BJPS

Brazilian Journal of Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902017000115237

Article

Synthesis and *in silico* study of 2-furyl(4-{4-[(substituted) sulfonyl]benzyl}-1-piperazinyl)methanone derivatives as suitable therapeutic agents

Ghulam Hussain[1], Muhammad Athar Abbasi[1,*], Aziz-ur-Rehman[1], Sabahat Zahra Siddiqui[1], Syed Adnan Ali Shah[2,3], Muhammad Ashraf[3], Qurat-ul-Ain[4], Irshad Ahmad[5], Rabia Malik[5], Muhammad Arif Lodhi[6], Farman Ali Khan[6], Muhammad Shahid[7], Hina Fatima[7]

[1]Department of Chemistry, Government College University, Lahore, Pakistan,[2]Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia, [3]Atta-ur-Rahman Institute for Natural Products Discovery (AuRIns), Universiti Teknologi MARA, Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia, [4]Department of Chemistry, The Islamia University of Bahawalpur, Bahawalpur, Pakistan, [5]Department of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan. [6]Department of Biochemistry, Abdul Wali Khan University, Mardan, Pakistan, [7]Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan

In the study presented here, a new series of 2-furyl(4-{4-[(substituted)sulfonyl]benzyl}-1-piperazinyl) methanone derivatives was targeted. The synthesis was initiated by the treatment of different secondary amines (**1a-h**) with 4-bromomethylbenzenesulfonyl chloride (**2**) to obtain various 1-{[4-(bromomethyl) phenyl]sulfonyl}amines (**3a-h**). 2-Furyl(1-piperazinyl)methanone (2-furoyl-1-piperazine; **4**) was then dissolved in acetonitrile, with the addition of K_2CO_3, and the mixture was refluxed for activation. This activated molecule was further treated with equi-molar amounts of **3a-h** to form targeted 2-furyl(4-{4-[(substituted)sulfonyl]benzyl}-1-piperazinyl)methanone derivatives (**5a-h**) in the same reaction set up. The structure confirmation of all the synthesized compounds was carried out by EI-MS, IR and ^{1}H-NMR spectral analysis. The compounds showed good enzyme inhibitory activity. Compound **5h** showed excellent inhibitory effect against acetyl- and butyrylcholinesterase with respective IC_{50} values of 2.91±0.001 and 4.35±0.004 μM, compared to eserine, a reference standard with IC_{50} values of 0.04±0.0001 and 0.85±0.001 μM, respectively, against these enzymes. All synthesized molecules were active against almost all Gram-positive and Gram-negative bacterial strains tested. The cytotoxicity of the molecules was also checked to determine their utility as possible therapeutic agents.

Uniterms: Piperazine derivatives/antimicrobial activity. Piperazine derivatives/*in silico.* Piperazine derivatives/Cholinesterase assays. Piperazine derivatives/ hemolytic activity.

INTRODUCTION

Sulfonamides have received a lot of attention in the literature because of their exciting biological properties and their role as pharmacophores of considerable historical importance (Abbasi *et al.*, 2016a, b). Heterocyclic sulfonamides have been found to be carbonic anhydrase inhibitors (Surpuran *et al.*, 1998; Di Fiore *et al.,* 2010; Smaine *et al.*, 2008) and antibacterial (Gadad *et al.*, 2000) and anticancer, antiinflammatory and analgesic (Sondhi *et al.*, 2000) agents. Furthermore, the piperazine core has displayed a wide spectrum of pharmacological activities and is part of a number of drugs that are preclinical and clinical candidates (Welsch, Snyder, Stockwell, 2010; Hussain *et al*., 2016).

Cholinesterases (acetylcholinesterase, AChE (EC 3.1.1.7)), butyrylcholinesterase, BChE (EC 3.1.1.8)), belong to the class of serine hydrolases and are responsible for the inactivation of acetylcholine at cholinergic synapses. The main effect of AChE and BChE is to catalyze the hydrolysis of the neurotransmitter acetylcholine and termination of the nerve impulse at cholinergic synapses

***Correspondence:** M. A. Abbasi. Department of Chemistry. Government College University, Lahore, Pakistan. Tel: (+92)-42-111000010 - Ext. 266. E-mail: atrabbasi@yahoo.com; abbasi@gcu.edu.pk

(Cygler *et al.*, 1993). BChE is extensively present in Alzheimer's plaques (Gauthier, 2001). Cholinesterases play an important role in Alzheimer's disease, and so their inhibitors are of great importance for the treatment of such diseases.

The bioactivity of piperazine and sulfamoyl moieties prompted us to synthesize some new molecules bearing these moieties together. The compounds synthesized were screened to explore their enzyme inhibitory and antibacterial potential. Moreover, we also carried out cytotoxicity and molecular docking studies to determine their utility as possible therapeutic agents in drug development programs.

MATERIAL AND METHODS

General

Chemicals were purchased from Sigma Aldrich and Alfa Aesar (Germany), and solvents of analytical grade were from local suppliers. Melting points were taken uncorrected on a Griffin and George apparatus using the open capillary tube method. Thin layer chromatography (TLC) using ethylacetate:*n*-hexane (30:70) as mobile phase, with detection at 254 nm, was used to determine the initial purity of the compounds. IR spectra were recorded on a Jasco-320-A spectrometer by using the KBr pellet method. ^{1}H-NMR spectra were recorded at 500 MHz in $CDCl_3$ using a Bruker spectrometer. EIMS spectra were recorded with a JMS-HX-110 spectrometer.

Synthesis of 1-{[4-(bromomethyl)phenyl]sulfonyl} amines (3a-h)

Different secondary amines (**1a-h**; 15.0 mmol) were suspended in 15 mL of distilled water in an iodine flask. The pH was adjusted to 9-10 with 10% Na_2CO_3, and 4-bromomethylbenzenesulfonyl chloride (**2**; 15.0 mmol) was added dropwise to the reaction mixture in 2-5 min. After complete addition, the iodine flask was vigorously shaken (manually) until the formation of solid precipitates. The progress of the reaction was monitored by TLC. The solid obtained was filtered, washed with distilled water and dried to yield the corresponding electrophiles 1-{[4-(bromomethyl)phenyl]sulfonyl}amines **3a-h**.

Synthesis of 2-furyl(4-{4-[(substituted)sulfonyl] benzyl}-1-piperazinyl)methanone derivatives (5a-h)

2-Furyl(1-piperazinyl)methanone (2-furoyl-1-piperazine; **4**; 0.1 g, 0.0045 mol) was dissolved in acetonitrile (20-30 mL) in a 100-mL round-bottom flask. Solid K_2CO_3 (0.0135 mol) was added and the mixture was refluxed for 0.5 h to activate compound **4**. The desired electrophiles 1-{[4-(bromomethyl)phenyl] sulfonyl}amines **3a-h**, 0.0045 mol, were added separately in each reaction. The mixture was refluxed for 4-5 h for completion. TLC was carried out to check reaction completion. Distilled water was added to the reaction mixture to obtain the precipitates, which were filtered, washed and dried to yield the desired products 2-furyl(4-{4-[(substituted)sulfonyl]benzyl}-1-piperazinyl) methanone derivatives **5a-h**.

*2-Furyl{4-[4-(4-morpholinylsulfonyl)benzyl]-1-piperazinyl}methanone (**5a**)*

Off-white amorphous solid; Yield: 90%; m.p.: 139-141 °C; HRMS: $[M]^{\bullet+}$ 419.1517 (Calcd. for $C_{20}H_{25}N_3O_5S$; 419.1604); IR (KBr, cm^{-1}) υ_{max}: 3081 (C-H str. of aromatic ring), 2878 (C-H str. of aliphatic), 1650 (C=O str.), 1578 (C=C aromatic str.), 1428 (S=O), 1192 (C-O-C bond str.), 1118 (C-N-C bond str.); ^{1}H-NMR (500 MHz, $CDCl_3$, δ/ppm): 7.71 (d, J = 8.2 Hz, 2H, H-3'' & H-5''), 7.54 (d, J = 8.1 Hz, 2H, H-2'' & H-6''), 7.46 (distorted d, J = 1.5 Hz, 1H, H-5'), 6.99 (d, J = 3.4 Hz, 1H, H-3'), 6.47 (dd, J = 1.7, 3.4 Hz, 1H, H-4'), 3.82 (br.s, 4H, CH_2-2 & CH_2-6), 3.76-3.74 (m, 4H, CH_2-3''' & CH_2-5'''), 3.61 (s, 2H, CH_2-7''), 3.01 (m, 4H, CH_2-3 & CH_2-5), 2.51(m, 4H, CH_2-2''' & CH_2-6'''); EIMS (*m/z*): 419 $[M]^+$, 324 $[C_{15}H_{22}N_3O_3S]^+$, 323 $[C_{15}H_{21}N_3O_3S]^{\bullet+}$, 268 $[C_{16}H_{16}N_2O_2]^{\bullet+}$, 241 $[C_{11}H_{15}NO_3S]^{\bullet+}$, 240 $[C_{11}H_{14}NO_3S]^+$, 193 $[C_{10}H_{13}N_2O_2]^+$,179 $[C_9H_{11}N_2O_2]^+$, 175 $[C_6H_9NO_3S]^{\bullet+}$, 95 $[C_5H_3O_2]^+$, 86 $[C_4H_8NO]^+$.

