Synthesis of bioactive sulfonamides bearing piperidine nucleus with talented activity against cholinesterase.

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Abstract

In the present study, a series of new *N*-alkyl-*N*-(piperidin-1-yl)benzenesulfonamide (**1a-f)** and *N*-aryl/alkyl substitued-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (**3a-n)** derivatives were synthesized. These derivatives were prepared by reacting 1-amino piperidine with benzene sulfonyl chloride to afford parent compound *N*-(piperidin-1-yl)benzenesulfonamide **(1),** followed by substitution at nitrogen with different electrophilic reagents in the presence of sodium hydride to give a series of derivatives **1a-f** and **3a-n.** The structures of the synthesized compounds were confirmed based on ^{1}H-NMR, IR and mass spectral data. The synthesized compounds were screened against acetylcholinesterase (AChE), butyrylcholinesterase (BChE) enzymes and almost all the compounds exhibited promising activities.

Keywords: 1-aminopiperidine, benzenesulfonyl chloride, cholinesterase

INTRODUCTION

The piperidine nucleus is a ubiquitous structural feature of biologically active compounds and numerous secondary metabolites, for example (S)-pipecolic acid a non proteinogenic aminoacid associated with epilepsy (Sanchez-Sancho et al., 1998; Nithiya et al., 2011; Adger et al., 1996 and Daly et al., 1986). Piperidine bearing compounds have diverse applications in commercial and medicinal area. Piperidine and Pyrrolidine ring containing compounds were evaluated for their effect on plasma glucose level (Kozikowski et al., 1998). Insulin normalization and treatment of cocaine abuse (Brau et al., 2000). Sulfonamides are famous for enzyme inhibition such as carbonic anhydrase, cysteine protease, HIV protease and cyclooxygenase (Supuran et al., 2003). Worldwide

researchers are trying to synthesize new drugs with better pharmacokinetic and dynamic properties with less adverse effects.

Most of the drugs used for the treatment of Alzheimer's disease are acetylcholinesterase inhibitors. Acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (BChE, EC 3.1.1.8) comprise a family of enzymes which include serine hydrolases. The different specificities for substrates and inhibitors for these enzymes are due to the differences in amino acid residues of the active sites of AChE and BChE. The enzyme system 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 (Cygler et al., 1993 and Tougu 2001). It has been found that BChE is present in significantly higher quantities in Alzheimer's plaques than in the normal age related non dementia of brains. Antagonists of the histamine H_1 and H_2 receptors have been successful as blockbuster drugs for treating allergic conditions and gastric ulcers, respectively. Cholinesterase inhibitors increase the amount 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 (Gauthier 2001 and Bertaccini 1982). Lipoxygenase enzymes contain iron in their structural frame work and are involved in dioxygenation of lipids, consisting of poly unsaturated fatty acids. Lipoxygenases perform a key role in the synthesis of leukotrienes, which are responsible for pathophysiology of different allergic diseases. Lipoxygenase inhibitors are required to cure these allergic and inflammatory diseases (Roussaki et al., 2010 and Aziz-ur-Rehman et al., 2004)).

Pharmacological potential of the heterocyclic compounds motivated chemists to synthesize piperidine derivatives with improved biological activities (Li et al., 2007). In continuation of our previous work on sulfonamides as possible therapeutic entrants (Aziz-ur-Rehman et al., 2011), here we report the synthesis of new sulfonamides bearing piperidine moiety having talented to moderate inhibitory potential against butyrylcholinesterase enzyme.

MATERIAL AND METHODS

General experimental part

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-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.

1-aminopiperidine, benzenesulfonyl chloride, bromoacetyl bromide, substituted/ unsubstituted aromatic amines and the other electrophilic reagents were obtained from commercial suppliers. All the employed solvents were of analytical grade.

Procedure for the synthesis of N-(piperidin-1-yl)benzenesulfonamide in aqueous medium (1):

1-amino piperidine (**a**) (2.6 mL; 10.0 mmol) was suspended in 50 mL water and the pH was maintained at 9.0 by adding basic aqueous solution of a Na_2CO_3 at 0-5^oC. Then, benzenesulfonyl chloride (**b**) (2.9 mL; 10.0 mmol) was added in the reaction mass slowly over 10-15-min. After completion of the 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 2 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 compound **1** on drying.

General procedure for the synthesis of compounds 1a–f:

To a solution of compound **1** (0.2 g, 8.33 mmol) in *N*,*N*-dimethyl formamide (DMF) (5 mL) was added sodium hydride (0.01 g, 0.40 mmol) at 0–5 °C. After completion of the addition, the temperature of the reaction mass was raised to RT and stirred for 15 min. The corresponding alkyl halide (8.33 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 cooled to room temperature and quenched with cold water (200 mL). The obtained solid was filtered, washed with water and dried to yield the corresponding *N*-alkyl derivatives **1a**–**f**.

The corresponding alkyl halides used for the reactions were ethyl iodide, allyl iodide, benzyl chloride, 4-bromobenzyl bromide, 2-phenyl ethyl iodide and 3-phenyl propyl iodide.

