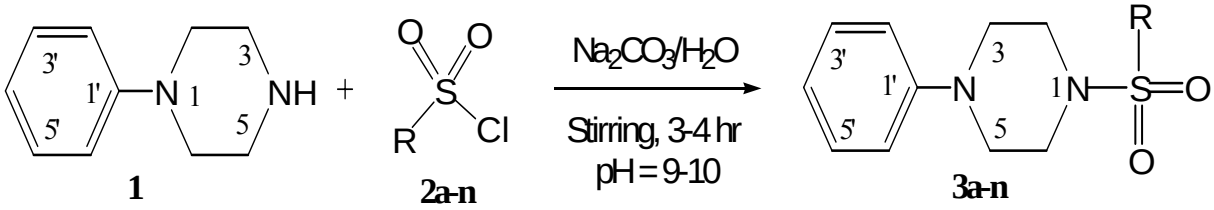
Yellow amorphous solid; Yield: 69.49%; m.p: 138-140^oC; Mol. formula: $C_{16}H_{16}N_4O_6S$; Mol. mass: 392 $gmol^{-1}$; IR (KBr) ν_{max}: 3064 (aromatic C-H stretching), 2903 (-CH_2 stretching), 1654 (aromatic C=C stretching), 1373 (S=O stretching); ^{1}H-NMR (400 MHz): δ 8.51 (dd, J= 8.4, 2.0 Hz, 1H, H-5"), 8.49 (d, J = 2.0 Hz, 1H, H-3"), 8.23 (d, J = 8.8 Hz, 1H, H-6"), 7.39-7.35 (m, 2H, H-2' to H-6'), 3.77-3.11 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ153.4 (C-1'), 149.7 (C-4"), 141.3 (C-2"), 140.3 (C-1"), 135.6 (C-3' & C-5'), 133.4 (C-5"), 130.9 (C-6"), 125.3 (C-3"), 122.4 (C-4'), 115.3 (C-2' & C-6'), 52.9 (C-3 & C-5), 48.4 (C-2 & C-6); EIMS: *m/z* 392 $[M]^{\bullet+}$, 328 $[C_{16}H_{16}N_4O_4]^{\bullet+}$, 167 $[C_6H_3N_2O_4]^+$, 161 $[C_{10}H_{13}N_2]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

1-[(Camphor-10-y)lsulfonyl]-4-phenylpiperazine (3m)

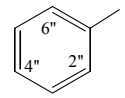
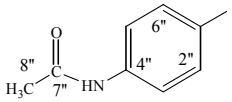
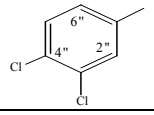
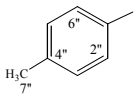
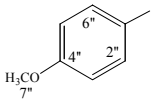
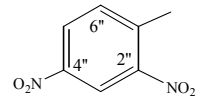
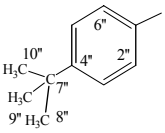
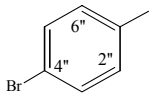
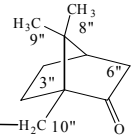
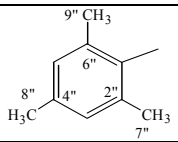
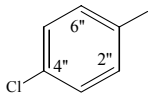
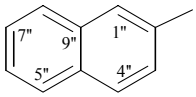
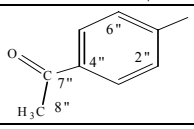
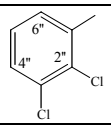
Off white shiny scales; Yield: 30.21%; m.p: 210^oC; Mol. formula: $C_{20}H_{28}N_2O_3S$; Mol. mass: 376 $gmol^{-1}$; IR (KBr) ν_{max}: 3097 (aromatic C-H stretching), 2914 (-CH_2 stretching), 1716 (C=O ketone stretching), 1667 (aromatic C=C stretching), 1387 (S=O stretching); ^{1}H-NMR (400MHz): δ 7.48 (t, J = 7.2 Hz, 2H, H-2' & H-6'), 7.05-6.95 (m, 3H, H-3' to H-5'), 4.02-3.36 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6), 3.12 (br.s, 1H, H_{eq}-6"), 2.85 (d, J =14.4 Hz, 1H, H_a-10"), 2.37 (d, J = 15.2 Hz, 1H, H_b-10"), 2.12-2.09 (m, 1H, H_{ax}-6"), 2.07-1.97 (m, 1H, H_{eq}-4"), 1.77-162 (m, 2H, H_{ax}-4", H_{ax}-5") 1.52-1.44 (m, 2H, H-3"), 1.08 (s, 3H, CH_3-9"), 0.87 (s, 3H, CH_3-8"); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ212.9 (C-1"), 152.8 (C-1'), 130.4 (C-3' & C-5'), 120.9 (C-4'), 116.3 (C-2' & C-6'), 59.7 (C-2"), 55.1 (C-10"), 52.8 (C-3 & C-5), 49.6 (C-7"), 47.5 (C-2 & C-6), 43.1 (C-5"), 42.6 (C-6"), 28.2 (C-3"), 26.5 (C-4"), 20.4 (C-9"), 17.9 (C-8"); EIMS: *m/z* 376 $[M]^{\bullet+}$, 312 $[C_{20}H_{28}N_2O]^{\bullet+}$, 215 $[C_{10}H_{15}O_3S]$, 161 $[C_{10}H_{13}N_2]^+$, 151 $[C_{10}H_{15}O]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.

