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**Chapter 8****Crystallographic investigation, quantum chemical calculations,  
Hirshfeld surface analysis and molecular docking of 2- [4- (acetyl  
amino sulphonyl) phenyl carbanoyl] benzoic acid**

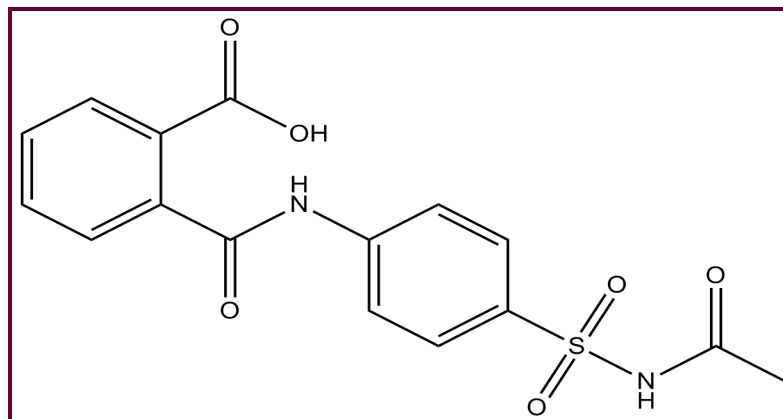
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## 8.1. Introduction

Phthalylsulfacetamide, 2-((4-([acetyl amino] sulfonyl) phenyl) amino) carbonyl) benzoic acid, a well-known sulfonamide used as leprostatic agent and to treat urinary tract infections. It has been investigated as a potential therapy for chloroquine-resistant malaria during pregnancy. The crystal structure of Phthalylsulfacetamide (PHSCA) is reported by T. P. Singh et al. [219]. The chemical structure of Phthalyl sulfacetamide is shown in **Figure 8.1**.



**Figure 8.1 Chemical Structure of PHSCA**

To compare the X-ray data with optimized geometry, to establish the intermolecular interactions as obtained by X-ray data and to correlate the structure-function relationship, Ab-initio MO calculation, Hirshfeld surface analysis and molecular docking studies are carried out by author.

## 8.2. Chemicals and Crystal Growth

Phthalylsulfacetamide is procured from Sigma-Aldrich and all solvents are purchased from Loba-Chemie. Transparent rectangular needle shaped diffraction quality single crystals are grown by slow evaporation technique using methanol as the solvent at room temperature. Photograph of grown crystal is shown in **Figure 8.2**.

## 8.3. X-ray Crystallographic Investigation

A suitable sample of single crystal of size  $(0.32 \times 0.16 \times 0.15)$  mm<sup>3</sup> is selected for crystallographic study. All diffraction measurements are performed at room temperature 296(2) K using graphite monochromated MoK $\alpha$  radiation of wavelength 0.71073 Å. The three

dimensional X-ray intensity data are collected from a crystal for  $\theta$  ranging from  $2.0^\circ$  to  $27.6^\circ$  using ( $\omega$ - $2\theta$ ) scan mode on a Bruker KAPPA APEX II CCD-4 diffractometer at Department of Physics, Sardar Patel University, Vallabh Vidyanagar. The cell refinement and data reduction are obtained using Bruker SAINT Programme. 15718 are the total number of measured reflections of which 3953 reflections are independent. Preliminary crystallographic data and details of the data collection and structure refinement are summarized in **Table 8.1** and **Table 8.2** respectively.



**Figure 8.2** Photograph of grown single crystals

**Table 8.1** Preliminary Crystallographic Data

Chemical name	: 2-[4-(Acetylaminosulphonyl) phenyl carbamoyl] benzoic Acid (Phthalylsulfacetamide)
Chemical formula	: $C_{16}H_{14}N_2O_6S$
Molecular weight	: 362.37 amu
Crystal system	: Monoclinic
Space group	: $P2_1/n$
a	: 7.9841(1) Å
b	: 12.8208(2) Å
c	: 16.6607(3) Å
$\alpha$	: $90.00(0)^\circ$
$\beta$	: $93.239(1)^\circ$
$\gamma$	: $90.00(0)^\circ$
Volume (V)	: 1702.71(5) Å <sup>3</sup>
Z	: 4
$\rho_c$	: 1.414 Mg/m <sup>3</sup>
$\mu(\text{mm}^{-1})$	: 0.23
F(000)	: 752

