Journal of Advanced Scientific Research
Available online through http://www.sciensage.info
ISSN 0976-9595
Research Article

CRYSTAL STRUCTURE, HIRSHFELD SURFACE, DFT AND MOLECULAR DOCKING STUDIES OF (Z)-METHYL 2-((N-(2-FORMYLPHENYL)-4-METHYLPHENYLSULFONAMIDO) METHYL)-3-(4-METHOXYPHENYL) ACRYLATE

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ABSTRACT
Sulfonamide derivative was identified as potential as penicillin-binding protein 2X (PBP-2X) inhibitor and this paper describes the in-depth structural analysis. Sulfonamide compounds were analyzed by various methods such as single-crystal X-ray diffraction, Hirshfeld surface analysis, and density functional theory, respectively. Hirshfeld surface analysis indicated that H…H, C-H…C, C-H…N, and especially C-H…O hydrogen bond interactions are the primary contributors to the intermolecular stabilization in the crystal. The sulfonamide structure was explained by X-ray structure determination and it was optimized by the DFT method with 6-311++G(d,p) basis set in the ground state. The first-order hyperpolarizability was calculated at same level of theory. FMO's, MEP, Mulliken charges were also calculated and analyzed in detail. Molecular docking experiments revealed important intermolecular interactions between the sulfonamide derivative and penicillin-binding protein 2X. These results indicate that sulfonamide may be considered for further drug design endeavors.

Keywords: XRD, Hirshfeld surfaces, DFT method, Molecular docking.

1. INTRODUCTION
Sulfonamide compounds are an important class of therapeutic agents in recent medicinal field [1]. Sulfonamide derivatives are among the first drug of ampicillin and gentamycin as chemotherapeutic agents in bacterial infections by *E.coli* in human, the organic synthetic compounds proficient of inhibiting the growth of bacteria that require PABA (para-amino benzoic acid) which is similar to sulfanilamide. Among the vast families of sulfonamides being currently investigated, N-substituted sulfonamides are one of the outstanding groups because of their broad biological spectrum. Sulfonamide compounds are well recognized that toxicological and pharmacological properties are improved to form of their metal complexes. The coordination of sulfonamide compounds has undergone noticeable development in recent years due to their interesting properties of these substances.

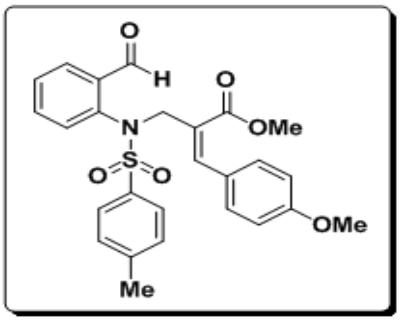
In this work, we synthesized series novel sulfonamide derivative containing nitro groups. The compounds characterized experimentally and theoretically using different techniques. Additionally, a molecular docking study of compound was investigated. The sulfonamide derivative was determined by X-ray diffraction studies, and further study by intermolecular contact, fingerprint plots and molecular surface contours (dnorm, di and de) provide by Hirshfeld surface analysis method. Theoretical investigations were estimated by using DFT method with B3LYP/6-311++G(d,p) basis set. The dipole moment (μ), polarizability (α_0) and the first hyperpolarizability (β_0) were calculated so as to explore the impact of π-electron system and exhibition NLO active material. The frontier molecular orbitals of HOMO and LUMO investigation have been utilized to explain data in regards to ionization potential (IP), electron affinity (EA), energy gap (ΔE), electronegativity (χ), electrophilicity index (w), hardness (η), softness (s) and are correlated. These parameters are confirming the charge transfer and chemical active regions within the molecule. MEP surface help to identify the chemical reactivity and

stability (electrophilic and nucleophilic attacks) of the molecule.

2. MATERIAL AND METHODS

2.1. Synthesis

A solution of *N*-(formylphenyl)(4-methylbenzene) sulfonamide (1 mmol, 0.275 g) and potassium carbonate (1.5 mmol, 0.207g) in acetonitrile solvent was stirred for 15 min at room temperature. To this solution, methyl (2Z)-2-(bromomethyl)-3-(4-methoxyphenyl)prop-2-enoate (1.2 mmol, 0.342g) was added dropwise till the addition was complete. After the completion of the reaction, as indicated by TLC, acetonitrile was evaporated. EtOAc (15 ml) and water (15 ml) were added to the crude mass. The organic layer was dried over anhydrous sodium sulfate. Removal of solvent led to the crude product, which was purified through pad of silica gel (100-200mesh) using ethylacetate and hexanes (1:9) as solvents. The pure title compound was obtained as a colourless solid (0.426g, 89% yield). Recrystallization was carried out using ethylacetate as solvent.



