INTRODUCTION

Sulfonamides were the first antibacterial agents used successfully for the treatment of infectious diseases in human beings. These were also employed for the treatment of various infections [1]; as antimicrobial, antithyroid, antitumor and antimalarial agents [2]; as inhibitor of carbonic anhydrase [2]; for the treatment of diabetes [3], HIV/AIDS [4] and bacterial infections in the animals [5]. Sulfonamides inhibit the formation of folic acid necessary for bacterial growth by competing with p-aminobenzoic acid for dihydropteroate synthase enzyme and ultimately inhibit the synthesis of purine and DNA [6].

Acetyl cholinesterase (AChE, EC 3.1.1.7) and butyryl cholinesterase (BChE, EC 3.1.1.8) belong to a group of enzymes including serine hydrolases and are key components of cholinergic brain synapses and neuromuscular...
junctons. These catalyze hydrolysis of neurotransmitter acetylcholine and terminate nerve impulse in cholinergic synapses [7]. BChE is present significantly in Alzheimer's plaques than the normal age related non dementia of brains. The cholinesterase inhibitors increase the amount of acetylcholine, for neuronal and neuromuscular transmission, reversibly or irreversibly [8].

The seeking of new cholinesterase and lipoxygenase enzyme inhibitors is thought to be an important strategy to inaugurate new drug candidates for the treatment of Alzheimer's disease and other related ones. The previous work by our group [9-12] has revealed that different structural changes in the molecule by substitution have a great influence on the biological activities. The objective of this work was to synthetize less toxic and more efficient sulfonamides against AChE, BChE and LOX enzymes, derived from 1-amino-2-phenylethane.

**EXPERIMENTAL**

**Materials and instruments**

Melting points of synthesized compounds were recorded with the help of Griffin and George melting apparatus. Purity of synthesized molecules was checked by thin layer chromatography (TLC) on G-25-UV plates coated with silica gel using ethyl acetate and n-hexane as solvent system. Detection wavelength was 254 nm by using ceric sulphate reagent. The IR spectra were recorded in KBr pellet method by using Jasco 320-A spectrophotometer with wave number taken in cm\(^{-1}\). CH\(_2\)OD was used to record \(^1\)H-NMR spectra on Bruker spectrometer working at 300 MHz. Mass spectra El-MS were recorded with the help of JMS-HX-110 spectrometer in Finnigan MAT-112 instrument. 1-Amino-2-phenylethane and substituted aryl sulfonyl chlorides were purchased from Merck and Alfa Aesar through local suppliers. The solvents employed in synthesis were of analytical grade.

**General procedure for the synthesis of different sulfonamides (3a-l)**

1-Amino-2-phenylethane (1; 0.1 mmol) was suspended in 100 mL distilled water in a 250 mL round bottom flask and pH was kept strictly 9-10 by the addition of 10% aqueous solution of Na\(_2\)CO\(_3\). The various aryl sulfonyl chlorides (2a-l) were added to the flask and the decrease in pH was avoided by the again addition of aq. Na\(_2\)CO\(_3\) solution. The reaction mixture was stirred for 3-4 hours 4-5 hours and monitored with TLC (n-hexane:EtOAc, 70:30) till the completion of reaction by single spot on TLC plate. After

\[
\begin{align*}
\text{Compd.} & \quad \text{R} & \quad \text{Compd.} & \quad \text{R} & \quad \text{Compd.} & \quad \text{R} \\
3a & \quad \text{H}_2\text{C} & \quad 3e & \quad \text{O} & \quad 3i & \quad \text{Cl} \\
3b & \quad \text{H}_2\text{C} & \quad 3f & \quad \text{H}_2\text{C} & \quad 3j & \quad \text{Cl} \\
3c & \quad \text{Cl} & \quad 3g & \quad \text{Br} & \quad 3k & \quad \text{O} & \quad \text{N} \\
3d & \quad \text{H}_2\text{C} & \quad 3h & \quad \text{Cl} & \quad 3l & \quad \text{N} & \quad \text{O} \\
3e & \quad \text{H}_2\text{C} & \quad 3i & \quad \text{Cl} & \quad 3j & \quad \text{Cl} \\
3f & \quad \text{H}_2\text{C} & \quad 3j & \quad \text{Cl} & \quad 3k & \quad \text{O} & \quad \text{N} \\
3g & \quad \text{Br} & \quad 3k & \quad \text{O} & \quad \text{N} & \quad \text{O} & \quad \text{N} \\
3h & \quad \text{Cl} & \quad 3l & \quad \text{N} & \quad \text{O} & \quad \text{N} & \quad \text{O}
\end{align*}
\]
confirmation by single spot, 3 mL of dilute HCl was added to adjust the pH of the reaction mixture to 3 - 4. The synthesized compounds were collected by filtration and washed with distilled water. The re-crystallization was carried out by methanol.