General procedure for the synthesis of compounds 2a–n:

The calculated amount of substituted aromatic amines/ aromatic alkyl amines (11.00 mmoles) was taken in an iodine flask containing 10 mL of distilled water and 5% Na_2CO_3 solution was added to adjust the pH 8.0 to 9.0. After adjusting the pH, the temperature of the reaction mass was maintained at 0-5^oC and stirred for 30 min. The bromoacetyl bromide (1 mL; 11.00 mmoles) was further poured drop wise in the reaction mass in 2-5 min at 0-5^oC. After completion of the addition, the iodine flask was vigorously shaken (manually) till the solid precipitates formed and the temperature of the reaction was allowed to rise slowly to room temperature. The solid precipitate was further stirred for 45 min. The progress of reaction completion was monitored by TLC (*n*-hexane : ethyl acetate : 70 : 30). After complete conversion, the obtained solid was filtered, washed with distilled water and dried to yield the corresponding electrophile *N*-aryl/alkyl-substituted-2-bromoacetamide **2a**–**n**.

General procedure for the synthesis of N-substituted-2-[(phenylsulfonyl) (piperidin-1-yl)amino] acetamide (3a–n):

To a solution of compound **1** (0.1 g, 0.40 mmol) in DMF (5 mL) was added sodium hydride (0.01 g, 0.40 mmol) in small portions over 2-5 min at 0–5 °C. After addition, the temperature was maintained at RT and stirred for 15 min. The corresponding *N*-substituted aryl/alkyl-2-bromoacetamide (0.09 g, 0.40 mmol) was added into the reaction mixture slowly and stirred for 10-15 min. The reaction mixture was then heated to 50^oC and stirred at this temperature 30-40 min; progress was monitored by TLC. After completion of reaction, mixture was cooled to RT and quenched with cold water (50 mL). The acquired precipitation was filtered, washed with water and dried to acquire the resultant derivatives. In some cases, the solid precipitation was not formed in the flask then compound was extracted through solvent extraction method by chloroform/ ethyl acetate to yield the corresponding *N*-substituted-2-[(phenylsulfonyl)(piperidin-1-yl)amino] acetamide **(3a–m)** derivatives.

SPECTRAL CHARACTERIZATION OF THE SYNTHESIZED COMPOUNDS:

***N*-(piperidin-1-yl) benzenesulfonamide (1):**

IR (KBr, cm^{-1}): ν_{max}: 3430 (N-H stretching), 3024 (C-H stretching of aromatic ring), 1546 (C=C stretching of aromatic ring), 1341 (-SO_{2-} stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.90

(dd, *J* = 8.7, 1.5 Hz, 2H, H-2' & H-6'), 7.65 (m, 2H, H-3' & H-5'), 7.52 (m, 1H, H-4'), 2.96 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.61 (m, 2H, CH_2-4), 1.44 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 240 (24%) $[M]^+$, 176 (37%), 156 (54%), 141 (100%).

***N*-ethyl-N-(piperidin-1-yl) benzenesulfonamide (1a):**

IR (KBr, cm^{-1}): ν_{max}: 2915 (-CH_2- stretching), 3029 (C-H stretching of aromatic ring), 1541 (C=C stretching of aromatic ring), 1337 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.90 (dd, *J* = 8.4, 1.2 Hz, 2H, H-2' & H-6'), 7.65 (m, 2H, H-3' & H-5'), 7.52 (m, 1H, H-4'), 2.95 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.61 (*m*, 2H, CH_2-4), 1.44 (m, 4H, CH_2-3 & CH_2-5), 3.20 (q, *J* = 7.5 Hz, 2H, CH_2-1''), 1.20 (t, *J* = 7.5, 3H, CH_3-2''). EIMS *m/z*: 268 (19%) $[M]^+$, 204 (34%), 184 (47%), 127 (100%).

***N*-Allyl-*N*-(piperidin-1-yl)benzenesulfonamide (1b):**

IR (KBr, cm^{-1}): ν_{max}: 2919 (-CH_2- stretching), 3035 (C-H stretching of aromatic ring), 1543 (C=C stretching of aromatic ring), 1335 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.90 (dd, *J* = 8.7, 1.5 Hz, 2H, H-2' & H-6'), 7.65 (m, 2H, H-3' & H-5'), 7.52 (m, 1H, H-4'), 5.78 (m, 1H, H-2''), 5.03 (dd, *J* =1.6, 17.3 Hz, 1H, H_b-3''), 4.96 (dd, *J* =1.2, 10.0 Hz, 1H, H_a-3''), 4.47 (s, 2H, CH_2-1''), 3.10 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.61 (m, 2H, CH_2-4), 1.44 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 280 (15%) $[M]^+$, 216 (35%), 239 (22%), 196 (55%), 139 (100%).

***N*-Benzyl-*N*-(piperidin-1-yl)benzenesulfonamide (1c):**

IR (KBr, cm^{-1}): ν_{max}: 2919 (-CH_2- stretching), 3035 (C-H stretching of aromatic ring), 1543 (C=C stretching of aromatic ring), 1335 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.90 (dd, *J* = 8.7, 1.5 Hz, 2H, H-2' & H-6'), 7.65 (m, 2H, H-3' & H-5'), 7.52 (m, 1H, H-4'), 7.48 (m, 2H, H-3'' & H-5''), 7.25 (m, 1H, H-4''), 7.11 (d, *J* = 7.00 Hz, 2H, H-2'' & H-6''), 4.47 (s, 2H, CH_2-7''), 3.10 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.61 (m, 2H, CH_2-4), 1.44 (m, 4H, CH_2-3 & CH_2-5), EIMS *m/z*: 330 (23%) $[M]^+$, 266 (44%), 239 (25%), 246 (65%), 91 (100%).

