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Original Research Article

Sulfonamide Derivatives of 2-Amino-1-phenylethane as Suitable Cholinesterase Inhibitors

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Abstract

Purpose: *To evaluate the enzyme inhibition activity of N-substituted sulfamoyl derivatives of 2-amino-1-phenylethane as probable new drug candidates for the treatment of Alzheimer's diseases.*
Methods: *A series of sulfamoyl derivatives, 3a-l, of 1-amino-2-phenylethane (1) were synthesized by reacting with various aryl sulfonyl chlorides, 2a-l, in the presence of aqueous Na_2CO_3 solution under definite pH control. All the synthesized molecules were screened against three enzymes, acetyl cholinesterase (AChE), butyryl cholinesterase (BChE) and lipoxygenase (LOX). The synthesized derivatives were further characterized by infra-red spectroscopy (IR), nuclear magnetic resonance (^{1}H-NMR) and electron ionization–mass spectrometry (EI-MS) for structure elucidation.*
Results: Screening against acetyl cholinesterase (AChE), butyryl cholinesterase (BChE) and lipoxygenase (LOX) showed these molecules to be suitable inhibitors of cholinesterase enzymes, AChE and BChE, relative to eserine, the reference standard. The molecule, 3c, remained effective with 50 % inhibitory concentration (IC_{50}) value of 82.93 ± 0.15 µM (relative to eserine with IC_{50} value of 0.04 ± 0.0001 µM) against AChE; similarly 3d was active against BChE with IC_{50} value of 45.65 ± 0.48 µM compared to eserine with IC_{50} value of 0.85 ± 0.00 µM. The molecule, 3f, was inactive against all the three enzymes.
Conclusion: *Overall, the results indicate that these compounds are active against cholinesterase enzymes but less potent against lipoxygenase enzyme.*

Keywords: *1-Amino-2-phenylethane, Aryl sulfonyl chlorides, Cholinesterase enzymes, Lipoxygenase*

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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

junctions. 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 synthesize less toxic and more efficient sulfonamides against AChE, BChE and LOX enzymes, derived from 1-amino-2-phenylethane.

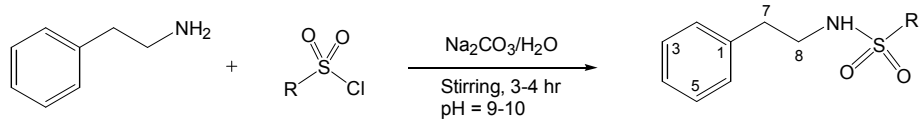
EXPERIMENTAL

Materials and instruments

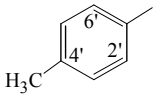
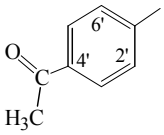
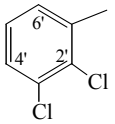
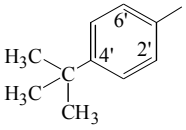
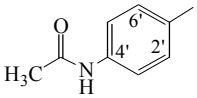
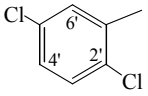
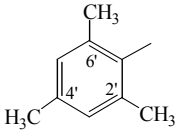
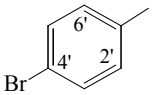
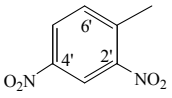
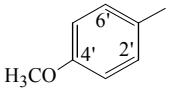
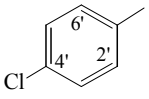
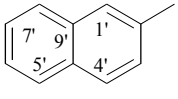
Melting points of synthesized compounds were recorded with the help of Griffin and George melting apparatus. Purity of synthesized molecules was checked by thin layer chromatography (TLC) on G-25-UV plates coated with silica gel using ethyl acetate and *n*-hexane as solvent system. Detection wavelength 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_3OD was used to record ^{1}H-NMR spectra on Bruker spectrometer working at 300 MHz. Mass spectra EI-MS were recorded with the help of JMS-HX-110 spectrometer in Finnigan MAT-112 instrument. 1-Amino-2-pheylethane 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_2CO_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_2CO_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



1 **2a-l** **3a-l**

Compd.	R	Compd.	R	Compd.	R
3a		**3e**		**3i**	
3b		**3f**		**3j**	
3c		**3g**		**3k**	
3d		**3h**		**3l**	

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 Na_2HPO_4 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 ºC. The reaction was started by the addition of 10 µL (0.5 mM $well^{-1}$) substrate (acetylthiocholine iodide for AChE and butyrylthiocholine chloride for BChE) and 10 µL DTNB (0.5 mM $well^{-1}$). After 15 min of incubation at 37 ºC, 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.

$$\text{Inhibition (\%)} = \{(Ac - At)/Ac\}100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

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

IC_{50} values were calculated using EZ–Fit Enzyme Kinetics software (Perrella Scientific Inc. Amherst, USA). IC_{50} values were calculated from the graph by a serial dilution of compounds to different concentrations. These are mean of three independent experiments.

