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Enzyme inhibition and antioxidant potential of new synthesized sulfonamides; synthesis, single crystal and molecular docking

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ABSTRACT

This study describes the synthesis of four (**1-4**) new phenylalanine based sulfonamides from benzene sulfonyl chlorides. The progress of the reaction was monitored on TLC and after completion; the products were subjected to various analyses that indicated the synthesis of the targeted molecules. The structure of sulfonamide **1** was elucidated on the basis of Single Crystal X-Ray Diffraction technique. While other sulfonamides were characterized with FTIR spectroscopy. The sulfonamide (**1-4**) were subjected to Density Functional Theory for optimization of the structures and to calculate the bond angle and bond length of the crystalline molecule (**1**). The DFT and SCXRD results are in close agreement with each other. All compounds were subjected to radical scavenging and enzyme inhibition studies. The compound **1** exhibited moderate antioxidant activity (38.04 %). Enzyme inhibition potential was checked against three enzymes; trypsin, acetylcholine esterase and butyrylcholine esterase using in-vitro models. This study indicated that 2-(4-acetamidophenylsulfonamido)-3-phenylpropanoic acid (**1**) was found most active among all the synthetic molecules. It exhibited inhibition of 54.07%, 72.42and 57.18 % against AChE, BChE and trypsin respectively. Docking studies of the four sulfonamides were also done with Molecular Operating Environment, which depicted good docking scores. In-silico studies also suggested good enzyme inhibition potential of these understudied molecules.

1. Introduction

In 1930's, the importance of sulfonamides in pharmaceutical industries was traced as an outcome of research [1]. Recently, in medicinal chemistry sulfonamides are being widely used. In 2011 pharmaceuticals are co-administered with a sulfonamide containing drugs [2]. Sulfonamides are essential components in pharmaceutical industry, being commonly used as anti-inflammatory, anticancer and anti-viral agents [3]. In general, synthesis of sulfonamides under mild conditions is fruitful for organic chemists, although new efforts have been made for the improvement of new sulfonamides synthesis [4]. The conservative method for the synthesis of sulfonamides from sulfonyl chlorides and amino groups is recently used because of the simplicity and reactivity of this method [5]. Thousands of chemical modifications are studied after sulfanilamide discovery. The most favorable results were obtained from the compounds in which one hydrogen atom of the SO_2NH_2 group was replaced by aryl ring [6]. Recently more than twenty thousand sulfonamides have been synthesized. This synthesis is based on the discovery of new compounds by varying substitutions starting from aliphatic to aryl moiety, resulting the alteration of the pharmacological properties [7].

Phenylalanine is an aromatic amino acid and important component of many proteins, which plays vital role in biological systems. The main sources of this amino acid are fish, meat, milk and cheese. It acts as essential part of neurotransmitters such as tyramine and dopamine thus acts as main part of neurological processes. Derivatives of phenylalanine are also used as antimicrobial agents [8]. It is used to treat various psychological diseases due to its main role in neuropeptide structure [8,9]. In this work, we have synthesized four new sulfonamides from phenylalanine and different sulfonyl chloride. The synthesized sulfonamides were subjected to anti-radical and enzyme inhibition studies.

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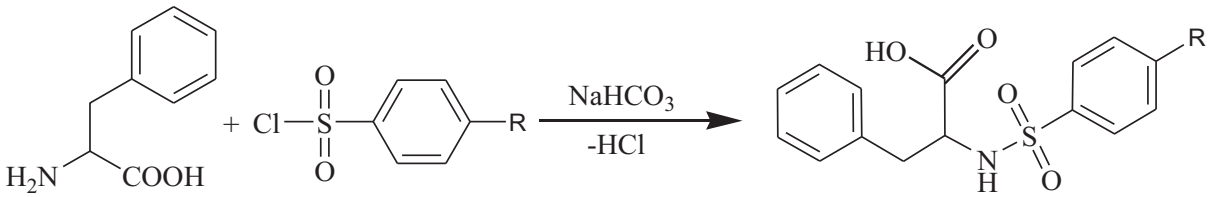

R = -N-CO-CH_3; **1**, R = Br; **2**, R = -CH_3; **3**, R = H; **4**

Scheme 1. Synthesis of sulfonamides

2. Methods and materials

2.1. Chemicals and solvents

The chemicals and reagents used in this research work were purchased from Alfa-Aesar and Sigma. Solvents such as THF, DMSO, methanol, ammonia and ethanol were used of analytical grade and purchased from Merck chemicals. UV/VIS spectrophotometer (UV-2300) of Shimadzu while FTIR of Perkin-Elmer was used for biological studies and characterization of the synthesized compounds respectively.

2.2. Synthesis of sulfonamides (1-4)

The targeted sulfonamides were synthesized according to reported method of Danish *et al.*, (2015) with some modifications [10]. Phenylalanine (1.0 mmol) and sulfonyl chlorides (1.0 mmol) were added to 30 mL distilled water. The mixture was heated at 35°C and pH was maintained at 9 with help of 1.0 M sodium bicarbonate. The reaction was monitored on TLC and after completion of the reaction, 5.0 mL of 1.0 M HCl was added, resulting in precipitate formation (Scheme 1). The product was washed with excess of distilled water and dried in oven at low temperature.

2.3. Crystallography

The compound was synthesized and crystallized to understand the geometrical arrangements of atoms in the molecule in its respective unit cell. Sample material was observed under the microscope to find the best suitable single crystal for data collection. The selected sample was glued over a glass fiber tip absorbed in a wax supported by a hollow copper rod with magnetic base. This holder was mounted on Agilent SuperNova (Dual source) Agilent Technologies Diffractometer, equipped with graphite-monochromatic Cu/Mo Kα radiation for data collection. The data collection was accomplished using CrysAlisPro software at 296 K under the Mo Kα radiation [12]. The structure solution was performed using SHELXS–97 [13] and refined by full–matrix least–squares methods on F2 using SHELXL–97 [13], in-built with WinGX [14]. All non–hydrogen atoms were refined anisotropically by full–matrix least squares methods [13]. Figures were drawn using PLATON [14] and ORTEP-3 [15]. All the C-H hydrogen atoms were positioned geometrically and treated as riding atoms where C–H = 0.93 Å and Uiso(H) = 1.2 *U*eq(C) for aromatic carbon atoms. The C-H bond distance are 0.96Å, 0.97Å and 0.98Å for methyl, methylene and methine groups respectively. *U*iso(H) was set to 1.5 times the *U*eq(C) for methyl carbon atoms while it was set to 1.2*U*eq(C) for methylene and methine carbon atoms. The N-H = 0.68(7)-0.84(6) Å, hydrogen atoms were located with difference fourier map and refined with *U*iso (H) = 1.2 *U*eq(N). The O-H = 0.89(7) Å, hydrogen atoms were also located with difference fourier map and refined with *U*iso (H) = 1.5 *U*eq(O). The cif has been submitted [1] to the CCDC and the assigned CCDC number is 1861457 for compound 1. The data can be obtained free of cost from the office of the CCDC is at 12 Union Road, Cambridge CB2 1EZ.