***N*-(4-bromobenzyl)-*N*-(piperidin-1-yl)benzenesulfonamide (1d):**

IR (KBr, cm^{-1}): ν_{max}: 2923 (-CH_2- stretching), 3029 (C-H stretching of aromatic ring), 1549 (C=C stretching of aromatic ring), 1329 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.68 (dd, *J* = 8.7, 1.5 Hz, 2H, H-2' & H-6'), 7.54 (m, 2H, H-3' & H-5'), 7.46 (d, *J* = 8.0 Hz, 2H, H-3'' & H-5''), 7.39 (m, 1H, H-4'), 7.02 (d, *J* = 8.0 Hz, 2H, H-2'' & H-6''), 4.47 (s, 2H, CH_2-7''), 3.14 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.71 (m, 2H, CH_2-4), 1.56 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 409 (13%) $[M]^+$, 345 (29%), 325 (33%), 268 (49%), 171 (100%).

***N*-[(2- Phenylethyl)-*N*-Pipiridino benzene sulfonamide (1e):**

IR (KBr, cm^{-1}): ν_{max}: 2921 (-CH_2- stretching), 3034 (C-H stretching of aromatic ring), 1541 (C=C stretching of aromatic ring), 1332 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.86 (dd, 2H, *J* = 7.2, 1.5 Hz, H-2' & H-6'), 7.69 (m, 2H, H-3' & H-5'), 7.61 (m, 1H, H-4'), 7.17-7.21 (m, 5H, H-2''' to H-6'''), 3.55 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 3.15 (t, *J* = 5.4 Hz, 2H, CH_2-8''), 2.55 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 2.66 (t, *J* = 5.4 Hz, 2H, CH_2-7''), 1.61 (m, 2H, CH_2-4), 1.44 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 344 (16%) $[M]^+$, 280 (35%), 239 (54%), 260 (74%), 105 (100%).

***N*-(3-phenylpropyl)-*N*-(piperidin-1-yl)benzenesulfonamide (1f):**

IR (KBr, cm^{-1}): ν_{max}: 2917 (-CH_2- stretching), 3037 (C-H stretching of aromatic ring), 1543 (C=C stretching of aromatic ring), 1323 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.86 (dd, *J* = 7.2, 1.5 Hz, 2H, H-2' & H-6'), 7.69 (m, 2H, H-3' & H-5'), 7.61 (m, 1H, H-4'), 7.17 (m, 5H, H-2'' to H-6''), 3.55 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 3.15 (t, *J* = 5.4 Hz, 2H, CH_2-9''), 2.55 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 2.66 (t, *J* = 5.4 Hz, 2H, CH_2-7''), 1.93 (m, 2H, CH_2-8''), 1.61 (m, 2H, CH_2-4), 1.44 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 358 (16%) $[M]^+$, 294 (35%), 274 (54%), 239 (74%), 141 (100%).

***N*-(2-methylphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3a):**

IR (KBr, cm^{-1}): ν_{max}: 3450 (N-H stretching), 3015 (C-H stretching of aromatic ring), 2912 (-CH_2- stretching), 1526 (C=C stretching of aromatic ring), 1337 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.09 (s, 1H, N-H), 7.98 (dd, *J* = 8.7, 1.5 Hz, 2H, H-2' & H-6'), 7.73 (m, 2H, H-3' & H-5'), 7.61 (m, 1H, H-4'), 7.11-7.28 (m, 4H, H-3''' to H-6'''), 4.04 (s, 2H, CH_2-2''), 3.14 (t, *J* =

5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 2.19 (s, 3H, CH_3-2'''), 1.71 (m, 2H, CH_2-4), 1.56 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 387 (16%) $[M]^+$, 323 (35%), 372 (54%), 281 (74%), 105 (100%).

***N*-(2-Methoxyphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3b):**

IR (KBr, cm^{-1}): ν_{max}: 3443 (N-H stretching), 3019 (C-H stretching of aromatic ring), 2923 (-CH_2-stretching), 1531 (C=C stretching of aromatic ring), 1325 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.02 (*s*, 1H, N-H), 7.74 (dd, *J* = 6.6, 1.8 Hz, 2H, H-2', H-6'), 7.61 (m, 2H, H-3' & H-5'), 6.95-6.99 (m, 4H, H-3''' to H-6'''), 6.80 (m, 1H, H-4'), 3.90 (s, 3H, CH_3-2'''), 4.09 (s, 2H, CH_2-2''), 2.96 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.71 (m, 2H, CH_2-4), 1.61 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (13%) $[M]^+$, 372 (43%), 281 (49%), 239 (71%), 141 (100%).

***N*-(3-Methoxyphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3c):**

IR (KBr, cm^{-1}): ν_{max}: 3440 (N-H stretching), 3021 (C-H stretching of aromatic ring), 2920 (-CH_2-stretching), 1529 (C=C stretching of aromatic ring), 1323 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.13 (*s*, 1H, N-H), 7.72 (dd, *J* = 6.6, 1.8 Hz, 2H, H-2' & H-6'), 7.63 (m, 2H, H-3' & H-5'), 7.23 (m, 1H, H-4'), 7.11 (t, *J* = 8.1 Hz, 1H, H-5'''), 7.09 (dd, *J* = 8.1, 1.2 Hz, 1H, H-6'''), 6.76 (d, *J* = 1.5 Hz, 1H, H-2'''), 6.52 (dd, *J* = 8.1, 1.2 Hz, 1H, H-4'''), 4.15 (s, 2H, CH_2-2''), 3.92 (s, 3H, CH_3-3'''), 2.92 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.43 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.73 (m, 2H, CH_2-4), 1.60 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (10%) $[M]^+$, 372 (32%), 281 (54%), 239 (61%), 141 (100%).