**Table 8.2 Intensity Data Collection and Refinement Parameters**

Instrument	: Bruker Kappa Apex-II CCD 4 diffractometer
Temperature	: 296 K
Radiation type	: MoK $\alpha$
Radiation source	: fine-focus sealed tube
Wavelength ( $\lambda$ )	: 0.71073 Å
Measurement method	: $\omega$ -2 $\theta$ scans
Measured reflections	: 15718
Independent reflections	: 3953 (3202 reflections with $I > 2\sigma(I)$ )
Limiting indices	: $-10 \leq h \leq 10$ ; $-16 \leq k \leq 13$ ; $-20 \leq l \leq 21$
$\theta$ range for data collection ( $^\circ$ )	: 2.0 $^\circ$ to 27.6 $^\circ$
Refinement method	: Full Matrix Least Square of $ F ^2$
Number of parameters	: 270
Final R indices [ $I > 2\sigma(I)$ ]	: $R_1 = 0.043$ , $wR_2 = 0.118$
R indices (all data)	: $R_1 = 0.055$ , $wR_2 = 0.125$
Goodness of fit (S)	: 1.05
Largest diff. peak and hole (e Å $^{-3}$ )	: 0.34 and -0.29
Software used to data collection	: Bruker Kappa Apex-II
Software used to cell refinement	: Bruker SAINT
Software used to solve the structure	: SHELXS-97
Software used to refine the structure	: SHELXL-97
Software used for Molecular Graphics	: PLUTON and ORTEP-3

### 8.3.1. Structure Solution and Refinement

SHELXS-97, built-in WinGX programme package is used to determine the phases and to locate the atomic positions and SHELXL-97 for refinement of the data to obtain a precise model of the structure. SHELXS-97 parameters of the set which could give the correct solution of the structure are

$$\begin{array}{lll} \text{Filter} = 0.002 & \text{NQAL} = 0.000 & \text{CFOM} = 0.004 \\ \text{R(ALPHA)} = 0.004 & \text{M(ABS)} = 1.054 & \end{array}$$

The phases obtained from the set are incorporated to generate an E-map. The value of  $R_{\text{int}}=0.0288$  and  $R_{\text{sigma}}=0.0260$  show that the quality of data is satisfactory. A trial model of the structure is developed using the significant high intense peaks. All the non-hydrogen atoms are refined anisotropically till  $R[F^2 > 2\sigma(F^2)]$  reduced to 0.043. The hydrogen atoms are located from difference Fourier map. Final R value is 0.043 for 3202 ( $I > 2\sigma(I)$ ) reflections and 270 parameters. The weighting scheme employed is of the type  $W = 1/[\sigma^2(F_o^2) + (0.0629P)^2 + 0.5997P]$  where  $P = (F_o^2 + 2F_c^2)/3$  with goodness of fit  $S = 1.05$ .

Highest and lowest electron density peaks ' $\Delta\rho$ ' are 0.340 and -0.29 eÅ<sup>-3</sup> respectively. The final positional parameters of non-hydrogen atoms with equivalent isotropic thermal parameters are listed in **Table 8.3**. **Table 8.4** summarizes the positional co-ordinates of hydrogen atoms with isotropic thermal parameters. The anisotropic thermal parameters of non-hydrogen atoms are given in **Table 8.5**.

**Table 8.3 Fractional co-ordinates of the non-hydrogen atoms and equivalent isotropic displacement parameters (Å<sup>2</sup>) with estimated standard deviation in parentheses**

$$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$$

Atom	x	y	z	U <sub>eq</sub>
S1	0.04019(5)	0.61383(4)	0.80067(3)	0.03787(5)
O1	0.17671(2)	0.56810(3)	0.84762(9)	0.0524(4)
O2	-0.01230(2)	0.56908(2)	0.72501(9)	0.0527(4)
O3	0.1771(2)	0.78316(4)	0.90407(9)	0.0591(4)
O4	-0.44328(2)	0.67611(2)	1.12379(8)	0.0508(4)
O5	-0.51463(2)	0.88225(2)	1.03065(9)	0.0498(4)
O6	-0.7225(2)	0.99854(2)	1.02515(2)	0.0645(5)
N1	-0.5541(2)	0.65970(4)	0.99514(9)	0.0404(4)
N2	0.0897(2)	0.73528(3)	0.77842(2)	0.0396(4)
C1	-0.1330(2)	0.62380(4)	0.86027(2)	0.0355(4)
C2	-0.1156(2)	0.61050(2)	0.94235(2)	0.0427(4)
C3	-0.2540(2)	0.61807(2)	0.98847(2)	0.0441(5)
C4	-0.4098(2)	0.64233(2)	0.95240(2)	0.0363(4)
C5	-0.4263(3)	0.6520(2)	0.86886(2)	0.0532(6)
C6	-0.2894(2)	0.6428(2)	0.82307(2)	0.0510(5)
C7	-0.5593(2)	0.68823(2)	1.07359(2)	0.0375(4)
C8	-0.7258(2)	0.73079(2)	1.09598(2)	0.0379(4)
C9	-0.7776(2)	0.83246(5)	1.07797(2)	0.0387(4)
C10	-0.9374(3)	0.86475(2)	1.09586(3)	0.0482(5)
C11	-1.0438(3)	0.7980(2)	1.13289(2)	0.0575(6)
C12	-0.9902(3)	0.6992(2)	1.15416(4)	0.0576(6)
C13	-0.8331(3)	0.66514(2)	1.13550(3)	0.0496(5)
C14	-0.6585(2)	0.90644(2)	1.04196(2)	0.0417(4)
C15	0.1460(2)	0.80775(2)	0.83475(2)	0.0428(4)
C16	0.1627(4)	0.9161(2)	0.80400(6)	0.0736(8)