Table 1
Physical characteristics of synthesized compounds

Product code	Color	Solubility	Melting point (°C)
1	Off white	Ethanol	213
2	White	Ethanol	146
3	Shiny off white	Ethanol	170
4	Shiny off white	Ethanol	135

2.4. Antioxidant activity

Antioxidant potential of the synthesized sulfonamides was checked according to the method of Shahwar *et al.*, (2012) using

Table 2
Fundamental IR vibrations of sulfonamide and metal complexes

Code	$\upsilon NH_{(str)}$ (cm^{-1})	υCOO (cm^{-1})		$\Delta\upsilon$ (cm^{-1})	$\upsilon S{=}O$ (cm^{-1})		υM-O (cm^{-1})
		Asym	sym		asym	sym	
1	3270	1625	1413	212	1345	1187	-
2	3284	1602	1462	208	1332	1175	-
3	3283	1668	1427	241	1329	1149	-
4	3335	1688	1433	255	1354	1178	-

Table 3
Crystal data and structure refinement of compound 1

Identification code	16117
Empirical formula	$C_{17}H_{18}N_2O_5S$
Formula weight	362.39
Temperature/K	296.15
Crystal system	monoclinic
Space group	$P2_1$
a/Å	5.1258(7)
b/Å	20.257(2)
c/Å	8.4164(11)
α/°	90
β/°	102.272(14)
γ/°	90
Volume/Å^3	853.93(19)
Z	2
ρ_{calc}mg/mm^3	1.409
μ/mm^{-1}	0.220
F(000)	380.0
Crystal size/mm^3	0.28 × 0.24 × 0.19
2θ range for data collection	6.382 to 58.626°
Index ranges	-7 ≤ h ≤ 6, -25 ≤ k ≤ 27, -5 ≤ l ≤ 11
Reflections collected	3937
Independent reflections	3203[R(int) = 0.0334]
Data/restraints/parameters	3203/1/238
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0586, wR_2 = 0.1467
Final R indexes [all data]	R_1 = 0.0704, wR_2 = 0.1583
Largest diff. peak/hole / e Å^{-3}	0.39/-0.42
Flack parameter	-0.05(16)

Table 4
Bond lengths of compound **1**

Atom	Atom	Length/Å SCXRD	DFT	Atom	Atom	Length/Å SCXRD	DFT
S1	O1	1.427(4)	1.64237	C3	C4	1.385(8)	1.41152
S1	O2	1.438(4)	1.63087	C4	C5	1.395(8)	1.40982
S1	N1	1.595(5)	1.76510	C5	C6	1.391(8)	1.39693
S1	C1	1.768(5)	1.86675	C7	C8	1.540(8)	1.56111
O3	C15	1.201(7)	1.23495	C7	C15	1.509(7)	1.52081
O4	C15	1.319(7)	1.37073	C8	C9	1.518(8)	1.51622
O5	C16	1.218(7)	1.24661	C9	C10	1.383(9)	1.40705
N1	C7	1.454(7)	1.46359	C9	C14	1.373(9)	1.40596
N2	C4	1.407(7)	1.41005	C10	C11	1.401(11)	1.39926
N2	C16	1.345(7)	1.38733	C11	C12	1.380(13)	1.40014
C1	C2	1.394(7)	1.39403	C12	C13	1.340(12)	1.39959
C1	C6	1.367(8)	1.39056	C13	C14	1.376(9)	1.39921
C2	C3	1.384(8)	1.39279	C16	C17	1.499(8)	1.51607

Table 5
Bond angles of compound **1**

Atom	Atom	Atom	Angle/° SCXRD	DFT	Atom	Atom	Atom	Angle/° SCXRD	DFT
O1	S1	O2	119.8(2)	118.51539	N1	C7	C8	111.8(4)	109.93070
O1	S1	N1	107.2(2)	106.49301	N1	C7	C15	109.8(4)	111.50243
O1	S1	C1	106.3(2)	111.76934	C15	C7	C8	113.0(4)	111.91659
O2	S1	N1	107.0(2)	109.26027	C9	C8	C7	113.5(4)	114.23832
O2	S1	C1	107.2(2)	107.71999	C10	C9	C8	121.3(6)	120.63841
N1	S1	C1	108.9(3)	101.76433	C14	C9	C8	121.0(5)	120.69827
C7	N1	S1	121.3(4)	118.69977	C14	C9	C10	117.7(6)	118.66097
C16	N2	C4	128.9(5)	128.62795	C9	C10	C11	120.4(8)	120.62675
C2	C1	S1	120.0(4)	117.61360	C12	C11	C10	119.8(8)	120.18945
C6	C1	S1	119.8(4)	119.35150	C13	C12	C11	119.4(8)	119.66436
C6	C1	C2	120.1(5)	122.98636	C12	C13	C14	121.2(8)	120.10549
C3	C2	C1	118.8(5)	117.74519	C9	C14	C13	121.5(7)	120.75229
C2	C3	C4	121.4(5)	120.84468	O3	C15	O4	124.0(5)	122.56776
C3	C4	N2	117.4(5)	117.05055	O3	C15	C7	124.7(5)	125.62457
C3	C4	C5	119.2(5)	119.90615	O4	C15	C7	111.2(4)	111.79098
C5	C4	N2	123.3(5)	123.04312	O5	C16	N2	123.4(5)	123.43723
C6	C5	C4	119.1(5)	119.44756	O5	C16	C17	122.4(5)	121.77978
C1	C6	C5	121.2(5)	119.06372	N2	C16	C17	114.2(5)	114.77316

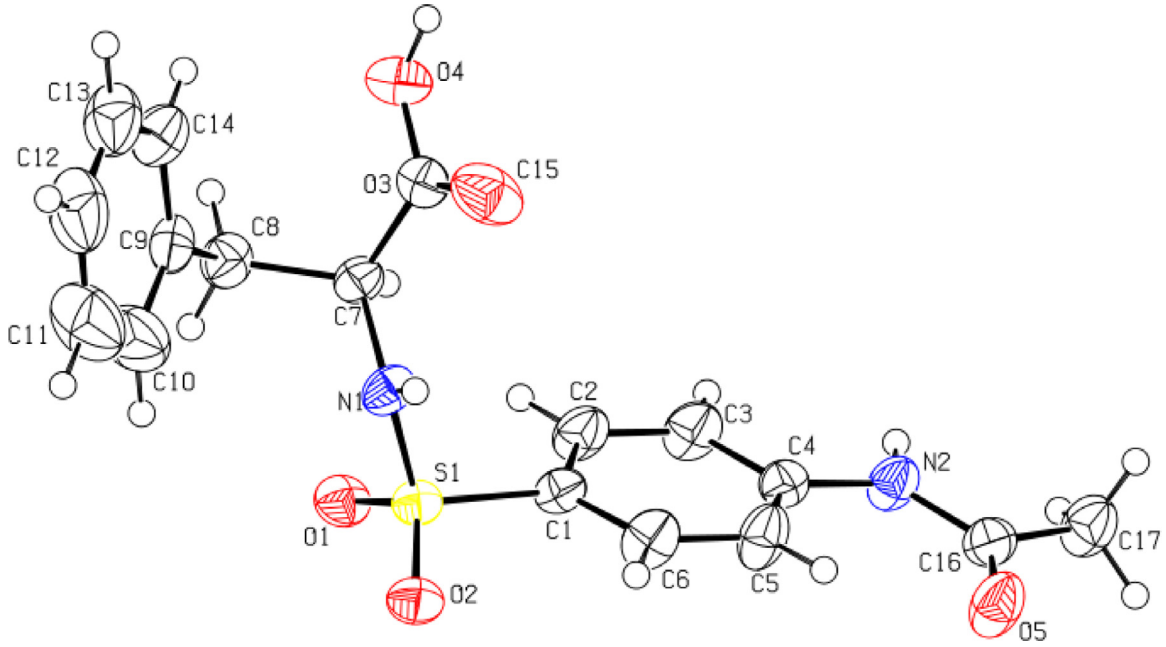

Fig. 1. Crystal structure of 2-(4-acetamidophenylsulfonamido)-3-phenylpropanoic acid (1), thermal ellipsoids were drawn at 50% probability level.