*(4-{4-[(3,5-dimethyl-4-morpholinyl)sulfonyl]benzyl}-1-piperazinyl)(2-Furyl)methanone (**5b**)*

White amorphous solid; Yield: 87%; m.p.: 151-153 °C; HRMS: $[M]^{\bullet+}$ 447.1823 (Calcd. for $C_{22}H_{29}N_3O_5S$; 447.1876); IR (KBr, cm^{-1}) υ_{max}: 3089 (C-H str. of aromatic ring), 2878 (C-H str. of aliphatic), 1652 (C=O str.), 1587 (C=C aromatic str.), 1435 (S=O), 1193 (C-O-C bond str.), 1119 (C-N-C bond str.); ^{1}H-NMR (500 MHz, $CDCl_3$, δ/ppm): 7.75 (d, J = 8.1 Hz, 2H, H-3'' & H-5''), 7.56 (d, J = 8.1 Hz, 2H, H-2'' & H-6''), 7.49 (distorted d, J = 1.6 Hz, 1H, H-5'), 7.05 (d, J = 3.4 Hz, 1H, H-3'), 6.48 (dd, J = 1.6, 3.4 Hz, 1H, H-4'), 3.85 (br.s, 4H, CH_2-2 & CH_2-6), 3.82 (m, 4H, CH_2-2''' & CH_2-6'''), 3.76-3.74 (m, 2H, CH-3''' & CH-5'''), 3.60 (s, 2H, CH_2-7''), 3.09 (m, 4H, CH_2-3 & CH_2-5), 1.35 (s, 6H, CH_3-7''' & CH_3-8'''); EIMS (*m/z*): 447 $[M]^+$, 352 $[C_{17}H_{26}N_3O_3S]^+$, 351 $[C_{17}H_{25}N_3O_3S]^{\bullet+}$, 268 $[C_{16}H_{16}N_2O_2]^{\bullet+}$, 269 $[C_{13}H_{19}NO_3S]^{\bullet+}$, 268 $[C_{13}H_{19}NO_3S]^+$, 193 $[C_{10}H_{13}N_2O_2]^+$,179 $[C_9H_{11}N_2O_2]^+$, 203 $[C_8H_{13}NO_3S]^{\bullet+}$, 95 $[C_5H_3O_2]^+$, 114 $[C_6H_{12}NO]^+$.

*2-Furyl{4-[4-(1-piperidinylsulfonyl)benzyl]-1-piperazinyl}methanone (**5c**)*

Light brown crystalline solid; Yield: 91 %; m.p.: 60-62 °C; HRMS: $[M]^{\bullet+}$ 417.1726 (Calcd. for $C_{21}H_{27}N_3O_4S$; 417.1748); IR (KBr, cm^{-1}) υ_{max}: 3086 (C-H str. of aromatic ring), 2878 (C-H str. of aliphatic), 1659 (C=O str.), 1576 (C=C aromatic str.), 1426 (S=O), 1191 (C-O-C bond str.), 1109 (C-N-C bond str.); ^{1}H-NMR (500 MHz, $CDCl_3$, δ/ ppm): 7.68 (d, J = 8.2 Hz, 2H, H-3'' & H-5''), 7.47 (d, J = 8.1 Hz, 2H, H-2'' & H-6''), 7.50-7.47 (merged s, 1H, H-5'), 6.97 (d, J = 3.3 Hz, 1H, H-3'), 6.47 (dd, J = 1.7, 3.3 Hz, 1H, H-4'), 3.76 (br.s, 4H, CH_2-2 & CH_2-6), 3.52 (s, 2H, CH_2-7''), 2.98 (m, 4H, CH_2-3 & CH_2-5), 2.92 (m, 4H, CH_2-2''' & CH_2-6'''), 1.59(m, 4H, CH_2-3''' & CH_2-5'''), 1.50 (m, 2H, CH_2-4'''); EIMS (*m/z*): 417 $[M]^+$, 322 $[C_{16}H_{24}N_3O_2S]^+$, 321 $[C_{16}H_{23}N_3O_2S]^{\bullet+}$, 268 $[C_{16}H_{16}N_2O_2]^{\bullet+}$, 239 $[C_{12}H_{17}NO_2S]^{\bullet+}$, 238 $[C_{12}H_{16}NO_2S]^+$, 193 $[C_{10}H_{13}N_2O_2]^+$,179 $[C_9H_{11}N_2O_2]^+$, 173 $[C_7H_{11}NO_2S]^{\bullet+}$, 95 $[C_5H_3O_2]^+$, 84 $[C_5H_{10}N]^+$.

*2-Furyl(4-{4-[(2-methyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)methanone (**5d**)*

Brown amorphous solid; Yield: 85 %; m.p.: 81-83 °C; HRMS: $[M]^{\bullet+}$ 431.1873 (Calcd. for $C_{22}H_{29}N_3O_4S$; 431.1889); IR (KBr, cm^{-1}) υ_{max}: 3092 (C-H str. of aromatic ring), 2880 (C-H str. of aliphatic), 1663 (C=O str.), 1584 (C=C aromatic str.), 1433 (S=O), 1195 (C-O-C bond str.), 1121 (C-N-C bond str.); ^{1}H-NMR (500 MHz, $CDCl_3$, δ/ ppm): 7.60 (d, J = 8.2 Hz, 2H, H-3'' & H-5''), 7.45 (d, J = 8.2 Hz, 2H, H-2'' & H-6''), 7.48 (distorted d, J = 1.5 Hz, 1H, H-5'), 6.98 (d, J = 3.4 Hz, 1H, H-3'), 6.49 (dd, J = 1.5, 3.3 Hz, 1H, H-4'), 3.79 (br.s, 4H, CH_2-2 & CH_2-6), 3.59 (s, 2H, CH_2-7''), 2.99 (m, 4H, CH_2-3 & CH_2-5), 2.92 (m, 1H, CH_2-2'''), 2.75 (m, 2H, CH_2-6'''), 1.95-1.46 (m, 6H, CH_2-3''' - CH_2-5'''), 0.96 (s, 3H, CH_3-7'''); EIMS (*m/z*): 431$[M]^+$, 336 $[C_{17}H_{26}N_3O_2S]^+$, 335 $[C_{17}H_{25}N_3O_2S]^{\bullet+}$, 268 $[C_{16}H_{16}N_2O_2]^{\bullet+}$, 253 $[C_{13}H_{19}NO_2S]^{\bullet+}$, 252 $[C_{13}H_{18}NO_2S]^+$, 193 $[C_{10}H_{13}N_2O_2]^+$,179 $[C_9H_{11}N_2O_2]^+$, 187 $[C_8H_{13}NO_2S]^{\bullet+}$, 95 $[C_5H_3O_2]^+$, 98 $[C_6H_{12}N]^+$.