**Enzyme inhibition assays**

**Cholinesterase assay**

The AChE and BChE inhibition activity were carried out according to the method reported in the literature [13] with minor changes. Volume of the reaction mixture was 100 µL containing 60 µL Na₂HPO₄ buffer (50 mM, pH 7.7), 10 µL test compound (0.5 mM well⁻¹) and 10 µL (0.5 unit well⁻¹) BChE or 0.005 unit well⁻¹ AChE enzyme. The contents were mixed, pre-read at 405 nm and pre-incubated for 10 min at 37 °C. The reaction was started by the addition of 10 µL (0.5 mM well⁻¹) substrate (acetylthiocholine iodide for AChE and butryrylthiocholine chloride for BChE) and 10 µL DTNB (0.5 mM well⁻¹). After 15 min of incubation at 37 °C, 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. Inhibition was calculated using Eq 1.

\[ \text{Inhibition (\%)} = \frac{(\text{Ac} - \text{At})}{\text{Ac}} \times 100 \]  

where Ac = absorbance of control and At = absorbance of test compound.

**Lipoxigenase assay**

Lipoxygenase (LOX) activity was assayed according to the method of Baylac & Racine [14] with slight modifications. Total volume of lipoxygenase assay mixture was 200 µL containing 150 µL Na₂HPO₄ buffer (100 mM & pH 8.0), 10 µL test compound (0.5 mM well⁻¹) and 15 µL (600 units well⁻¹) enzyme. The contents were mixed, pre-read at 234 nm and pre-incubated 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 experiments were performed in triplicates. The positive and negative controls were included in the assay. Baicalein (0.5 mM well⁻¹) was used as a positive control. The percentage inhibition (%) and IC₅₀ values were calculated by the same method as described for cholinesterase enzymes.

**Statistical analysis**

All the measurements were carried out in triplicate and statistical analysis was performed by Microsoft Excel 2010. The results are presented as mean ± SEM with 90% CL.

**RESULTS**

**Chemistry**

The molecules, 3a-l, were synthesized by coupling 1-amino-2-phenylethane (1) with different aryl sulfonyl chlorides (2a-l) in a weak basic aqueous media with dynamic pH control. The products were yielded after stirring of 4-5 hours and isolated by filtration after acidifying up to pH of 4-5. Acidic pH is necessary for good yield of the products but high acidity has negative effect. The structural analysis was performed through spectral data.

**Spectral characterization of the synthesized molecules**

(3a-l)N-(2-Phenylethyl)-4-methylbenzene sulphonamide (3a)

White crystalline solid; Yield: 94.72 %; m.p.: 98 °C; Mol. formula: C₁₅H₁₇NO₂S; Mol. mass: 275 gmol⁻¹; IR (KBr, cm⁻¹) νmax: 3310 (N-H stretching), 2930 (C-H stretching of aromatic ring), 2740 (-CH₂ stretching), 1601 (C=C stretching of aromatic ring), 1320 (S=O stretching); ¹H-NMR (300 MHz, CDCl₃): δ ppm 7.68 (d, J = 8.1 Hz, 2H, H-2', H-6'), 7.33 (d, J = 8.1 Hz, 2H, H-3', H-5'), 7.23 (dd, J = 7.5, 1.5 Hz, 2H, H-2, H-6); 7.15 (t, J = 7.8 Hz, 1H, H-4), 7.09 (dd, J = 7.8, 1.2 Hz, 2H, H-3, H-5), 3.03 (t, J = 7.8 Hz, 2H, H-8), 2.69 (t, J = 7.2 Hz, 2H, H-7), 2.40 (s, 3H, CH₃-4); EIMS: (m/z): 275 [M⁺], 155 [C₆H₄SO₂]⁺, 120 [C₈H₁₀N]⁺, 105 [C₇H₉]⁺, 91 [C₆H₇]⁺, 77 [C₅H₅]⁺, 65 [C₄H₄]⁺, 51 [C₃H₃]⁺.

