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Research Article

SYNTHESIS, SPECTRAL CHARACTERIZATION AND STRUCTURE-ACTIVITY RELATIONSHIP STUDIES ON SOME SULFONAMIDES BEARING PIPERIDINE NUCLEUS

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ABSTRACT

In the present study, a series of sulfonamides (**3a-k**) were synthesized by the coupling of different sulfonyl chloride (**1a-k**) with 4-(piperidin-1-yl)aniline (**2**) under dynamic pH control in aqueous media. Further, each of the synthesized sulfonamide treated with electrophile, ethyl iodide yielded *N*-ethyl substituted sulfonamides (**5a-k**) in the presence of sodium hydride (NaH) and dimethyl formamide (DMF). The structures of all the synthesized compounds were characterized by IR, EI-MS and ^{1}H-NMR spectra. To study the structure-activity relationship, these compounds were assayed for their antioxidant activities and other biological activities via screening them against acetylcholinesterase, butyrylcholinesterase and lipoxygenase enzymes. It was observed from the results that the *N*-ethyl substitution retarded their inhibitory potential while the unsubstituted molecules were relatively more suitable target for the treatment of Alzheimer's disease.

Keywords: 4-(piperidin-1-yl) aniline, Sulfonamides, Enzyme inhibition activity, ^{1}H-NMR and EI-MS.

INTRODUCTION

Several thousand of piperidine compounds have been cited in clinical and preclinical studies. Besides the appealing structural features, these compounds are also of pharmaceutical attention as they exhibit an extensive range of biological activities. The Piperidine nucleus is a ubiquitous structural feature in several pharmacologically active compounds, for example berberine and hydrastine which are natural medicinally important alkaloids.[1-4] There are loads of piperidine containing compounds which possess remarkable biological and medicinal properties.[5,6] Piperidine has diverse applications in commercial and curative area. Piperidine and Pyrrolidine nucleus containing compounds showed their appreciable effect on plasma glucose level[7], Insulin normalization, cure of cocaine abuse.[8]

Piperidine is also active as local anesthetics, such as mepivacaine, ropivacaine, and bupivacaine are extensively used in clinical practice.[9,10] Sulfonamides are in use as restorative agents from many years. Very first use of sulfonamides was as antibacterial agent, but their uses have unmitigated to treat other diseases. Sulfonamides are also prominent for enzyme inhibition such as carbonic anhydrase, cysteine protease, HIV protease and cyclooxygenase.[11] Moreover; sulfonamides have extensive potential to other therapeutic applications i.e. in cancer chemotherapy, hypoglyceamia, and diuretics.[12] Pharmacological potential of these heterocyclic compounds provoked chemists to synthesized piperidine derivatives with enhanced biological activities.[13]

Acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (BChE, EC 3.1.1.8) consist of an enzymes family which includes serine hydrolases. The diverse specificities for the substrates and inhibitors for these enzymes are due to the differences in amino acid residues of the active sites of AChE and BChE. Actually the system of enzyme is responsible for the termination of acetylcholine at cholinergic synapses. These are key components of cholinergic brain synapses and neuromuscular junctions. The major function of AChE and BChE is to catalyze the hydrolysis of the neurotransmitter acetylcholine and termination of the nerve impulse in cholinergic synapses.[14,15] It has been found that BChE is present in appreciably higher quantity in Alzheimer's plaques than in the normal age linked dementia of brains. H_1 and H_2 receptor antagonists possess AChE inhibitory activities. Cholinesterase inhibitors raise the quantity of acetylcholine available for neuronal and neuromuscular transmission through their ability to reversibly or irreversibly. Hence, the search for new cholinesterase inhibitors is considered an important and ongoing strategy to introduce new drug candidates for the treatment of Alzheimer's disease and other related diseases.[16,17]

The present work is a successful effort to synthesize such novel compounds exhibiting diverse and improved pharmacological potential. We have synthesized the sulfonamides of piperidine to fuse two highly biological actives classes with an objective to search new contenders of drug having significant enhanced activity and could be helpful in controlling many degenerative diseases.

MATERIALS AND METHODS

Reagents

Melting points of the synthesized compounds were recorded on a Griffin and George melting point apparatus by open capillary tube and were uncorrected. Purity was checked on thin layer chromatography (TLC) on pre-coated silica gel G-25-UV_{254} plates with different solvent systems using ethyl acetate and *n*-hexane giving single spot. Detection was carried out at 254 nm, and by ceric sulphate reagent. The I.R. spectra were recorded in KBr pellet method on a Jasco-320-A spectrophotometer (wave number in cm^{-1}). Nuclear magnetic resonance spectra were recorded in CD_3OD on a Bruker spectrometers operating at 300 MHz. Chemical shifts are given in ppm. Mass spectra (EIMS) were recorded on a JMS-HX-110 spectrometer, with a data system.

4-(piperidine-1-yl)aniline, sulfonyl chlorides and ethyl iodide were obtained from commercial suppliers. All the employed solvents were of analytical grade.

General procedure for the synthesis of *N*-(4-piperidin-1-ylphenyl)sulfonamides in aqueous medium (3a-k)

4-(piperidine-1-yl)aniline (**2**) (0.5 mL, 0.47 mmol) was suspended in 10 mL water and the pH was maintained at 9.0 by adding basic aqueous solution of a Na_2CO_3 at 0-5°C. Then, sulfonyl chlorides **1a-k** (0.47 mmol) was added in the reaction mass slowly over 10-15-min. After complete addition, the temperature of the reaction mixture was allowed to rise slowly to room temperature. The reaction mixture was stirred and monitored with TLC for the completion of reaction. Then conc. HCl (around 0.5 mL) was added slowly to adjust the pH to 2.0. The reaction mass was cooled to room temperature (RT), filtered and the solid washed with distilled water to afford the title compounds **3a-k** on drying.

General procedure for the synthesis of *N*-ethyl substituted sulfonamides (5a–k)

To an individual solution of compounds **3a-k (**0.02 g, 0.83 mmol) in *N,N*-dimethyl formamide (DMF) (0.5 mL), sodium hydride (0.001 g, 0.040 mmol) was added at room temperature and stirred for 15 min. The ethyl iodide (**4**) (0.061ml, 0.83 mmol) was added into the

reaction mixture and stirred for 30-40 min. The reaction mass was then monitored by TLC. After complete conversion, the reaction mass was quenched with cold water (20 mL). The obtained solid was filtered, washed with distilled water and dried to yield the corresponding *N*-ethyl sulfonamide derivatives **5a–k**.