*2-Furyl(4-{4-[(3-methyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)methanone (**5e**)*

Brown amorphous solid; Yield: 80%; m.p.: 80-82 °C; HRMS: $[M]^{\bullet+}$ 431.1873 (Calcd. for $C_{22}H_{29}N_3O_4S$; 431.1889); IR (KBr, cm^{-1}) υ_{max}: 3089 (C-H str. of aromatic ring), 2876 (C-H str. of aliphatic), 1654 (C=O str.), 1579 (C=C aromatic str.), 1431 (S=O), 1189 (C-O-C bond str.), 1115 (C-N-C bond str.); ^{1}H-NMR (500 MHz, $CDCl_3$, δ/ ppm): 7.69 (d, J = 8.1 Hz, 2H, H-3'' & H-5''), 7.45 (d, J = 8.1 Hz, 2H, H-2'' & H-6''), 7.51 (distorted d, J = 1.4 Hz, 1H, H-5'), 7.03 (d, J = 3.3 Hz, 1H, H-3'), 6.43 (dd, J = 1.5, 3.3 Hz, 1H, H-4'), 3.84 (br.s, 4H, CH_2-2 & CH_2-6), 3.46 (s, 2H, CH_2-7''), 3.07 (m, 4H, CH_2-3 & CH_2-5), 2.90-2.60 (m, 4H, CH_2-2''' & CH_2-6'''), 1.75 (m, 1H, CH_2-3'''), 1.81-1.48 (m, 4H, CH_2-4''' & CH_2-5'''), 0.98 (s, 3H, CH_3-7'''); EIMS (*m/z*): 431$[M]^+$, 336 $[C_{17}H_{26}N_3O_2S]^+$, 335 $[C_{17}H_{25}N_3O_2S]^{\bullet+}$, 268 $[C_{16}H_{16}N_2O_2]^{\bullet+}$, 253 $[C_{13}H_{19}NO_2S]^{\bullet+}$, 252 $[C_{13}H_{18}NO_2S]^+$, 193 $[C_{10}H_{13}N_2O_2]^+$,179 $[C_9H_{11}N_2O_2]^+$, 187 $[C_8H_{13}NO_2S]^{\bullet+}$, 95 $[C_5H_3O_2]^+$, 98 $[C_6H_{12}N]^+$.

*2-Furyl(4-{4-[(4-methyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)methanone (**5f**)*

Light brown amorphous solid; Yield: 87%; m.p.: 86-88 °C; HRMS: $[M]^{\bullet+}$ 431.1873 (Calcd. for $C_{22}H_{29}N_3O_4S$; 431.1889); IR (KBr, cm^{-1}) υ_{max}: 3086 (C-H str. of aromatic ring), 2877 (C-H str. of aliphatic), 1657 (C=O str.), 1580 (C=C aromatic str.), 1430 (S=O), 1190 (C-O-C bond str.), 1116 (C-N-C bond str.); ^{1}H-NMR (500 MHz, $CDCl_3$, δ/ ppm): 7.62 (d, J = 8.0 Hz, 2H, H-3'' & H-5''), 7.54 (d, J = 8.1 Hz, 2H, H-2'' & H-6''), 7.46 (distorted d, J = 1.7 Hz, 1H, H-5'), 6.90 (d, J = 3.5 Hz, 1H, H-3'), 6.40 (dd, J = 1.7, 3.4 Hz, 1H, H-4'), 3.79 (br.s, 4H, CH_2-2 & CH_2-6), 3.55 (s, 2H, CH_2-7''), 2.91 (m, 4H, CH_2-3 & CH_2-5), 2.92-2.67 (m, 4H, CH_2-2''' & CH_2-6'''), 1.64-1.52(m, 4H, CH_2-3''' & CH_2-5'''), 1.54(m, 1H, CH_2-4'''), 0.99 (s, 3H, CH_3-7'''); EIMS (*m/z*): 431$[M]^+$, 336 $[C_{17}H_{26}N_3O_2S]^+$, 335 $[C_{17}H_{25}N_3O_2S]^{\bullet+}$, 268 $[C_{16}H_{16}N_2O_2]^{\bullet+}$, 253 $[C_{13}H_{19}NO_2S]^{\bullet+}$, 252 $[C_{13}H_{18}NO_2S]^+$, 193 $[C_{10}H_{13}N_2O_2]^+$,179 $[C_9H_{11}N_2O_2]^+$, 187 $[C_8H_{13}NO_2S]^{\bullet+}$, 95 $[C_5H_3O_2]^+$, 98 $[C_6H_{12}N]^+$.

*2-Furyl(4-{4-[(2,6-dimethyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)(2- methanone (**5g**)*

Light brown amorphous solid; Yield: 78%; m.p.: 91-93 °C; HRMS: $[M]^{\bullet+}$ 445.2037 (Calcd. for $C_{23}H_{31}N_3O_4S$; 445.2057); IR (KBr, cm^{-1}) υ_{max}: 3089 (C-H str. of aromatic ring), 2873 (C-H str. of aliphatic), 1658 (C=O str.), 1581 (C=C aromatic str.), 1437 (S=O), 1181 (C-O-C bond str.), 1117 (C-N-C bond str.); ^{1}H-NMR (500 MHz, $CDCl_3$, δ/ ppm): 7.65 (d, J = 8.2 Hz, 2H, H-3'' & H-5''), 7.49 (d, J = 8.1 Hz, 2H, H-2'' & H-6''), 7.56 (distorted d, J = 1.5 Hz, 1H, H-5'), 6.95 (d, J = 3.3 Hz, 1H, H-3'), 6.48 (dd, J = 1.5, 3.3 Hz, 1H, H-4'), 3.79 (br.s, 4H, CH_2-2 & CH_2-6), 3.54 (s, 2H, CH_2-7''), 2.93 (m, 4H, CH_2-3 & CH_2-5), 2.98 (m, 2H, CH_2-2''' & CH_2-6'''), 1.67-1.45 (m, 4H, CH_2-3''' & CH_2-5'''), 0.96 (s, 6H, CH_3-7''' & CH_3-8'''); EIMS (*m/z*): 445 $[M]^+$, 350 $[C_{18}H_{28}N_3O_2S]^+$, 349 $[C_{18}H_{27}N_3O_2S]^{\bullet+}$, 268 $[C_{16}H_{16}N_2O_2]^{\bullet+}$, 267 $[C_{14}H_{21}NO_2S]^{\bullet+}$, 266 $[C_{14}H_{20}NO_2S]^+$, 193 $[C_{10}H_{13}N_2O_2]^+$,179 $[C_9H_{11}N_2O_2]^+$, 201 $[C_9H_{15}NO_2S]^{\bullet+}$, 95 $[C_5H_3O_2]^+$, 112 $[C_7H_{14}N]^+$.

*2-Furyl-(4-{4-[(3,5-dimethyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinylmethanone (**5h**)*

Off-white amorphous solid; Yield: 89 %; m.p.: 90-92

°C; HRMS: $[M]^{\bullet+}$ 445.2037 (Calcd. for $C_{23}H_{31}N_3O_4S$; 445.2057); IR (KBr, cm^{-1}) υ_{max}: 3085 (C-H str. of aromatic ring), 2872 (C-H str. of aliphatic), 1650 (C=O str.), 1588 (C=C aromatic str.), 1435 (S=O), 1183 (C-O-C bond str.), 1111 (C-N-C bond str.); ^{1}H-NMR (500 MHz, $CDCl_3$, δ/ppm): 7.71 (d, J = 8.2 Hz, 2H, H-3'' & H-5''), 7.45 (d, J = 8.0 Hz, 2H, H-2'' & H-6''), 7.46 (distorted d, J = 1.4 Hz, 1H, H-5'), 6.90 (d, J = 3.2 Hz, 1H, H-3'), 6.45 (dd, J = 1.5, 3.4 Hz, 1H, H-4'), 3.72 (br.s, 4H, CH_2-2 & CH_2-6), 3.45 (s, 2H, CH_2-7''), 2.89 (m, 4H, CH_2-3 & CH_2-5), 2.90-2.61 (m, 4H, CH_2-2''' & CH_2-6'''), 1.59-1.50 (m, 2H, CH_2-3''' & CH_2-5'''), 1.45-1.34 (m, 2H, CH_2-4'''), 1.01 (s, 6H, CH_3-7''' & CH_3-8'''); EIMS (*m/z*): 445 $[M]^+$, 350 $[C_{18}H_{28}N_3O_2S]^+$, 349 $[C_{18}H_{27}N_3O_2S]^{\bullet+}$, 268 $[C_{16}H_{16}N_2O_2]^{\bullet+}$, 267 $[C_{14}H_{21}NO_2S]^{\bullet+}$, 266 $[C_{14}H_{20}NO_2S]^+$, 193 $[C_{10}H_{13}N_2O_2]^+$,179 $[C_9H_{11}N_2O_2]^+$, 201 $[C_9H_{15}NO_2S]^{\bullet+}$, 95 $[C_5H_3O_2]^+$, 112 $[C_7H_{14}N]^+$.

Biological activity assays

Cholinesterase assays

The AChE and BChE inhibition study was performed according to an established method (Ellman *et al.*, 1961). The percent inhibition was calculated by the following equation:

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

The IC_{50} (concentration at which there is 50% enzyme inhibition) of compounds was calculated using EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA).