**Table 8.4 Fractional co-ordinate of hydrogen atoms and isotropic displacement parameters ( $\text{\AA}^2$ ) with estimated standard deviation in parentheses**

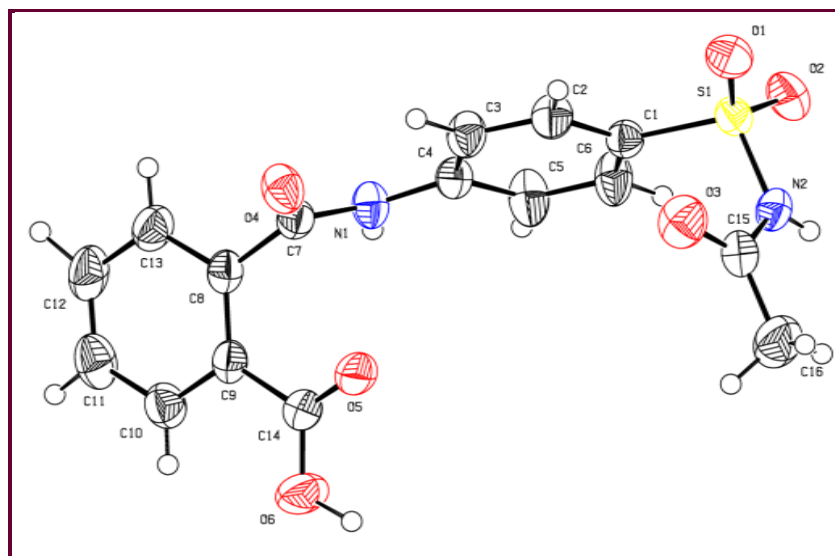
Atom	x	y	z	$U_{\text{iso}}$
H1	-0.640(3)	0.672(2)	0.9660(2)	0.065(8)
H2	-0.013(3)	0.5979(2)	0.9686(2)	0.056(7)
H2A	0.066(3)	0.7514(2)	0.7339(2)	0.045(6)
H3	-0.239(3)	0.6096(2)	1.0461(2)	0.051(6)
H5	-0.529(3)	0.669(2)	0.8441(2)	0.081(9)
H6	-0.301(3)	0.6544(2)	0.7682(5)	0.057(6)
H6A	-0.634(4)	1.044(3)	1.003(2)	0.105(2)
H10	-0.967(3)	0.932(2)	1.0863(4)	0.055(7)
H11	-1.156(3)	0.823(2)	1.1410(5)	0.069(8)
H12	-1.048(4)	0.643(2)	1.1848(8)	0.083(9)
H13	-0.796(3)	0.598(2)	1.1505(4)	0.057(7)
H16A	0.1316	0.9177	0.7475	0.11
H16B	0.2769	0.9388	0.8127	0.11
H16C	0.0905	0.9617	0.8319	0.11

**Table 8.5 Anisotropic displacement parameters ( $\text{\AA}^2$ ) of non-hydrogen atoms with estimated standard deviation in parentheses**