Spectral Characterization of the Synthesized Compounds

***N*-[4-(Piperidin-1-yl)phenyl]benzenesulfonamide (3a)**

Dirty green powder; Yield: 90%; M.p.132-134°C. Molecular formula: $C_{17}H_{20}N_2O_2S$; Mol. Wt. 316g. IR (KBr, cm^{-1}) ν_{max}: 3429 (N-H stretching), 3023 (C-H stretching of aromatic ring), 1546 (C=C aromatic stretching), 1341 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.68 (dd, J = 2.5, 8.4 Hz, 2H, H-2″ & H-6″), 7.46-7.41 (m, 1H, H-4″), 7.54-7.51 (m, 2H, H-3″ & H-5″), 6.92 (d, J = 9.0 Hz, H-2 & 6), 6.82 (d, J = 9.0 Hz, H-3 & 5), 3.05 (t, J = 5.7 Hz, 2H, H_{ax}-2′ & H_{ax}-6′), 2.55 (t, J = 5.7 Hz, 2H, H_{eq}-2′ & H_{eq}-6′), 1.70 (m, 2H, CH_2-4′), 1.58 (m, 4H, CH_2-3′ & CH_2-5′). EIMS: *m/z* 316 (19%) $[M]^+$, 252 (21%), 175 (37%), 156 (24%), 141 (100%).

***N*-[4-(Piperidin-1-yl) phenyl]-4-methylbenzenesulfonamide (3b)**

Grey sticky solid; Yield: 89%; Molecular formula: $C_{18}H_{22}N_2O_2S$; Mol. Wt. 330g IR (KBr, cm^{-1}) ν_{max}: 3424 (N-H stretching), 3018 (C-H stretching of aromatic ring), 1539 (C=C aromatic stretching), 1349 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.56 (d, J = 8.4 Hz, 2H, H-2″ & H-6″), 7.26 (d, J = 8.4 Hz, 2H, H-3″ & 5″), 6.93 (d, J = 9.0 Hz, H-2 & 6), 6.85 (d, J = 9.0 Hz, H-3 & 5), 3.07 (t, J = 5.1 Hz, 2H, H_{ax}-2′ & H_{ax}-6′), 2.95 (t, J = 5.1 Hz, 2H, H_{eq}-2′ & H_{eq}-6′), 2.35 (s, 3H, CH_3-4″), 1.68 (m, 2H, CH_2-4′), 1.56 (m, 4H, CH_2-3′ & CH_2-5′). EIMS: *m/z* 330 (13%) $[M]^+$, 266 (22%), 175(42%), 155 (51%), 91(100%; loss of tropylium ion fragment).

***N*-[4-(Piperidin-1-yl)phenyl]-1-phenylmethanesulfonamide (3c)**

Black shiny solid; Yield: 87.5%; m.p 263-265°C, Molecular formula: $C_{18}H_{22}N_2O_2S$; Mol. Wt. 330g. IR (KBr, cm^{-1}) ν_{max}: 3417 (N-H stretching), 3034 (C-H stretching of aromatic ring), 1557 (C=C aromatic stretching), 1235 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.43 (m, 5H, H-2" to H-6"), 6.96 (d, J = 8.4 Hz, H-2 & 6), 6.70 (d, J = 8.4 Hz, H-3 & 5), 4.40 (s, 2H, SO_2-CH_2), 3.10 (t, J = 5.4 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.87 (t, J = 5.4 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 1.70 (m, 2H, CH_2-4′), 1.59 (m, 4H, CH_2-3′ & CH_2-5′). EIMS: *m/z* 330 (13%) $[M]^+$, 266 (22%), 175(42%), 155 (51%), 91(100%; loss of tropylium ion fragment).

***N*-[4-{(4-Piperidin-1-yl)phenyl)acetamido]benzenesulfonamide (3d)**

Bottled green sticky solid; Yield: 85%; Molecular formula: $C_{19}H_{23}N_3O_3S$; Mol. Wt. 373g. IR (KBr, cm^{-1}) ν_{max}: 3423 (N-H stretching), 3031 (C-H stretching of aromatic ring), 1543 (C=C aromatic stretching), 1337 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.62 (d, J = 8.7 Hz, 2H, H-2" & H-6"), 7.35 (d, J = 8.7 Hz, 2H, H-3" & 5"), 6.92 (d, J = 9.0 Hz, 2H, H-2 & 6), 6.82 (d, J = 9.0 Hz, 2H, H-3 & 5), 3.53 (t, J = 5.4 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 3.07 (t, J = 5.4 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 2.12 (s, 3H, CO-CH_3) 1.70 (m, 2H, CH_2-4'), 1.58 (m, 4H, CH_2-3' & CH_2-5'). EIMS: *m/z* 373 (13%) $[M]^+$, 330 (27%), 309 (12%), 175 (32%), 155 (100%).

***N*-[4-(Piperidin-1-yl)phenyl]-4-acetylbenzenesulfonamide (3e)**

Aqua green solid; Yield: 77%; m.p 140-142°C, Molecular formula: $C_{19}H_{22}N_2O_3S$; Mol. Wt. 358g. IR (KBr, cm^{-1}) ν_{max}: 3427 (N-H stretching), 3021 (C-H stretching of aromatic ring), 1549 (C=C aromatic stretching), 1347 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 8.05 (d, J = 8.7 Hz, 2H, H-2" & H-6"), 7.93 (d, J = 8.7 Hz, 2H, H-3" & 5"), 7.81 (d, J = 8.4 Hz, 2H, H-2 & 6), 7.00 (d, J = 8.4 Hz, 2H, H-3 & 5), 3.40 (t, J = 5.4 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.87 (t, J = 5.4 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 2.59 (s, 3H, CO-CH_3) 1.70 (m, 2H, CH_2-4'), 1.59 (m, 4H, CH_2-3' & CH_2-5'). EIMS: *m/z* 358 (15%) $[M]^+$, 294 (23%), 315 (40%), 183 (19%), 119 (100%).

***N*-[4-(Piperidin-1-yl)phenyl]-2,4,6-trimethylbenzenesulfonamide (3f)**

Black shiny sticky solid; Yield: 88%; Molecular formula: $C_{20}H_{26}N_2O_2S$; Mol. Wt. 358g. IR (KBr, cm^{-1}) ν_{max}: 3427 (N-H stretching), 3021 (C-H stretching of aromatic ring), 1547 (C=C aromatic stretching), 1331 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.20 (d, J = 9.0 Hz, 2H, H-2 & 6), 7.12 (d, J = 9.0 Hz, 2H, H-3 & 5), 6.85 (s, 2H, H-3″ & H-5″), 3.47 (t, J = 5.1 Hz, 2H, H_{ax}-2′ & H_{ax}-6′), 2.86 (t, J = 5.1 Hz, 2H, H_{eq}-2′ & H_{eq}-6′), 2.60 (s, CH_3 -4″) 1.95 (m, 2H, CH_2-4′), 1.67 (m, 4H, CH_2-3′ & CH_2-5′). EIMS: *m/z* 358 (7%) $[M]^+$, 294 (19%), 183 (23%), 175 (19%), 119 (100%).

