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Research Article

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Lattice Energy Calculation and Molecular Docking Studies of 2-([(4-([Acetylamino]sulfonyl)phenyl)amino]carbonyl)benzoic acid

Sanjay M. Tailor*, Kinjal D. Patel and Urmila H. Patel

Department of Physics, Sardar Patel University, Vallabh Vidyanagar -388 120, Gujarat, India

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ABSTRACT

2-([(4-([Acetylamino]sulfonyl)phenyl)amino]carbonyl)benzoic acid (Phthalyl sulfacetamide) belongs to well known member of antimicrobial sulfonamide family. The lattice energy of molecular structure of Phthalyl sulfacetamide are calculated using simple atom-atom potential energy functions, using coulombic terms with point-charge parameters, and using the PIXEL formulation, which is based on integral sums over the molecular electron density to obtain coulombic, polarization, dispersion and repulsion lattice energies. To calculate the lattice energy of molecular pair, those are involved in intermolecular interactions established by X-ray data, are picked up. Protein-ligand interaction plays an important role in structural based drugs design. Docking studies are carried out on Phthalyl sulfacetamide to understand the structure function relationship. The selected receptors are docked with Phthalyl sulfacetamide and the interaction energy value obtained using GLIDE utility from Schrodinger software. The observation from docking results suggests that the Phthalyl sulfacetamide binds well with 4X45 having G-score value -10.19.

Keywords: Phthalyl sulfacetamide, Interaction energy, CLP package, Docking, Glide score

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INTRODUCTION

Sulfonamide is the general term for the derivatives of p-Amino benzene sulfonamide [1-3]. The crystal structure of 2-([(4-([Acetylamino]sulfonyl)phenyl)amino]carbonyl)benzoic acid (Phthalyl sulfacetamide) is reported by T. P. Singh et al. [4]. We have collected data independently from the crystal grown by us. The chemical structure of Phthalyl sulfacetamide is shown in Figure 1. A robust theory of crystal packing should proceed by a quantitative evaluation of the potentials between molecules. These potentials arise from electrical interactions among electrons and nuclei, are being proposed for their calculation [5]. Since the nature of weak intermolecular interactions and its influences in the crystal packing appeared as unpredictable in nature, therefore careful but systematic studies of its nature has become an important prerequisite in the area of crystal engineering [6]. The nature and quantitative contribution of intermolecular interaction towards crystal packing for title molecule by Hirshfeld Surface analysis is reported earlier by us [7]. To establish that molecular packing revealed from the X-ray data are in most stable conformation, the energies associated with the intermolecular interactions and the nature of interactions are calculated using PIXEL by extracting only those molecular pair, involved in the crystal packing which reveals that the strongest hydrogen bond have the minimum lattice energy.

Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex [8]. It aims to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized. Two approaches are particularly popular within the molecular docking community. One approach (shape complementarily) uses a matching technique that describes the protein and the ligand as complementary surfaces [9-11]. The second approach simulates the actual docking process in which the ligand-protein pair wise interaction energies are calculated [12]. Protein–ligand interactions are essential for all processes happening in living

organisms. The results of docking can be used to find inhibitors for specific target proteins and thus to design new drugs.

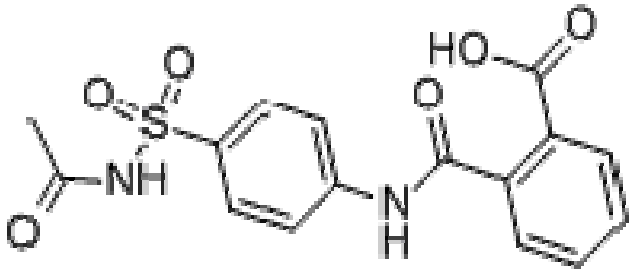

Figure 1: Chemical Structure of Phthalyl sulfacetamide

EXPERIMENTAL SECTION

Detailed quantitative analysis of the crystal packing have been performed with calculation of the interaction energies of the extracted molecular pairs from the crystal packing using PIXELC module in Coulomb-London–Pauli (CLP) computer program package [13].