Atom	$U^{11}$	$U^{22}$	$U^{33}$	$U^{12}$	$U^{13}$	$U^{23}$
S1	0.0360(2)	0.0408(3)	0.0372(2)	0.00627(2)	0.0062(2)	-0.00003(8)
O1	0.0409(7)	0.0575(9)	0.0589(9)	0.0156(6)	0.0045(6)	0.0102(7)
O2	0.0568(9)	0.0561(9)	0.0457(8)	0.0025(7)	0.0090(6)	-0.0141(7)
O3	0.0691(2)	0.0680(2)	0.0392(8)	-0.0048(8)	-0.0052(7)	-0.0040(7)
O4	0.0526(8)	0.0664(2)	0.0333(7)	0.0093(7)	0.0000(6)	-0.0042(6)
O5	0.0419(7)	0.0444(8)	0.0649(9)	-0.0035(6)	0.0186(7)	0.0097(7)
O6	0.0517(9)	0.0443(9)	0.0995(3)	0.0017(7)	0.0225(9)	0.0201(9)
N1	0.0345(8)	0.0561(2)	0.0306(8)	-0.0015(7)	0.0023(6)	-0.0019(7)
N2	0.0440(9)	0.0467(2)	0.0283(8)	-0.0006(7)	0.0041(6)	0.0048(7)
C1	0.0337(8)	0.0380(2)	0.0351(9)	0.0013(7)	0.0040(7)	0.0025(7)
C2	0.0348(9)	0.0566(2)	0.0361(9)	0.0061(8)	-0.0025(7)	0.0061(8)
C3	0.0426(2)	0.0602(3)	0.0293(9)	0.0053(9)	-0.0003(7)	0.0051(8)
C4	0.0350(9)	0.0421(2)	0.0318(8)	-0.0028(7)	0.0025(7)	-0.0010(7)
C5	0.0340(2)	0.0919(8)	0.0331(2)	0.0075(2)	-0.0023(8)	0.0019(2)
C6	0.0397(2)	0.0844(7)	0.0287(9)	0.0084(2)	0.0009(8)	0.0050(9)
C7	0.0427(9)	0.0375(2)	0.0325(9)	-0.0035(7)	0.0044(7)	-0.0001(7)
C8	0.0398(9)	0.0440(2)	0.0304(8)	-0.0069(8)	0.0056(7)	-0.0028(7)
C9	0.0387(9)	0.0441(2)	0.0342(9)	-0.0054(8)	0.0092(7)	-0.0011(7)
C10	0.0435(2)	0.0507(3)	0.0513(2)	-0.0013(9)	0.0114(9)	-0.0037(2)
C11	0.0395(2)	0.0722(6)	0.0622(4)	-0.0094(2)	0.0168(2)	-0.0106(2)
C12	0.0529(2)	0.0648(5)	0.0573(3)	-0.0230(2)	0.0208(2)	-0.0032(2)
C13	0.0572(2)	0.0453(2)	0.0474(2)	-0.0128(2)	0.0128(9)	0.0008(9)
C14	0.0427(2)	0.0411(2)	0.0421(2)	-0.0015(8)	0.0085(8)	0.0034(8)
C15	0.0399(2)	0.0527(2)	0.0364(9)	-0.0019(8)	0.0081(8)	-0.0029(8)
C16	0.112(2)	0.0539(5)	0.0565(4)	-0.0186(5)	0.0221(4)	-0.0050(2)

### 8.3.2. Crystal Structure of Phthalylsulfacetamide

Phthalylsulfacetamide,  $C_{16}H_{14}N_2O_6S$ , (PHSCA) crystallizes in monoclinic space group  $P2_1/n$  with  $Z=4$ . An ‘ORTEP’ view of the molecule indicating atomic numbering scheme (thermal ellipsoids drawn at 50% probability level) is displayed in the **Figure 8.3**.



**Figure 8.3** ORTEP diagram of the title compound showing thermal displacement ellipsoids drawn at 50% probability level

#### Molecular Dimension

Bond length involving non-hydrogen atoms, as obtained by X-ray data with estimated standard deviation in parentheses and by theoretical calculations at the B3LYP/6-311G level of theory, are summarized in **Table 8.6** and bond length involving hydrogen atoms as obtained by X-ray data, are tabulated in **Table 8.7**. **Table 8.8** presents the bond angle involving non hydrogen atoms with estimated standard deviation in parentheses as obtained by X-ray data and by theoretical calculation at the B3LYP/6-311G level of theory. Molecular dimension of phenyl rings are normal: bond length of phenyl rings (C1–C6) and (C8–C13) varies from 1.374 Å to 1.395 Å. The tetrahedral geometry around sulfur atom is distorted from its ideal value of 109°, the angle varies from 104.1(9)° to 119.7(9)°.