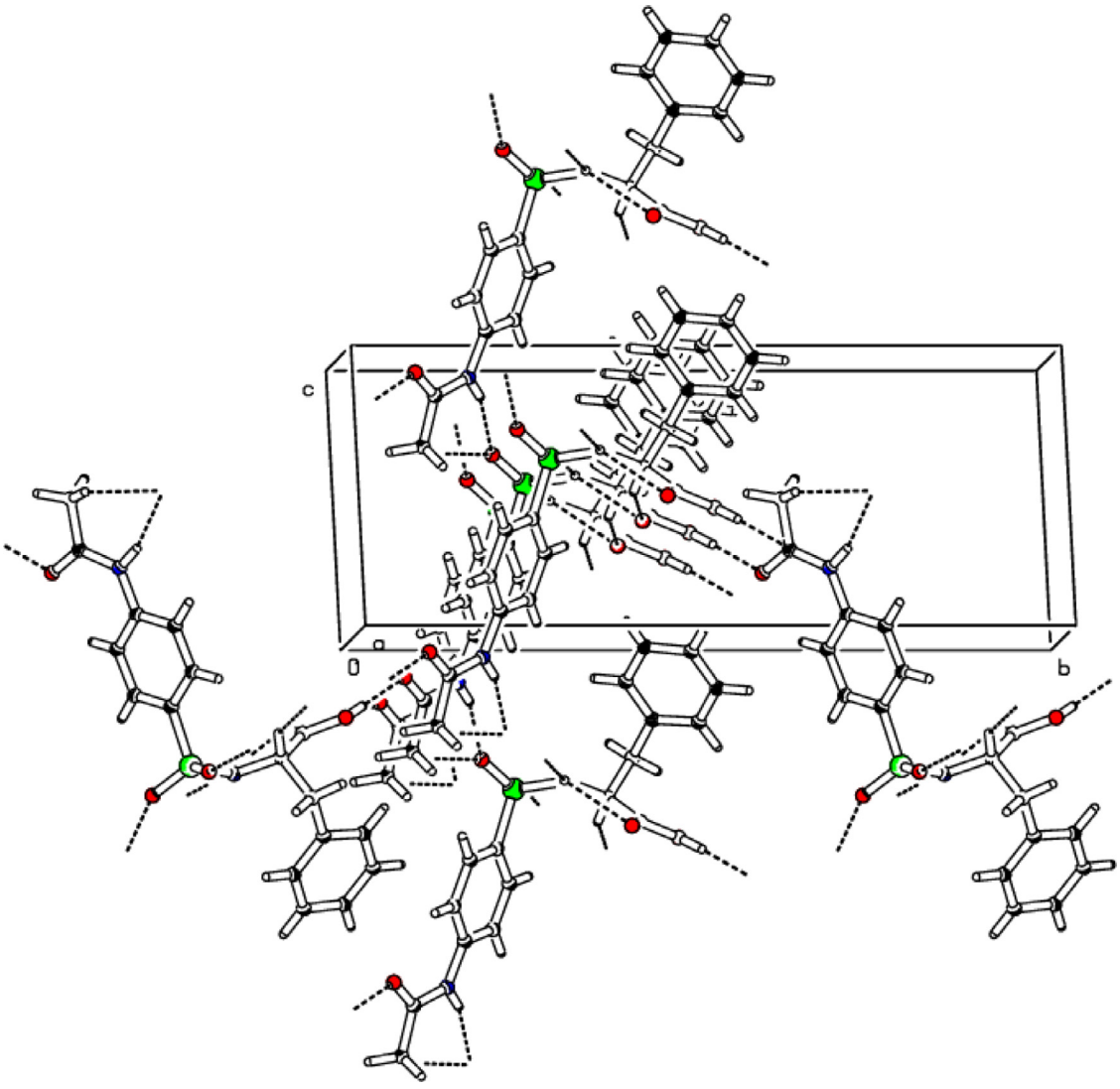

Fig. 2. Packing diagram of (1:1) 2-(4-acetamidophenylsulfonamido)-3-phenylpropanoic acid (1)

DPPH as free radical [16]. 2.0 mL of methanolic solution of DPPH (25.0 mg/mL) was mixed with 100 µL of sample (5 mg/mL). Test tubes were mixed and kept in dark for half an hour. The decrease in absorbance was measured at 517 nm using Gallic acid as reference standard. The scavenging of free radical was calculated using following formula;

$$\%\text{Inhibition} = \frac{\text{Absorbance(blank)} - \text{Absorbance(test)}}{\text{Absorbance(blank)}} \times 100$$

2.5. Enzyme Inhibition Activity

2.5.1. Acetylcholine esterase assay

Inhibition study of AChE was done by methodology introduced by Raza *et al*., (2019) [17]. Synthesized compound (100 µL) and enzyme was mixed followed by incubation for 15 minutes. After incubation substrate, buffer and DTNB solution were added in the mixture and kept the test tubes in incubator for 30 minutes at 37°C. The absorbance was recorded with spectrophotometer. At 410 nm, the inhibition percentage value was determined by following formula:

$$\%age\ inhibition = [(E - S)/E] \times\ 100$$

Where E shows the absorbance of enzyme without sample and S shows the activity of enzyme with sample.

2.5.2. Butyrylcholine esterase inhibition assay

BChE inhibition study of the synthesized compound was carried using *in vitro* model of Raza *et al*., 2019 [17]. Enzyme (BChE) and

Table 6
Antioxidant activity of the synthesized compounds

Sample code	Absorbance	%age inhibition
1	0.3534	38.04
2	0.5216	8.49
3	0.4317	15.47
4	0.4202	19.26

Table 7
Enzyme inhibition activity of the synthesized compounds

Sample Code	Enzyme inhibition (%age)		
	Trypsin	AChE	BChE
1	57.18	54.07	72.42
2	45.24	51.16	49.27
3	43.27	39.64	46.57
4	42.09	45.24	48.36