The receptors for the structure of Phthalyl sulfacetamide and sulfonamide derivatives are referred from different journals and retrieved from PDB website [14] and those proteins are selected whose structures have been determined using a biophysical technique such as X-ray crystallography. A scoring function can discriminate correct (experimentally observed) docking complex structure from incorrect ones. The structure of the suitable protein structure and potential ligands serve as inputs to a docking program. Phthalyl sulfacetamide is procured from Sigma-Aldrich company and three dimensional structure has been investigated by X-ray diffraction. The corresponding shelxl file has been converted into PDB file using WINGX software. This PDB structure is used for the docking studies with different receptors using GLIDE [15-17] module of Schrodinger software. The title molecule is subjected full minimization with OPLS_2005 force field using "LigPrep" module. The structure of receptors are imported and refined by "Protein Preparation Wizard". Energy minimization is done by using OPLS_AA force field and refinement is carried out until average mean square deviation of the non hydrogen atoms reached 0.3Å and resulting optimized structure is used for docking. Receptor grid is generated and enclosed by a box at the receptor residue. Finally, prepared ligand and receptor is docked with "Ligand Docking" utility.

RESULTS AND DISCUSSION

Lattice Energy Calculation

The coulombic, polarization, dispersion and repulsion contributions to the total lattice energies for title compound are tabulated in Table 1. Different molecular pairs of title molecule involved in intermolecular interactions as obtained from crystal structure data along with their respective interaction energies are presented in Table 2.

Table 1: Total Lattice energies (kcal mol^{-1}) partitioned into coulombic, polarization dispersion and repulsion contribution using CLP for Phthalyl sulfacetamide

E_{Coul}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}
-46.75	-21.98	-44.33	56.08	-56.98

Table 2: PIXEL interaction energies (kcal mol^{-1}) between molecular pairs related by a symmetry operation and the associated intermolecular interactions

Mol. Pair	Centroids distance	E_{Coul} kcal/mol	E_{Pol} kcal/mol	E_{Disp} kcal/mol	E_{Rep} kcal/mol	E_{Tot} kcal/mol	Symmetry	Important interactions
I	7.672	-33.75	-18.23	-10.95	45.08	-17.88	-x-1, -y+2, -z+2	O6–H6A···O5
II	7.984	-9.98	-4.18	-12.73	11.9	-14.98	x-1, y, z	N1–H1···O3, C5–H5···O1, N1–H1···O1
III	7.984	-9.98	-4.18	-12.73	11.9	-14.98	x+1, y, z	Cg(2)–Cg(1)
IV	6.451	-5.05	-1.58	-10.75	4.65	-12.73	-x-1, -y+1, -z+2	C12–H12···O1
V	9.463	-12.7	-5.78	-10.00	15.83	-12.65	x+1/2, -y+3/2, z-1/2	C16–H16A···O4, N2–H2A···O4, C6–H6··· Cg(2)
Cg(1) represents centroid of phenyl ring (C1-C2-C3-C4-C5-C6) and Cg(2) represents centroid of phenyl ring (C8-C9-C10-C11-C12-C13).								

Molecular stability is due to intermolecular interaction between symmetry related molecular pairs– both the intermolecular interactions and molecular pair are established from X-ray result. X-ray crystallographic investigations of title compound reveals that intermolecular interactions are involved in stability of the structure. The Table 3 summarizes the details of intermolecular interaction along with symmetry code as obtained from X-ray [7]. The ORTEP [18] diagram of the title compound with numbering scheme is elucidated in Figure 2. The results show that the intermolecular interaction O6–H6A···O5 is the strongest among all in terms of hydrogen bond length and angle. Figure 3: III is the molecular packing of title compound, displaying strong dimeric O6–H6A···O5 hydrogen bond (Figure 3: motif I) which results in the formation of a pseudo ring of graph set motif $R_2^2(8)$ [19] at each center of inversion point. The calculated interaction energy for this specific interaction is -17.88 kcal mol^{-1} (with major contribution from coulombic) being the lowest among all, is very well match with the X-ray data. The next minimum lattice energy is -14.98 kcal mol^{-1} (with major contribution from dispersion), as calculated from PIXEL– is due to the joined contribution from N1–H1···O3,C5–H5···O1 and N1–H1···O1 interactions (Figure 3: motif II marked with circular region c) at x-1, y, z and from plannar stacking interaction at x+1, y, z. The next minimum stabilization energy (-12.73 $kcalmol^{-1}$) is due to C12–H12···O. The least contributed molecular pair involves N2–H2A···O4, C16–H16A···O4 and C6–H6···C(2) with interaction energy of -12.65 kcal mol^{-1} (Figure 3: motif II denoted by circular region b). The molecular packing view for molecular pair II to V are shown in Figure 3: IV down the ab plane.