**Table 8.6 Bond length (Å) involving non-hydrogen atoms with estimated standard deviation in parentheses as obtained by X-ray data and by theoretical calculations (B3LYP /6-311G level of theory)**

Bond length	X-ray	B3LYP	Bond length	X-ray	B3LYP
S1—O1	1.429(2)	1.622	C1—C6	1.384(3)	1.388
S1—O2	1.426(2)	1.640	C2—C3	1.385(3)	1.394
S1—N2	1.653(2)	1.848	C3—C4	1.388(2)	1.408
S1—C1	1.753(2)	1.873	C4—C5	1.395(3)	1.409
O3—C15	1.209(2)	1.241	C6—C5	1.373(3)	1.389
O4—C7	1.222(2)	1.243	C7—C8	1.503(2)	1.513
O5—C14	1.216(2)	1.236	C8—C9	1.395(3)	1.411
O6—C14	1.310(2)	1.379	C8—C13	1.391(3)	1.399
N1—C7	1.362(2)	1.378	C9—C10	1.390(3)	1.404
N1—C4	1.406(2)	1.408	C10—C11	1.376(3)	1.392
N2—C15	1.377(2)	1.379	C11—C12	1.374(4)	1.396
C14—C9	1.491(2)	1.476	C13—C12	1.383(3)	1.396
C1—C2	1.377(2)	1.386	C15—C16	1.494(3)	1.513

**Table 8.7 Bond length (Å) involving hydrogen atoms as obtained by X-ray data**

Bond length	X-ray	Bond length	X-ray
O6—H6A	0.98 (4)	C10—H10	0.93 (3)
N1—H1	0.86 (3)	C11—H11	0.97 (3)
N2—H2A	0.78 (2)	C12—H12	1.03 (3)
C2—H2	0.90 (2)	C13—H13	0.95 (2)
C3—H3	0.95 (2)	C16—H16C	0.87 (4)
C5—H5	0.93 (3)	C16—H16B	0.87 (4)
C6—H6	0.93 (2)	C16—H16A	1.01 (6)



**Table 8.8 Bond angle (°) involving non-hydrogen atoms with estimated standard deviation in parentheses as obtained by X-ray data and by theoretical calculations (B3LYP /6-311G level of theory)**

Bond angle	X-ray	B3LYP	Bond angle	X-ray	B3LYP
O1—S1—O2	119.7(9)	121.67	C2—C1—C6	120.3(2)	123.68
O1—S1—N2	108.9(9)	110.17	C2—C1—S1	120.9(2)	119.59
O1—S1—C1	108.7(8)	110.62	C2—C3—C4	119.9(2)	119.77
O2—S1—N2	104.1(9)	99.30	C3—C4—C5	118.9(2)	119.91
O2—S1—C1	109.1(8)	108.31	C4—C5—C6	120.9(2)	120.62
O3—C15—N2	121.2(2)	121.98	C6—C1—S1	118.7(2)	116.70
O3—C15—C16	123.7(2)	123.18	C7—C8—C9	122.7(2)	123.56
O4—C7—N1	124.0(2)	124.27	C7—N1—C4	126.8(2)	128.56
O4—C7—C8	121.6(2)	120.96	C7—C8—C13	118.3(2)	117.11
O5—C14—O6	123.9(2)	121.27	C8—C9—C10	119.7 (2)	119.66
O5—C14—C9	121.9(2)	125.57	C8—C9—C14	119.6(16)	120.12
O6—C14—C9	114.2(2)	113.15	C8—C13—C12	120.4(2)	120.80
N1—C7—C8	114.2(2)	114.54	C9—C8—C13	118.9(2)	119.11
N1—C4—C3	123.8(2)	122.98	C9—C10—C10	120.5(2)	120.58
N1—C4—C5	117.2(2)	117.11	C10—C9—C14	120.6(2)	120.21
N2—S1—C1	105.3(8)	105.12	C10—C11—C12	119.9(2)	119.81
N2—C15—C16	115.1(2)	114.84	C11—C12—C13	120.3(2)	120.03
C1—C2—C3	120.2(2)	118.36	C15—N2—S1	123.7(2)	123.47
C1—C6—C5	119.5(2)	117.66			

### Molecular Conformation

The equation of few significant least-square planes, along with the displacement of the relevant atoms from the mean planes and the dihedral angle between the different mean planes are presented in **Table 8.9** which reveal that both the phenyl rings are effectively planar. Molecular conformation described by few torsional angles about significant bond obtained by X-ray data (with estimated standard deviation in parentheses) and by theoretical calculation at the B3LYP/6-311G levels of theory are tabulated in **Table 8.10**. The dihedral angle between two phenyl rings [(C1-C6) & (C8-C13)] is  $62.23(10)^\circ$  and  $52.29^\circ$  by B3LYP method. The torsional angle C9–C8–C7–N1 of  $-78.5(2)^\circ$  describes the rotation of phenyl ring. Similarly, N2–C1–N1–S1 of  $22.4(13)^\circ$  represents the rotation of phenyl ring attached to sulfonyl group.