***N*-[4-(Piperidin-1-yl)phenyl]-4-chlorobenzenesulfonamide (3g)**

Dirty green solid; Yield: 89%; m.p 150-152°C, Molecular formula: $C_{17}H_{19}ClN_2O_2S$; Mol. Wt. 350g. IR (KBr, cm^{-1}) ν_{max}: 3419 (N-H stretching), 3031 (C-H stretching of aromatic ring), 1543 (C=C aromatic stretching), 1337 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.64 (d, J = 8.7 Hz, 2H, H-2" & H-6"), 7.47 (d, J = 8.7 Hz, 2H, H-3" & 5"), 6.93 (d, J = 9.0 Hz, 2H, H-2 & 6), 6.85 (d, J = 9.0 Hz, 2H, H-3 & 5), 3.08 (t, J = 5.1 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.88 (t, J = 5.1 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 1.67 (m, 2H, CH_2-4'), 1.57 (m, 4H, CH_2-3' & CH_2-5'). EIMS: *m/z* 350 (19%) $[M]^+$, 286 (29%), 190 (42%), 175 (51%), 111 (100%).

***N*-[4-(Piperidin-1-yl)phenyl]-2,3-dihydro-1,4-benzodioxine-6-sulfonamide (3h)**

Royl blue sticky solid; Yield: 86.5%; Molecular formula: $C_{19}H_{22}N_2O_4S$; Mol. Wt. 374g. IR (KBr, cm^{-1}) ν_{max}: 3429 (N-H stretching), 3023 (C-H stretching of aromatic ring), 1546 (C=C aromatic stretching), 1341 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.29 (dd, J = 2.0, 8.4 Hz, 1H, H-1"), 7.25 (d, J = 8.4 Hz, 1H, H-2"), 7.21 (d, J = 8.4Hz, 1H, H- 6"), 6.90 (d, J = 9.0 Hz, 2H, H-2 & 6), 6.84 (d, J = 9.0 Hz, 2H, H-3 & 5), 4.30-4.34 (m, 4H, O-CH_2-CH_2-O), 3.43 (t, J = 5.4 Hz, 2H, H_{ax}-2′ & H_{ax}-6′), 2.98 (t, J = 5.4 Hz, 2H, H_{eq}-2′ & H_{eq}-6′), 1.67 (m, 2H, CH_2-4′), 1.57 (m, 4H, CH_2-3′ & CH_2-5′). EIMS: *m/z* 374 (13%) $[M]^+$, 310 (17%), 199 (37%), 175 (45%), 135 (100%).

***N*-[4-(Piperidin-1-yl)phenyl]-3,5-dichloro-2-hydroxybenzenesulfo - namide (3i)**

Magenta shiny crystals; Yield: 90%; m.p 200-202°C, Molecular formula: $C_{17}H_{18}Cl_2N_2O_3S$; Mol. Wt. 401g. IR (KBr, cm^{-1}) ν_{max}: 3421 (N-H stretching), 3025 (C-H stretching of aromatic ring), 1547 (C=C aromatic stretching), 1343 (-SO_2- stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.70 (d, J = 2.7 Hz, 1H, H-6"), 7.61 (d, J = 2.7 Hz, 1H, H-4"), 7.53 (d, J = 7.2 Hz, 2H, H-2 & 6), 7.37 (d, J = 7.2 Hz, 2H, H-3 & 5), 3.66 (t, J = 5.1 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 3.54 (t, J = 5.1 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 2.05 (m, 2H, CH_2-4'), 1.81 (m, 4H, CH_2-3' & CH_2-5'). EIMS: *m/z* 401 (19%) $[M]^+$, 337 (29%), 241 (42%), 175 (51%), 161 (100%).

***N*-[4-(Piperidin-1-yl)phenyl]camphor-8-sulfonamide (3j)**

Buff sticky solid; Yield: 84%; Molecular formula: $C_{21}H_{30}N_2O_3S$; Mol. Wt. 390g IR (KBr, cm^{-1}) ν_{max}: 3429 (N-H stretching), 3023 (C-H stretching of aromatic ring), 1546 (C=C aromatic stretching), 1341 (-SO_2- stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 6.93 (d, J = 9.0 Hz, 2H, H-2 & 6), 6.85 (d, J = 9.0 Hz, 2H, H-3 & 5), 3.51 (m, 2H, CH_2-SO_2), 3.08 (t, J = 5.1 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.88 (t, J = 5.1 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 1.67 (m, 2H, CH_2-4'), 1.60-2.51 (m, 7H, $CHCH_2CH_2CHCH$ of camphor), 1.57 (m, 4H, CH_2-3' & CH_2-5'), 1.05 (s, 3H, -CH_3 of camphor), 0.82 (s, 3H, -CH_3 of camphor). EIMS: *m/z* 390 (19%) $[M]^+$, 326 (29%), 215 (42%), 175 (51%), 151(100%).

***N*-[4-(Piperidin-1-yl)phenyl]butane-1-sulfonamide (3k)**

Light green sticky solid; Yield: 87%; Molecular formula: $C_{15}H_{24}N_2O_2S$; Mol. Wt. 296g. IR (KBr, cm^{-1}) ν_{max}: 3427 (N-H stretching), 3021 (C-H stretching of aromatic ring), 1543 (C=C aromatic stretching), 1343 (-SO_2- stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 6.92 (d, J = 8.2 Hz, 2H, H-2 & 6), 6.82 (d, J = 8.2 Hz, 2H, H-3 & 5), 3.10 (t, J = 5.4 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.97 (t, J = 5.4 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 2.91 (t, J = 7.0 Hz, 2H, CH_2-1"), 2.05 (m, 2H, CH_2-4'), 1.81 (m, 4H, CH_2-3' & CH_2-5'),1.68-1.48 (m, 4H, CH_2-2" to CH_2-3"), 0.94 (t, J = 3.6 Hz, 3H, CH_3-4"). EIMS: *m/z* 296 (19%) $[M]^+$, 232 (29%), 175 (42%), 121 (100%).