***N*-(4-Methoxyphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3d):**

IR (KBr, cm^{-1}): ν_{max}: 3439 (N-H stretching), 3015 (C-H stretching of aromatic ring), 2925 (-CH_2-stretching), 1531 (C=C stretching of aromatic ring), 1329 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.19 (s, 1H, N-H), 7.80 (dd, *J* = 6.6, 1.8 Hz, 2H, H-2' & H-6'), 7.65 (m, 2H, H-3' & H-5'), 7.28 (m, 1H, H-4'), 6.85 (d, *J* = 9.0 Hz, 2H, H-2''' & H-6'''), 6.67 (d, *J* = 8.7 Hz, 2H, H-5''' & H-3'''), 4.07 (s, 2H, CH_2-2''), 3.91 (s, 3H, CH_3-4'''), 2.94 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 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*: 401 (17%) $[M]^+$, 372 (28%), 281 (51%), 239 (54%), 141 (100%).

***N*-Methyl-*N*-(4-hydroxyphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3e):**

IR (KBr, cm^{-1}): ν_{max}: 3029 (C-H stretching of aromatic ring), 2940 (-CH_2- stretching), 1537 (C=C stretching of aromatic ring), 1319 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.79 (dd, *J* = 6.6, 1.8 Hz, 2H, H-2' & H-6'), 7.62 (m, 2H, H-3' & H-5'), 7.30 (m, 1H, H-4'), 6.91 (d, *J* = 9.0 Hz, 2H, H-2''' & H-6'''), 6.71 (d, *J* = 8.7 Hz, 2H, H-3''' & H-5'''), 4.13 (s, 2H, CH_2-2''), 3.17 (s, 3H, CH_3-7), 2.93 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.45 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.69 (m, 2H, CH_2-4), 1.55 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 403 (13%) $[M]^+$, 339 (27%), 281 (57%), 239 (71%), 93 (100%).

***N*-benzyl-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3f):**

IR (KBr, cm^{-1}): ν_{max}: 3431 (N-H stretching), 3018 (C-H stretching of aromatic ring), 2945 (-CH_2-stretching), 1529 (C=C stretching of aromatic ring), 1323 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.10 (*s*, 1H, N-H), 7.90 (dd, *J* = 6.7, 1.5 Hz, 2H, H-2' & H-6'), 7.60-7.63 (m, 5H, H-2''' to H-6'''), 7.54 (m, 2H, H-3' & H-5'), 7.27 (m, 1H, H-4'), 4.35 (s, 2H, CH_2-2''), 3.24 (s, 2H, CH_2-7'''), 2.95 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.61 (*m*, 2H, CH_2-4), 1.56 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 387 (23%) $[M]^+$, 323 (45%), 303 (59%), 281 (73%), 91 (100%).

***N*-(2-phenylethyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3g):**

IR (KBr, cm^{-1}): ν_{max}: 3437 (N-H stretching), 3023 (C-H stretching of aromatic ring), 2932 (-CH_2-stretching), 1521 (C=C stretching of aromatic ring), 1327 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.19 (1H, s, N-H), 7.91 (2H, dd, *J* = 6.7, 1.5 Hz, H-2' & H-6'), 7.53 (2H, m, H-3' & H-5'), 7.19-7.26 (m, 2H, H-2''' to H-6'''), 7.26 (m, 1H, H-4'), 4.33 (s, 2H, CH_2-2''), 3.22 (t, *J* = 6.5 Hz, 2H, CH_2-8'''), 2.94 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.76 (t, *J* = 6.5 Hz, 2H, CH_2-7'''), 2.48 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.59 (m, 2H, CH_2-4), 1.53 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (17%) $[M]^+$, 337 (31%), 317 (69%), 105 (84%), 91 (100%).

***N*-(2-methoxy-5-chlorophenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3h):**

IR (KBr, cm^{-1}): ν_{max}: 3429 (N-H stretching), 3019 (C-H stretching of aromatic ring), 2943 (-CH_2-stretching), 1535(C=C stretching of aromatic ring), 1325 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.25 (s, 1H, N-H), 8.32 (d, *J* = 2.4 Hz, 1H, H-6'''), 7. 89 (dd, *J* = 7.2, 1.5 Hz,

2H, H-2', H-6'), 7.73 (m, 2H, H-3', H-5'), 7.61 (m, 1H, H-4'), 7.01 (dd, *J* = 8.7, 2.1 Hz, 1H, H-4'''), 6.94 (d, *J* = 8.7 Hz, 1H, H-3'''), 3.90 (s, 2H, CH_2-2''), 2.95 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, J = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.61 (m, 2H, CH_2-4), 1.44 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 437 (13%) $[M]^+$, 373 (25%), 353 (59%), 281 (73%), 141 (100%).