**Table 8.9 Equation of least-square planes along with the displacement of relevant atoms and the dihedral angle between different planes with standard deviation in parentheses**

(1) C1-C2-C3-C4-C5-C6			
$0.1671(9)x + 0.9806(2)y + 0.1028(9)z = 5.1397(17)$			
C1	-0.016(2)	C4	-0.023(2)
C2	0.001(2)	C5	0.008 (3)
C3	0.019(3)	C6	0.012(3)
(2) C8-C9-C10-C11-C12-C13			
$0.3210(8)x + 0.3278(9)y + 0.8886(4)z = 1.584(7)$			
C8	0.018(2)	C11	0.016(2)
C9	-0.016(2)	C12	-0.014(2)
C10	-0.001(2)	C13	-0.003(2)
Dihedral angle between LSQ- planes			
Plane	X-ray	B3LYP	
(C1-C6) & (C8-C13)	$62.23(10)^\circ$	$52.29^\circ$	

**Table 8.10 Few torsional angles ( $^\circ$ ) with estimated standard deviation in parentheses**

	X-ray	B3LYP		X-ray	B3LYP
C7—N1—C4—C3	22.4(3)	4.52	S1—N2—C15—O3	6.9(3)	-10.26
N1—C7—C8—C9	-78.5(2)	-93.62	O1—S1—N2—C15	-51.95(2)	-53.07
O6—C14—C9—C8	177.9(2)	-171.56	N2—S1—C1—C6	78.16(2)	98.36
C4—N1—C7—C8	163.1(2)	-179.14			

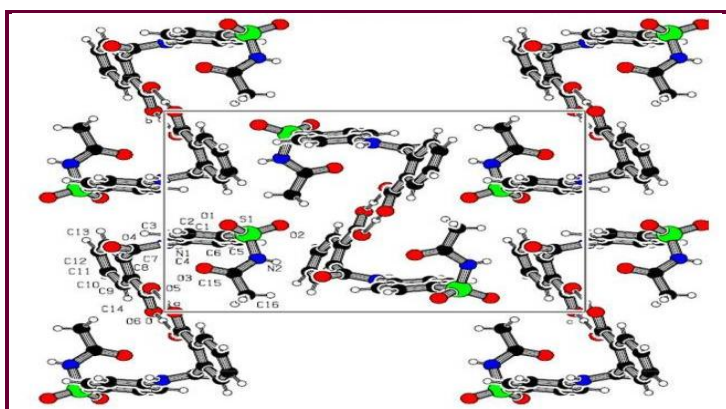
### 8.3.3. Hydrogen Bonding and Molecular Packing

Analysis of hydrogen bonding pattern of the title compound shows the presence of C-H... $\pi$ ,  $\pi$ ... $\pi$  and N-H...O intermolecular hydrogen bond interactions in the structure. The intermolecular hydrogen bond interactions, calculated from PARST and PLUTON software, are summarized in **Table 8.11**.