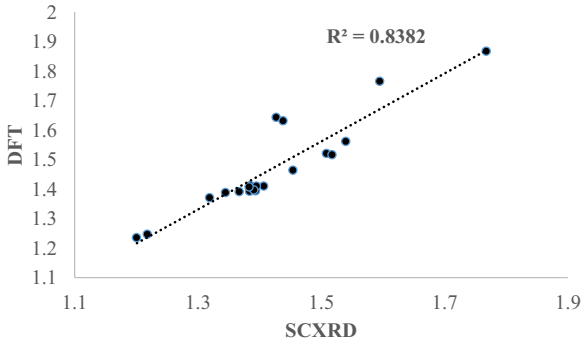

Fig. 3. Correlation of bond length (DFT and SCXRD) of compound 1

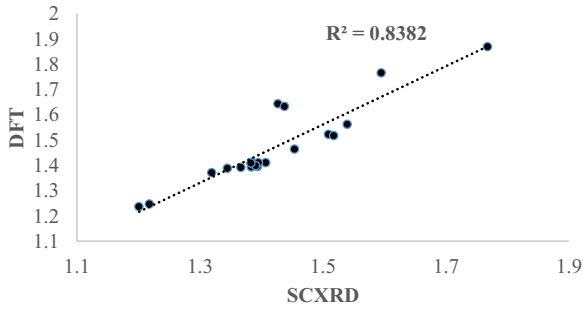

Fig. 4. Correlation of bond angle (DFT and SCXRD) of compound 1

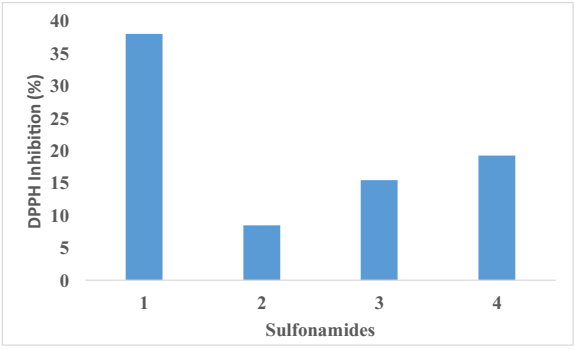

Fig. 5. Antioxidant activity of the synthesized compounds

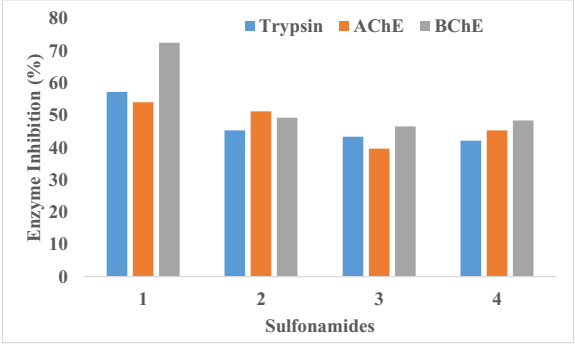

Fig. 6. Enzyme inhibition activity of the synthesized compounds

understudy compound (100 µL) was mixed well for 10 minutes, followed by the addition of substrate. 100 µL buffer of pH 7.8 and DTNB were also added in test and control sample. The mixture was incubated at 37°C for 30 minutes and absorbance was measured with UV/VIS spectrophotometer. The results were presented in inhibition (% age), calculated through below mentioned formula.

$$\%age\ inhibition = [(E - S)/E] \times 100$$

Where E shows the absorbance of enzyme without sample and S shows the activity of enzyme with sample.

2.5.3. Trypsin inhibition activity

In order to check the trypsin inhibitory potential of the synthesized compounds, spectrophotometric method of Raza *et al*,. (2013) was used [18]. The compound and enzyme were mixed together and waited for 10 minutes. 50 µL substrate and 100 µL tris buffer of 8.5 pH were added in the mixture. The mixture was incubated at 40°C for 25 minutes and absorbance was determined. The percentage inhibition was calculated using formula as discussed in above section.

$$\%age\ inhibition = [(E - S)/E] \times 100$$

Where E shows the absorbance of enzyme without sample and S shows the activity of enzyme with sample.

2.6. Docking studies

Docking studies on synthesized compounds were carried according to method of Raza *et al.*, (2019) with Molecular Operating Environment (MOE) docking program version 2016.08 [17]. During docking, crystal structures of AChE and BChE with PDB codes 1EVE and 1P0I were selected respectively. The docking' view and 3D interactions of the ligands at active sites of enzymes with graphical representations were seen with discovery studio visualizer [19].

2.7. Computational studies

DFT calculations were carried out for all synthesized compounds having nitrogen, sulfur, oxygen and carbon in their structures using Gaussian 09 software [15,20]. The initial geometries were obtained from crystallographic data of compound **1** [21]. B3LYP density functional and 6-31G(d,p) basis set were used for optimization and calculations.

3. Results and discussion

New phenylalanine based sulfonamides were synthesized according to reported method of our research group [10,11]. The physical appearance and melting point suggested the synthesis of the targeted compounds. The physical properties of new sulfonamide such as color, solubility, melting points, and appearance were checked and tabulated in Table 1. Solubility the sulfonamides were checked in ethanol, methanol and in DMSO.

3.1. Infrared spectroscopy

Most valuable analytical technique is infrared spectroscopy in which any type of sample such as solids, liquids, gases, solutions, films and fibers can be analyzed. IR spectra have been recorded in the range between 4000-400 cm^{-1}. Stretching frequencies of different functional groups have been identified at ν(S=O), ν(C-H), ν(C=O), ν(N-H), ν(S=O), and ν(O-H) and clear shifting of absorption bands observed as shown in Table 2. In sulfonamide ligand N-H peak appear in 3342–3220 cm^{-1} while in phenylalanine NH_2 bands appear in 3550-3300 cm^{-1} this difference shows the removal of one N-H bond from NH_2 and the appearance of N-S peak confirms the formation of sulfonamide ligand [22]. $\nu(S{=}O)_{asym}$ and $\nu(S{=}O)_{sym}$ stretching shows sharp peaks at 1300-1375 and 1124-1190 cm^{-1}. Similarly, the stretching of ν(S-N) and ν(C-S) appears at 920-956 cm^{-1} and 830-860 cm^{-1} respectively [23]. These peaks suggested the synthesis of the under studied compounds.

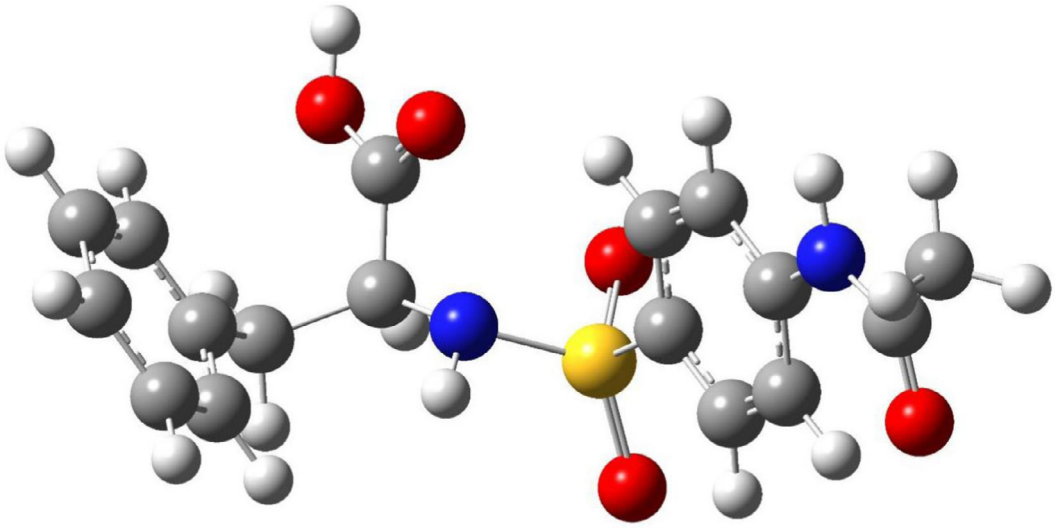

Fig. 7. Optimized structure of crystalline sulfonamide (1)