***N*-(2,3-dimethylphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3i):**

IR (KBr, cm^{-1}): ν_{max}: 3440 (N-H stretching), 3032 (C-H stretching of aromatic ring), 2941 (-CH_2- stretching), 1523 (C=C stretching of aromatic ring), 1318 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.17 (*s*, 1H, N-H), 7.98 (dd, *J* = 8.7, 1.5 Hz, 2H, H-2' & H-6'), 7.73 (m, 2H, H-3' & H-5'), 7.61 (m, 1H, H-4'), 7.32 (d, *J* = 7.5, 1H, H-6'''), 7.05-7.10 (m, 2H, H-4''' & H-5'''), 4.02 (s, 2H, CH_2-2''), 3.14 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 2.28 (s, 3H, CH_3-3'''), 2.14 (s, 3H, CH_3-2'''), 1.71 (2H, m, CH_2-4), 1.56 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (15%) $[M]^+$, 337 (19%), 317 (43%), 141 (100%), 105 (61%).

***N*-(2,4-dimethylphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3j):**

IR (KBr, cm^{-1}): ν_{max}: 3438 (N-H stretching), 3029 (C-H stretching of aromatic ring), 2939 (-CH_2- stretching), 1521 (C=C stretching of aromatic ring), 1315 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.45 (s, 1H, N-H), 7.97 (dd, *J* = 7.2, 1.5 Hz, 2H, H-2' & H-6'), 7.71 (m, 2H, H-3' & H-5'), 7.61 (m, 1H, H-4'), 7.43 (d, *J* = 8.1 Hz, 1H, H-6'''), 7.10 (d, *J* = 8.1 Hz, 1H, H-5'''), 6.78 (d, *J* = 1.5, 1H, H-3'''), 4.10 (s, 2H, CH_2-2''), 2.99 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.49 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.61 (m, 2H, CH_2-4), 1.44 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (13%) $[M]^+$, 337 (21%), 317 (31%), 141 (100%), 105 (58%),

***N*-(2,5-dimethylphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3k):**

IR (KBr, cm^{-1}): ν_{max}: 3448 (N-H stretching), 3029 (C-H stretching of aromatic ring), 2935 (-CH_2- stretching), 1519 (C=C stretching of aromatic ring), 1313 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 11.40 (s, 1H, N-H), 8.01 (d, *J* = 1.5 Hz, 1H, H-6'''), 7.73 (dd, *J* = 8.7, 1.5 Hz, 2H, H-2' & H-6'), 7.58 (m, 2H, H-3' & H-5'), 7.08 (m, 1H, H-4'), 6.91 (d, *J* = 7.5 Hz, 2H, H-4''''), 6.87 (d, *J* = 7.5 Hz, 2H, H-3'''), 4.17 (s, 2H, CH_2-2''), 2.96 (t, *J* = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, *J* = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 2.20 (s, 6H, CH_3-2''' & CH_3-5'''), 3.62 (s, 2H, CH_2-2''), 1.59 (m, 2H, CH_2-4), 1.41 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (19%) $[M]^+$, 337 (23%), 317 (35%), 141 (100%), 105 (59%),

***N*-(2,6-dimethylphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3l):**

IR (KBr, cm^{-1}): ν_{max}: 3441 (N-H stretching), 3033 (C-H stretching of aromatic ring), 2942 (-CH_2-stretching), 1521 (C=C stretching of aromatic ring), 1319 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.97 (dd, J = 8.7, 1.5Hz, 2H, H-2' & H-6'), 7.73 (m, 2H, H-3' & H-5'), 7.61 (m, 1H H-4'), 7.06 (m, 3H, H-3''' to H-5'''), 2.96 (t, J = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 3.98 (*s*, 2H, CH_2-2''), 2.47 (t, J = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 2.20 (s, 6H, CH_3-2''' & CH_3-6'''), 2.16 (s, 2H, CH_2-2''), 1.57 (m, 2H, CH_2-4), 1.42 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (23%) $[M]^+$, 337 (45%), 317 (21%), 141 (100%), 105 (45%).

***N*-(3,4-dimethylphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3m):**

IR (KBr, cm^{-1}): ν_{max}: 3437 (N-H stretching), 3028 (C-H stretching of aromatic ring), 2937 (-CH_2-stretching), 1520 (C=C stretching of aromatic ring), 1313 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.73 (dd, J = 6.6, 1.8 Hz, 2H, H-2' & H-6'), 7.63 (m, 2H, H-3' & H-5'), 7.30 (m, 1H, H-4'), 7.16 (d, J = 8.1 Hz, 2H, H-6'''), 7.02 (d, J = 8.1 Hz, 1H, H-5'''), 6.76 (s, 1H, H-2'''), 3.99 (s, 2H, CH_2-2''), 2.96 (t, J = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, J = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 2.23 (s, 3H, CH_3-3'''), 2.20 (s, 3H, CH_3-4'''), 1.62 (m, 2H, CH_2-4), 1.45 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (13%) $[M]^+$, 337 (35%), 317 (44%), 141 (100%), 105 (31%).

***N*-(3,5-dimethylphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (3n):**

IR (KBr, cm^{-1}): ν_{max}: 3441 (N-H stretching), 3021 (C-H stretching of aromatic ring), 2931 (-CH_2-stretching), 1511 (C=C stretching of aromatic ring), 1311 (-SO_2- stretching), ^{1}H-NMR (300 MHz, CD_3OD, δ / ppm): 7.73 (dd, J = 6.6, 1.8 Hz, 2H, H-2' & H-6'), 7.63 (m, 2H, H-3' & H-5'), 7.22 (s, 2H, H-2''' & H-6'''), 6.76 (s, 1H, H-4'''), 4.01 (s, 2H, CH_2-2''), 2.96 (t, J = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, J = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 2.26 (s, 6H, CH_3-3''' & CH_3-6'''), 1.69 (m, 2H, CH_2-4), 1.41 (m, 4H, CH_2-3 & CH_2-5). EIMS *m/z*: 401 (10%) $[M]^+$, 337 (20%), 317 (34%), 141 (100%), 105 (51%).