N-(2-Phenylethyl)-4-(1,1,1-trimethyl) methyl benzenesulphonamide (3b)

Brownish black crystalline solid; Yield: 94.18%; m.p.: 112 °C; Mol. formula: C₁₅H₂₃NO₂S; Mol. mass: 317 gmol⁻¹; IR (KBr, cm⁻¹) νmax: 3301 (N-H stretching), 2927 (C-H stretching of aromatic ring), 2701 (-CH₂ stretching), 1617 (C=C stretching of aromatic ring), 1320 (S=O stretching); ¹H-NMR (300 MHz, CDCl₃): δ ppm 7.73 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.61 (d, J = 8.4 Hz, H-3', H-5'), 7.23 (d, J = 7.5 Hz, 2H, H-2, H-6), 7.16 (t, J = 7.5 Hz, 1H, H-4), 7.09 (d, J = 6.9 Hz, H-3, H-5), 3.05 (t, J = 7.2 Hz, H-8), 2.70 (t, J = 7.2 Hz, H-8), 2.64 (t, J = 7.2 Hz, H-7), 2.40 (s, 3H, CH₃-4); EIMS: (m/z): 317 [M⁺], 155 [C₆H₄SO₂]⁺, 120 [C₈H₁₀N]⁺, 105 [C₇H₉]⁺, 91 [C₆H₇]⁺, 77 [C₅H₅]⁺, 65 [C₄H₄]⁺, 51 [C₃H₃]⁺.
N-(2-Phenylethyl)-2,4,6-trimethylbenzene sulfonamide (3c)
Brownish black viscous liquid; Yield: 94.77%; Mol. formula: C_{17}H_{20}NO_{2}S; Mol. mass: 303 gmol^{-1}; IR (KBr, cm^{-1}) v_{max}: 3345 (N-H stretching), 2941 (C-H stretching of aromatic ring), 2711 (C-H stretching), 1635 (C=C stretching of aromatic ring), 1305 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): \( \delta \)ppm 7.18 (dd, J = 7.5, 2.4 Hz, 2H, H-2, H-6), 7.11-6.97 (m, 3H, H-3 to H-5), 6.95 (s, 2H, H-3, H-5), 3.06 (t, J = 7.2 Hz, 2H, H-8), 2.64 (t, J = 7.5 Hz, 2H, H-7), 2.63 (s, 6H, CH3-2', CH3-6'), 2.26 (s, 3H, CH3-4'); EIMS (m/z): 303 [M]+, 183 [C_{11}H_{13}O]^{+}, 119 [C_{7}H_{11}]^{+}, 120 [C_{6}H_{10}N]^{+}, 105 [C_{6}H_{5}]^{+}, 91 [C_{7}H_{5}]^{+}, 77 [C_{6}H_{4}]^{+}, 65 [C_{6}H_{3}]^{+}, 51 [C_{6}H_{3}]^{+}.