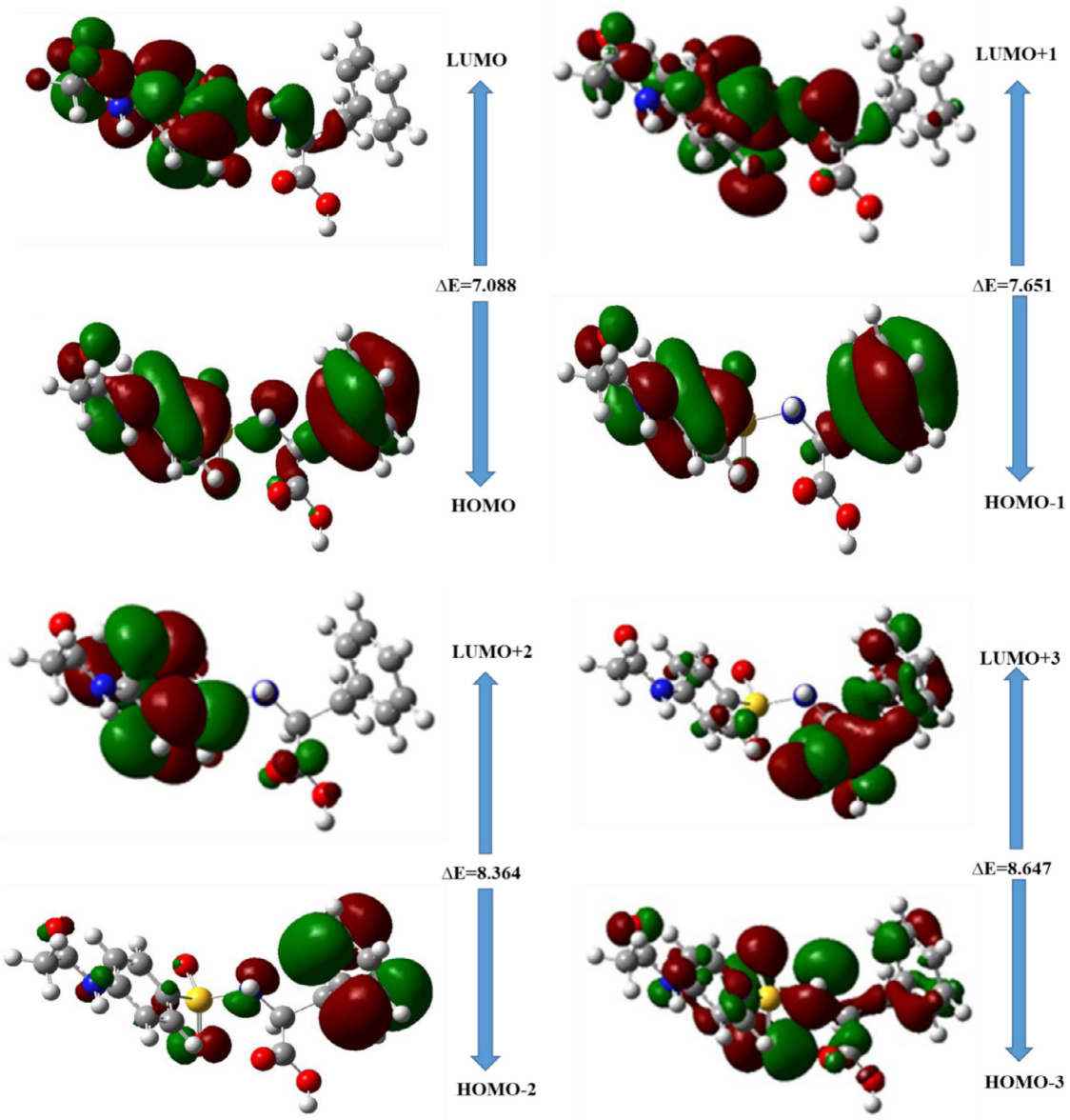

Fig. 8. HOMO-LUMO energy difference of compound 1

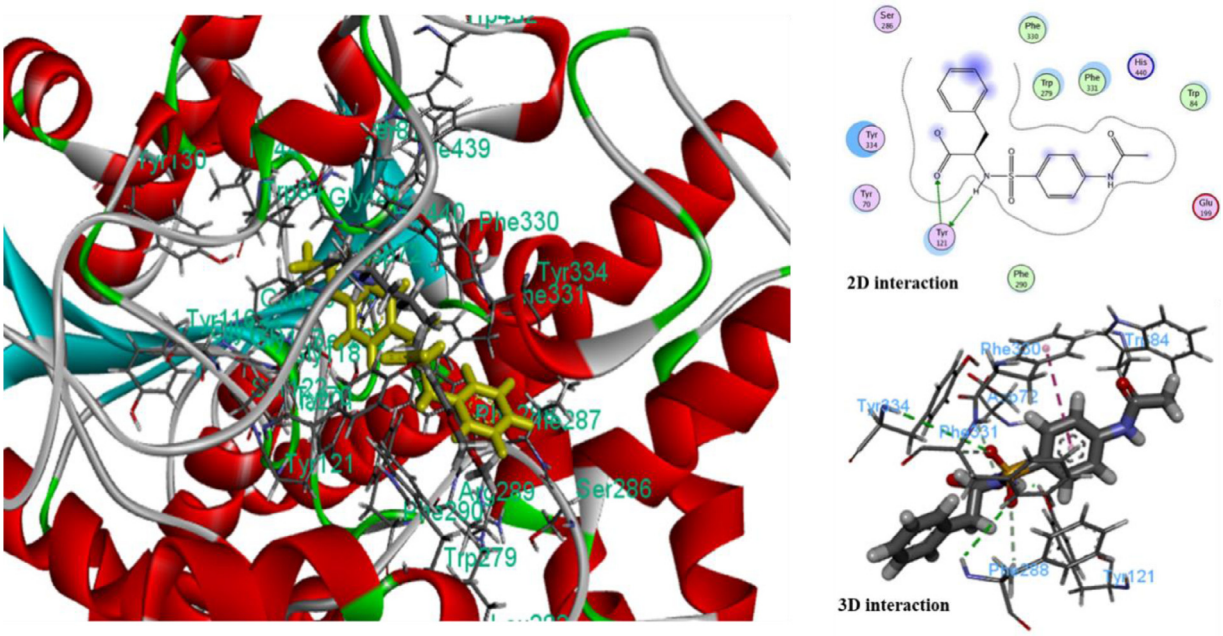

Fig. 9. Docking pose of compound 1 on the active site of AChE

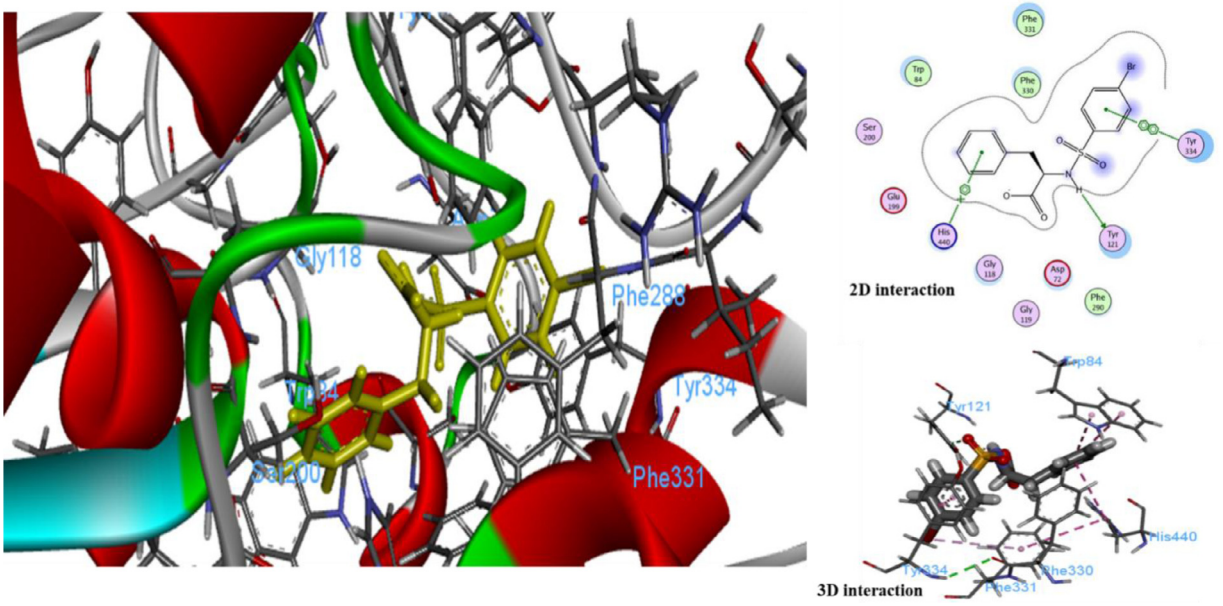

Fig. 10. Docking pose of compound 2 on the active site of AChE

3.2. X-Ray analysis of 2-(4-acetamidophenylsulfonamido)-3-phenylpropanoic acid (1)

2-(4-acetylamino) phenylsulfonylamino)-3-phenylpropanoic acid molecule was crystalized in monoclinic, a = 5.1258(7) Å, b = 20.257(2) Å, c = 8.4164(11) Å, β = 102.272(14)°, V = 853.93(19) Å^3. The data was collected at T = 296.15 K with space group $P2_1$ (no. 4), Z = 2 (Table 3). The final wR_2 was 0.1583 (all data) and R_1 was 0.0586 (I > 2\s(I)). The dihedral angle between the planes produced through two aromatic rings is 73.787 (2)°. The *N*–acetyl group is oriented at dihedral angle of 10.408 (4)° with respect to aromatic ring (C1-C6). The S atom adopted distorted tetrahedral geometry with <O1-S1-O2 = 119.80(1)°. The carboxylic group (O4/C15/O5) is twisted by 62.363(5)° with respect to the benzyl ring (C9-C14). The intermolecular hydrogen bonding connects the molecules to form three dimensional networks along the base vectors (0 0 1), (1 0 0) and (0 1 0). The bond angle and bond length of the crystalline molecule