2.2. X-Ray Crystallography

Intensity data of the sulfonamide compound were collected using on a BRUKER KAPPA AREA diffractometer [2] at room temperature (296 °K) using graphite-monochromated MoKα radiation (λ = 0.71073 Å) by applying the X-scan process. Data collection and cell refinement were carried out using APEXS [2] while data reduction was applied using SAINT [3]. The structures were solved by direct methods using SHELXS97 [3] and refined with full-matrix least-squares calculations on using SHELXL [3] implemented in WinGX program suit the molecular graphics for drawing ORTEP plots using PLATON [4]. All H atoms were inserted in idealized positions and treated using a riding model for compound, fixing the bond lengths at 0.86 and 0.93 Å for NH and aromatic CH atoms, respectively. The displacement parameters of the H atoms were fixed at U (1.5U for NH and aromatic CH) of their parent atoms. The H atoms were positioned geometrically and refined using a riding model: N-H = 0.86 Å, C-H = 0.93-0.98 Å with U(C) for methyl H atoms and = 1.2Ueq (N, C) for other H atoms.

2.3. Computational Study

The molecular structure of the Sulfo compound optimized by DFT method with a hybrid functional B3LYP (Becke's three parameter hybrid functional using the LYP correlation functional) and the 6-311++G(d,p) level of theory. The entire calculations were performed with Gaussian 09W [5] program package. Moreover, in order to show NLO activity of sulfo molecule, the dipole moment, linear polarizability and first order hyperpolarizability were obtained from molecular polarizabilities based on theoretical calculations. NBO analysis was carried out so as to elucidate inter- and intra-molecular interactions in the title molecule. The electronic properties such as dipole moment (μ), E_{HOMO}, E_{LUMO}, HOMO-LUMO energy gap (ΔE), Mulliken charges and physico-chemical properties were calculated at same level of theory. The molecular electrostatic potential and inter-molecular interactions in the crystal structure of sulfo compound, a Hirshfeld surface (HS) analysis and two dimensional finger plots [6, 7] was carried out using CrystalExplorer17.5 [8].

2.4. Molecular Modelling

Sulfonamide compounds as anti-bacterial agent is selected as a ligand for molecular docking. Penicillin-binding protein (PBP2X) was taken as the target protein for docking studies of sulfonamides. The aim of this study is to analyze by docking methods the interaction of sulphonamide derivatives with the PBP-2X in order to characterize their antimicrobial potential. In the present investigation, we performed the docking studies of synthesized compound of sulfonamides with target protein penicillin-binding proteins (PBP-2X).

The crystal structure of the target protein, penicillin-binding protein 2X in complex [9] was downloaded from the PDB (id: 1QMF) with the specific resolution. The 2D ligand of sulfonamide compound studied: Methyl (2Z)-2-{[N-(2-formylphenyl)(4-methylbenzene)sulfonamido] methyl}-3-(4-methoxy phenyl) prop-2-enoate, their structures were drawn using Chemsketch.

The study of sulfonamide compound are screened using high throughput screening, and further subjected to AutoDock tools [10] is used as a primary docking engine. Docking calculations were carried out on penicillin-binding protein 2X as a protein model [11]. Essential

hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools. The pictures were taken using PyMOL [12], and Chimera [13].

3. RESULTS AND DISCUSSION

3.1. Structural Analysis

The synthesized sulfonamide compound was confirmed by single crystal X-ray diffraction determination. The ORTEP plot of sulfonamide compound with the atomic numbering scheme and thermal ellipsoidal plots were depicted in fig. 1.

The conformational states of the sulfonamide molecules under analysis depend on the mobility of the bridge, connecting between 4-methylbenzene (C8-C13/C14) and 4-methoxy phenyl(C1-C6/C7/O1) moieties. In order to describe the conformational state, we have chosen three parameters [14], the angle between the SO_2 group and 4-methylbenzene (C8-C13/C14) and 4-methoxy phenyl(C1-C6/C7/O1) moieties, describing the S1-N1 bond mobility, and the torsion angle, which characterizes the location of 2-formylphenyl(C18-C23/O4/C24) and prop-2-enoate(C16/C25/O5/O6/ C26) relative to the NH group.