Table 3: Hydrogen bond interactions with their symmetry codes

D–H···A	D–H (Å)	H···A (Å)	D–A (Å)	D–H···A (°)	Symmetry code
O6–H6A···O5	1.005(3)	1.638(3)	2.643(2)	178.3(3)	-x+1,-y+2,-z+2
N1–H1···O3	0.832(2)	2.248(3)	3.007(2)	151.8(2)	x-1,+y,+z
C5–H5···O1	0.920(2)	2.685(3)	3.347(3)	129.60(2)	x-1,+y,+z
N1–H1···O1	0.832(2)	2.736(3)	3.382(2)	135.7(2)	x-1,+y,+z
C12–H12···O1	1.012(3)	2.931(3)	3.735(3)	136.92(2)	-x-1,-y+1,-z+2
C16–H16A···O4	0.96(3)	2.432(2)	3.293(3)	149.1(2)	x+1/2,-y+3/2,+z-1/2
N2–H2A···O4	0.782(2)	2.054(2)	2.814(2)	163.9(2)	x+1/2,-y+3/2,+z-1/2

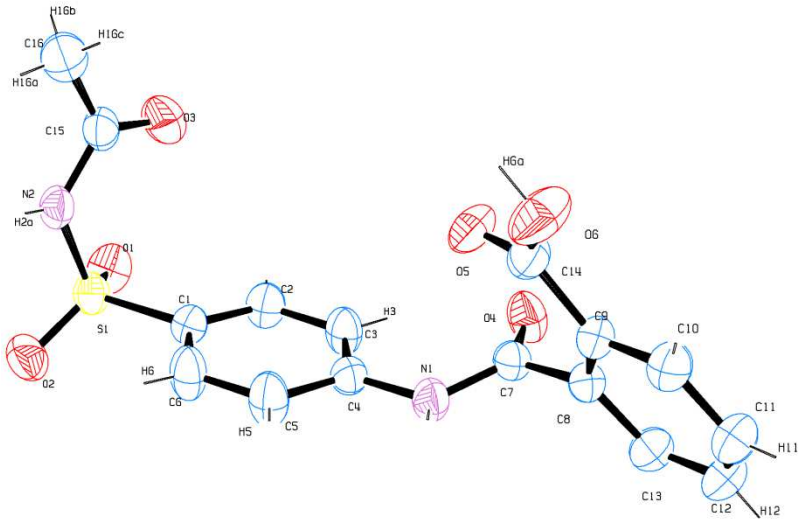

Figure 2: The ORTEP diagram of title compound with numbering scheme

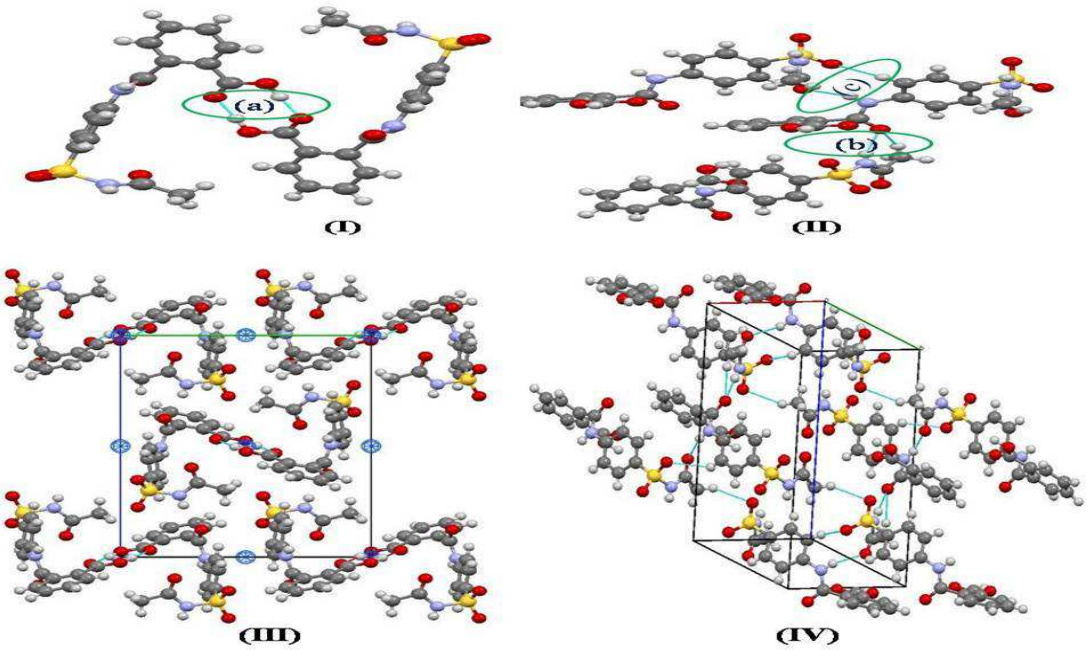

Figure 3: Selected molecular pairs from Table 2: (I) O6–H6A···O5 intermolecular interactions forming a dimer ring (denoted by circular region a) (II) N–H···O and C–H···O intermolecular interactions (III) Packing of molecular dimer O6–H6A···O5 along a axis (IV) Packing of molecules down the ab plane via N–H···O, C–H···O hydrogen bonds

Molecular Docking

GLIDE docking method has been applied to build a binding affinity model for title molecule with different receptors. For the predication of results mainly three parameters are considered which are Glide score, Glide energy and H-bond. On the basis of these parameters the binding affinity of ligand towards the receptors are discussed. The more negative value of G-score indicates the good binding affinity of the ligand with receptor. The minimum energy for the formation of complex between ligand and receptor indicates the good binding affinity. More, H-bond in the structure shows ligand having good binding mode to receptor. Table 4 summarizes the glide score and glide energy of title molecule with different receptors.