Antibacterial activity

The antibacterial activity test was performed in sterile 96-wells microplates under aseptic environments**.** The method is rooted in the principle that microbial cell number increases as the microbial growth proceeds in a log phase of growth, which results in increased absorbance of broth medium (Kaspady *et al.*, 2009; Yang *et al.*, 2006). Three Gram-negative (*Salmonella typhi, Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram-positive bacteria (*Bacillus subtilis, Staphylococcus aureus*) were included in the study. The organisms were maintained on stock culture agar medium. The test samples with suitable solvents and dilutions were pipette into wells (20 µg/well). Overnight maintained fresh bacterial culture after suitable dilution with fresh nutrient broth was poured into wells (180 µL). The initial absorbance of the culture was strictly maintained between 0.12-0.19 at 540 nm. The total volume in each well was kept to 200 µL. The incubation was done at 37 °C for 16-24 hours with lid on the microplate. The absorbance was measured, before and after incubation and the difference was noted as an index of bacterial growth at 540 nm by using microplate reader. The percent inhibition was calculated by using the formula:

$$\text{Inhibition (\%)} = \frac{X - Y}{X} \times 100$$

where X is absorbance in control with bacterial culture and Y is absorbance in test sample. Results are mean of triplicate (n=3, ± SEM). Ciprofloxacin was taken as standard.

Statistical analysis

The results are written as mean ± SEM after performance in three-folds and statistical analysis by Microsoft Excel 2010. Minimum inhibitory concentration (MIC) was calculated by using different dilutions (ranging 5-30 µg/well) and EZFit Perrella Scientific Inc. Amherst USA software.

Hemolytic activity

Hemolytic activity was evaluated by a previously reported method (Sharma, Sharma, 2001; Powell, Catranis, Maynard, 2000). Human blood was obtained from volunteers according to the Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad, Pakistan. After centrifugation, separation and washing, the % RBCs lysis was computed by noting the absorbance.

Molecular docking

To predict the bioactive conformations, various compounds (ligands) were docked into the binding pockets of the selected proteins (enzymes) by using the default parameters of MOE-Dock program.

Ligand preparation

The three-dimensional (3D) structures of the compounds synthesized were modeled by using the Build program of MOE 2009-10. The energies of the compounds were then minimized by using the default parameter of MOE energy minimization algorithm (gradients: 0.05, force field: MMFF94X). Database was created in which all the compounds (3D structures) were saved in the mdb file format for the next step of docking.

Receptor protein preparation

The 3D structures of receptor protein molecules

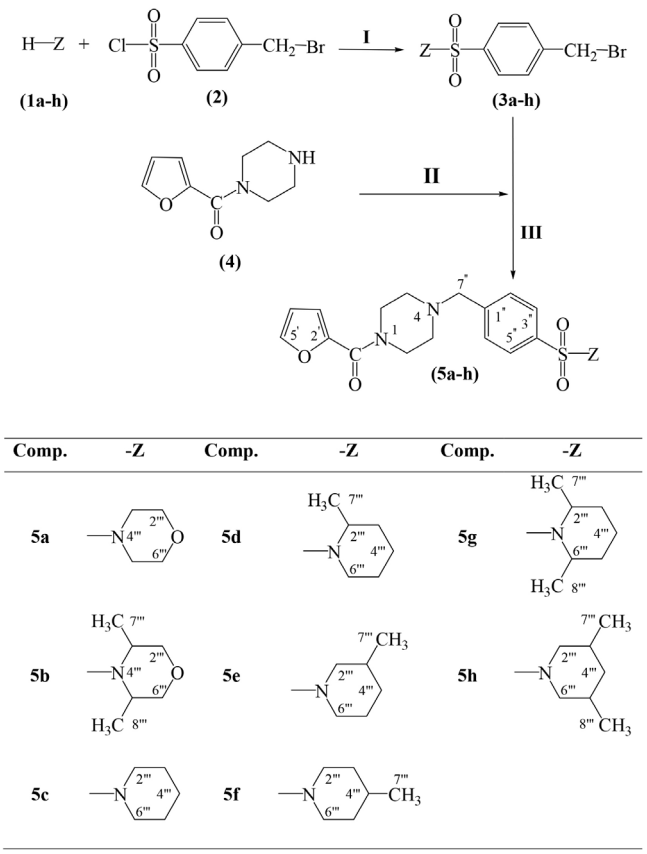
of AChE (PDB ID code: 1Zi3; Resolution: 1.69Å) and BChE (PDB ID code: 1POP; Resolution: 2.30Å) were downloaded from Protein Data Bank. All water molecules were removed from the receptor proteins and 3D protonation was carried out by using Protonate 3D Option. Protein molecules were energy minimized by using the default parameters of MOE 2009-10 energy minimization algorithm (gradient: 0.05, Force Field: MMFF94X). By using default parameters of MOE-Dock Program, all the ligands were docked into binding sites of the above proteins. Re-docking procedure was also used to increase the validity of docking protocol (Bostro, Greenwood, Gottfries, 2003).

RESULTS AND DISCUSSION

The purpose of the present study was to synthesize new molecules and to evaluate their biological activities against different enzymes and various bacterial strains. In addition, the cytotoxicity of the new compounds was also evaluated. Different 2-furyl(4-{4-[(substituted) sulfonyl]benzyl}-1-piperazinyl)methanone derivatives (**5a-h**) were synthesized in various steps as described in **Scheme 1**. The synthesis was carried out by the treatment of different secondary amines (**1a-h**) with 4-bromomethylbenzenesulfonyl chloride (**2**) to obtain solid electrophiles, **3a-h**, which were collected through filtration. 2-Furyl(1-piperazinyl)methanone (2-furoyl-1-piperazine; **4**) was then dissolved in acetonitrile and K_2CO_3 added, and the mixture was refluxed for 0.5 h for activation of this molecule. This solution was mixed with an equimolar amount of 1-{[4-(bromomethyl)phenyl] sulfonyl}amines (**3a-h**), to form the target 2-furyl(4-{4-[(substituted)sulfonyl]benzyl}-1-piperazinyl)methanones (**5a-h**).

Chemistry

The structural analysis of one of the compounds is discussed here in detail for the benefit of the reader. Compound **5c** was synthesized as a light brown crystalline solid with a melting point of 60-62 °C and molecular formula of $C_{21}H_{27}N_3O_4S$, which was confirmed by EI-MS with a $[M]^+$ peak of 417. The distinct peak at *m/z* 95 was related to the furan-2-carbaldehyde part of the molecule. The fragmentation pattern of this molecule is outlined in Figure 1. In the IR spectrum, characteristic peaks appeared at 3086 (C-H stretch of aromatic ring), 2878 (C-H stretch of aliphatic), 1659 (C=O stretch), 1576 (C=C aromatic stretch), 1426 (S=O), 1191 (C-O-C bond stretch) and 1109 (C-N-C bond stretch), confirming the presence of sulfonamide and 2-furoyl-1-piperazine ring.



SCHEME 1 - Outline for the synthesis of 2-Furyl(4-{4-[(substituted)sulfonyl]benzyl}-1-piperazinyl)methanone derivatives (**5a-h**). **Reagents and conditions:** (**I**) 10% Na_2CO_3, pH 9-10, Stirring at room temperature for 3-4 hours; (**II**) Acetonitrile, K_2CO_3, reflux for 0.5 hours (**III**) Reflux for 4-5 hours after addition of electrophiles, **3a-h**, separately one by one in each reaction.