Table 8.11 Intermolecular interaction and symmetry code

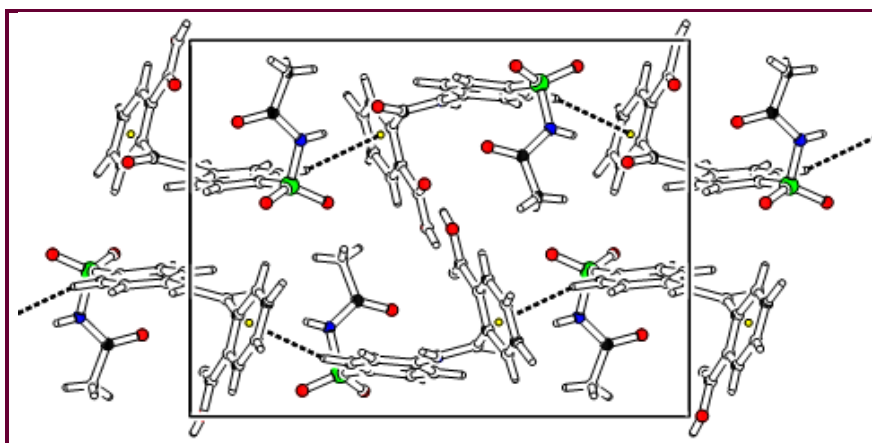
A. Hydrogen bond interactions					
D–H...A	(D–H) Å	(H–A) Å	(D–A) Å	(D–H...A)°	
O6–H6A...O5 <sup>(i)</sup>	1.005(3)	1.638(3)	2.643(2)	165(2)	
N2–H2A...O4 <sup>(iii)</sup>	0.782(2)	2.054(2)	2.814(2)	163.9(2)	
N1–H1...O3 <sup>(iii)</sup>	0.832(2)	2.248(3)	3.007(2)	150(2)	
C5–H5...O <sup>(iii)</sup> 1	0.920(2)	2.685(3)	3.347(3)	176(3)	
N1–H1...O1 <sup>(iii)</sup>	0.832(2)	2.736(3)	3.382(2)	103.9(2)	
C12–H12...O1 <sup>(iv)</sup>	1.012(3)	2.931(3)	3.735(3)	119.0(2)	
C16–H16A...O4 <sup>(ii)</sup>	0.96(3)	2.432(2)	3.293(3)	100.7(2)	
B. $\pi$ - $\pi$ interaction					
Cg(I)–Cg(J)	Cg(I)...Cg(J) Å	A	$\beta$	$\gamma$	Cg(J)...P Å
Cg(2)–Cg(1) <sup>(v)</sup>	4.8411(11)	0	52.7	52.7	3.6252(9)
C. C–H... $\pi$ interaction					
C–H(I) ...Cg(J)	d(H–Cg) Å	d(C–Cg) Å	$\gamma$ °	Y–X...Cg°	H...P Å
C6–H6...Cg(2) <sup>(ii)</sup>	2.79(2)	3.693(2)	7.94	164.5(19)	2.76
<b>Symmetry Code:</b> (i) -x-1,-y+2,-z+2; (ii) x+1/2,-y+3/2,+z-1/2; (iii) x-1,+y,+z; (iv) -x-1,-y+1,-z+2; (v) x+1, y, z					
Note: Cg (1) and Cg (2) represents the centroid of the phenyl rings (C1-C6) & (C8-C13) respectively					

O–H...O, N–H...O and C–H...O intermolecular interactions are responsible for the stability of crystal packing. Acetyl oxygen atom (O3) at x-1,+y,+z acts as an acceptor to sulfonyl nitrogen atom (N1). In intermolecular interaction O6–H6A...O5, the oxygen atom of carboxylic group forms the dimer ring of graph set motif R (8) at each center of inversion point in which the O6 atom acts as a donor to O5 atom of the symmetry related molecule at -x-1,-y+2,-z+2 shown in **Figure 8.4**.



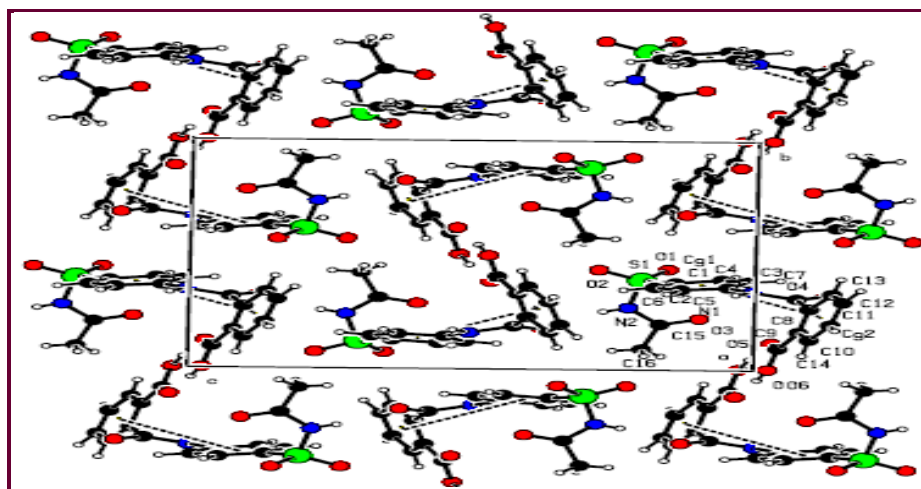
**Figure 8.4** A part of molecular packing diagram displaying O6–H6A...O5 intermolecular interactions

The molecular packing is also influenced by intermolecular C–H... $\pi$  interactions as shown in **Figure 8.5**. The six membered phenyl ring (C1–C6) oriented in such a manner that it facilitates the formation of C–H... $\pi$  interaction—The C6 via H6 acts as donor to Cg(2) of the symmetry related ( $x+1/2, -y+3/2, z-1/2$ ) phenyl ring in an intermolecular interaction such that the distance C6–H6...Cg(2) = 3.693(4) Å.