The S1 atoms showed a distorted tetrahedral geometry, with O3-S1-O2 [119.38(9)°] and N1-S1-C8 [107.13 (8)°] angles were deviating from ideal tetrahedral values are attributed to the Thrope-Ingold effect [15]. The S1-O3, S2-O2, S1-N1 and S1-C8 bond lengths were 1.4234(18) Å, 1.4246(16) Å, 1.6490(15) Å and 1.751(2) Å were comparable [16].

The sulfonamide moiety connected by two moieties, both the moieties are planar conformation, 4-methyl-benzene (C8-C13/C14) with maximum deviation of atom C14 0.020(3) Å and 4-methoxy phenyl (C1-C6/C7/O1) with maximum deviation of atom C7-0.015(3) Å, respectively.

The dihedral angle between 4-methylbenzene (C8-C13 /C14) and 4-methoxy phenyl (C1-C6/C7/O1) rings, which connected by sulfonamide moiety, the respective angles are 81.82(8) & 70.69 (7)° are axially oriented.

The S1-N1 bond connected with 2-formylphenyl (C18-C23/O4/C24) & prop-2-enoate (C16/C25/O5/O6/ C26), respectively. The 2-formylphenyl ring has planar conformation with maximum deviation of atom C24 [-0.026(3)Å], and the prop-2-enoate group assumes equatorial orientation. Which can be confirmed through torsion angle values of [O5/ C25/O6/C26= -2.4(3) ° & C16/C25/O6/C26= 177.10(17)°], respectively.

In the crystal structure, molecules were linked into two centrosymmetric dimers via C-H…O hydrogen bonds (fig. 2). The crystal packing was also stabilized by intermolecular C19-H19…O5^{i} and C24-H24A…O4^{ii} bonds linked two different molecules together R^2_2 (14) & R^2_2(6) hydrogen bonding motif (fig. 2).

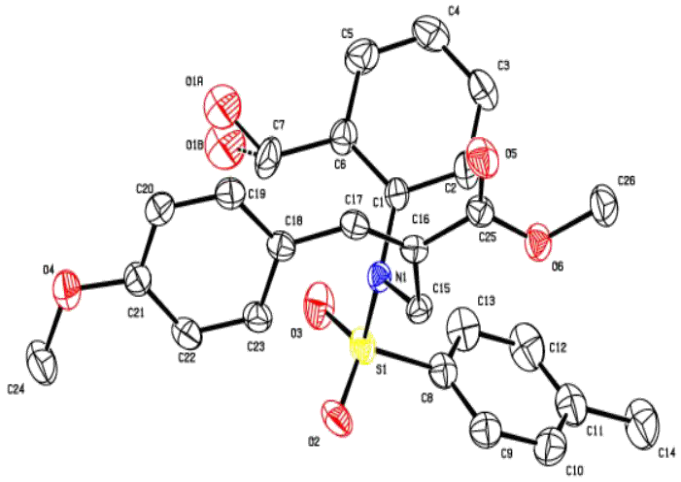


Fig. 1: The molecular structure of the title molecule (Sulfo), with atom labeling and displacement ellipsoids are drawn at the 30% probability level

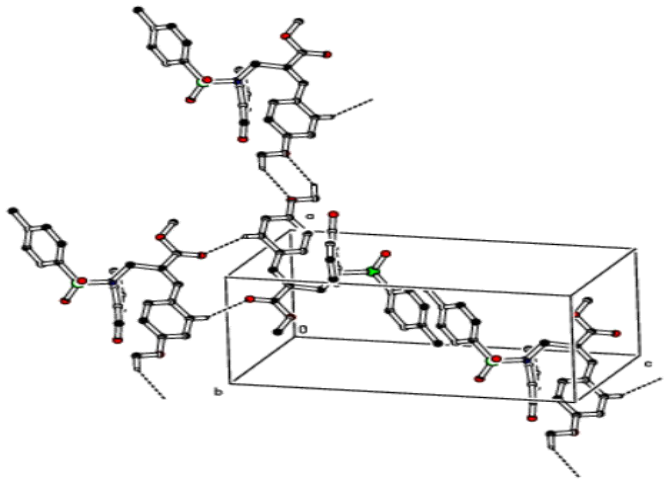


Fig. 2: The crystal packing of the title compound (Sulfo), viewed along the *b*-axis. R^2_2(14) dimer hydrogen bonds are shown as dashed line

3.2. Hirshfeld Surface Analysis

Hirshfeld Surface Analysis plotted over d_{norm} /shape index /curvedness and fragment patch are explained in fig. 3(a-d). The white surface area indicates contacts with distances equal to the sum of the van der Waals radii, and

the red colour indicates positive potential and blue colour indicates negative potential, the colours indicate distances shorter in close contact or longer (distinct contact) than the van der Waals radii, respectively. The blue spot indicate the positive electrostatic potential of hydrogen bond donors and red spot indicate the negative electrostatic potential of hydrogen-bond acceptors, respectively [17, 18].