***N*-Ethyl-*N*-[4-(piperidin-1-yl)phenyl]benzenesulfonamide (5a)**

Violet sticky solid; Yield: 80%; Molecular formula: $C_{19}H_{24}N_2O_2S$; Mol. Wt. 344g. IR (KBr, cm^{-1}) ν_{max}: 3028 (C-H stretching of aromatic ring), 1542 (C=C aromatic stretching), 1344 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.64 (dd, *J* = 2.5, 8.4 Hz, 2H, H-2" & H-6"), 7.42-7.39 (m, 1H, H-4"), 7.52-7.54 (m, 2H, H-3" & H-5"), 6.91 (d, *J* = 9.0 Hz, H-2 & 6), 6.83 (d, *J* = 9.0 Hz, H-3 & 5), 3.61 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.05 (t, *J* = 5.7 Hz, 2H, H_{ax}-2′ & H_{ax}-6′), 2.55 (t, *J* = 5.7 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 1.70 (m, 2H, CH_2-4'), 1.58 (m, 4H, CH_2-3' & CH_2-5'), 1.05 (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS: *m/z* 344 (12%) $[M]^+$, 280 (31%), 203 (24%), 141(100%).

_N_-Ethyl-_N_-[4-(Piperidin-1-yl)phenyl]-4-methylbenzene sulfonamide (5b)

Black sticky solid; Yield: 86.5%; Molecular formula: $C_{20}H_{26}N_2O_2S$; Mol. Wt. 358g. IR (KBr, cm^{-1}) ν_{max}: 3021 (C-H stretching of aromatic ring), 1542 (C=C aromatic stretching), 1344 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.58 (d, *J* = 8.4 Hz, 2H, H-2" & H-6"), 7.24 (d, *J* = 8.4 Hz, 2H, H-3" & 5"), 6.91 (d, *J* = 9.0 Hz, H-2 & 6), 6.83 (d, *J* = 9.0 Hz, H-3 & 5), 3.60 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.12 (t, *J* = 5.1 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.99 (t, *J* = 5.1 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 2.38 (s, 3H, CH_3-4"), 1.69 (m, 2H, CH_2-4'), 1.57 (m, 4H, CH_2-3' & CH_2-5'), 1.03 (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS *m/z*: 358 (8%) $[M]^+$, 294(12%), 203(31%), 155 (26%), 91(100%; loss of tropylium ion fragment).

_N_-Ethyl-_N_-[4-(Piperidin-1-yl)phenyl]-1-phenylmethane sulfonamide (5c)

Black sticky solid; Yield: 85%; Molecular formula: $C_{20}H_{26}N_2O_2S$; Mol. Wt. 359g. IR (KBr, cm^{-1}) ν_{max}: 3021 (C-H stretching of aromatic ring), 1557 (C=C aromatic stretching), 1331 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.44 (m, 5H, H-2" to H-6"), 6.93 (d, *J* = 8.4 Hz, H-2 & 6), 6.71 (d, *J* = 8.4 Hz, H-3 & 5), 4.42 (s, 2H, SO_2-CH_2), 3.59 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.11 (t, *J* = 5.4 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.89 (t, *J* = 5.4 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 1.75 (m, 2H, CH_2-4′), 1.57 (m, 4H, CH_2-3′ & CH_2-5′), 1.01 (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS: *m/z* 358 (5%) $[M]^+$, 294(23%), 203(39%), 155 (21%), 91(100%; loss of tropylium ion fragment).

_N_-Ethyl-_N_-[4-{4-(piperidin-1-yl)phenyl)acetamido]benzene sulfonamide (5d)

Shumpain sticky solid; Yield: 81%; Molecular formula: $C_{21}H_{27}N_3O_3S$; Mol. Wt. 401g. IR (KBr, cm^{-1}) ν_{max}: 3019 (C-H stretching of aromatic ring), 1537 (C=C aromatic stretching), 1333 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.65 (d, *J* = 8.7 Hz, 2H, H-2" & H-6"), 7.39 (d, *J* = 8.7 Hz, 2H, H-3" & 5"), 6.90 (d, *J* = 9.0 Hz, 2H, H-2 & 6), 6.81 (d, *J* = 9.0 Hz, 2H, H-3 & 5), 3.63 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.55 (t, *J* = 5.4 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 3.05 (t, *J* = 5.4 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 2.17 (s, 3H, CO-CH_3) 1.71 (m, 2H, CH_2-4'), 1.55 (m, 4H, CH_2-3' & CH_2-5'), 1.07 (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS *m/z*: 401 (7%) $[M]^+$, 358 (17%), 337 (52%), 203 (22%), 155 (100%).

_N_-Ethyl-_N_-(4-piperidin-1-ylphenyl)-4-acetylbenzenesulfonamide (5e)

Sea-green sticky solid; Yield: 78%; m.p 87-89 °C, Molecular formula: $C_{21}H_{26}N_2O_3S$; Mol. Wt. 386g. IR (KBr, cm^{-1}) ν_{max}: 3019 (C-H stretching of aromatic ring), 1537 (C=C aromatic stretching), 1335 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 8.01 (d, *J* = 8.7 Hz, 2H, H-2" & H-6"), 7.97 (d, *J* = 8.7 Hz, 2H, H-3" & 5"), 7.81 (d, *J* = 8.4 Hz, 2H, H-2 & 6), 7.01 (d, *J* = 8.4 Hz, 2H, H-3 & 5), 3.59 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.43 (t, *J* = 5.4 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.89 (t, *J* = 5.4 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 2.57 (s, 3H, CO-CH_3) 1.71 (m, 2H, CH_2-4'), 1.57 (m, 4H, CH_2-3' & CH_2-5'), 1.10 (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS *m/z*: 386 (15%) $[M]^+$, 343 (23%), 322 (40%), 203 (19%), 119 (100%).

_N_-Ethyl-_N_-(4-piperidin-1-ylphenyl)-2,4,6-trimethylbenzenesulfonamide (5f)

Black sticky solid; Yield: 88%; Molecular formula: $C_{22}H_{30}N_2O_2S$; Mol. Wt. 386g. IR (KBr, cm^{-1}) ν_{max}: 3021 (C-H stretching of aromatic ring), 1543 (C=C aromatic stretching), 1340 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.19 (d, *J* = 9.0 Hz, 2H, H-2 & 6), 7.13 (d, *J* = 9.0 Hz, 2H, H-3 & 5), 6.87 (s, 2H, H-3″ & H-5″), 3.63 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.45 (t, *J* = 5.1 Hz, 2H, H_{ax}-2′ & H_{ax}-6′), 2.83 (t, *J* = 5.1 Hz, 2H, H_{eq}-2′ & H_{eq}-6′), 2.63 (s, CH_3 -4″) 1.97 (m, 2H, CH_2-4′), 1.63 (m, 4H, CH_2-3′ & CH_2-5′), 1.03 (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS: *m/z* 386 (7%) $[M]^+$, 322 (19%), 203 (23%), 183 (19%), 119 (100%).