In ^{1}H-NMR spectrum, two signals of aromatic protons appeared at δ 7.68 (d, J = 8.2 Hz, 2H, H-3'' & H-5''), 7.47 (d, J = 8.1 Hz, 2H, H-2'' & H-6''), which were typical for 1,4-disubstituted aromatic ring. The furan ring showed three peaks in the aromatic region at δ 7.50-7.47 (merged s, 1H, H-5'), 6.97 (d, J = 3.3 Hz, 1H, H-3') and 6.47 (dd, J = 1.7, 3.3 Hz, 1H, H-4'). In the aliphatic region, signals appeared for a piperazine ring at δ 3.76 (br.s, 4H, CH_2-2 & CH_2-6) and 2.98 (m, 4H, CH_2-3 & CH_2-5) for piperazine ring at δ 3.52 (s, 2H, CH_2-7'') and signals for a piperidine ring at δ 2.92 (m, 4H, CH_2-2''' & CH_2-6'''), 1.59 (m, 4H, CH_2-3''' & CH_2-5''') and 1.50 (m, 2H, CH_2-4''') with attached sulfonamide group. The EIMS and ^{1}H-NMR spectra of this molecule are shown in Figure 2 and Figure 3, respectively. These spectral data confirmed thev structure of this molecule as *2-furyl{4-[4-(1-piperidinylsulfonyl)benzyl]-1-piperazinyl}methanone*. Similarly, the structures of all the synthesized molecules,

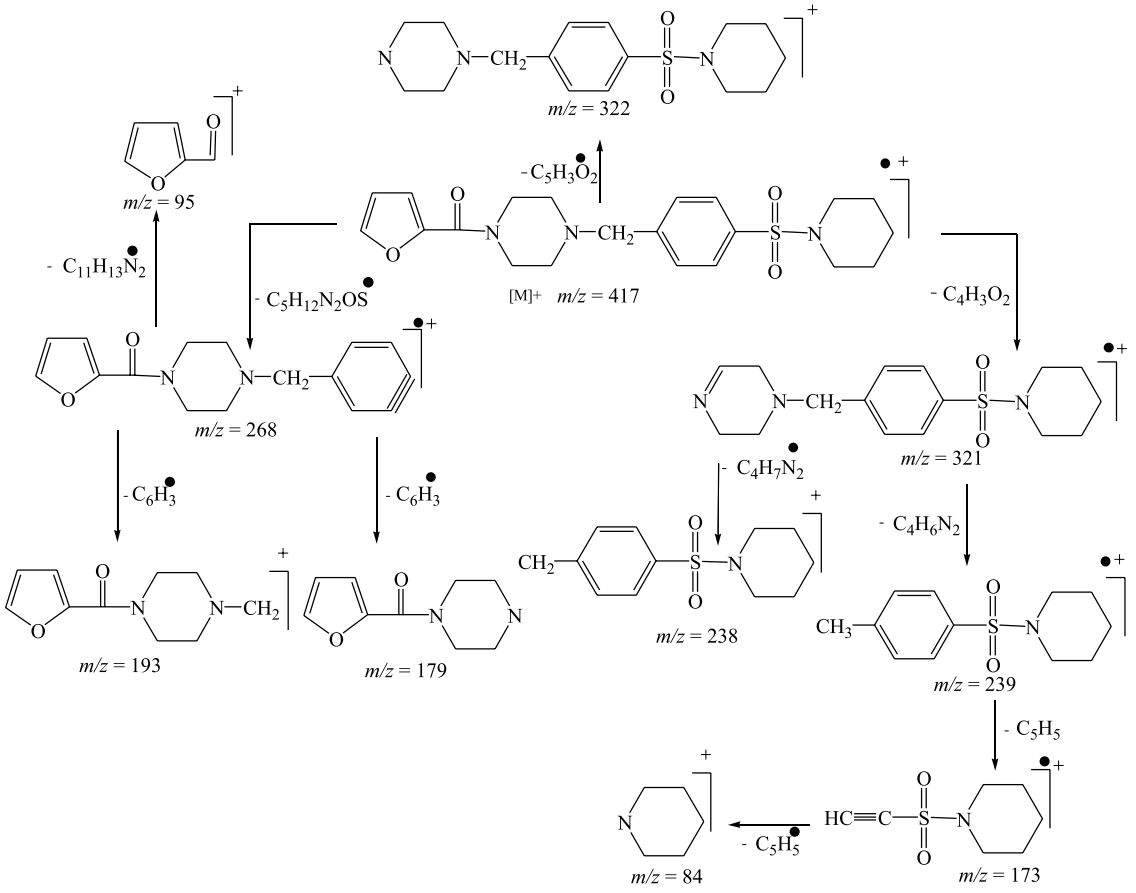


FIGURE 1 - Proposed mass fragmentation pattern of *2-furyl{4-[4-(1-piperidinylsulfonyl)benzyl]-1-piperazinyl}methanone* (**5c**).

5a-h, were characterized by their IR, ^{1}H-NMR and EI-MS spectral analysis.

Biological activities

Cholinesterase assays

The results of screening the compounds against cholinesterase are given as % inhibition and IC_{50} in Table I.

Against AChE, (4-{4-[(3,5-dimethyl-1-piperidinyl) sulfonyl]benzyl}-1-piperazinyl)(2-furyl)methanone (**5h**) was found to be an excellent inhibitor with an IC_{50} of 2.91 ± 0.001 µM, compared to eserine, a reference standard with an IC_{50} of 0.04 ± 0.0001 µM, probably due to the presence of the 3,5-dimethyl-1-piperidinyl group. Among the other molecules, 2-furyl(4-{4-[(4-methyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)methanone (**5f**) and 2-furyl(4-{4-[(2-methyl-1-piperidinyl)sulfonyl] benzyl}-1-piperazinyl)methanone (**5d**), with IC_{50} values of 13.72 ± 0.06 and 33.42 ± 0.05 µM, respectively, were found to be excellent inhibitors probably due to the presence of 4-methyl-1-piperidinyl and 2-methyl-1-piperidinyl groups.

With regard to BChE, 4-{4-[(3,5-dimethyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)(2-Furyl) methanone (**5h**) and 2furyl(4-{4-[(3-methyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)methanone (**5e**) both showed very comparable inhibitory potential compared to the standard used against, as evident from their IC_{50} values. The results are given in Table I. The IC_{50} values of these compounds were calculated to be 4.35 ± 0.004 and 8.33 ± 0.007 µM, respectively, compared to eserine with an IC_{50} of 0.85 ± 0.001 µM. The significant inhibitory potential of these molecules could have been attributed to the substitution of 3,5-dimethyl-1-piperidinyl and 3-methyl-1-piperidinyl groups. In the future these molecules can be further investigated to introduce new drug candidates.

Antibacterial activity (in vitro)

All the compounds synthesized were screened against various Gram-positive and Gram-negative bacterial strains, and most of them were found to be potent inhibitors. The results are tabulated as % inhibition and MIC values in Tables II and III, respectively.

Against *S. typhi*, 2-furyl(4-{4-[(3-methyl-1-

TABLE I - Bioactivity studies of different 2-furyl(4-{4-[(substituted)sulfonyl]benzyl}-1-piperazinyl)methanone derivatives (**5a-h**)

Compound	AChE		BChE		Hemolytic activity
	Inhibition %	IC_{50} (µM)	Inhibition %	IC_{50} (µM)	%
5a	35.67±0.16	-	41.25±0.15	-	30.12
5b	28.99±0.18	-	42.22±0.11	-	6.82
5c	76.23±0.14	51.21±0.03	52.34±0.13	372.92±0.05	10.87
5d	78.15±0.16	33.42±0.05	75.61±0.14	52.41±0.06	32.55
5e	65.45±0.11	125.28±0.08	92.44±0.12	8.33±0.007	1.66
5f	82.33±0.03	13.72±0.06	55.28±0.16	259.25±0.19	5.99
5g	63.27±0.19	165.23±0.09	57.55±0.14	217.38±0.17	35.98
5h	91.93±0.03	2.91±0.001	89.76±0.08	4.35±0.004	1.79
Eserine	**91.27±1.17**	**0.04±0.0001**	**82.82±1.09**	**0.85±0.0001**	
PBS					**0.09**
Triton					**100**

NOTE: All compounds were dissolved in methanol and experiments were performed in triplicate (mean ± SEM, n=3). AChE = acetylcholinesterase, BChE = butyrylcholinesterase

TABLE II - Antibacterial activity (% inhibition) of different 2-furyl(4-{4-[(substituted)sulfonyl]benzyl}-1-piperazinyl)methanone derivatives (**5a-h**)

Compound	Inhibition (%)				
	S. typhi (-)	*E. coli (-)*	*P. aeruginosa (-)*	*B. subtilis (+)*	*S. aureus (+)*
5a	74.48±0.97	73.65±0.68	58.37±0.80	72.93±0.23	38.38±0.62
5b	74.23±0.95	68.45±0.63	61.21±0.43	75.23±0.43	46.29±0.52
5c	69.57±0.41	59.35±0.85	52.79±0.50	62.77±0.83	44.00±0.29
5d	75.76±0.32	61.30±0.45	54.99±0.15	68.30±0.70	42.80±0.91
5e	77.73±0.14	57.40±0.60	42.99±0.19	54.67±0.65	47.90±0.42
5f	78.58±0.32	58.95±0.74	54.39±0.27	63.27±0.20	45.76±0.57
5g	67.14±0.29	63.13±0.53	73.84±0.17	66.43±0.82	45.23±0.73
5h	65.30±0.83	70.87±0.46	66.36±0.82	74.61±0.18	44.13±0.49
Ciprofloxacin	**91.05±0.68**	**92.32±0.42**	**92.50±0.34**	**92.02±053**	**91.44±0.64**