N-(2-Phenylethyl)-4-acetamidobenzene sulfonamide (3f)
Yellowish white crystalline solid; Yield: 91.21%; m.p.: 107 °C; Mol. formula: C_{16}H_{15}N_{2}O_{2}S; Mol. mass: 318 gmol^{-1}; IR (KBr, cm^{-1}) v_{max}: 3301 (N-H stretching), 2921 (C-H stretching of aromatic ring), 2715 (C-H stretching), 1615 (C=C stretching of aromatic ring), 1311 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): \( \delta \)ppm 7.52 (d, J = 8.1 Hz, 2H, H-3', H-5'), 7.32 (d, J = 8.4 Hz, 2H, H-2', H-6'), 7.23 (d, J = 7.2 Hz, 2H, H-2, H-6), 7.15 (t, J = 6.9 Hz, 1H, H-4), 7.09 (t, J = 7.2 Hz, 2H, H-7), 2.13 (s, 3H, CH3CONH-4'); EIMS (m/z): 318 [M]+, 198 [C_{14}H_{20}SO_{4}N]^{+}, 134 [C_{10}H_{14}O_{2}N]^{+}, 120 [C_{9}H_{12}N]^{+}, 105 [C_{8}H_{5}]^{+}, 91 [C_{7}H_{5}]^{+}, 77 [C_{6}H_{4}]^{+}, 65 [C_{6}H_{3}]^{+}, 51 [C_{6}H_{3}]^{+}.

N-(2-Phenylethyl)-4-aminoacetophenone (3b)
White crystalline solid; Yield: 94.24%; m.p.: 194 °C; Mol. formula: C_{16}H_{16}NO_{2}; Mol. mass: 295 gmol^{-1}; IR (KBr, cm^{-1}) v_{max}: 3278 (N-H stretching), 2913 (C-H stretching of aromatic ring), 2714 (C-H stretching), 1614 (C=C stretching of aromatic ring), 1310 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): \( \delta \)ppm 7.59 (d, J = 8.7 Hz, 2H, H-2', H-6'), 7.52 (d, J = 8.4 Hz, 2H, H-3', H-5'), 7.23 (d, J = 7.2, 2H, H-2, H-6), 7.17 (t, J = 7.2 Hz, 1H, H-4), 7.10 (d, J = 7.2 Hz, 2H, H-3, H-5), 3.09 (t, J = 7.2 Hz, 2H, H-8), 2.72 (t, J = 7.5 Hz, 2H, H-7); EIMS (m/z): 297 [M+2]^{+}, 295 [M]^{+}, 220 [C_{15}H_{17}BrSO_{2}]^{+}, 156 [C_{10}H_{13}Br]^{+}, 120 [C_{9}H_{12}N]^{+}, 105 [C_{8}H_{5}]^{+}, 91 [C_{7}H_{5}]^{+}, 77 [C_{6}H_{4}]^{+}, 65 [C_{6}H_{3}]^{+}, 51 [C_{6}H_{3}]^{+}.

N-(2-Phenylethyl)-4-aminophenylbenzene sulfonamide (3g)
White crystalline solid; Yield: 92.31%; m.p.: 115 °C; Mol. formula: C_{16}H_{15}NO_{2}S; Mol. mass: 329 gmol^{-1}; IR (KBr, cm^{-1}) v_{max}: 3331 (N-H stretching), 2901 (C-H stretching of aromatic ring), 2705 (C-H stretching), 1599 (C=C stretching of aromatic ring), 1301 (S=O stretching); ^{1}H-NMR
(300 MHz, CD3OD): δ ppm 7.95 (dd, J = 7.8, 1.5 Hz, 1H, H-6'), 7.71 (dd, J = 8.1, 1.5 Hz, 1H, H-4'), 7.40 (t, J = 8.1 Hz, 1H, H-5'), 7.40 (t, J = 8.1 Hz, 1H, H-5), 7.19 (d, J = 6.9 Hz, 2H, H-2, H-6), 7.12 (t, J = 6.9 Hz, 1H, H-1), 7.06 (dd, J = 7.8, 1.2 Hz, 2H, H-3, H-5), 3.19 (t, J = 7.2 Hz, 2H, H-2), 2.70 (t, J = 7.2 Hz, 2H, H-7); EIMS (m/z): 333 [M+H]+, 331 [M+H]+, 297 [M+H]+, 296 [M+H]+, 255 [M+H]+, 238 [M+H]+, 105 [C6H5]+, 91 [C6H5]+, 77 [C6H5]+, 65 [C6H5]+, 51 [C6H5]+.