_N_-Ethyl-_N_-(4-piperidin-1-ylphenyl)-4-chlorobenzenesulfonamide (5g)

Dark green sticky solid; Yield: 85%; m.p 90-93°C, Molecular formula: $C_{19}H_{23}ClN_2O_2S$; Mol. Wt. 378g. IR (KBr, cm^{-1}) ν_{max}: 3033 (C-H stretching of aromatic ring), 1541 (C=C aromatic stretching), 1337 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.61 (d, *J* = 8.7 Hz, 2H, H-2" & H-6"), 7.49 (d, *J* = 8.7 Hz, 2H, H-3" & 5"), 6.91 (d, *J* = 9.0 Hz, 2H, H-2 & 6), 6.87 (d, *J* = 9.0 Hz, 2H, H-3 & 5), 3.63 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.07 (t, *J* = 5.1 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.89 (t, *J* = 5.1 Hz, 2H, H_{eq}-2' & H_{eq}-6'),1.65 (m, 2H, CH_2-4'), 1.59 (m, 4H, CH_2-3' & CH_2-5'), 1.0q (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS: *m/z* 378 (7%) $[M]^+$, 314 (17%), 203 (27%), 175 (15%), 111 (100%).

_N_-Ethyl-_N_-(4-piperidin-1-ylphenyl)-2,3-dihydro-1,4-benzodioxine-6-sulfonamide (5h)

Deep blue sticky solid; Yield: 86%; Molecular formula: $C_{21}H_{26}N_2O_4S$; Mol. Wt. 402g. IR (KBr, cm^{-1}) ν_{max}: 3029 (C-H stretching of aromatic ring), 1541 (C=C aromatic stretching), 1333 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.33 (dd, *J* = 2.0, 8.4 Hz, 1H, H-1"), 7.27 (d, *J* = 8.4 Hz, 1H, H-2"), 7.20 (d, *J* = 8.4Hz, 1H, H- 6"), 6.91 (d, *J* = 9.0 Hz, 2H, H-2 & 6), 6.83 (d, *J* = 9.0 Hz, 2H, H-3 & 5), 4.31-4.35 (m, 4H, O-CH_2-CH_2-O), 3.63 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.45 (t, *J* = 5.4 Hz, 2H, H_{ax}-2′ & H_{ax}-6′), 2.99 (t, *J* = 5.4 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 1.66 (m, 2H, CH_2-4'), 1.59 (m, 4H, CH_2-3' & CH_2-5'), 1.01 (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS: *m/z* 402 (11%) $[M]^+$, 338 (14%), 203 (27%), 199 (35%), 135 (100%).

_N_-Ethyl-_N_-[4-(Piperidin-1-yl)phenyl]-3,5-dichloro-2-hydroxy benzenesulfonamide (5i)

Purple coloured sticky solid; Yield: 89%; Molecular formula: $C_{19}H_{22}Cl_2N_2O_3S$; Mol. Wt. 429g. IR (KBr, cm^{-1}) ν_{max}: 3035 (C-H stretching of aromatic ring), 1527 (C=C aromatic stretching), 1335 (-SO_{2-} stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.73 (d, *J* = 2.7 Hz, 1H, H-6"), 7.67 (d, *J* = 2.7 Hz, 1H, H-4"), 7.51 (d, *J* = 7.2 Hz, 2H, H-2 & 6), 7.35 (d, *J* = 7.2 Hz, 2H, H-3 & 5), 3.65 (t, *J* = 5.1 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 3.63 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.57 (t, *J* = 5.1 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 2.01 (m, 2H, CH_2-4'), 1.83 (m, 4H, CH_2-3' & CH_2-5'), 1.03 (t, *J* = 7.2 Hz, 3H, CH_3-2'"). EIMS: *m/z* 401 (13%) $[M]^+$, 365 (22%), 269 (15%), 203 (65%), 161 (100%).

_N_-Ethyl-_N_-[4-(Piperidin-1-yl)phenyl]camphor-8-sulfonamide (5j)

Black sticky solid; Yield: 64%; Molecular formula: $C_{23}H_{34}N_2O_3S$; Mol. Wt. 418g. IR (KBr, cm^{-1}) ν_{max}: 3025 (C-H stretching of aromatic ring), 1539 (C=C stretching of aromatic ring), 1335 (-SO2-stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 6.91 (d, *J* = 9.0 Hz, 2H, H-2 & 6), 6.83 (d, *J* = 9.0 Hz, 2H, H-3 & 5), 3.60 (q, *J* = 7.2 Hz, 2H, CH_2-1'", 3.53 (m, 2H, CH_2-SO_2), 3.09 (t, *J* = 5.1 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.79 (t, *J* = 5.1 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 1.69 (m, 2H, CH_2-4'), 1.62-2.53 (m, 7H, $CHCH_2CH_2CHCH$ of camphor), 1.51 (m, 4H, CH_2-3' & CH_2-5'), 1.07 (t, *J* = 7.2 Hz, 3H, CH_3-2'"), 1.01 (s, 3H, -CH_3 of camphor), 0.82 (s, 3H, -CH_3 of camphor). EIMS: *m/z* 390 (4%) $[M]^+$, 354 (17%), 215 (22%), 203 (31%), 151(100%).

_N_-Ethyl-_N_-[4-(Piperidin-1-yl)phenyl]butane-1-sulfonamide (5k)

Green sticky solid; Yield: 82%; Molecular formula: $C_{17}H_{18}N_2O_2S$; Mol. Wt. 324g. IR (KBr, cm^{-1}) ν_{max}: 3021 (C-H stretching of aromatic ring), 1535 (C=C aromatic stretching), 1343 (-SO_2 stretching); ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 6.91 (d, *J* = 8.2 Hz, 2H, H-2 & 6), 6.85 (d, *J* = 8.2 Hz, 2H, H-3 & 5), 3.63 (q, *J* = 7.2 Hz, 2H, CH_2-1'"), 3.11 (t, *J* = 5.4 Hz, 2H, H_{ax}-2′ & $_{Hax}$-6′), 2.99 (t, *J* = 5.4 Hz, 2H, H_{eq}-2′ & H_{eq}-6′), 2.93 (t, *J* = 7.0 Hz, 2H, CH_2-1"), 2.01 (m, 2H, CH_2-4′), 1.83 (m, 4H, CH_2-3′ & CH_2-5′), 1.63-1.49 (m, 4H, CH_2-2" to CH_2-3"), 1.00 (t, *J* = 7.2 Hz, 3H, CH_3-2'"), 0.91 (t, *J* = 3.6 Hz, 3H, CH_3-4″). EIMS: *m/z* 324 (11%) $[M]^+$, 260 (17%), 203(35%), 121 (100%).