1-[(Naphthalen-2-yl)sulfonyl]-4-phenylpiperazine (3n)

Off white amorphous solid; Yield: 60.31%; m.p.; 88^oC; Mol. formula: $C_{20}H_{20}N_2O_2S$; Mol. mass: 352 $gmol^{-1}$; IR (KBr) ν_{max}: 3060 (aromatic C-H stretching), 2910 (-CH_2 stretching), 1655 (aromatic C=C stretching), 1375 (S=O stretching); ^{1}H-NMR (400 MHz): δ 8.05 (d, J=8.4 Hz, 1H, H-8"), 7.99 (d, J=1.6 Hz, 1H, H-1"), 7.96 (d, J=8.4 Hz, 1H, H-5"),7.90 (d, J=8.0 Hz, 1H, H-4"), 7.74-7.60 (m, 5H, H-2' & H-6'), 7.72 (dd, J=8.4, 1.6 Hz, 1H, H-7"), 7.67 (d, J=7.2 Hz, 1H, H-3"), 7.39 (dd, J=7.2, 2.8 Hz, 1H, H-6"), 3.89-3.11 (m, 8H, CH_2-2, CH_2-3, CH_2-5, CH_2-6); ^{13}C-NMR ($CDCl_3$, 100MHz): δ151.5(C-1'), 138.1(C-10"), 137.6(C-2"), 136.9(C-5"), 135.4(C-7"), 130.5(C-4"), 129.7 (C-8"), 128.1(C-3' & C-5'), 127.7(C-9"), 127.4(C-6"), 124.9(C-1"), 123.0(C-3"), 121.7(C-4'), 115.3(C-2' & C-6'), 53.1(C-3 & C-5), 49.0(C-2 & C-6); EIMS: *m/z* 352 $[M]^{\bullet+}$,288$[C_{20}H_{20}N_2]^{\bullet+}$, 191$[C_{10}H_7SO_2]^+$, 161 $[C_{10}H_{13}N_2]^+$, 127 $[C_{10}H_7]^+$, 101 $[C_8H_5]^+$, 77 $[C_6H_5]^+$, 51 $[C_4H_3]^+$.



1 **2a-n** **3a-n**

Com.	R	Com.	R	Com.	R
2a, 3a		2f, 3f		2k, 3k	
2b, 3b		2g, 3g		2l, 3l	
2c, 3c		2h, 3h		2m, 3m	
2d, 3d		2i, 3i		2n, 3n	
2e, 3e		2j, 3j			

Scheme 1: Outline for the synthesis of 1-arylsulfonyl-4-phenylpiperazine derivatives

Enzyme inhibition assays

α-Glucosidase assay

The enzyme inhibitory activity against *α*-glucosidase was performed according to cited method (Chapdelaine *et al*., 1978). Phosphate buffer saline (50mM, pH 6.8, 70µL), test compound (0.5mM, 10 µL) and enzyme (0.057 units, 10 µL) were taken to make total volume of 100µL, mixed well and pre-incubated for 10 min at 37ºC and absorbance was taken at 400nm. 10µL of substrate (*p*-nitrophenylglucopyranoside (0.5mM) was added to start the reaction and after incubation for 30 min at 37ºC, absorbance was noted again at 400 nm at microplate reader (Synergy HT). The change in absorbance was used as index for the measurement of % age inhibition. Acarbose was used as positive control. All the experiments were performed in triplicates. The inhibition (%) was calculated by the following equation:

$$\%\ age\ Inhibition = \frac{Control - Test}{Control} \times 100$$

EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA) was used to calculate IC_{50} values of the compounds. Serial dilutions of the compounds from 0.5 to 0.015625mM were employed for determination of IC_{50} values. Values used for graph were mean of 3 independent experiments which were used to calculate IC_{50} value.