TABLE III - Antibacterial activity (MIC) and hemolytic activity of the different 2-furyl(4-{4-[(substituted)sulfonyl]benzyl}-1-piperazinyl)methanone derivatives (**5a-h**)

Compound	MIC (µM)				
	S. typhi (-)	*E. coli(-)*	*P. aeruginosa (-)*	*B. subtilis (+)*	*S. aureus (+)*
5a	9.13±0.28	9.86±0.35	15.28±0.66	9.56±0.82	_
5b	9.19±0.74	10.58±0.42	14.53±0.74	9.25±0.18	_
5c	10.31±0.25	15.95±0.63	18.33±0.61	14.87±0.56	_
5d	9.10±0.69	14.89±0.79	17.85±0.85	10.14±0.62	_
5e	8.58±0.26	16.96±0.11	_	17.92±0.45	_
5f	8.62±0.44	16.75±0.52	18.76±0.12	11.41±0.56	_
5g	13.84±0.19	12.35±0.39	9.10±0.43	16.91±0.29	_
5h	10.51±0.76	12.24±0.84	13.61±0.96	11.58±0.93	_
Ciprofloxacin	**7.45±0.58**	**7.16±0.58**	**7.14±0.18**	**7.29±0.90**	**7.80±0.19**

piperidinyl)sulfonyl]benzyl}-1-piperazinyl)methanone (**5e**) and 2-furyl(4-{4-[(4-methyl-1-piperidinyl)sulfonyl] benzyl}-1-piperazinyl)methanone (**5f**) had the lowest MIC values, 8.58 ± 0.26 and 8.62 ± 0.44 µM, respectively, most probably due to the presence of 3-methyl-1-piperidinyl and 4-methyl-1-piperidinyl. In the case of *E. coli*, 2-furyl{4-[4-(4-morpholinylsulfonyl)benzyl]-1-piperazinyl}methanone (**5a**) showed the lowest MIC value of 9.86 ± 0.35 µM, likely because of the presence of the 4-morpholinyl group. In the case of *P. aeroginosa*, (4-{4-[(2,6-dimethyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)(2-furyl)methanone (**5g**) exhibited the lowest MIC value of 9.10 ± 0.43 µM, which might have been due to presence of the 2,6-dimethyl-1-piperidinyl group. Against *B. subtilis*, (4-{4-[(3,5-dimethyl-4-morpholinyl) sulfonyl]benzyl}-1-piperazinyl)(2-furyl)methanone (**5b**) showed the lowest MIC value of 9.25 ± 0.18 µM, presumably owing to the presence of the 3,5-dimethyl-4-morpholinyl group. Surprisingly, all molecules tested were inactive against *S. aureus*.

Hemolytic activity

The highest hemolytic activity was shown by **5g** (35.98%), higher than the positive control (Triton X-100). The lowest activity was shown by **5e** (1.66%) but higher than the negative control (PBS), as shown in Table I. Some of these molecules might be further tested for their application in drug designing programs because of moderate toxicity.

Computational Docking

It is clear from Figure 2 (2D and 3D) that compound **5h** was deeply bound in the binding pockets of AChE by making two important interactions with the amino acid residues Asp211 and Trp300. Asp211 interacted strongly with the nitrogen of the piperazine ring of the ligand through Mn^{++}, giving a bond length of 2.19 Å. A second arene-arene interaction was made between Trp300 and furyl rings with a bond distance of 3.60 Å. Val210, Asp302, Glu303 and Phe121 were also present in the nearby vicinity.

Similarly, molecule **5f** showed two interactions with this enzyme. Lys125 interacted strongly with the sulfonyl oxygen of the ligand through side chain donor interaction. The bond length calculated was 2.57 Å. Tyr126 made an arene-arene interaction with the benzyl ring of the compound, giving a bond distance of 3.77 Å, as shown in Figure 3 (2D and 3D).

The *in silico* study with butyrylcholinesterase (BChE) revealed that **5h** also and another compound, **5e,** exhibited considerable interaction. It was inferred that

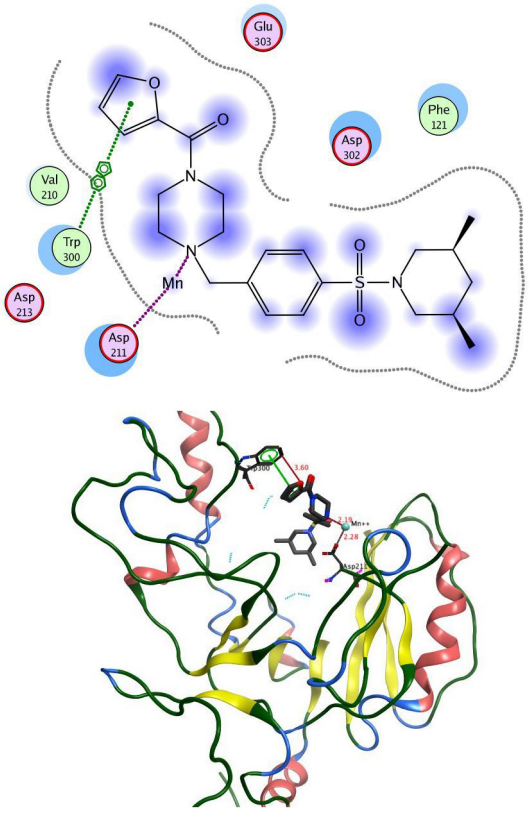


FIGURE 2 - The 2D and 3D interaction analysis of 4-{4-[(3,5-dimethyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl)(2-furyl)methanone (**5h**) with acetylcholinesterase.

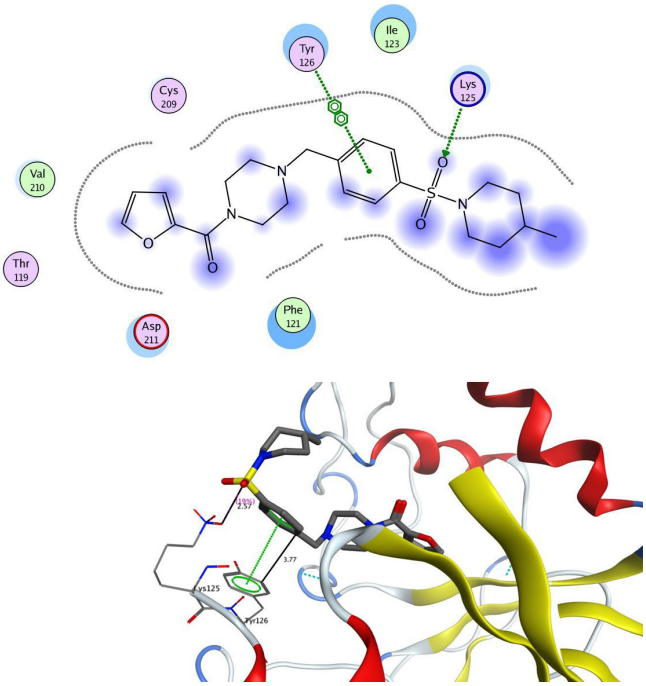


FIGURE 3 - The 2D and 3D interaction analysis of 2-furyl(4-{4-[(4-methyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl) methanone (**5f**) with acetylcholinesterase.

5h exhibited two interactions. The first side chain donor interaction was between Thr120 and the sulfonyl oxygen with a distance of 3.53 Å, while the second arene-cation interaction was between His438 and the furoyl ring of the ligand with a bond length of 3.8 9Å (Figure 4; 2D and 3D).

In the same way, compound **5e** had two interactions with the active site residues Thr120 and Trp82. Thr120 had a strong side chain donor interaction with the sulfonyl oxygen, showing a bond distance of 3.56 Å, but Trp82 produced an arene-arene interaction with the furoyl ring, showing a bond length of 4.06Å **(**Figure 5; 2D and 3D). Met437, Gly116 and His438 were also present very close to the ligand.