Acetylcholinesterase assay

The AChE inhibition activity was performed according to the method (Ellman et al., 1961) with slight modifications. Total volume of the reaction mixture was 100 µL. It contained 60 µL Na_2H PO_4 buffer with concentration of 50 mM and pH 7.7. Ten 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

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

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

Butyrylcholinesterase assay

The BChE inhibition activity was performed addording to the method (Ellman et al., 1961) with slight modifications. Total volume of the reaction mixture was 100 µL containing 60 µL, Na_2H PO_4 buffer, 50 mM and pH 7.7. Ten 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.

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

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

Lipoxygenase assay

Lipoxygenase (LOX) activity was assayed addording to the method (Tappel 1953; Evans 1987 and Baylac et al., 2003) 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.

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

Where Control = Total enzyme activity without inhibitor

Test = Activity in the presence of test compound

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

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

In the undertaken research, a series of heterocyclic compounds containing piperidine nucleus was synthesized as scheme-1. The parent compound *N*-(piperidin-1-yl)benzenesulfonamide **(1)**, was prepared by a process similar to the known literature procedure (Deng et al., 2006 and Jafarpour et al., 2011) using benzenesulfonyl chloride (**a**) and 1-amino piperidine (**b**). Reaction of **1** with different electrophiles yielded a series of *N*-alkyl-*N*-(piperidin-1-yl)benzenesulfonamide (**1a-f)** and *N*-aryl/alkyl substitued-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (**3a-n)** as represented in Scheme 1. Synthesis of all derivatives **1a-f** and **3a-n** was performed in DMF (*N*,*N*-dimethylformamide) using sodium hydride (NaH) as the base. Complete conversion was achieved within 30 to 70 min by stirring. The products were isolated by adding cold water in the reaction mixture and filtering off the precipitated solid. In some cases, compound was taken out through solvent extraction method by chloroform/ ethyl acetate. Parent compound **1** was synthesized as light yellow powder. The molecular formula $C_{18}H_{17}N_3O_3S$ was established by HR-MS showing molecular ion peak at *m/z* 240.3230. The IR spectrum showed absorption bands at 3430 cm^{-1}, 3024 cm^{-1}, 1546 cm^{-1} and 1341 cm^{-1} which were assigned to, SO_2-N-H (stretching of sulfonamide), C-H (aromatic stretching), C=C (stretching of aromatic ring) and -SO_2- (stretching of sulfonyl group)

respectively. The EI-MS gave characteristic peaks at *m/z* 176 and 156 which were attributed to the loss of SO_2 (sulfonyl) and 1-piperidinyl groups respectively. In the aromatic region of the ^{1}H-NMR spectrum signals appeared at δ 7.90 (dd, J = 8.7, 1.5 Hz, 2H, H-2' & H-6'), 7.65 (m, 2H, H-3' & H-5') and 7.52 (m, 1H, H-4') which were assigned to the mono substituted benzenesulfonyl ring. In the aliphatic region of the ^{1}H-NMR spectrum, signals appeared at 2.96 (t, J = 5.4 Hz, 2H, H_{ax}-2 & H_{ax}-6), 2.47 (t, J = 5.4 Hz, 2H, H_{eq}-2 & H_{eq}-6), 1.61 (m, 2H, CH_2-4) and 1.44 (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 **1** was assigned as *N*-(piperidin-1-yl)benzenesulfonamide. Similarly, the structure of other compounds was characterized by ^{1}H-NMR, IR and mass spectral data as described in experimental section. The physical data of all the synthesized compounds has been shown in table-1.

Pharmacology

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. It is obvious from Table-2 that compounds *N*-allyl-*N*-(piperidin-1-yl)benzenesulfonamide **(1b)** and *N*-benzyl-*N*-(piperidin-1-yl)benzenesulfonamide **(1c)** were showed promising inhibitory potential against butyrylcholinesterase enzyme having IC_{50} value of 4.4±0.03 and 4.21±0.11 μmol/L respectively, relative to Eserine, a reference standard with IC_{50} value of 0.85±0.001 μmol/L, probably due to the *N*-substitution of allyl and benzyl groups respectively in these molecules. Similarly, from a series of *N*-substituted 2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide **(3a-n)**, the compound which showed talented inhibitory activity was *N*-methyl-*N*-(4-hydroxyphenyl)-2-[(phenylsulfonyl)(piperidin-1-yl)amino]acetamide (**3e**) having IC_{50} value of 5.31±0.04 μmol/L as compared to reference standard. The enhanced activity might be due to the substitution of *N*-methyl-*N*-(4-hydroxyphenyl)acetamide which is probably more complimentary for the inhibition of butyrylcholinesterase enzyme. The other acetamides which showed good inhibitory potential against butyrylcholinesterase enzyme were **3l, 3d, 3g, 3a,** and **3j** having IC_{50} value of 15.91±0.02, 17.11±0.14, 17.62±0.21, 18.11±0.24 and 18.31±0.13 μmol/L respectively, perhaps due to the substitution of *N*-(2,6-dimethylphenyl)acetamide, *N*-(4-Methoxyphenyl)acetamide, *N*-(2-phenylethyl)acetamide, *N*-(2-methylphenyl)acetamide and *N*-(2,4-dimethylphenyl)acetamide groups respectively in these molecules. The screening of acetamides (**3a-n)** against