is shown in Tables 4 and 5. The carboxylic group connects the molecules in *zig-zag* manner along *b* axes. Newly synthesized ligand has stable 3-dimensional structure as shown in (Figs. 1 and 2).

3.3. Antioxidant study

Antioxidants are those substances that quench the activity of free radicals. They deteriorate the activity of reactive oxygen in biological system. Reactive oxygen group include H_2O_2, ·OH and

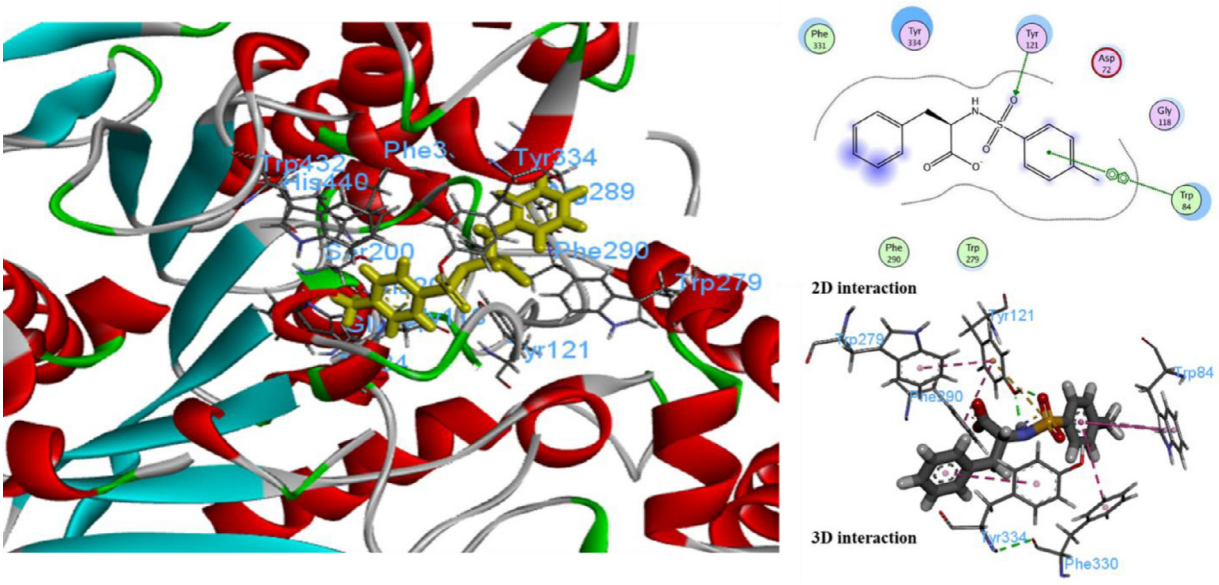

Fig. 11. Docking pose of compound 3 on the active site of AChE

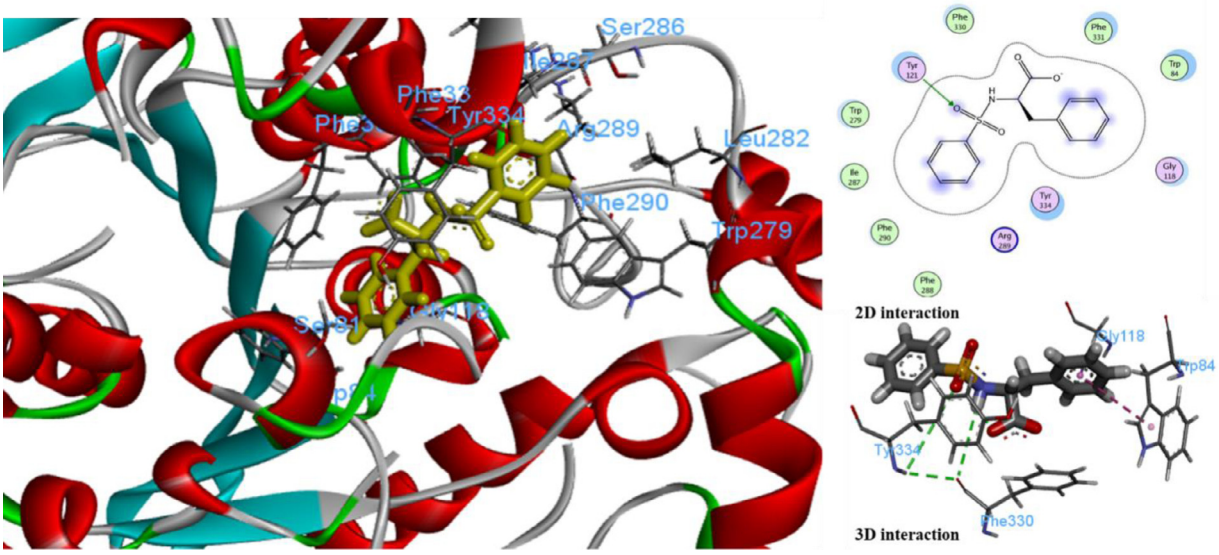

Fig. 12. Docking pose of compound 4 on the active site of AChE

$O_2^{\cdot -}$. Over stress of oxidant species in our body causes major diseases in living system [24]. Generally, diphenyl-1-picrylhydrazyl (DPPH) at room temperature in methanol gives violet color and acts as a stable free radical and its maximum absorbance occurs at 517nm. When it combines with antioxidants, its free radical activity is reduced and color changes from purple to yellow. Newly synthesized compounds and its complexes were studied for their antioxidant activity against DPPH. The compound **1** exhibited highest antiradical activity (38.04 %) among the tested compounds. While remaining depicted low to moderate inhibition of DPPH as shown in Table 6 and Fig. 5.