Table 4: Docking results of Phthalyl sulfacetamide with different receptors

Receptors	4X45	4X30	4MJO	3UA8
Glide Score	-10.19	-9.969	-10.07	-8.917
Glide Energy (kcal/mol)	-55.412	-62.65	-47.256	-71.885

Figure 4 represents hydrogen bond interaction between receptors with title molecule. Out of vast family of receptor four receptors 4X45 (transferase), 4X30 (transport protein), 4MJO (hydrolase inhibitor) and 3UA8 (transport protein/ anagonist) are docked with title molecule and give good G-score. The binding sites of proteins after GLIDE docking with title molecule are depicted in Figure 5. The title molecule is found to have high docking score of -10.19 and energy -55.41 kcal/mo l with 4X45 receptor. The title molecule interacts with 4X45 proteins at sites: THR 135, THR132, SER 102, ARG 67 and VAL 25 (Figure 5a). The 4X30 receptor give G-score of -9.969 with glide energy -62.65 kcal/mol. Phthalyl Sulfacetamide interacts with ASN 273, ARG 378 and H_2O protein sites of 4X30 (Figure 5b). The 4MJO receptor is hydrolase inhibitor showing G-score of -10.07 with glide energy -47.25 kcal/mol. The protein sites LYS 112, VAL 160 and ASP 178 interacts with title molecule (Figure 5c). The 3UA8 receptor is transport protein, docked with title molecule which results with -8.917 glide score and-71.88kcal/mol glide energy. It forms hydrogen bond with title molecule via H_2O, GLU 13, GLU 193, TYR 220and ARG 96 protein sites (Figure 5d).