**N-(2-Phenylethyl)-2,5-dichlorobenzene sulfonamide (3j)**

Yellowish white crystalline solid: Yield: 93.21%; m.p.: 101 °C; Mol. formula: C16H13Cl2NO4S; Mol. mass: 329 g/mol; IR (KBr, cm⁻¹) νmax: 3319 (N-H stretching), 2912 (C-H stretching of aromatic ring), 2719 (-CH2 stretching), 1621 (C=C stretching of aromatic ring), 1321 (S=O stretching), 1159 (N=O stretching), 1086 (C–O stretching), 778 (CH3 bending), 768 (CH2 bending), 756 (CH3 rocking), 740 (CH2 rocking), 691 (CH3 wagging), 607 (CH2 wagging).

**N-(2-Phenylethyl)-2,4-dinitrobenzene sulfonamide (3k)**

Yellowish white crystalline solid: Yield: 91.34%; m.p.: 101 °C; Mol. formula: C16H13NO4S; Mol. mass: 351 g/mol; IR (KBr, cm⁻¹) νmax: 3311 (N-H stretching), 2931 (C-H stretching of aromatic ring), 2725 (-CH2 stretching), 1607 (C=C stretching of aromatic ring), 1313 (S=O stretching), 1159 (N=O stretching), 1086 (C–O stretching), 778 (CH3 bending), 768 (CH2 bending), 756 (CH3 rocking), 740 (CH2 rocking), 691 (CH3 wagging), 607 (CH2 wagging).

**N-(2-Phenylethyl)naphthalen-2-ylsulfonamide (3l)**

Yellow crystalline solid: Yield: 94.51%; m.p.: 92 °C; Mol. formula: C16H13NO4S; Mol. mass: 311 g/mol; IR (KBr, cm⁻¹) νmax: 3340 (N-H stretching), 2915 (C-H stretching of aromatic ring), 2731 (-CH2 stretching), 1619 (C=C stretching of aromatic ring), 1319 (S=O stretching), 1159 (N=O stretching), 1086 (C–O stretching), 778 (CH3 bending), 768 (CH2 bending), 756 (CH3 rocking), 740 (CH2 rocking), 691 (CH3 wagging), 607 (CH2 wagging).

**Enzyme inhibition activity**

A series of sulfonamides derived from 1-amino-2-phenylethylamine was synthesized by the protocol sketched in scheme 1 and evaluated for anti-enzymatic activity by screening against acetyl cholinesterase (AChE), butyryl cholinesterase (BChE) and lipooxygenase (LOX) enzymes. The enzyme inhibition activity of the sulfonamide prepared by the reaction of 2-phenylethylamine and benzenesulfonyl chloride and its derivatives has been previously evaluated by our group [15]. Here, we further prepared sulfonyl derivatives of 1-amino-2-phenylethylamine (2-phenylethylamine) to evaluate their biological activities in search of new suitable molecules. The results indicate that these molecules are suitable inhibitors of both cholinesterase enzymes but moderately active against lipooxygenase enzyme.