The overall two-dimensional fingerprint plot and those delineated into HH, HO/OH, HC/CH, CC, CO/OC and OO contacts [19] are illustrated in fig. 4(a-f), respectively, together with their relative contributions to the Hirshfeld surface. The most important interaction is HH(49.6%), HO/OH(30.3%), HC/CH(15.8%), CC (3.3%),CO/OC(0.8%) and OO(0.2%), contributing to the overall crystal packing.

The Hirshfeld surface analysis demonstrate the importance of hydrogen bond contacts in the crystal packing. The more number of hydrogen bond HH, HC/CH and HO/OH interactions suggest that van der Waals interactions and hydrogen bonding play the major roles in the crystal packing [20].

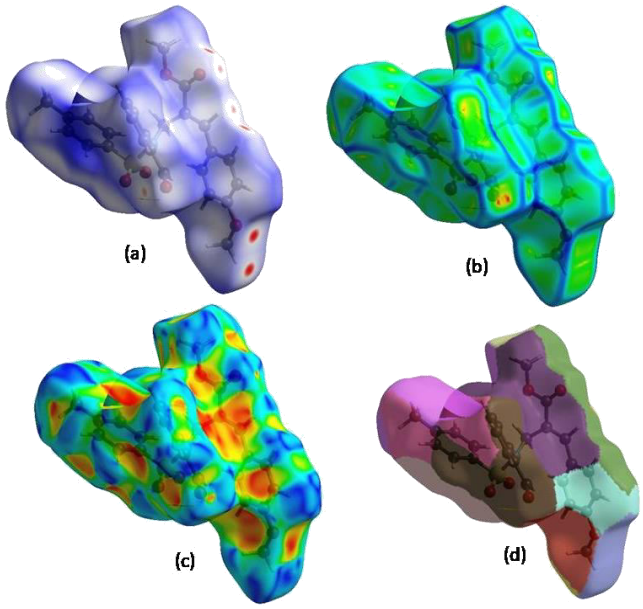


Fig. 3(a-d): View of the three-dimensional Hirshfeld surface of the title compound (Sulfo) plotted over (a) dnorm; (b) shape index; (c) curvedness and (d) fragment patch