Lipoxygenase 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 Na_3PO_4 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 reactions 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 IC_{50} 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 sulfonamide (3a)*

White crystalline solid; Yield: 94.72 %; m.p.: 98 °C; Mol. formula: $C_{15}H_{17}NO_2S$; Mol. mass: 275 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3310 (N-H stretching), 2930 (C-H stretching of aromatic ring), 2740 (-CH_2 stretching), 1601 (C=C stretching of aromatic ring), 1320 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): 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, CH_3-4); EIMS: (*m/z*): 275 $[M]^+$, 155 $[C_7H_7SO_2]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

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

Brownish black crystalline solid; Yield: 94.18%; m.p.: 112 °C; Mol. formula: $C_{18}H_{23}NO_2S$; Mol. mass: 317 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3301 (N-H stretching), 2927 (C-H stretching of aromatic ring), 2701 (-CH_2 stretching), 1617 (C=C stretching of aromatic ring), 1301 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): 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*

= 7.8 Hz, H-7), 1.34 (s, 9H, $(CH_3)_3$C-4'); EIMS (*m/z*): 317 $[M]^+$, 197 $[C_{10}H_{13}SO_2]^+$, 133 $[C_{10}H_{13}]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

N-(2-Phenylethyl)-2,4,6-trimethylbenzene sulfonamide (3c)

Brownish black viscous liquid; Yield: 94.77%; Mol. formula: $C_{17}H_{21}NO_2S$; Mol. mass: 303 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3345 (N-H stretching), 2941 (C-H stretching of aromatic ring), 2711 (-CH_2 stretching), 1635 (C=C stretching of aromatic ring), 1305 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): δ/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, CH_3-2', CH_3-6'), 2.26 (s, 3H, CH_3-4'); EIMS (*m/z*): 303 $[M]^+$, 183 $[C_9H_{11}O_2S]^+$, 119 $[C_9H_{11}]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

N-(2-Phenylethyl)-4-methoxybenzene sulfonamide (3d)

Brown thick viscous liquid; Yield: 92.14%; Mol. formula: $C_{15}H_{17}NO_3S$; Mol. mass: 291 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3332 (N-H stretching), 2946 (C-H stretching of aromatic ring), 2740 (-CH_2 stretching), 1620 (C=C stretching of aromatic ring), 1320 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): δ/ppm 7.72 (d, *J* = 9.0 Hz, 2H, H-2', H-6'), 7.21 (d, *J* = 7.5 Hz, H-2, H-6), 7.16 (t, *J* = 8.1 Hz, 1H, H-4), 7.11 (dd, *J* = 8.1, 1.5 Hz, 2H, 2H, H-3, H-5), 7.04 (d, *J* = 9.0 Hz, H-3', H-5'), 3.85 (s, 3H, CH_3O-4'), 3.03 (t, *J* = 7.8 Hz, 2H, H-8), 2.70 (t, *J* = 7.8 Hz, 2H, H-7); EIMS (*m/z*): 291 $[M]^+$, 171 $[C_7H_7O_3S]^+$, 107 $[C_7H_7O]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

N-(2-Phenylethyl)-4-acetylbenzene sulfonamide (3e)

White crystalline solid; Yield: 94.21%; m.p.: 121 °C; Mol. formula: $C_{16}H_{17}NO_3S$; Mol. mass: 303 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3341 (N-H stretching), 2921 (C-H-stretching of aromatic ring), 2707 (-CH_2 stretching), 1605 (C=C stretching of aromatic ring), 1321 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): δ/ppm 8.09 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 8.02 (d, *J* = 8.7 Hz, H-3', H-5'), 7.63 (d, *J* = 8.4 Hz, 2H, H-2, H-6), 7.26-7.13 (m, 3H, H-3 to H-5), 3.07 (t, *J* = 7.2 Hz, H-8), 2.92 (t, *J* = 7.2 Hz, H-7), 1.50 (s, 3H, CH_3CO-4'); EIMS (*m/z*): 303 $[M]^+$, 183 $[C_8H_7SO_3]^+$, 120 $[C_8H_{10}N]^+$, 119 $[C_8H_7O]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

N-(2-Phenylethyl)-4-acetamidobenzene sulfonamide (3f)