acetylcholinesterase enzyme depicted that the two compounds **3l** and **3d** exhibited good inhibitory potential having IC_{50} 19.11±0.32 and 21.31±0.64 μmol/L, relative to Eserine, a reference standard with IC_{50} value of 0.04±0.001 μmol/L. However, only few compounds (Table-1) showed very weak inhibition against lipoxygenase enzyme but all other compounds remained inactive.

CONCLUSION:

The proposed structures of the synthesized compounds are well supported by spectroscopic data. From the enzyme inhibition data (Table-2), it was obvious that three compounds **1b, 1c & 3e** possessed talented activity against butyrylcholinesterase enzyme and the other synthesized compounds showed moderate to weak activity against acetylcholinesterase and lipoxygenase enzymes which was evident from their IC_{50} values, relative to the standards used. Hence, on the basis of aforesaid results, it was generally concluded that these derivatives seem relatively more suitable drug candidates for the treatment of Alzheimer's disease and other associated diseases.

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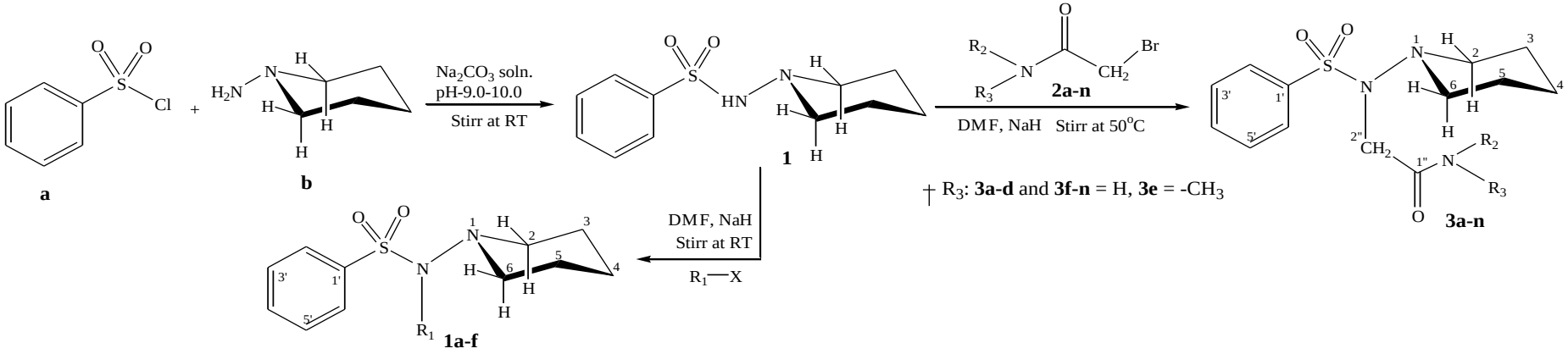

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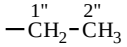
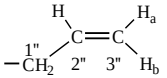
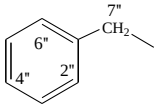
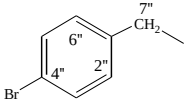
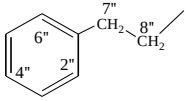
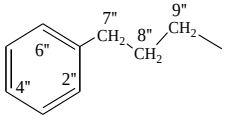
1a	
1b	
1c	
1d	
1e	
1f	

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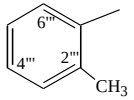
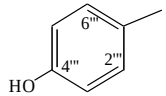
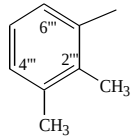
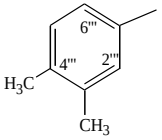
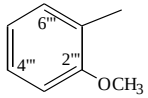
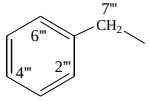
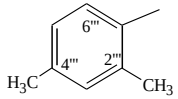
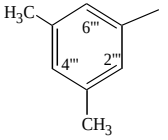
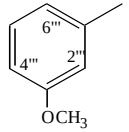
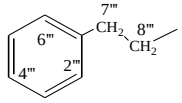
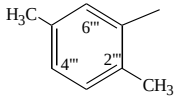
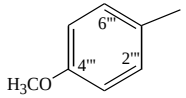
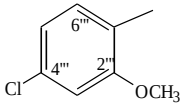
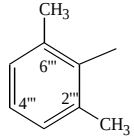
3a		3e		3i		3m	
3b		3f		3j		3n	
3c		3g		3k			
3d		3h		3l			

Scheme-1: Synthetic scheme of sulfonamides bearing piperidine nucleus.

Table 1: The physical data of the synthesized compounds.