Lipoxygenase (LOX) assay

Enzyme inhibitory activity against LOX was done according to the method reported (Baylac and Racine *et al*., 2003). Sodium phosphate buffer (100mM; pH 8.0, 150µL), test compound (10µL) and purified LOX enzyme (15µL) was taken to make total volume of 200µL. The mixture was thoroughly mixed, pre-incubated for 10min at 25°C and absorbance was taken at 234 nm. Substrate solution (25 µL) was then added to start the reaction. The change in absorbance was noted at 234 nm after 6 minutes. All the experiments were done in triplicates. The negative ans positive controls were used in the assay. Quercetin (0.5mM well^{-1}) was employed as a positive control. The % age inhibition and IC_{50} values were calculated by the same method as mentioned in *α*-glucosidase assay.

Acetyl cholinesterase (AChE) and butyryl cholinesterase (BChE) assays

The enzyme inhibition studies for AChE & BChE were performed according to the cited method (Ellman *et al*. 1961). The reaction mixture was prepared by Na_2HPO_4 buffer (50mM and pH 7.7, 60µL), test compound (0.5 mM well^{-1}, 10µL), followed by the addition of enzyme (0.005 unit well$^{-1,}$ 10µL) to make total volume of 100µL. The contents were mixed, pre incubated for 10minuts at 37ºC pre read at 405nm. 10µL of the substrate (acetylthiocholine iodide/ butyrylthiocholine iodide) in

0.5 mM/well and 10µL DTNB (0.5mM/well were added to start the reaction. The reaction contents were incubated for 15minuts at 37ºC and the absorbance was measured at 405nm. These experiments were carried out in triplicate. Eserine (0.5mM/well) was employed as a positive control. The % age inhibition and IC_{50} values were calculated by the same method as described in *α*-glucosidase assay.

STATISTICAL ANALYSIS

All the experiments were carried out in triplicate. Statistical analysis was performed using Microsoft Excel 2010 and the results are offered as mean ± SEM.

Computational method

Preparation of receptor protein

The protein molecules included in our study, α-glucosidase (PDB code: 3NO4; resolution: 2.02Å), lipoxygenase (LOX; PDB code: 1IK3; resolution: 2.0Å), acetyl cholinesterase (AChE; PDB code: 1GQR; resolution: 2.2Å) and butyryl cholinesterase (BChE; PDB ID code: 1POP; resolution: 2.30Å) were obtained from Protein Data Bank. Water molecules were removed and the 3D protonation of the protein molecules were carried out. The energies of the protein molecules were minimized using MOE software. The parameters used for energy minimization were; Force Field: MMFF94X+Solvation, gradient: 0.05 and Chiral Constraint: Current Geometry. When the root mean square gradient falls below the 0.05 the Energy minimization was terminated. The initial and final energy of protein were calculated (in kcal/mol) by GizMOE using MMFF94X force field with conjugant gradient method. The template used for Docking was the minimized structure of the protein.

Molecular docking

MOE docking program was used to find the binding mode of ligand molecule with the protein molecule and to analyze the correct conformation of the ligand, so as to obtain minimum energy structure (Wadood *et al*., 2014). Molecular docking was carried out for all the synthesized molecules against *α*-glucosidase, LOX, AChE and BChE enzymes to find out the mode of interaction between binding site and inhibitor molecules.

Validation of docking protocol

In order to validate the accuracy of MOE-Dock program, the co crystallized ligand of all the mentioned enzymes were extracted and re-docked into the binding pocket of receptor proteins. The RMSD differences between docked and co-crystallized ligand were found in between 0.823 to 1.091Å respectively which is less than 2Å. It confirms that our docking protocol is optimized and can be used for further studies.

RESULTS

The research work was conducted to synthesize a new series of 1-arylsulfonyl-4-Phenylpiperazine (3a-n) synthesized by the protocol depicted in scheme-1. The reaction procedures with conditions are discussed in experimental section. The proposed structures of all the compounds were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR and EI-MS techniques. The synthesized compounds were evaluated for their anti-enzymatic potentials against *α*-glucosidase, LOX, AChE and BChE enzymes (table 1) because of their role in inflammatory and other degenerative diseases.