Enzyme Inhibition Assays

Acetylcholinesterase Assay

The AChE inhibition activity was performed according to the method[18] with slight modifications. Total volume of the reaction mixture was 100 µL. It contained 60 µL Na_2HPO_4 buffer with concentration of 50 mM and pH 7.7. 10 µL test compound (0.5 mM well^{-1}) was added, followed by the addition of 10 µL (0.005 unit well^{-1}) enzyme. The contents were mixed and pre-read at 405 nm. Then contents were pre-incubated for 10 min at 37ºC. The reaction was initiated by the addition of 10 µL of 0.5 mM well^{-1} substrate (acetylthiocholine iodide), followed by the addition of 10 µL DTNB (0.5 mM well^{-1}). After 15 min of incubation at 37ºC absorbance was measured at 405 nm using 96-well plate reader Synergy HT, Biotek, USA. All experiments were carried out with their respective controls in triplicate. Eserine (0.5 mM well^{-1}) was used as a positive control. The percent inhibition was calculated by the help of following equation

$$\text{Inhibition (\%)} = \frac{Control - Test}{Control} \times 100$$

IC_{50} values were calculated using EZ–Fit Enzyme kinetics software (Perrella Scientific Inc. Amherst, USA).

Butyrylcholinesterase Assay

The BChE inhibition activity was performed according to the method[18] with slight modifications. Total volume of the reaction mixture was 100 µL containing 60 µL, Na_2HPO_4 buffer, 50 mM and pH 7.7. 10 µL test compound 0.5 mM well^{-1} was added followed by the addition of 10 µL (0.5 unit well^{-1}) BChE (Sigma Inc.). The contents were mixed and pre-read at 405 nm and then pre-incubated for 10 min at 37ºC. The reaction was initiated by the addition of 10 µL of 0.5 mM well^{-1} substrate (butyrylthiocholine chloride). Followed by the addition of 10 µL DTNB, 0.5 mM well^{-1}. After 15 min of incubation at 37ºC, absorbance was measured at 405 nm using 96-well plate reader Synergy HT, Biotek, USA. All experiments were carried out with their respective controls in triplicate. Eserine (0.5 mM well^{-1}) was used as positive control. The percent inhibition was calculated by the help of following equation.

$$\text{Inhibition (\%)} = \frac{Control - Test}{Control} \times 100$$

IC_{50} values were calculated using EZ–Fit Enzyme kinetics software (Perrella Scientific Inc. Amherst, USA).

Lipoxygenase Assay

Lipoxygenase (LOX) activity was assayed according to the method[19-21] with slight modifications. A total volume of 200 µL lipoxygenase assay mixture contained 150 µL sodium phosphate buffer (100 mM, pH 8.0), 10 µL test compound and 15 µL purified lipoxygenase enzyme (600 units well^{-1},Sigma Inc.). The contents were mixed and pre-read at 234 nm and preincubated for 10 minutes at 25°C. The reaction was initiated by addition of 25 µL substrate solution. The change in absorbance was observed after 6 min at 234 nm using 96-well plate reader Synergy HT, Biotek, USA. All reactions were performed in triplicates. The positive and negative controls were included in the assay. Baicalin (0.5 mM well^{-1}) was used as a positive control. The percentage inhibition (%) was calculated by formula given below.

$$\text{Inhibition (\%)} = \frac{Control - Test}{Control} \times 100$$

Where Control =Total enzyme activity without inhibitor

Test = Activity in the presence of test compound

IC_{50} values were calculated using EZ–Fit Enzyme Kinetics software (Perrella Scientific Inc. Amherst, USA).

DPPH Assay

The stable 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) was used for the determination of antioxidant activity. Different concentrations of compounds in respective solvents were added at an equal volume (10µl) to 90 µl of 100 µM methanolic DPPH in a total volume of 100 µl in 96-well plates. The contents were mixed and incubated at 37°C for 30 minutes. The absorbance was measured at 517nm using Synergy HT BioTek® USA microplate reader. Quercetin and L-ascorbic acid were used as standard antioxidants. The experiments were carried out in triplicates. IC_{50} values were calculated using EZ-Fit5 Perrella Scientific Inc. Amherst USA software. The decrease in absorbance indicates increased radical scavenging activity which was determined by the following formula.[22]

$$\text{Antiradical activity (\% Inhibition)} = \frac{Control - Test}{Control} \times 100$$

Statistical Analysis

All the measurements were done in triplicate and statistical analysis was performed by Microsoft Excel 2003. Results are presented as mean ± sem.