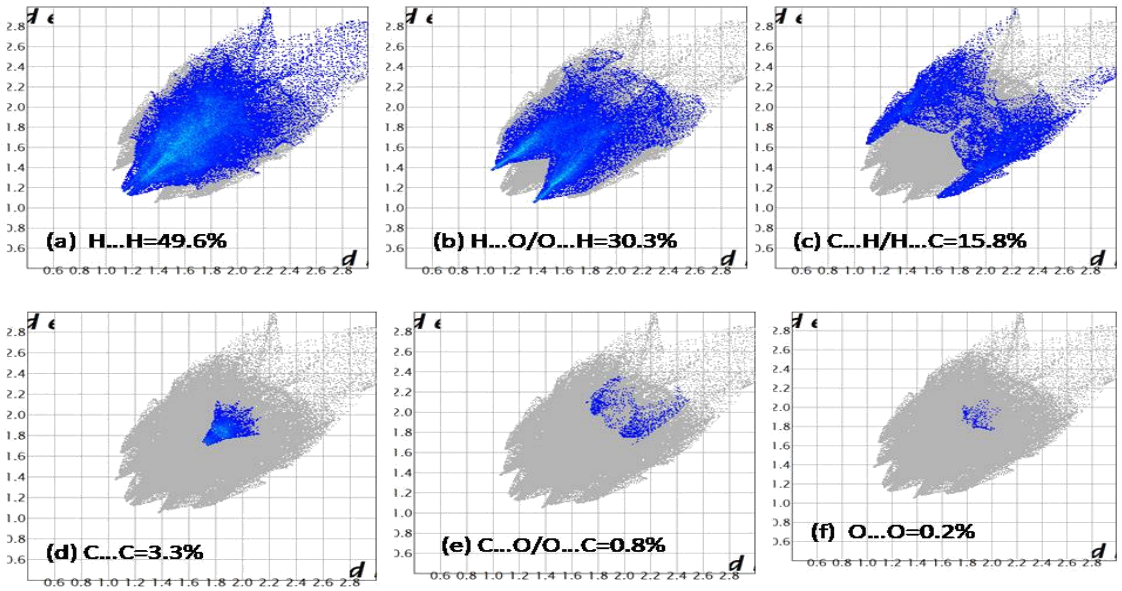


Fig. 4(a-f): The full two-dimensional fingerprint plots for the title compound (Sulfo), showing (a) H…H(49.6%); (b) H…O/O…H(30.3%); (c) C…H/H..C (15.8%); (d) C…C(3.3%); (e) C…O/O…C(0.8%) and (f) O..O (0.2%) interactions

3.3. Density Functional Theory

3.3.1. NLO Property

The hyperpolarizability (β_0), dipole moment (μ), anisotropy of the polarizability (Δ_α) and polarizability (α_0) were calculated using B3LYP/6-311++G(d,p) basis set of finite field approach. The complete equations for calculating the magnitude of the total static dipole moment (μ), the mean polarizability (α_{tot}) and the mean hyperpolarizability (β_0), using the x, y, z components [21, 22] are defined as follows:

$$\mu = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2}$$

$$\alpha_0 = \frac{\alpha_{xx} + \alpha_{yy} + \alpha_{zz}}{3}$$

$$\Delta\alpha = 2^{-1/2}\left[(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6(\alpha_{xy}^2 + \alpha_{yz}^2 + \alpha_{xz}^2)\right]^{1/2}$$

$$\beta_0 = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2}$$

Theoretical investigation plays an important role in understanding the structural property relationship, which is able to assist in designing novel NLO materials. The higher values of dipole moment, molecular polarizability and hyperpolarizability are important for more active NLO properties and these values are listed in table 1.

Table 1: The NLO measurements of Sulfo

Parameters	B3LYP/6-311++G(d,p)
Dipole moment μ	**Debye**
μ_x	1.1172417
μ_y	0.6027424
μ_z	0.4736392
μ	1.35493 **Debye**
Polarizability α_0	**x*10^{-30}esu***
α_{xx}	275.8273827
α_{xy}	19.5734865
α_{yy}	131.3725594
α_{xz}	-59.7968282
α_{yz}	-41.9138373
α_{zz}	363.6715689
α_0	0.52842**x10^{-30}esu**
Hyperpolarizability β_0	**x*10^{-30}esu***
β_{xxx}	392.5381425
β_{xxy}	184.2769439
β_{xyy}	51.4869976
β_{yyy}	-17.9266124
β_{xxz}	-881.6248493
β_{xyz}	-267.4768971
β_{yyz}	-55.6742148
β_{xzz}	1811.7237392
β_{yzz}	232.4197358
β_{zzz}	-840.2751985
β_0	24.04978**x10^{-30}esu**

Standard value for urea μ*=1.3732 Debye,* β_0*=0.3728x10^{-30}esu:* ***esu****-electrostatic unit*

The molecular dipole moment (μ), molecular polarizability and hyperpolarizability are calculated about 1.35493 (Debye), 0.52842 and 24.04978x10^{-30} esu, respectively. The β_0 value of the Sulfo compound is sixty five times greater than that of urea. Hence, our title molecule is an interesting object for Non-linear optical property.

3.3.2. HOMO - LUMO Analysis

The optimized molecular structure of Sulfo is shown in fig. 5 adopted with numbering scheme. HOMO-LUMO orbitals are likewise called frontier orbitals (FMOs) as they lie at the outermost boundaries of the electrons of the molecule. The frontier orbital gap helps to characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule. Energy of the HOMO is directly related to the ionization potential, LUMO is directly related to the electron affinity. The difference in energy between transition levels is called as energy gap, which is responsible for the stability of the structures [23].