DISCUSSION

Chemistry

1-phenylpiperazine (1) and various arylsulfonyl chlorides (2a-n) were coupled in a weak basic aqueous medium and dynamic pH control to synthesize 1-arylsulfonyl-4-phenylpiperazine derivatives (3a-n). The solid sodium carbonate was added to neutralize hydrochloric acid formed during nucleophilic condensation of 1 and 2a-n. The presence of HCl suppresses the nucleophilic character of 1. The resulting products were separated out through filtration after acidifying the reaction mixture. The low acidity is recommended for better yield. The structural characterization was done through spectral data and found well simpatico as demonstration (Scheme 1). For example, the Compound 3a was pepared as white amorphous powder. Its yield was found 70.74% and m. p. was noted as 128^{o}C. IR spectrum confirmed the presence of aromatic rings by two absorption bands at 3050 cm^{-1} for C-H stretching and at 1650 cm^{-1} for C=C stretching and piperazine by one absorption band of -CH_2 stretching at 2900 cm^{-1}. Sulfonyl group was recognized at 1380 cm^{-1} by S=O stretching. Molecular formula of this compound was established by EI-MS depicting molecular ion peak at *m/z* 302 and also by assignment of the number of protons through integration curve in its ^{1}H-NMR spectrum. 1-phenylpiperazine cation appeared as fragment peak at *m/z* 161 in EI-MS spectrum. The fragments at *m/z* 77 and 51 also indicated the presence of phenyl ring. The cation from benzenesulfonyl group was also observed at *m/z* 141. In ^{1}H-NMR spectrum, three signals; a downfield triplet due to vicinity of strong electron withdrawing sulfonyl group at *δ* 7.84 with coupling constant 7.2 Hz for two deshielded protons of H-2" & H-6", an upfield doublet at *δ* 7.62 having integration for one proton, present at para position of benzene ring and a more upfield doublet resonating at *δ* 7.51 with integration for two meta protons of benzene ring affirmed the phenylsulfonyl group in the molecule. Two multiplets in the range of *δ* 7.29-7.24 and *δ* 3.31-3.19 were assigned to five protons of phenyl ring attached to piperazine moiety and eight protons of piperazine ring itself, respectively. In the ^{13}C-NMR spectrum, ten signals appeared and their multiplicity was resolved with the help of distorsionless enhancement by polarization transfer (DEPT) spectra, disclosing the presence of two quaternary carbons, ten methine carbons and four methylene carbons. Downfield