**Table 1: Enzyme inhibition activities of synthesized compounds (3a-4)**

| Compd. | AChE (μM) | IC50 (μM) | %Inhibition | BChE (μM) | IC50 (μM) | %Inhibition | LOX (μM) | IC50 (μM) | %Inhibition |
|--------|-----------|-----------|-------------|-----------|-----------|-------------|----------|-----------|-------------|
| 3a     | 82.34±3.76| 402.65±1.59| 69.04±2.98  | 204.14±1.95| 81.45±0.31| 251.07±0.65|
| 3b     | 77.94±2.90| 324.35±1.23| 64.25±3.67  | 229.26±1.72| 27.63±0.67 | -           |          |          |             |
| 3c     | 86.92±2.51| 263.32±1.55| 66.65±2.92  | 143.15±0.81| 33.90±0.54| -           |          |          |             |
| 3d     | 2.95±0.22 | 115.45±1.23| 86.71±2.25  | 45.65±0.48 | 38.61±0.27| -           |          |          |             |
| 3e     | 82.25±3.96| 184.15±0.62| 70.02±3.24  | 212.65±1.85| 66.27±0.51| 342.76±0.78|
| 3f     | 23.67±3.69 | -         | 13.01±3.67  | -         | 16.23±0.19| -           |          |          |             |
| 3g     | 45.52±3.98| >500       | 70.71±2.45  | 294.13±1.63| 60.90±0.34| 356.87±0.59|
| 3h     | 55.14±3.22| 382.21±1.67| 71.16±2.73  | 233.24±1.83| 64.36±0.27| 374.14±0.97|
| 3i     | 92.23±2.31| 362.55±1.94| 78.96±3.51  | 254.75±1.63| 22.31±0.17| -           |          |          |             |
| 3j     | 85.16±2.52| 326.44±1.43| 81.75±2.35  | 234.85±1.69| 5.45±0.77 | -           |          |          |             |
| 3k     | 56.33±2.55| 421.12±1.78| 84.67±3.50  | 129.57±0.75| 59.27±0.41| 364.43±0.91|
| 3l     | 88.52±2.76| 185.15±0.56| 80.76±3.79  | 162.39±0.94| 69.60±0.61| 330.43±0.85|

*ACHE = acetyl cholinesterase; BChE = butyryl cholinesterase; LOX = lipooxygenase; a = eserine; b = baicalein*
DISCUSSION

Compound 3a was obtained as white crystalline solid having yield of 92.72 % and m.p. of 98 °C. IR spectrum supported the presence of sulfamoyl group by stretching of N-H bond at 3310 cm⁻¹ and that of S=O group at 1320 cm⁻¹. Molecular formula was also established by EI-MS molecular ion peak at m/z 275 and also by counting the number of protons in ¹H-NMR spectrum. EI-MS gave two prominent fragment peaks at m/z 155 for toluene sulfonyl cation and at m/z 120 for the cation of phenylethyl amino group.

In the ¹H-NMR spectrum, two doublets appeared at δ 7.68 (d, J = 8.1 Hz, 2H, H-2', H-6') for two protons in the vicinity of strong electron withdrawing sulfonyl group and 7.33 (d, J = 8.1 Hz, 2H, H-2, H-6), 7.15 (t, J = 7.8 Hz, 1H, H-4) and 7.09 (dd, J = 7.8, 1.2 Hz, 2H, H-3, H-5) were assigned for five proton substituted at ortho, para and meta position in the benzene ring. The signals appearing in aliphatic region at δ 3.03 (t, J = 7.8 Hz, 2H, H-8) and 2.69 (t, J = 7.2 Hz, 2H, H-7) confirmed the presence of two adjacent methylene groups in the molecule; and at δ 2.40 (s, 3H, CH₃-4) supported the presence of methyl group attached at para position of benzene ring linked with sulfonyl group. On the basis of these evidences, the structure of 3a was named as N-(2-phenylethyl)-4-methylbenzenesulfonamide. Likewise the structures of other synthesized compounds (3b-1) were corroborated by ¹H-NMR, IR and mass spectra data.

The screening of the synthesized molecules against acetyl cholinesterase (AChE) revealed that the most of the molecules exhibited inhibition potential except 3d, 3f and 3g as shown by their IC₅₀ values. Among these molecules, N-(2-phenylethyl)-2, 4, 6-trimethylbenzenesulfonamide (3c) was highly active. This molecule showed the inhibition potential probably because of the presence of trimethyl substituted benzene ring which exhibited more interaction with the active site of the enzyme to block it. The order of inhibition potential of all the molecules was found to be as, 3c > 3e > 3i > 3b > 3j > 3l > 3h > 3a > 3k.

Butyryl cholinesterase enzyme was inhibited by almost all the molecules with higher IC₅₀ values relatively but still 3f was inactive. The most active molecule was N-(2-phenylethyl)-4-methoxy benzenesulfonamide (3d) and the most credibly due to p-substituted methoxy benzyl group which exhibited H-bonding and also π – π interactions with amino acid residues associated with the active site of this enzyme. The activity of the molecules was in the following rank order: 3d > 3k > 3c > 3l > 3e > 3b > 3j > 3i > 3l > 3d > 3f. The synthesized compounds showed moderate activities against lipoxygenase enzyme. The high IC₅₀ values of the active molecules against this enzyme indicate that they were less active. The rank order of inhibition of the molecules was 3a > 3l > 3e > 3h > 3g > 3k. Half of the molecules of the synthesized series were inactive.