The ionization potential is determined from the energy difference between the energy of the compound derived from electron-transfer (radical cation) and the respective neutral compound; IP = E_{cation}-En; IP = -E_{HOMO}, while the electron affinity is computed from the energy difference between the neutral molecule and the anion molecule: EA = En-E_{anion}; EA = -E_{LUMO}, respectively. The other important quantities such as electro negativity (χ), hardness (η), softness (ζ), and Electrophilicity index (ω) are deduced from ionization potential and electron affinity values [24, 25] using the following equations:

$$\text{Electro negativity } (\chi)\ \mu \approx -\chi = -\frac{IP+EA}{2}$$

$$\text{Chemical hardness } (\eta) \approx -\frac{IP-EA}{2}$$

$$\text{Softness } (\zeta) = \frac{1}{\eta}$$

$$\text{and Electrophilicity index } (\omega) = \frac{x2}{2\eta}$$

In our present molecule, the HOMO, LUMO and band gap energies are calculated in gas phase: -5.81232 eV, -2.71856 eV, and 3.09376 eV, respectively. The smaller energy gap of HOMO-LUMO explains the eventual charge transfer interaction taking place within the molecule, which influences the biological activity of the molecule. The HOMO is located over sulfonamide and propinoate moiety and LUMO is located over 4-methoxy phenyl and prop-2-enoate moiety. The HOMO-LUMO picture is shown in fig. 6. The energy

values of HOMO, LUMO, energy gap, electron affinity, electrophilicity index, chemical hardness and softness of the title molecule are listed in table 2.

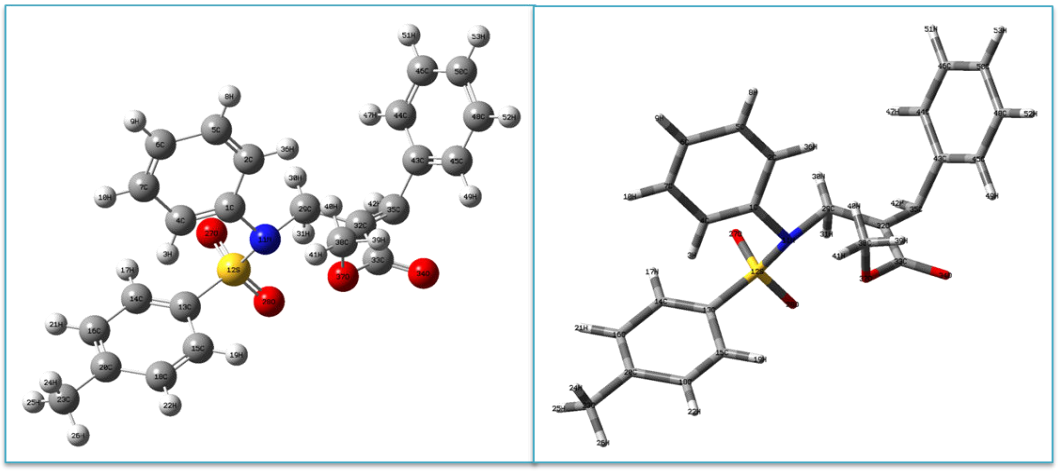


Fig. 5: The optimized molecular structure of Sulfo

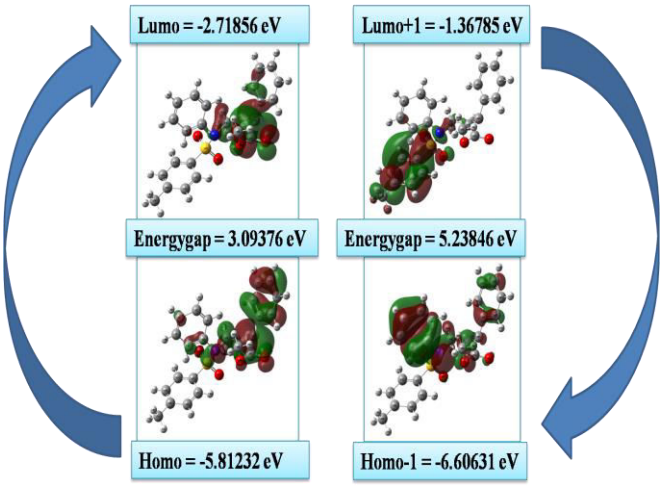


Fig. 6: The Frontier molecular orbitals of Sulfo

Table 2: The Physico-chemical properties of Sulfo

Parameters	Values
HOMO	-5.81232 eV
LUMO	-2.71856 eV
Homo-Lumo Energy gap	3.09376 eV
HOMO-1	-6.60631 eV
LUMO+1	-1.36785 eV
Homo-1-Lumo+1 Energy gap	5.23846 eV
Ionization potential (IP)	5.81232 eV
Electron affinity (EA)	2.71856 eV
Electrophilicity Index (ω)	2.94043
Chemical Potential (μ)	4.26544
Electro negativity (χ)	-4.26544
Hardness (η)	-3.09376