3.4. Enzyme inhibition activity

Enzymes are natural biocatalysts, which control the performance of metabolic activity of living organisms. In order to control the over activity of the enzyme, study of new molecules as enzyme inhibitor is very important field of this century. Researchers throughout the world are engaged in synthesizing new molecules having good enzyme inhibition potential. ACh (acetylcholine) plays important role in the activity of central nervous system. It acts as neurotransmitter that conveys the message between neurons through synapses. AChE breaks acetylcholine and deficiency of this enzyme leads serious diseases, such as, memory loss and some nervous system problems, leading Alzheimer's disease. So, the treatment of Alzheimer's disease, AChE inhibitors are best drugs [25]. The compound **1** showed maximum activity (72.42 %) among all the tested sulfonamides against BChE while minimum response (39.64 %) against AChE was exhibited by **3** as shown in Table 7 and Fig. 6. BChE is another enzyme having key role in brain after AChE. All synthesized sulfonamide ligands along their metal complexes were also screened against BChE. The activity of the sulfonamide is 72.42 %, 49.27 %, 46.57 % and 48.36 % for **1, 2, 3** and **4** respectively. Furthermore, synthetic compounds were also subjected to trypsin inhibition study using in-vitro model. The order of reactivity among the sulfonamides is; **1** > **2** > **3** > **4**. It was summarized that about all compounds showed moderate to good inhibition potential which

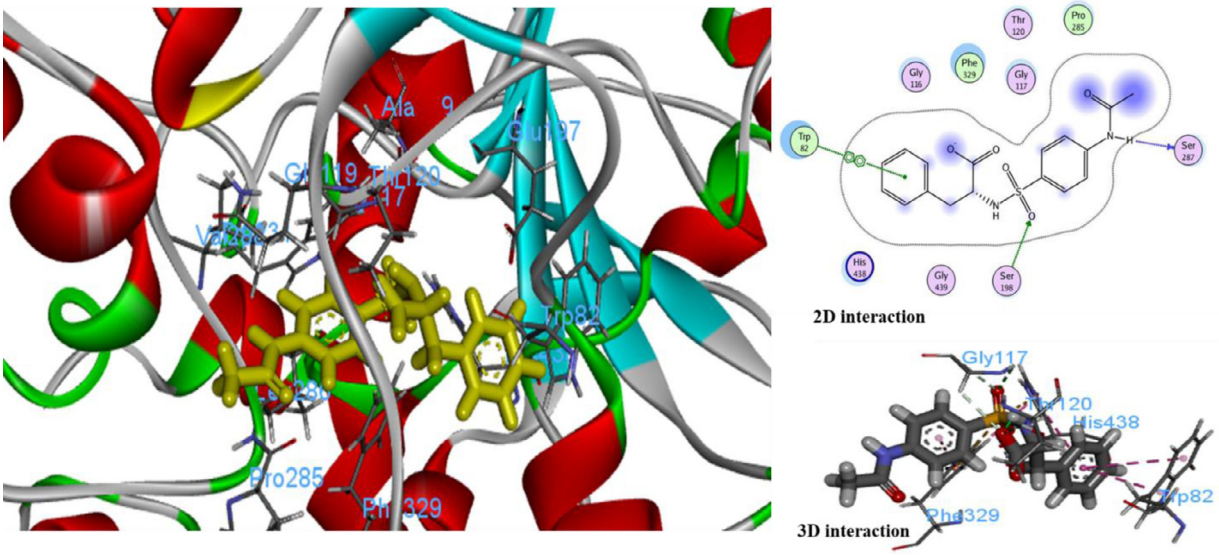

Fig. 13. Docking pose of compound 1 on the active site of BChE

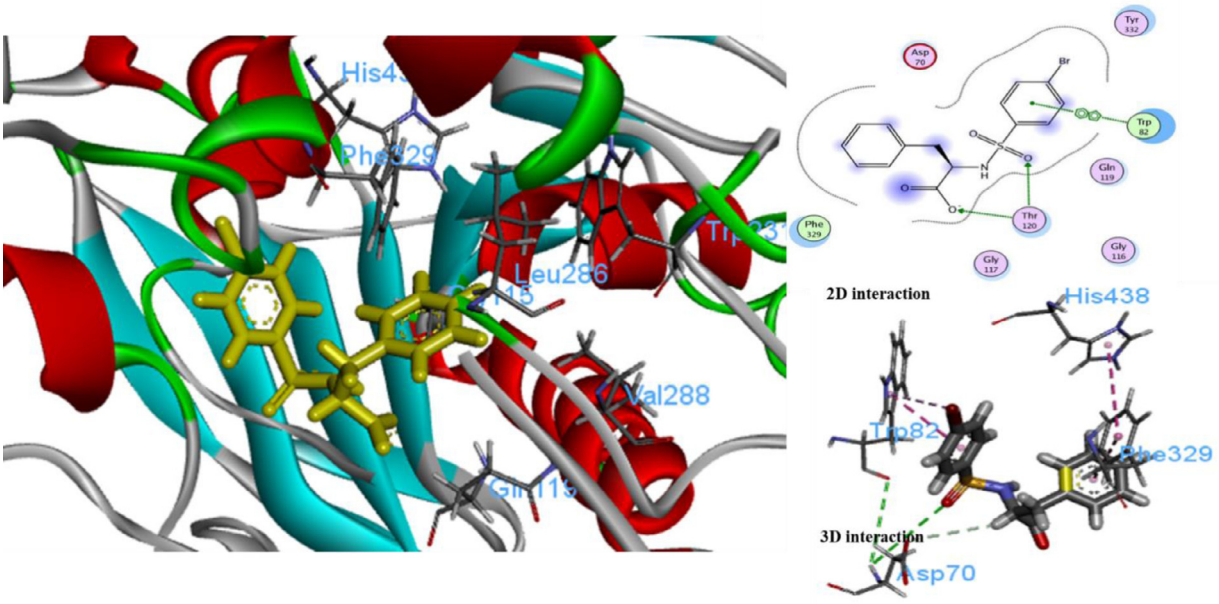

Fig. 14. Docking pose of compound 2 on the active site of BChE

indicated that they may behave as therapeutic agents after fulfil others parameters.

3.5. Density functional theory

The crystalline sulfonamide (**1**) was subjected to density functional theory for optimization and other DFT calculations using B3LYP density functional and 6-31g basis set. The optimized structure of **1** is shown in Fig. 7 which is similar to the SCXRD structure in geometry. The bond lengths and bond angle calculations from DFT studies were also matched with data obtained from XRD analysis. It was found that both are in close agreements that indicated that DFT also supported the crystal structure of the targeted molecule. Maximum deviation in bond length is about 0.2 Å for S1-O1 and S1-O2. The SCXRD bond length in S1-O1 is 1.427 Å and in S1-O2 is 1.438 Å while in DFT these are 1.64237 Å and 1.63087 Å respectively (Table 4 and Fig. 3). Similarly, the bond angle in XRD result of O1-S1-C1 is 106.3° and of N1-S1-C1 is 108.9°, which is slightly different from DFT calculations (111.76934° and 101.76433° respectively) as shown in Table 5 and Fig. 4. The HOMO and LUMO orbitals along energy difference between orbitals of the understudied molecule were also drawn using Gaussian 6 software. The energy difference between HOMO and LUMO is 7.088 eV, HOMO-1 and LUMO+1 is 7.651 eV, HOMO-2 and LUMO+2 is 8.364 eV while between HOMO-3 and LUMO+3 is 8.647 eV as shown in Fig. 8.