CONCLUSION

The synthesized compounds were confirmed by spectral data. It was evident from enzyme inhibition analysis that compound **5h** exhibited potent inhibitory activity against AChE and BChE, with IC_{50} of 2.91 ± 0.001 and 4.35±0.004 µM, respectively, as compared to the standard eserine, with IC_{50} of 0.04 ± 0.0001 and 0.85 ± 0.001 µM, which could be attributed to the presence of the 3,5-dimethyl-1-piperidinyl group in this molecule. These results were fully supported by their *in silico* study. Putting *S. aureus* aside, all of the synthesized molecules were active against the Gram-positive and Gram-negative bacterial strains tested, except compound **5e**, which was inactive against *P. aeroginosa*. The hemolytic study was also carried out to evaluate the cytotoxicity profile of the synthesized molecules. It was inferred from the results that most of molecules were moderately toxic. Hence, these molecules could be recommended as suitable therapeutic entrants in a drug development program for the pharmaceutical industry.

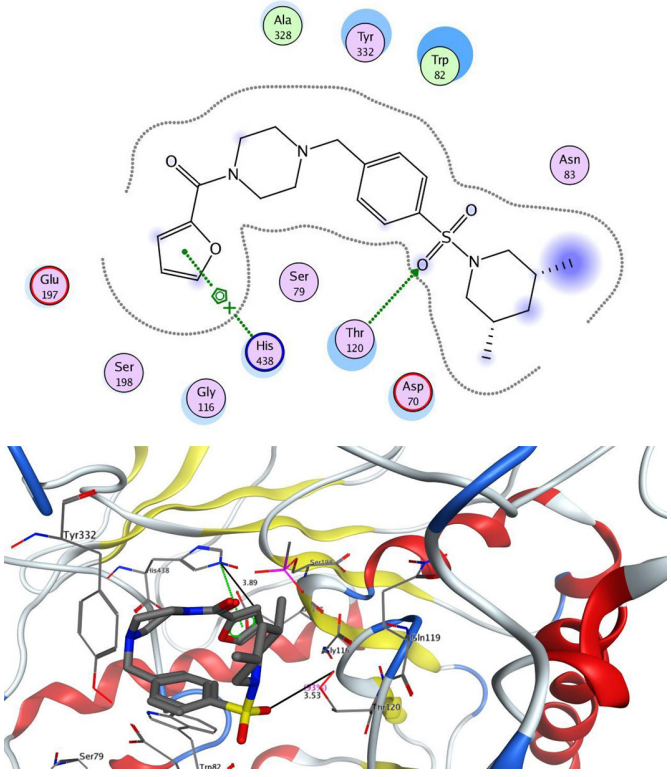


FIGURE 4 - The 2D and 3D interaction analysis of 4-{4-[(3,5-dimethyl-1-piperidinyl)sulfonyl] benzyl}-1-piperazinyl)(2-furyl)methanone (**5h**) against butrylcholinesterase.

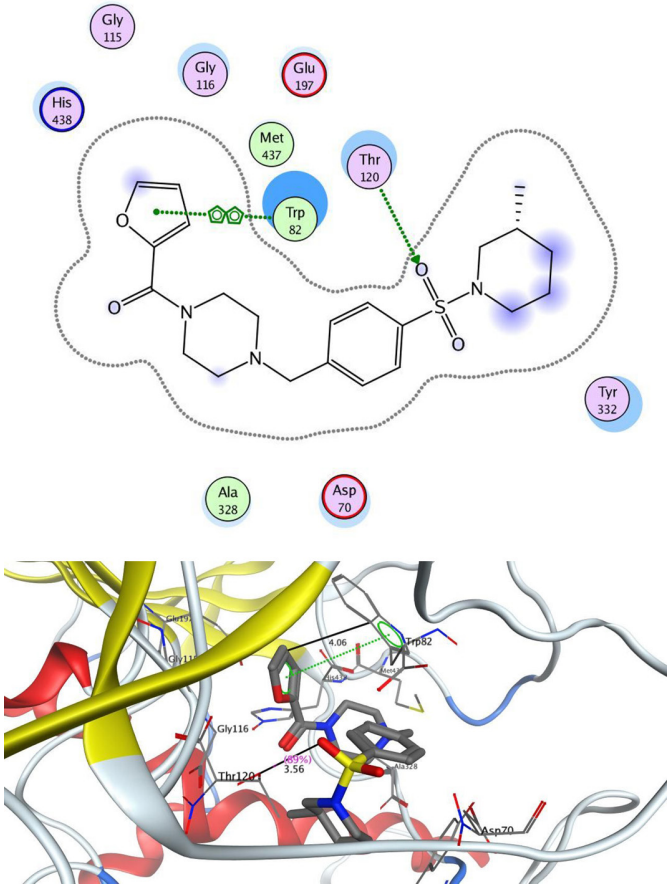


FIGURE 5 - The 2D and 3D interaction analysis of 2-furyl(4-{4-[(3-methyl-1-piperidinyl)sulfonyl]benzyl}-1-piperazinyl) methanone (**5e**) with butrylcholinesterase.

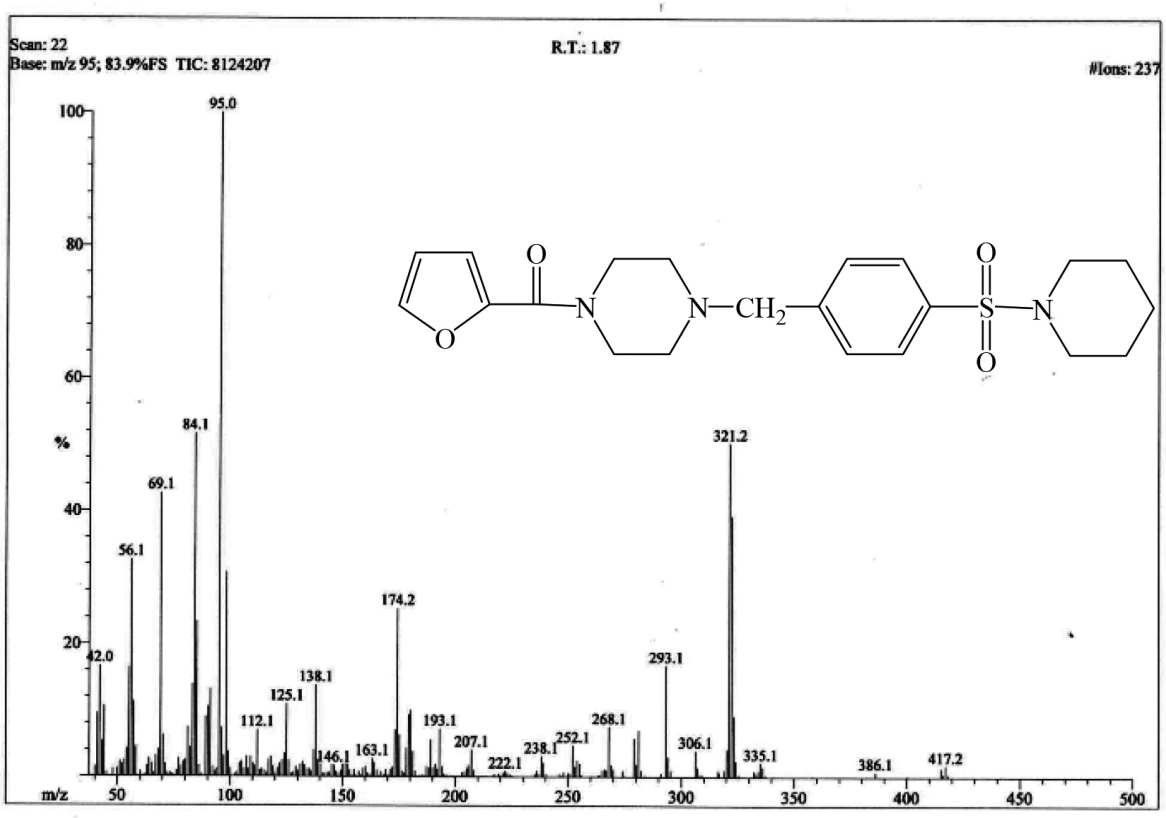


FIGURE 6 - EIMS spectrum of 2-furyl{4-[4-(1-piperidinylsulfonyl)benzyl]-1-piperazinyl}methanone (**5c**).