Samples	Appearance	Melting point (°C)	Molecular formula	% of Yield
1	Light yellow powder	55-57	$C_{11}H_{16}N_2O_2S$	90
1a	Brownish orange sticky liquid	-	$C_{13}H_{20}N_2O_2S$	79
1b	Brown sticky solid	-	$C_{14}H_{20}N_2O_2S$	83
1c	Mustard sticky solid	-	$C_{18}H_{22}N_2O_2S$	80
1d	Light yellow sticky solid	-	$C_{18}H_{21}BrN_2O_2S$	72
1e	Greenish black sticky solid	-	$C_{19}H_{24}N_2O_2S$	81
1f	Mustard sticky solid	-	$C_{20}H_{26}N_2O_2S$	75
3a	Dark Brown sticky solid	-	$C_{20}H_{25}N_3O_3S$	85
3b	Rust sticky solid	-	$C_{20}H_{25}N_3O_4S$	77
3c	Rust sticky solid	-	$C_{20}H_{25}N_3O_4S$	87
3d	Brown sticky solid	-	$C_{20}H_{25}N_3O_4S$	68
3e	Rust sticky solid	-	$C_{20}H_{25}N_3O_4S$	87
3f	Mustard sticky solid	-	$C_{20}H_{25}N_3O_3S$	80
3g	Rust sticky solid	-	$C_{21}H_{27}N_3O_3S$	72
3h	Light brown sticky solid	-	$C_{21}H_{24}ClN_3O_4S$	87
3i	Lemon yellow sticky solid	-	$C_{21}H_{27}N_3O_3S$	89
3j	Dark brown sticky solid	-	$C_{21}H_{27}N_3O_3S$	65
3k	Mustard crystals	139-141	$C_{21}H_{27}N_3O_3S$	89
3l	Buff powder	135-137	$C_{21}H_{27}N_3O_3S$	73
3m	Yellow powder	130-133	$C_{21}H_{27}N_3O_3S$	89
3n	Lemon yellow sticky solid	-	$C_{21}H_{27}N_3O_3S$	67

Table 2: Bioactivities study of synthesized compounds

C. No.	BChE			AChE			LOX		
	Conc./well (mM)	**Inhibition (%)**	**IC_{50} µM**	**Conc. (mM)**	**Inhibition (%)**	**IC_{50} (µmol.)**	**Conc./well (mM)**	**Inhibition (%)**	**IC_{50} µM**
1	0.5	30.74±0.42	NIL	0.5	39.49±0.21	NIL	0.5	57.96±0.22	329.31±0.08
1a	0.5	80.67±0.11	87.51±0.04	0.5	85.98±0.32	39.21±0.04	0.5	50.06±0.63	<400
1b	0.25	95.68±0.41	4.4±0.03	0.5	83.90±0.14	23.21±0.17	0.5	42.17±0.31	NIL
1c	0.5	95.19±0.32	4.21±0.11	0.5	75.09±0.54	60.41±0.31	0.5	48.51±0.98	NIL
1d	0.5	80.33±0.31	89.21±0.014	0.5	67.85±0.25	185.21±0.39	0.5	40.69±0.34	NIL
1e	0.5	95.53±0.64	16.21±0.54	0.5	78.69±0.42	69.71±0.36	0.5	42.95±0.26	NIL
1f	0.5	94.09±0.34	17.42±0.08	0.25	82.01±0.73	147.51±0.35	0.5	49.42±0.63	NIL
3a	0.25	96.35±0.04	18.11±0.24	0.5	86.74±0.19	32.71±0.05	0.5	67.73±0.11	339.11±0.18
3b	0.5	91.47±0.82	34.41±0.52	0.5	86.46±0.94	190.52±0.52	0.5	66.11±0.37	181.31±0.09
3c	0.5	89.79±0.45	137.24±0.05	0.5	82.01±0.43	35.31±0.24	0.5	48.90±0.69	NIL
3d	0.5	94.76±0.15	17.11±0.14	0.5	94.03±0.71	21.31±0.64	0.5	28.33±0.01	NIL
3e	0.5	94.94±0.14	5.31±0.04	0.5	62.88±0.54	159.82±0.44	0.5	93.75±0.55	183.21±0.06
3f	0.5	88.10±0.27	35.41±0.71	0.5	51.99±0.31	399.11±0.47	0.5	40.94±0.52	NIL
3g	0.5	94.99±0.11	17.62±0.21	0.5	76.23±0.19	69.66±0.06	0.5	47.61±0.53	NIL
3h	0.5	70.71±0.64	71.21±0.05	0.5	65.53±0.01	311.11±0.17	0.25	42.09±0.34	NIL
3i	0.5	89.43±0.25	37.31±0.14	0.5	49.81±0.37	NIL	0.5	75.77±0.38	225.21±0.31
3j	0.5	91.49±0.44	18.31±0.13	0.5	79.92±0.38	35.92±0.81	0.5	39.46±0.31	NIL
3k	0.5	88.32±0.88	67.91±0.71	0.5	51.23±0.54	401.41±0.65	0.5	49.94±0.71	NIL
3l	0.5	92.98±0.57	15.91±0.02	0.5	88.64±0.92	19.11±0.32	0.5	70.28±0.52	236.41±0.95
3m	0.5	90.99±0.51	138.61±0.47	0.5	75.66±0.64	247.61±0.71	0.5	47.22±0.29	NIL
3n	0.5	90.03±0.05	136.91±0.71	0.5	90.52±0.85	137.11±0.08	0.25	66.84±0.54	188.21±0.15
Control	**Eserine**		**0.85±0.001**	**Eserine**		**0.04±0.001**	**Baicalein**		**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).
LOX = Lipoxygenase.
AChE = Acetyl cholinesterase.
BChE = Butyryl cholinesterase.