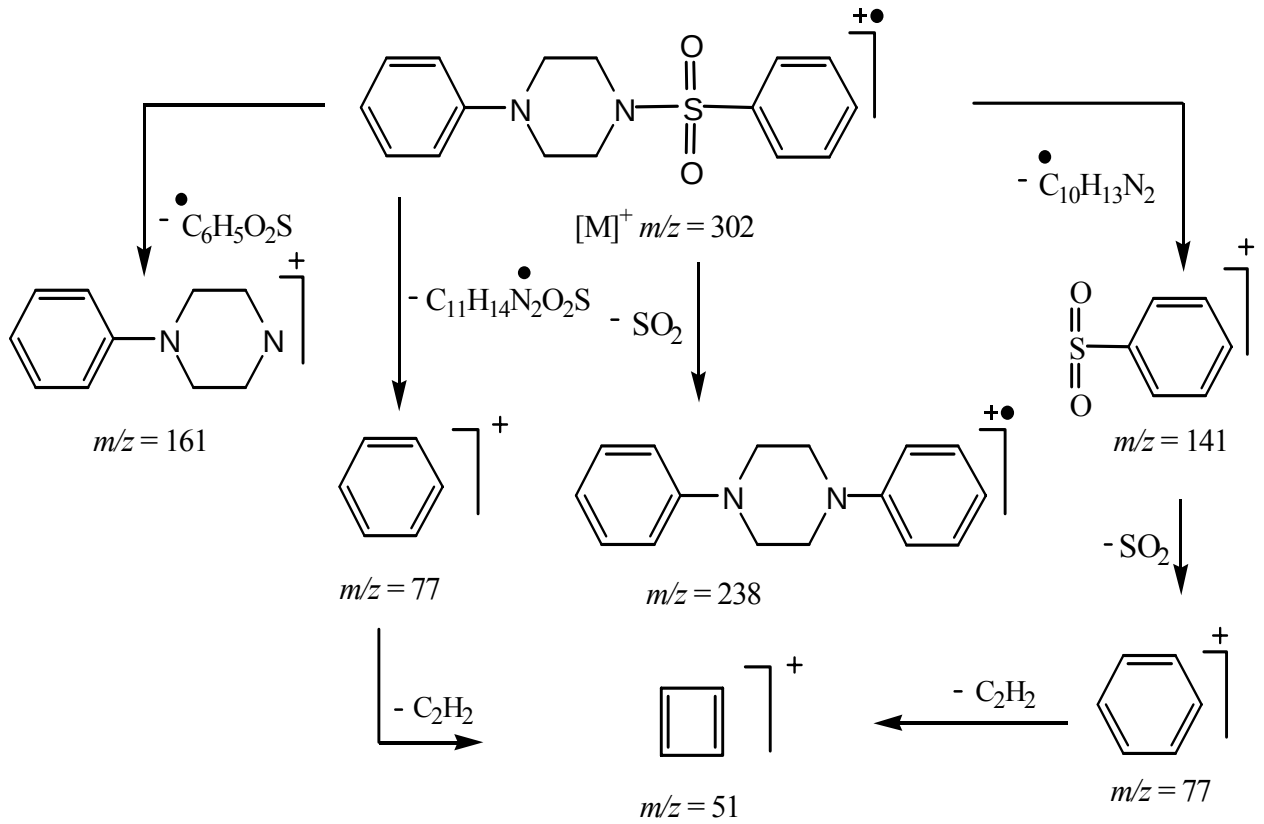


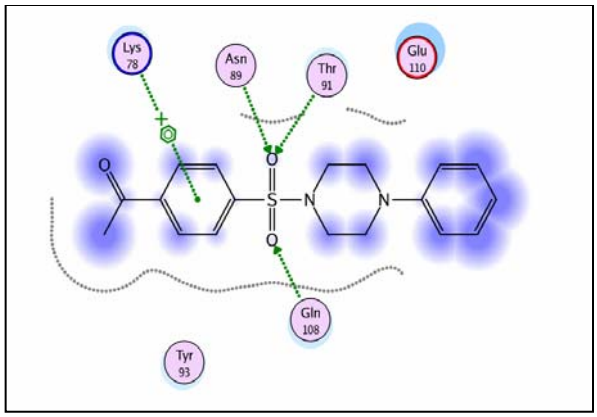
Fig. 1: Mass fragmentation pattern of 1-(Phenylsulfonyl)-4-phenylpiperazine (3a).

signals appearing at δ 151.2 and 145.2 were assigned to C-1' and C-1" which are two quaternary carbons of two phenyl rings, one attached to piperazine moiety and other to sulfonyl group, respectively. Three signals for five methine carbons of phenyl ring attached to sulfonyl group appeared at δ 133.4 forC-4", 130.1 for C-3"& C-5') and at δ 127.3 for C-2", C-6". Similarly, the three signals resonating at δ 128.4 for C-3' & C-5', 122.7 for C-4' and 116.1 for C-2' & C-6' were assigned to phenyl group attached to piperazine ring. The four methylene carbons of piperazine ring were characterized by two signals at δ 53.3 for C-3 & C-5 and 47.5 for C-2, C-6. On the basis of these evidences, the structure of 3a was named, 1-(phenylsulfonyl)-4-phenylpiperazine. Likewise the structures of other synthesized compounds (3b-n) were corroborated by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra data, as described in experimental section. For convenience, the mass fragmentation pattern of 1-(phenylsulfonyl)-4-phenylpiperazine (3a) is also sketched in (fig. 1).