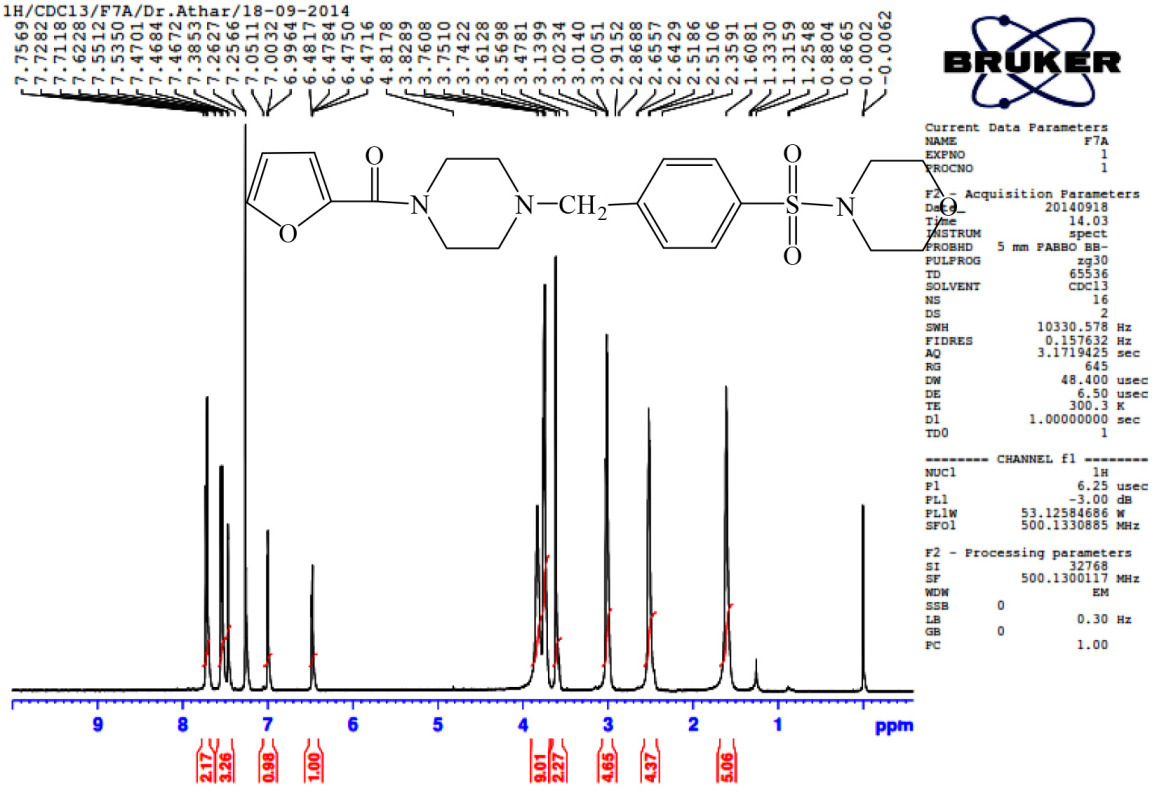


FIGURE 7 - ^{1}H-NMR spectrum of -furyl{4-[4-(4-morpholinylsulfonyl)benzyl]-1-piperazinyl}methanone (**5a**).

REFERENCES

ABBASI, M.A.; TARIQ, S.; AZIZ-UR-REHMAN; SIDDIQUI, S.Z.; AHMAD, I.; MALIK, R.; SHAH, S.A.A. Synthesis of some new *N*-substituted-2,3-dihydro-[1,4]-benzodioxin-6-yl)-4-acetamidobenzenesulfonamides as valuable antibacterial agents. *Russ. J. Bioorg. Chem.*, v.42, p.198-209, 2016.

ABBASI, M.A.; ISLAM, M.; AZIZ-UR-REHMAN; RASOOL, S.; RUBAB, K.; HUSSAIN, G.; AHMAD, I.; ASHRAF, M.; SHAHID, M.; SHAH, S.A.A. Synthesis, characterization, antibacterial, α-glucosidase inhibition and hemolytic studies on some new *N*-(2,3-dimethylphenyl)benzenesulfonamide derivatives. *Trop. J. Pharm. Res*., v.15, p.591-598, 2016.

BOSTRO, M.J.; GREENWOOD, J.R.; GOTTFRIES, J. Assessing the performance of OMEGA with respect to retrieving bioactive conformations. *Mol. Graph. Model*., v.21, p.449-462, 2003.

CYGLER, M.; SCHRAG, J.D.; SUSSMAN, J.; HAREL, L.; SILMAN, M.I.; GENTRY, M.K. Relationship between sequence conservation and three dimentional structure in a large family of esterases, lipases and related proteins. *Protein Sci.*, v.2, p.366-388, 1993.

DI FIORE, A.; MONTI, S.M.; INNOCENTI, A.; WINUMA, J.Y.; DE SIMONE, G.; SUPURAN, C.T. Carbonic anhydrase inhibitors: Crystallographic and solution binding studies for the interaction of a boroncontaining aromatic sulfamide with mammalian isoforms I–XV. *Bioorg. Med. Chem. Lett.,* v.20, p.3601-3605, 2010.

ELLMAN, G.L.; COURTNEY, K.D.; ANDRES, V.; FEATHERSTONE, R.M. A new and rapid calorimetric determination of acetylcholinesterase activity. *Bio. Pharm.*, v.7, p.88-95, 1961.

GADAD, A.K.; MAHAJANSHETTI, C.S.; NIMBALKAR, S.; RAICHURKAR, A. Synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide derivatives. *Eur. J. Med. Chem.,* v.35, p.853-857, 2000.

GAUTHIER, S. Cholinergic adverse effects of cholinesterase inhibitors in Alzheimer's disease. *Drug Aging*, v.18, p.853-862, 2001.

HUSSAIN, G.; ABBASI, M.A.; AZIZ-UR-REHMAN; SIDDIQUI, S.Z.; ASHRAF, M.; NOREEN, A.; LODHI, M.A.; KHAN, F.A.; SHAHID, M.; MUSHTAQ, Z.; SHAH, S.A.A. Synthesis and molecular docking study of some new 4-{[4-(2-furoyl)-1-piperazinyl]methyl}-*N*-(substituted-phenyl)benzamides as possible therapeutic entrants for Alzheimer's disease. *Med. Chem.*, v.6, p.129-136, 2016.

KASPADY, M.; NARAYANASWAMY, V.K.; RAJU, M.; RAO, G.K. Synthesis, antibacterial activity of 2,4-disubstituted oxazoles and thiazoles as bioesters. *Lett. Drug Des.. Disc*., v.6, p.21-28, 2009.

POWELL, W.A.; CATRANIS, C.M.; MAYNARD, C.A. Design of self-processing antimicrobial peptide for plant protection. *Lett. Appl. Microbiol.,* v.31, p.163-168, 2000.

SHARMA, P.; SHARMA, J.D. *In vitro* hemolysis of human erythrocytes by plant extracts with antiplasmodial activity. *J. Ethnopharmacol.,* v.74, p.239-243, 2001.

SMAINE, F.Z.; PACCHIANO, F.; RAMI, M.; BARRAGAN-MONTERO, V.; VULLO, D.; SCOZZAFAVA, A.; WINUMA, J.Y.; SUPURAN, C.T. Carbonic anhydrase inhibitors: 2-Substituted-1,3,4-thiadiazole-5-sulfamides act as powerful and selective inhibitors of the mitochondrial isozymes VA and VB over the cytosolic and membrane-associated carbonic anhydrases I, II and IV. *Bioorg. Med. Chem. Lett.,* v.18, p.6332-6335, 2008.

SONDHI, S.M.; JOHAR, M.; SINGHAL, N.; DASTIDAR, S.G.; SHUKLA, R.; RAGHUBIR, R. Synthesis and anticancer, anti-inflammatory and analgesic activity evaluation of some drugs and acridine derivatives. *Monatsh. Chem.*, v.131, p.511-520, 2000.

SURPURAN, C.T.; SCOZZAFAVA, A.; JURCA, B.C.; ILIES, M.A. Carbonic anhydrase inhibitors. Part 49.Synthesis of substituted ureido and thioureido derivatives of aromatic / heterocyclic sulfonamides with increased affinities for isozyme I. *Eur. J. Med. Chem.,* v.33, p.83-93, 1998.

WELSCH, M.E.; SNYDER S.A.; STOCKWELL, B.R. Privileged scaffolds for library design and drug discovery. *Curr. Opin. Chem. Biol.,* v.14, p.347-361, 2010.

YANG, C.R.; ZANG, Y.; JACOB, M.R.; KHAN, S.I.; ZHANG, Y.-J.; LI, X.-C. Antifungal activity of C-27 steroidal saponins. *Antimicrob. Agents Chemother.*, v.50, p.1710-1714, 2006.

Received for publication on 03rd December 2015
Accepted for publication on 06th October 2016