3.3.3. MEP Analysis

The molecular electrostatic potential surface was determined by B3LYP/6-311++G(d,p) basis set. MEP shows the electronic thickness and is helpful in acknowledgment locales for electrophilic assault and nucleophilic responses just as hydrogen bonding interactions. The different values of the electrostatic potential at the surface are represented by different colors. The negative areas (red, orange and yellow color) of MEP were related to electrophilic reactivity, the positive areas (blue color) ones to nucleophilic reactivity and green color is neutral regions. According to the MEP map in fig. 7, negative region of compound is mainly focused on oxygen, nitrogen and sulphur atoms with the highest red color intensity which is caused by the contribution of lone-pair electrons. Therefore they are suitable sites for electrophilic attack. The parts of the title compounds with pale red or yellow color are sites with weak interaction that including phenyl rings. The positive potential sites (blue color) are around the hydrogen atoms. In addition, Total density, Alpha density and ESP surfaces are shown in fig. 7.

3.4. Molecular Docking Studies

In the present analysis, *in silico* docking studies were performed using the crystal structure of penicillin-binding protein 2X to recognize the theoretical binding mode of sulfonamide derivative with the receptor binding site. Structure based drug design involves detailed knowledge of the binding sites of targets (such

as proteins) associated with the disease. Molecular docking is great promise in the field of computer based drug design which screens small molecules by orienting and scoring function of the binding protein. The top score docking pose was selected for analyzed sulfonamide compound compared with cocrystal, which was re-docked with the target protein using the same protocol.

The docking score and hydrogen bonding interactions of the sulfo compound and co-crystallized ligand are given in table 3. A view of the X-ray crystal structure of the title compound in the Penicillin-binding protein 2X Receptor active site showing the key hydrogen contacts between inhibitor and enzyme, is depicted in fig. 8. The co-crystallized ligand in the Penicillin-binding protein 2X Receptor active site showing the key hydrogen contacts between inhibitor and enzyme, is depicted in fig. 9. The surface diagram showing the title compound docked at the active site of Penicillin-binding protein 2X Receptor is depicted in fig. 10.

X-ray crystal structures confirmed the expected binding mode, and consideration of binding orientation and electronic properties enabled optimization to Sulfonamide as a more potent second-generation lead.

The docked molecule conformations suggest that the studied sulfonamide derivatives have favourable hydrogen bond interactions with the target penicillin binding protein 2X. The compounds have binding orientation and interaction with aminoacids like LYS241, GLY473, VAL471 and ASN544 present in the target protein penicillin binding protein 2X active site compared with the cocrystal ligand.

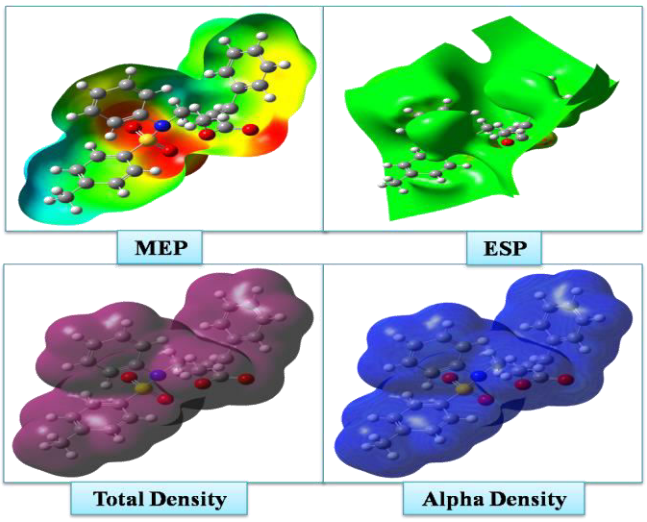


Fig. 7: The MEP, ESP, Total density and Alpha density surfaces of Sulfo

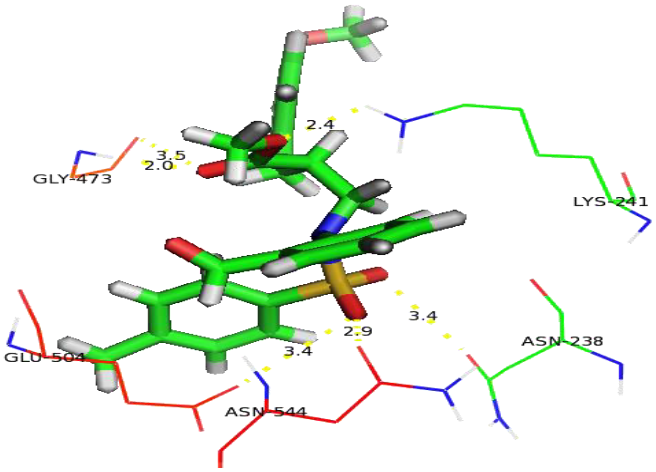


Fig. 8: The title compound in the Penicillin-binding protein 2X Receptor active site showing the key hydrogen contacts between Sulfonamide inhibitor and enzyme