3.6. Docking studies

The synthesized sulfonamides (**1-4**) were docked with AChE (PDB: 1EVE) and BChE (PDB: 1P0I) using MOE and different poses of the docking studies were viewed with Discovery Studio software. The 2D and 3D interaction pose of best fitted compound on active sites of both enzymes were presented in Fig.s 9–16. The

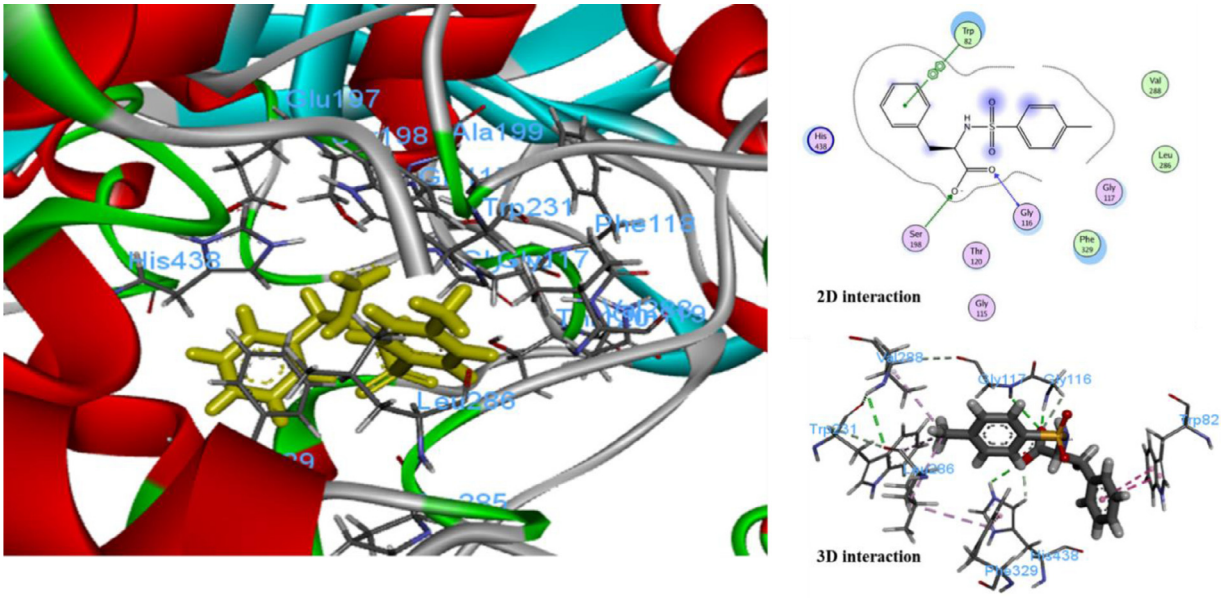

Fig. 15. Docking pose of compound 3 on the active site of BChE

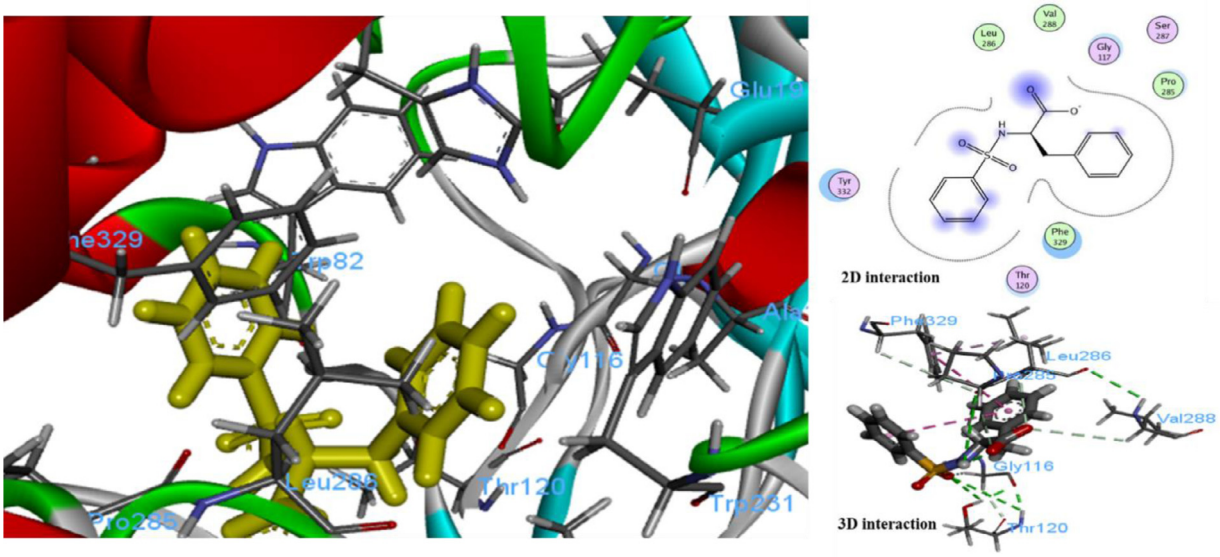

Fig. 16. Docking pose of compound 4 on the active site of BChE

Table 8
Docking score and binding affinity of the synthesized sulfonamides

Compounds	AChE Docking score	Binding affinity (Kcal/mol)	BChE Docking score	Binding affinity (Kcal/mol)
1	-6.4042	-5.5085	-5.6871	-3.6042
2	-7.3808	-5.5690	-6.5356	-5.0632
3	-6.6114	-5.8364	-5.1359	-5.7899
4	-6.2274	-6.7578	-5.6700	-5.2169

docking score and binding affinity of all compounds against each enzyme is summarized in Table 8.

The results presented in Table 8 indicated that under studied sulfonamides are moderate inhibitors of the esterase family which also suggested by the *in vitro* studies. It was depicted from results that on AChE, compound **1** showed interactions with Tyr121, Tyr334 and Phen288 residues through hydrogen bond interactions while with Phe330 via π-π interactions. Compound **2** depicted π-π interactions with Trp84 and Tyr334, alkyl-π interactions with His440 and Phe330 while showed hydrogen bond interaction with Tyr121 residue. π-π interactions with Trp84, Phe330 and Try334 while hydrogen bond interactions with Tyr121was depicted by **3**. Furthermore, compound **4** exhibited hydrogen bond interactions with Phe330, Tyr334 and Tyr121. It also interacts with Trp84 through π-π interaction. In case of BChE, compound **1, 2** and **3** showed strong interactions (π-π) with important residue Trp82 located on the active site. Hydrogen bond interactions with Ser198 and Thr120 was shown by **1** and **2** respectively. The compound **3**

and **4** exhibited weak interactions with His438 and Thr120 respectively.

4. Conclusion

The present project was designed to synthesize sulfonamides (**1-4**) according to reported method of our research group. The structures were confirmed with available spectral and XRD techniques. The compounds were also optimized via DFT and DFT calculations were used to compare the theoretical and experimental bond angle and bond length. It was depicted from both studies (experimental and theoretical) that both in close agreement. The HOMO and LUMO orbitals of the compound **1** are also drawn to determine the energy gap difference between these orbital. These studies suggested that such compounds may be used as nucleophile. The synthesized compounds were further evaluated using in-vitro models in the regard of anti-radical and enzyme inhibition potential. It was concluded that among all synthesized compounds, compound **1** is most active against DPPH as well as all tested enzymes (AChE, BChE and Trypsin). In silico study in the form of molecular docking were performed to evaluate the interactions of the targeted compounds on the studied enzymes. The 2D and 3D interactions models of the compounds showed that they could inhibit these enzymes remarkably. All the understudied models suggested that synthesized molecules might be incorporated in the medicinal chemistry after checking their other parameters.

Author contribution

Muhammad Danish and **Muhammad Asam Raza** have designed the whole project as supervisor, **Hurria Rani** has done the experimental work, **Arusa Akhtar** help in characterization and done docking studies, **Muhammad Nadeem Arshad** and **Abdullah M. Asiri** have done XRD analysis and collected the crystal data.

Declaration of Competing Interest

All authors declared that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.130608.

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