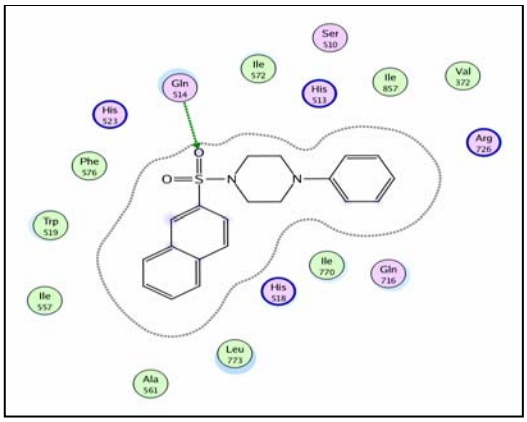
Enzyme inhibition study

The results of enzyme inhibition study against α-glucosidase, lipoxygenase, acetylcholinesterase and butyrylcholinesterase enzymes are presented as % age inhibition and IC_{50} values (table 1). A few compounds exhibited better activities against α-glucosidase enzyme. Acarbose was used as reference standard having percentage inhibition value of 92.23±0.14 and IC_{50} value of 36.25±0.12µM. Among all the compounds, 1-[(4-acetylphenyl)sulfonyl]-4-phenylpiperazine (3e) demonstrated the highest inhibition activity with lowest IC_{50} value of 68.13±0.27µM. This potency of 3e might be attributed to the acetyl group present at *para* position of phenyl ring attached to sulfonyl group. Compound, 1-[(3,4-dichlorophenyl)sulfonyl]-4-phenylpiperazine (3k) showed the second highest activity value at IC_{50} of 98.12±0.39 µM. The molecules, 1-{[4-(*tert*-butyl)phenyl] sulfonyl}-4-phenylpiperazine (3c) and 1-[(4-acetamidophenyl)sulfonyl]-4-phenylpiperazine (3f) also displayed comparatively moderate inhibition activity with IC_{50} value of 133.67±0.81 and 147.34±0.54µM respectively. The inhibition activity of 3c and 3f may be due to *ter*-butyl and acetamido groups respectively attached at *para* positions of phenyl ring of sulfonyl group. 1-(Naphthalen-2-ylsulfonyl)-4-phenylpiperazine (3n) also showed weaker activity having IC_{50} value of 162.31±0.14 supposed to be due to naphthalene moiety. Other compounds showed no activity at all. The active molecules exhibited the following order of activity 3e>3k>3c>3f>3n.

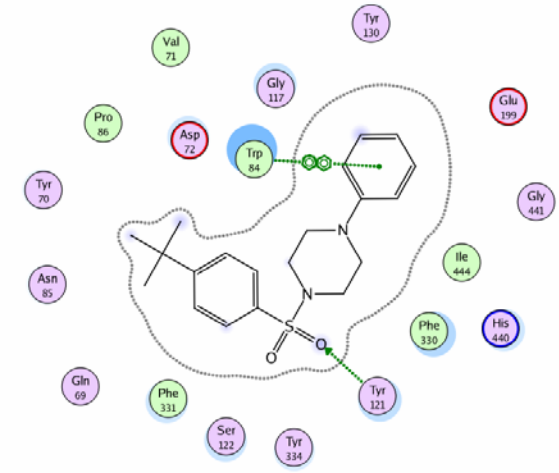
The enzyme inhibitory activity of the synthesized molecules against LOX enzyme exhibited that the molecule1-[(naphthalen-2-ylsulfonyl)]-4-phenylpiperazine (**3n**) showed moderate inhibition potential with IC_{50} value of 187.41±1.01 µM relative to reference standard, baicalein having IC_{50} value of 22.4±1.3µM. The molecule



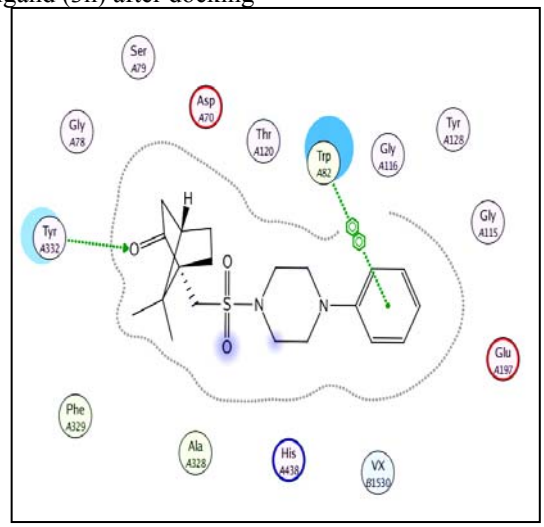
(a); 2D interacted image of α-glucosidase with the docked ligand (3e) after docking



(b); 2D interacted image of LOX with the docked ligand (3n) after docking



(c); 2D interacted image of AChE with the docked ligand (3c) after docking



(d); 2D interacted image of BChE with the docked ligand (3m) after docking

Fig. 2 (a): Binding modes of compound 3e against α-glucosidase (b); Binding modes of compound 3n against LOX (c); Binding modes of compound 3c against AChE (d); Binding modes of compound 3m against BChE.