CONCLUSION

The series of synthesized sulfonamides can be obtained in yield by a facile and benign method using water as reaction medium. Compound 3f remained inactive against all the three enzymes taken into account. Overall, the compounds are active against both cholinesterase enzymes but less potent against lipoxygenase enzyme. These findings may be helpful in the efforts to design and search for new drug candidates for Alzheimer's disease.

REFERENCES

1. Sarmah AK, Meyer MT, Boxall ABA. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. Chemosphere 2006; 65(5): 725-759.
2. Remko M, Lieth CWV. Theoretical study of gas phase acidity, pka, lipophilicity and solubility of some biologically active sulfonamides. Biorg Med Chem 2004; 12(20): 5395-5403.
3. Boyd AE. Sulfonyl urea receptors ion, channels and fruit flies. Diabetes 1988; 237: 847-850.
4. De Clercq E. New developments in anti-HIV chemotherapy. Curr Med Chem 2001; 8: 1543-1572.
5. Jerry S, Riviere J. Sulfonamides veterinary pharmacology and therapeutics, edn 8, Ed. Richard Towa State, University Press 2001.
6. El-Sayed NS, El-Bendary RE, El-Ashy SM, El-Kerdawy MM. Synthesis and antifumour activity of new sulfonamide derivatives of thiadiazole [3,2a] pyrimidines. Eur J Med Chem 2011; 46(9): 3714-3720.
7. Tougu V. Acetylecholinesterase: Mechanism of catalysis and inhibition. Curr Med Chem 2001; 1: 155-170.
8. Gauthier S. Cholinergic adverse effects of cholinesterase inhibitors in Alzheimer's disease. Drug Aging 2001; 18: 853-862.
9. Abbasi MA, Aziz-ur-Rehman, Muhmood T, Khan KM, Ashraf M, Ejaz SA, Arshad S. Synthesis structural characterization and biological screening of various sulfonamides derived from 2-amidines. J Chem Soc Pak 2013; 35(2): 404-410.
10. Aziz-ur-Rehman, Rasool S, Abbasi MA, Khan KM, Ashraf M, Afzal I. Synthesis, characterization and biological screening of some 4-O-substituted derivatives of N-(4-hydroxyphenyl)-N-methyl-4-methylbenzenesulfonamide. Asian J Pharm Bio Res 2012; 2(2): 100-105.
11. Aziz-ur-Rehman, Rasool S, Abbasi MA, Fatima A, Nafeesa K, Ahmad I, Afzal S. Synthesis, spectral analysis and biological screening of some new N-
(un)substituted N-(5-chloro-2-methoxyphenyl)-aryl sulfonamides. J Pharmacy Res 2013; 6: 559-564.

12. Aziz-ur-Rehman, Fatima A, Abbasi MA, Khan KM, Ashraf M, Ahmad I, Ejaz SA. Synthesis, characterization and biological screening of N-substituted-(5-chloro-2-methoxyphenyl)benzenesulfonamide. Asian J Chem 2013; 25(7): 3735-3740.

13. Ellman GL, Courtney KD, Andres V, Featherstone RM. A new and rapid calorimetric determination of acetylcholinesterase activity. Biochem Pharmacol 1961; 7: 88-90. Baylac S, Racine P. Inhibition of 5-lipoxygenase by essential oils and other natural fragrant extracts. Int J Aromather 2003; 13: 138-142.

14. Aziz-ur-Rehman, Afroz S, Abbasi MA, Tanveer W, Khan KM, Ashraf M, Afzal I, Ambreen N. Synthesis characterization and biological screening of sulfonamides derived from 2-phenylethylamine. Pak J Pharm Sci 2012; 25(4): 809-814.