White Crystalline Solid; Yield: 91.21%; m.p: 107 °C, Mol. formula: $C_{16}H_{18}N_2O_3S$; Mol. mass: 318 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3301 (N-H stretching), 2921 (C-H stretching of aromatic ring), 2715 (-CH_2 stretching), 1615 (C=C stretching of aromatic ring), 1311 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): δ/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, CH_3CONH-4'); EIMS (*m/z*): 318 $[M]^+$, 198 $[C_8H_8SO_3N]^+$, 134 $[C_8H_8ON]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

N-(2-Phenylethyl)-4-bromobenzene sulfonamide (3g)

Yellowish white crystalline solid; Yield: 94.40%; m.p.: 113 °C; Mol. formula: $C_{14}H_{14}BrNO_2S$; Mol. mass: 339 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3317 (N-H stretching), 2925 (C-H stretching of aromatic ring), 2701 (-CH_2 stretching), 1619 (C=C stretching of aromatic ring), 1301 (S=O stretching); ^{1}H-NMR (300 MHz, MeOD): δ/ppm 7.68 (d, *J* = 8.4 Hz, 2H, H-3', H-5'), 7.65 (d, *J* = 8.1 Hz, 2H, H-2', H-6'), 7.21-7.11 (m, 5H, H-2 to H-6), 3.08 (t, *J* = 6.9 Hz, 2H, H-8), 2.72 (t, *J* = 6.9 Hz, 2H, H-7); EIMS (*m/z*): 341 $[M+2]^+$, 339 $[M]^+$, 220 $[C_6H_4BrSO_2]^+$, 156 $[C_6H_4Br]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

N-(2-Phenylethyl)-4-chlorobenzene sulfonamide (3h)

White crystalline solid; Yield: 94.25%; m.p.: 101 °C; Mol. formula: $C_{14}H_{14}ClNO_2S$; Mol. mass: 295 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3327 (N-H stretching), 2913 (C-H stretching of aromatic ring), 2714 (-CH_2 stretching), 1614 (C=C stretching of aromatic ring), 1310 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): δ/ppm 7.75 (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 $[M]^+$, 175 $[C_6H_4SO_2Cl]^+$, 120 $[C_8H_{10}N]^+$, 111 $[C_6H_4Cl]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

N-(2-Phenylethyl)-2,3-dichlorobenzene sulfonamide (3i)

White crystalline solid; Yield: 92.31%; m.p.: 115 °C; Mol. formula: $C_{14}H_{13}Cl_2NO_2S$; Mol. mass: 329 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3331 (N-H stretching), 2901 (C-H stretching of aromatic ring), 2705 (-CH_2 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-4), 7.06 (dd, *J* = 7.8, 1.2 Hz, 2H, H-3, H-5), 3.19 (t, *J* = 7.2 Hz, 2H, H-8), 2.70 (t, *J* = 7.2 Hz, 2H, H-7); EIMS (*m/z*): 333 $[M+4]^+$, 331 $[M+2]^+$, 329 $[M]^+$, 209 $[C_6H_3O_2Cl_2S]^+$, 145 $[C_6H_3Cl_2]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

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

White crystalline solid; Yield: 93.21%; m.p.: 101 °C, Mol. formula: $C_{14}H_{13}Cl_2NO_2S$; Mol. mass: 329 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3319 (N-H stretching), 2912 (C-H stretching of aromatic ring), 2719 (-CH_2 stretching), 1621 (C=C stretching of aromatic ring), 1321 (S=O stretching), ^{1}H-NMR (300 MHz, CD3OD): δ/ppm 7.92 (d, *J* = 2.1 Hz, 1H, H-6'), 7.54 (dd, *J* = 8.4, 2.1 Hz, 1H, H-4'), 7.50 (d, *J* = 8.4 Hz, 1H, H-3'), 7.19 (d, *J* = 7.5 Hz, 2H, H-2, H-6), 7.12 (t, *J* = 7.5 Hz, 1H, H-4), 7.07 (dd, *J* = 8.1, 1.2 Hz, 2H, H-3, H-5), 3.29 (t, *J* = 7.5 Hz, 2H, H-8), 2.72 (t, *J* = 7.2 Hz, H-7); EIMS (*m/z*): 333 $[M+4]^+$, 331 $[M+2]^+$, 329 $[M]^+$, 209 $[C_6H_3Cl_2O_2S]^+$, 145 $[C_6H_3Cl_2]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

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

Yellowish white crystalline solid; Yield: 91.34%; m.p.: 101 °C; Mol. formula: $C_{14}H_{13}N_3O_6S$; Mol. mass: 351 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3311 (N-H stretching), 2931 (C-H stretching of aromatic ring), 2725 (-CH_2 stretching), 1607 (C=C stretching of aromatic ring), 1313 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): δ/ppm 8.62 (d, *J* = 2.4 Hz, 1H, H-3'), 8.44 (dd, *J* = 8.7, 2.1 Hz, H-5'), 8.09 (d, *J* = 8.7 Hz, 1H, H-6'), 7.15-7.03 (m, 5H, H-2 to H-6), 3.39 (t, *J* = 7.2 Hz, 2H, H-8), 2.78 (t, *J* = 6.9 Hz, 2H, H-7); EIMS (*m/z*): 351 $[M]^+$, 231 $[C_6H_3O_6N_2S]^+$, 167 $[C_6H_3O_4N_2]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