(**3n**) showed the inhibition potential probably because of naphthalene moiety of sulfonyl group, which may have exhibited more interaction with the active site of the enzyme. The compounds, 1-[(4-acetylphenyl)sulfonyl]-4-phenylpiperazine (**3e**) and1-[(4-acetamidophenyl) sulfonyl]-4-phenylpiperazine (3f) showed the weaker inhibition potential with IC_{50} values of 221.91±1.21µM and 239.61±1.29µM respectively. Activity of both these compounds may be due to the presence of acetyl and acetamido groups, respectively, attached at *para* position of phenylsulfonyl group. All other synthesized compounds remained inactive against LOX enzyme.

The enzyme inhibitory activity against AChE revealed that the molecule 1-{[4-(*tert*-butyl)phenyl]sulfonyl}-4-phenylpiperazine (3c) exhibited weak inhibition potential with IC_{50} value of 290.81±0.76µM relative to reference standard, eserine having IC_{50} value of 0.04±0.0001µM. This molecule showed the inhibition potential probably due to the *tert*-butyl moiety. Other compounds showed no activity at all. The active molecules exhibited the following order of activity 3c>3j>3n>3e>3i>3d.

The activity against BChE revealed that the 1-(Camphor-10-ylsulfonyl)-4-phenylpiperazine (3m) exhibited weaker inhibition potential with IC_{50} value of 193.18±0.29µM, and the molecules1-{[4-(*tert*-butyl)phenyl]sulfonyl}-4-phenylpiperazine (3c) also showed weaker inhibitory potential with IC_{50} value of 316.31±0.38µM relative to reference standard, eserine having IC_{50} value of 0.04±0.0001µM. Other compounds showed no activity at all. The active molecules exhibited the following order of activity 3m>3c>3i>3a>3n>3d>3l>3j.

Molecular docking

All the compounds were computationally docked against *α*-glucosidase, LOX, AChE and BChE, enzymes. The docking results of compound 3e revealed that the compound interacted well with the active site of the target protein of *α*-glucosidase enzyme. The amino acid residues Asn89, Thr91 showed polar H-bond interaction with same

sulfonyl oxygen atom and Gln108 interacted with other double bonded oxygen atom of sulfonylpiperazine moiety through H-bond donor interaction, whereas; Lys78 interacted through arene-cation bonding with acetophenone moiety. Other amino acid residues found in close environment were Glu110 and Tyr93. (fig. 2; a). One amino acid residue interacted with compound 3n against LOX as Gln514 which showed H-bond donor interaction via sulfonyl oxygen atom whereas; Ile770, His518, His513, Leu773 and Phe576 etc. were seen in vicinity of ligand molecule (fig. 2; b). The amino acid residue Tyr121 interacted strongly with the sulfonyl oxygen of the compound 3c through an H-bond donor when docked against AChE enzyme. Similarly the same compound showed somewhat weak arene-arene interaction with Trp84 amino acid residue. Gly117, Asp72, Phe330, Phe331 and Ile444 etc. were found close to the ligand (fig. 2; c).

The interaction analysis of compound 3m against BChE showed interaction of amino acid residue Tyr*A*332 with oxygen atom of dimethylbicycloheptane moiety through H-bond donor interaction while Trp*A*82 via arene-arene bonding with the terminal benzene ring. Gly*A*116, Thr*A*120, Asp*A*70 and Gly*A*115 were found in close contact to the ligand (fig. 2; d).

CONCLUSION

The series of the sulfonamides was synthesized in good yields and the proposed structures of the synthesized molecules were corroborated by the spectral data using IR, EI-MS, ^{1}H-NMR and ^{13}C-NMR spectral techniques. The results of anti-enzymatic activities of the synthesized molecules against *α*-glucosidase, lipoxygenase, acetyl and butyrylcholinesterase depicted that majority of them remained inactive against these enzymes. However, among the active molecules, 3e displayed moderate activity against *α*-glucosidase. The computational analysis data also supported the anti-enzymatic data. This molecule can be further evaluated for affectivity and related side effects to be used as new drug candidate for type-2 diabetes and related diseases.

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