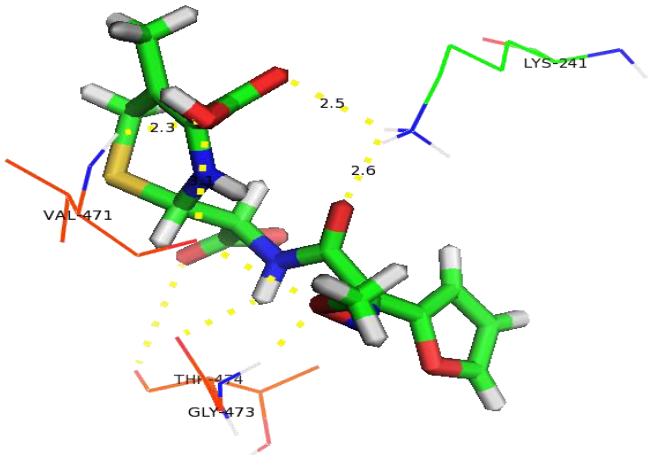


Fig. 9: The co-crystallized ligand (dexamethasone) in the Penicillin-binding protein 2X Receptor active site showing the key hydrogen contacts between inhibitor and enzyme

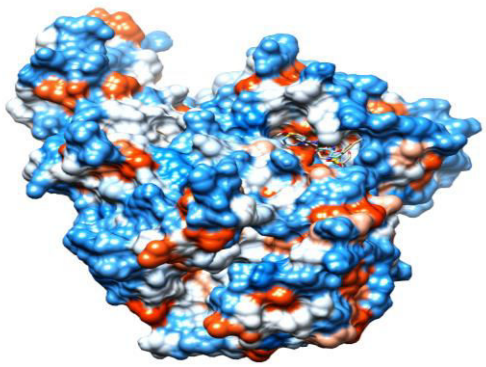


Fig. 10: Surface diagram showing the Sulfonamide docked at the active site of Penicillin-binding protein 2X Receptor

The title compound is shown to be effective inhibitor. In all these complex conformations the hydrogen bond interaction limits are 2.5 to 3.5 Å which shows a good interaction and hence most likely to result in a strong inhibition. The results show that the title compound having better binding energy and the co-crystallized ligand have comparable interactions.

Table 3: Hydrogen bond interactions of Isopropyl Myristate with amino acids at the active site of Penicillin-binding protein 2X Receptor

Compound	Docking Score	Hydrogen Bonding Interactions		
		Donor	Acceptor	Distance (Å)
Sulfonamide	-8.4	N-H[LYS241]	O*	**2.4**
		N-H[GLY473]	O*	**2.0**
		O-H	O*	**3.5**
Co-Crystal	-7.4	N-H[LYS241]	O*	2.5
		N-H	O*	2.6
		N-H[VAL471]	O*	2.3
		O-H	O*	3.1

4. CONCLUSION

The synthesized sulfonamide compound was structurally characterized and was determined by single crystal X-ray diffraction method and further we analyzed and examined by theoretical and experimental studies such as Hirshfeld surface analysis, Density functional theory and computational study of molecular docking. The Hirshfeld surface analyses and 2D-fingerprint plots were performed to understand the contributions of various inter atomic level contacts, which help to stabilize the molecular structures. The quantum chemical calculations has been carried out for the first time to the Sulfo molecule by DFT/B3LYP/6-311++G(d,p) basis set. The first order hyperpolarizability (β_0=24.04978 x10^{-30} esu) of Sulfo was calculated and found to be sixty five times greater than that of urea and hence the molecule has considerable good NLO activity. The Homo-Lumo energy gap was calculated about 3.09376 eV. The smaller energy gap of HOMO-LUMO explains the eventual charge transfer interaction taking place within the molecule, which influences the biological activity of the molecule. MEP surface analysis mentioned the active charge sites of the title molecule. Additionally the molecular modeling study of synthesized sulfonamide compound was carried out.

Conflict of interest

The authors declare that they have no conflicts of interest.

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