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

Yellow crystalline solid; Yield: 94.51%; m.p.: 92 °C; Mol. formula: $C_{18}H_{17}NO_2S$; Mol. mass: 311 $gmol^{-1}$; IR (KBr, cm^{-1}) ν_{max}: 3340 (N-H stretching), 2915 (C-H stretching of aromatic ring), 2731 (-CH_2 stretching), 1619 (C=C stretching of aromatic ring), 1319 (S=O stretching); ^{1}H-NMR (300 MHz, CD3OD): δ/ppm 8.37 (s, 1H, H-1'), 8.17 (t, *J* = 8.4 Hz, H-6'), 8.00 (d, *J* = 8.7 Hz, H-4'), 7.95 (d, *J* = 9.3 Hz, H-3'), 7.78 (dd, *J* = 8.7, 1.8 Hz, H-5'), 7.65 (dd, *J* = 7.2, 1.5 Hz, 1H, H-8'), 7.63 (dd, *J* = 6.9, 1.5 Hz, 1H, H-7'), 7.17 (dd, *J* = 7.2, 1.2 Hz, 2H, H-2, H-6), 7.11 (t, *J* = 6.9 Hz, 1H, H-4), 7.06 (d, *J* = 6.9 Hz, 2H, H-3, H-5), 3.18 (t, *J* = 7.2 Hz, 2H, H-8), 2.71 (t, *J* = 7.5 Hz, 2H, H-7); EIMS (*m/z*): 311 $[M]^+$, 191 $[C_{10}H_7SO_2]^+$, 127 $[C_{10}H_7]^+$, 120 $[C_8H_{10}N]^+$, 105 $[C_8H_9]^+$, 91 $[C_7H_7]^+$, 77 $[C_6H_5]^+$, 65 $[C_5H_5]^+$, 51 $[C_4H_3]^+$.

Enzyme inhibition activity

A series of sulfonamides derived from 1-amino-2-phenylethane 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 lipoxygenase (LOX) enzymes. The enzyme inhibition activity of the sulfonamide prepared by the reaction of 2-phenylethylamine and benzenesulfonyl chloride and its derivatives has previously been evaluated by our group [15]. Here, we further prepared sulfonyl derivatives of 1-amino-2-phenylethane (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 lipoxygenase enzyme.

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

Compd.	AChE		BChE		LOX	
	Inhibition (%)	IC_{50} (µM)	Inhibition (%)	IC_{50} (µM)	Inhibition (%)	IC_{50} (µM)
3a	82.34 ±3.76	402.65±1.59	69.04±2.98	304.14±1.95	81.45±0.31	251.07±0.65
3b	77.94±2.90	324.35±1.23	64.25±3.87	229.26±1.72	27.63±0.67	-
3c	86.92±2.51	82.93±0.15	66.65±2.92	143.15±0.81	33.90±0.54	-
3d	2.95±3.82	-	86.71±2.25	45.65±0.48	38.81±0.27	-
3e	82.25±3.96	184.15±0.62	79.02±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	347.14±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	326.41±1.43	81.75±2.35	234.85±1.69	5.45±0.77	-
3k	56.53±3.25	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
Control	**91.29±1.17[a]**	**0.04±0.0001[a]**	**82.82±1.09[a]**	**0.85±0.0001[a]**	**93.79±1.27[b]**	**22.4±1.3[b]**

AChE = acetyl cholinesterase; BChE = butyryl cholinesterase; LOX = lipoxygenase; a = eserine; b = baicalein

DISCUSSION

Compound **3a** was obtained as white crystalline solid having yield of 92.72 % and m.p. of 98 ^{o}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 ^{1}H-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 ^{1}H-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-3', H-5') for the other two protons of *p*-disubstituted benzene ring. The three signals appearing at δ 7.23 (dd, *J* = 7.5, 1.5 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, CH_3-4) 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-l**) were corroborated by ^{1}H-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 IC_{50} 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 > 3l > 3b > 3j > 3i > 3h > 3a > 3k**.

Butyryl cholinesterase enzyme was inhibited by almost all the molecules with higher IC_{50} 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 > 3h > 3j > 3i > 3g > 3a**.
The synthesized compounds showed moderate activities against lipoxygenase enzyme. The high IC_{50} 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.

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