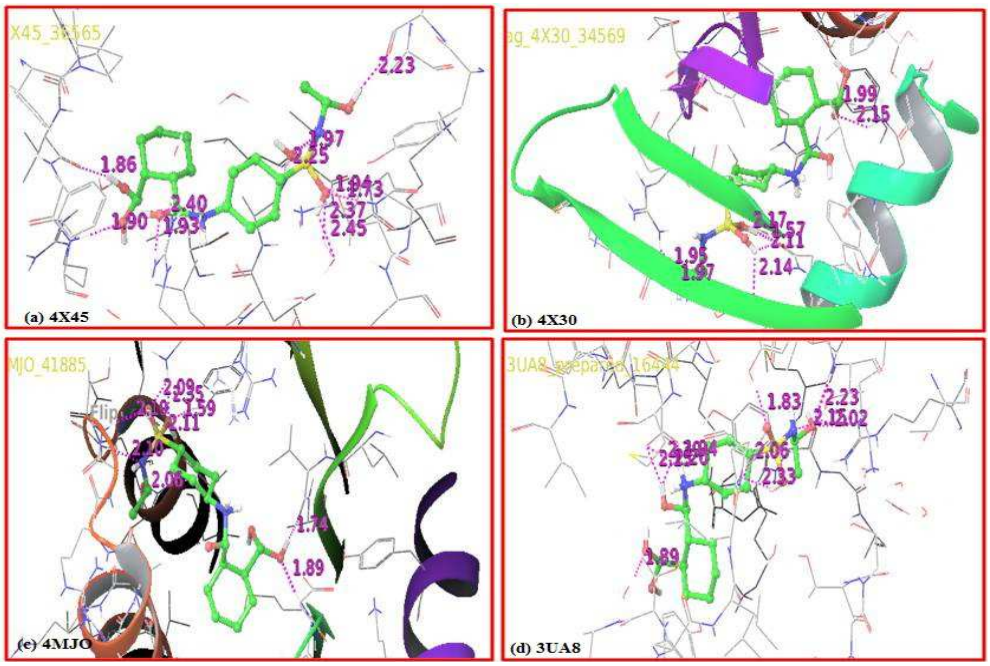

Figure 4: Interaction of Phthalyl sulfacetamide with (a) 4X45 (b) 4X30 (c) 4MJO and (d) 3UA8 receptors

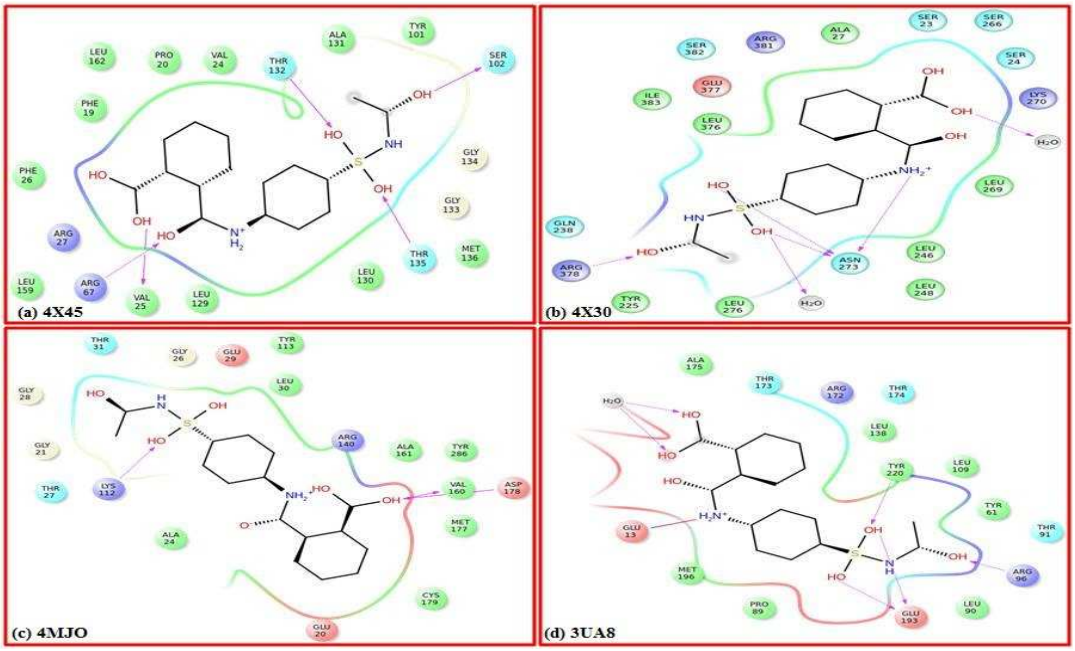

Figure 5: The binding sites of protein (a) 4X45 (b) 4X30 (c) 4MJO and (d) 3UA8 after GLIDE docking with title molecule

CONCLUSION

The complete analysis of the crystal packing with inputs from interaction energy calculations via PIXEL reveals that the stability of molecular packing is not only due to conventional hydrogen bond but also due to weak but significant C–H···O, C–H···π and π···π interactions. From docking score and glide energy we can say that title molecule having good binding affinity with 4X45 receptor and it may developed as a drug that can target the 4X45.

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