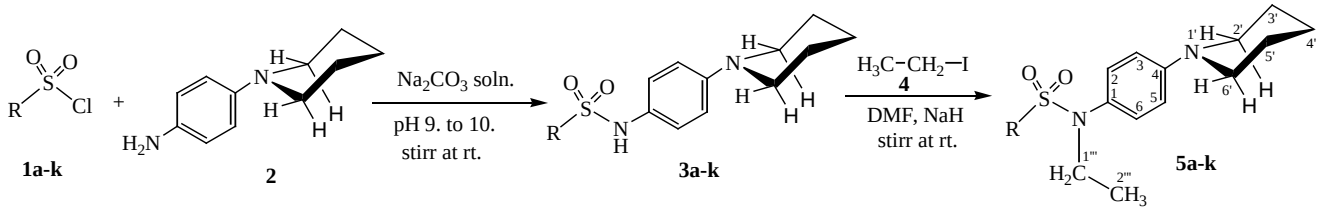
RESULTS AND DISCUSSION

The objective of our research work was to synthesize sulfonamides and further its *N*-ethyl substituted derivatives and to screen out their enzymatic activities. First, a series of sulfonamides (**3a-k**) were synthesized by the reaction of different sulfonyl chlorides (**1a-k**) with 4-(piperidin-1-yl)aniline (**2**) under dynamic pH control in aqueous media.[23,24] Further, *N*-ethyl substituted sulfonamides (**5a-k**) were obtained by treating each of the sulfonamide with electrophile, ethyl iodide in the presence of *N,N*-dimethyl formamide (DMF) and sodium hydride (NaH) which acts as a base. Reactants completely converted into products by simple stirring after 1-3 hrs. Precipitates were quenched by treating with cold water and recrystallized by using methanol (Scheme-1). Compound **3a** was synthesized as dirty green powder. The molecular formula $C_{17}H_{20}N_2O_2S$ was established by molecular ion peak at *m/z* 316 in EI-MS and by counting the number of protons in its ^{1}H-NMR spectrum. The IR spectrum showed absorption bands at 1441cm^{-1}, 3024 cm^{-1}, 3023 cm^{-1} and 1546 cm^{-1} which were assigned to, -SO_2 (stretching of sulfonyl group), SO_2-N-H (stretching of sulfonamide), C-H (aromatic stretching) and C=C (stretching of aromatic ring) respectively. The EI-MS gave a distinct peak at *m/z* 252 after the removal of -SO_2 group and further a peak was observed at *m/z* 141 which showed the presence of benzenesulfonyl group in the molecule. In the aromatic region of the ^{1}H-NMR spectrum signals appeared at δ 7.68 (dd, *J* = 2.5, 8.4 Hz, 2H, H-2" & H-6"), 7.46-7.41 (m, 1H, H-4") and 7.54-7.51 (m, 2H, H-3" & H-5") which were assigned to the mono substituted aromatic ring. The two signals appeared at δ 6.92 (d, *J* = 9.0 Hz, 2H, H-2 & 6) and 6.82 (d, *J* = 9.0 Hz, 2H, H-3 & 5), due to large coupling constant and each signal integrated two protons showed that the presence of para disubstituted aromatic ring. In the aliphatic region of the ^{1}H-NMR spectrum, signals appeared at 3.05 (t, *J* = 5.7 Hz, 2H, H_{ax}-2' & H_{ax}-6'), 2.55 (t, *J* = 5.7 Hz, 2H, H_{eq}-2' & H_{eq}-6'), 1.70 (m, 2H, CH_2-4') and 1.58 (m, 4H, CH_2-3' & CH_2-5') which indicated the presence of piperidine nucleus in the molecule. On the basis of above cumulative evidences, the structure of **3a** was assigned as *N*-[4-(Piperidin-1-yl)phenyl]benzenesulfonamide. Similarly, the structures of other compounds were characterized by ^{1}H-NMR, IR and mass spectral data as described in experimental section.

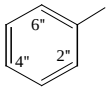
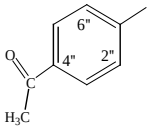
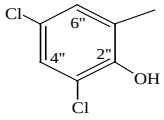
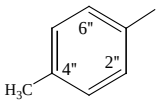
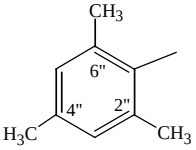
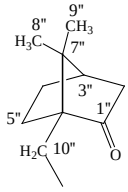
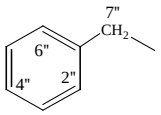
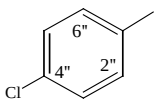
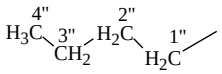
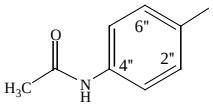
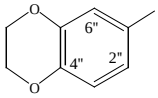
Enzyme inhibition activity

The screening of these synthesized compounds against acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and lipoxygenase (LOX) enzymes revealed that these molecules exhibited good inhibitory potential against acetylcholinesterase and butyrylcholinesterase as it was evident from their IC_{50} values. The results are depicted in Table-1 & Table-2. It is clearly evident from results in table-1 that the compounds *N*-[4-{(4-Piperidin-1-yl)phenyl)acetamido]benzenesulfonamide (**3d**) and *N*-(4-Piperidin-1-ylphenyl)-3,5-dichloro-2-hydroxybenzenesulfonamide **(3i)** were found to be promising inhibitors against acetylcholinesterase enzyme having IC_{50} value of 77.11±0.06 and 81.33±0.09 µmoles/L respectively, relative to Eserine, a reference standard with IC_{50} value of 0.04±0.001 µmoles, probably due to 4-acetamidophenyl and 2-hydroxy-3,5-dichloropheyl groups respectively in these molecules. From table-2, the compounds **5c, 5d** and **5f** were identified as good inhibitors having IC_{50} value of 35.41±0.15, 66.31±0.21 and 68.31±0.6309 µmoles/L respectively, as compared to reference standard. The enhanced activity might be due to *N*-substitution of

ethyl group in these sulfonamides. The screening against butyrylcholinesterase enzyme exposed that the compounds **3f** and **3b** (Table-1) exhibited talented inhibitory potential having IC_{50} value of 40.41±0.61 and 45.11±0.09 µmoles/L as compared to standard with IC_{50} value of 0.85±0.0001 µmoles/L, probably due to the present of 2,4,6-trimethylphenyl and 4-methylphenyl groups respectively in these molecules. However, some compounds (Table-1) showed weak inhibition against lipoxygenase enzyme but all other compounds remained inactive. Similarly the activity of compounds **5i** and **5j** (Table-2) showed excellent inhibitory potential having IC_{50} values of 27.11±0.21 and 35.61±0.05 µmoles/L respectively, as compared to reference standard. This enhanced activity might also be due to *N*-ethyl substitution of sulfonamides. DPPH is a stable free radical at room temperature. DPPH radical is scavenged by antioxidants through the donation of a proton and form reduced DPPH. The colour changes from violet to yellow after reduction of DPPH, and it can be quantified by decrease of absorbance at wavelength 517 nm. Radical scavenging activity increased with increasing percentage of the free radical inhibition. The colour change from violet to yellow and fall in absorbance of the stable radical DPPH was measured for three different concentrations of samples, and the results are shown in table-1. These results revealed that the compound *N*-[4-{4-(Piperidin-1-yl)phenyl)acetamido]benzenesulfonamide (**3d)** showed good % scavenging of DPPH. One more concrete information from the data (Table-1 & 2), reflected that all the *N*-ethyl substituted sulfonamides (**5a-k)** lose their antioxidant activity. The IC_{50} value for each sample was calculated from the curves plotted. IC_{50} is the concentration of samples causing 50 percent inhibition of absorbance and lower its value means greater antioxidant activity of the samples.



1a-k **2** **3a-k** **5a-k**

Compound	R	Compound	R	Compound	R
3a, 5a		**3e, 5e**		**3i, 5i**	
3b, 5b		**3f, 5f**		**3j, 5j**	
3c, 5c		**3g, 5g**		**3k, 5k**	
3d, 5d		**3h, 5h**			

Scheme 1: Outline for the synthesis of sulfonamides 3a-k & 5a-k

Table 1: Bioactivity studies of sulfonamides (3a-k)

Sample Code	DPPH		AchE		BchE		LOX	
	Inhibition (%) Conc./well (0.5 mM)	IC_{50} µM	Inhibition (%) Conc./well (0.5 mM)	IC_{50} (µmol.)	Inhibition (%) Conc./well (0.5 mM)	IC_{50} µM	Inhibition (%) Conc./well (0.5 mM)	IC_{50} µM
3a	24.78±0.51	139.41±0.18	71.64±0.11	132.21±0.04	93.67±0.12	51.61±0.04	11.27±0.01	NIL
3b	71.07±0.87	159.11±0.14	82.94±0.41	89.51±0.04	92.66±0.41	45.11±0.09	64.44±0.17	270.51±0.04
5c	76.31±0.49	134.41±0.51	69.08±0.44	110.71±0.62	88.19±0.23	81.11±0.03	69.60±0.19	304.91±0.01
3d	89.53±0.32	48.11±0.56	79.96±0.51	77.11±0.06	75.52±0.61	130.81±0.51	3.40±0.11	NIL
3e	77.14±0.13	134.51±0.08	79.32±0.05	125.71±0.21	95.91±0.99	39.81±0.71	39.20±0.13	NIL
3f	73.69±0.11	153.51±0.61	66.10±0.51	230.81±0.62	91.74±0.55	40.41±0.61	63.03±0.51	294.51±0.11
3g	75.67±0.21	142.71±0.21	78.89±0.24	214.11±0.71	83.71±0.52	122.21±0.26	75.23±0.41	142.71±0.21
3h	59.77±0.81	348.21±0.18	70.36±0.01	197.21±0.81	95.83±0.74	50.11±0.61	61.27±0.91	339.41±0.18
3i	69.92±0.17	184.11±0.25	82.52±0.14	81.33±0.09	79.38±0.26	143.41±0.33	19.84±0.62	NIL
3j	65.95±0.75	260.51±0.04	84.43±0.29	124.21±0.51	89.85±0.24	132.41±0.36	43.78±0.25	NIL
3k	83.59±0.89	117.51±0.15	87.21±0.11	113.11±0.25	94.29±0.48	47.61±0.62	61.38±0.89	324.11±0.15
Control	Quercetin 93.21±0.97	16.96±0.14	Eserine 91.29±1.17	0.04±0.001	Eserine 82.82±1.09	0.85±0.0001	Baicalein 93.79±1.27	22.4±1.3

Note: IC_{50} values (concentration at which there is 50% enzyme inhibition) of compounds were calculated using EZ–Fit Enzyme kinetics software (Perella Scientific Inc. Amherst, USA).

AChE = Acetyl cholinesterase; BChE = Butyrylcholinesterase; LOX = Lipoxygenase; DPPH = 1,1-diphenyl-2-picrylhydrazyl radical.

Table 2: Bioactivity studies of *N*-ethyl substituted sulfonamides (5a-k)

Sample Code	DPPH		AchE		BchE		LOX	
	Inhibition (%) Conc./well (0.5 mM)	IC_{50} µM	Inhibition (%) Conc./well (0.5 mM)	IC_{50} (µmol.)	Inhibition (%) Conc./well (0.5 mM)	IC_{50} µM	Inhibition (%) Conc./well (0.5 mM)	IC_{50} µM
5a	16.00±0.29	NIL	63.29±0.55	164.11±0.17	94.25±0.14	38.81±0.05	58.54±0.51	<300
5b	17.04±0.11	NIL	54.37±0.42	<300	80.87±0.44	99.51±0.18	58.74±0.71	<300
5c	34.07±0.08	NIL	93.45±0.15	35.41±0.15	92.96±0.23	60.41±0.15	29.73±0.11	NIL
5d	12.83±0.31	NIL	83.73±0.76	66.31±0.21	86.97±0.31	69.81±0.11	61.93±0.34	<300
5e	20.35±0.21	NIL	73.12±0.19	136.11±0.28	85.21±0.56	75.21±0.28	32.51±0.75	NIL
5f	16.08±0.42	NIL	88.69±0.67	68.31±0.63	97.18±0.45	54.71±0.63	59.16±0.34	<300
5g	14.31±0.27	NIL	83.04±0.16	138.71±0.36	83.80±0.17	135.51±0.36	31.69±0.28	NIL
5h	16.89±0.95	NIL	65.97±0.07	111.11±0.36	89.20±0.71	49.91±0.07	30.86±0.36	NIL
5i	17.99±0.29	NIL	72.62±0.11	133.61±0.71	94.60±0.05	27.11±0.21	54.22±0.19	<300
5j	16.00±0.29	NIL	63.29±0.55	164.11±0.17	94.25±0.14	38.81±0.05	58.54±0.51	<300
5k	13.94±0.53	NIL	64.46±0.61	138.61±0.17	69.31±0.21	142.61±0.17	33.23±0.86	NIL
Control	Quercetin 93.21±0.97	16.96±0.14	Eserine 91.29±1.17	0.04±0.001	Eserine 82.82±1.09	0.85±0.0001	Baicalein 93.79±1.27	22.4±1.3

Note: IC_{50} values (concentration at which there is 50% enzyme inhibition) of compounds were calculated using EZ–Fit Enzyme kinetics software (Perella Scientific Inc. Amherst, USA).

AChE = Acetyl cholinesterase; BChE = Butyrylcholinesterase; LOX = Lipoxygenase; DPPH = 1,1-diphenyl-2-picrylhydrazyl radical.

CONCLUSION

The proposed structures of the synthesized compounds are well supported by spectroscopic data. From the enzyme inhibition data (Table-1 & 2), it was obvious that the compounds possessed moderate to talented activity against acetylcholinesterase, butyrylcholinesterase and lipoxygenase enzymes which was evident from their IC_{50} values, relative to the standard used. All compounds showed good scavenging activity against DPPH but all *N*-ethyl substituted sulfonamides stayed inactive. Hence, on the basis of aforesaid results, it was generally concluded that the derivatives without *N*-ethyl substitution seem relatively more suitable drug candidates for the treatment of Alzheimer's disease and other associated diseases. These entrants can also be helpful for the treatment of a variety of disorders such as bronchial asthma, inflammation, cancer and autoimmune diseases.

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