**Figure 8.5** A part of molecular packing displaying C–H... $\pi$  interaction

Molecular stacking is further supported by  $\pi$ ... $\pi$  stacking interaction observed between the centroid of the phenyl ring (C1–C6) and that of phenyl ring (C8–C13) at  $x+1, y, z$  with their centroid separated by 4.8411(11) Å, shown in **Figure 8.6**.



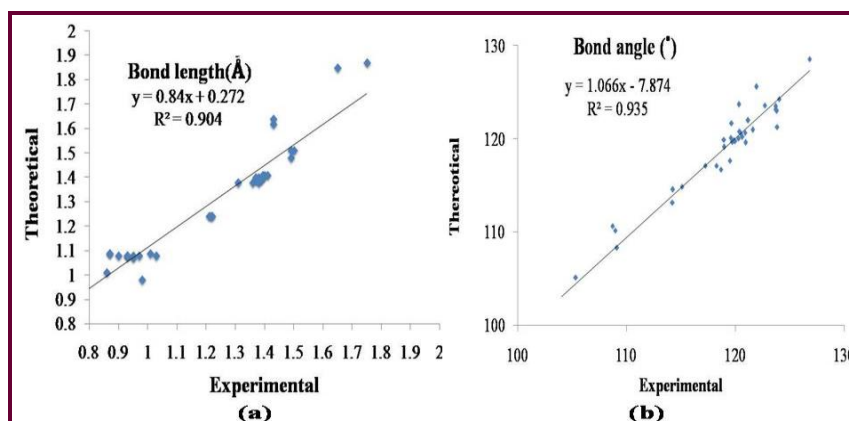
**Figure 8.6** A part of molecular packing showing  $\pi$ ... $\pi$  molecular packing interaction

## 8.4. Ab – initio and DFT Calculations

Density Functional theory method has been used to calculate all quantum chemical calculation using JAGUAR utility from Schrodinger software package. The geometry optimization, Mulliken charge distribution, dipole moment and HOMO-LUMO calculation have been performed using B3LYP method at 6-311G basis set.

### 8.4.1. Geometry Optimization Calculations

The optimized geometric parameters, obtained from B3LYP/6-311G calculations, are listed in **Table 8.6** and **Table 8.8**. The graphical representations for correlation coefficients for bond length and bond angle are depicted in **Figure 8.7**. The highest bond difference of 0.21 Å for the S1—C1 in B3LYP method where as the highest bond angle deviation of 4.75° occurred in the O2—S1—N2 angle in B3LYP method. The correlation coefficients for bond length and bond angle are 0.904 and 0.935 respectively. The root mean square error (RMSE) for bond length is 0.074 Å and for bond angle is 1.517°. All optimized bond lengths are slightly larger than those of experimental values. The observed discrepancies between the theoretical and experimental result may be attributed to different environments of the molecule, being isolated state in gas phase for theoretical study hence no influence of molecular interactions.



**Figure 8.7** Graphical representation of correlation between experimental versus theoretical (a) bond length and (b) bond angle

### 8.4.2. Mulliken Charge Distributions

The Mulliken charge distribution analysis, calculated using B3LYP method with basis set 6-311G level, are tabulated in **Table 8.12** and are presented in **Figure 8.8** which represents the

charges on the individual atoms. The atomic charge calculation for individual atoms by Mulliken charge distributions help to predict whether a particular atom will take part in hydrogen bond interactions or not. It is noticeable that all the oxygen and nitrogen atoms have negative charge and all hydrogen atoms have positive charge. One of the carboxylic oxygen (O6) is more negatively charged (-0.5762) than the other oxygen atoms present. Similarly, the nitrogen N1 is more negatively charged (-0.7863) than the other nitrogen atoms present. The hydrogen atom from carboxylic oxygen (H6A) has more positive charge (0.3393) than the other hydrogen atoms present. These observations suggest that oxygen and nitrogen act as electron acceptor and charge transfer take place from H to O and N. The carbon atom from acetyl group C15 is more positive (0.5709) than other positive carbons and aromatic C1 (-0.3391) is more negative than other negative carbon atoms. The presence of donor and acceptor atoms reveal the existence of intra and inter molecular hydrogen bonding interactions involve the specific atoms in the crystalline phase.

**Table 8.12 Mulliken charges (e) for atoms calculated by B3LYP method**

Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge
O5	-0.3655	H5	0.172376	O4	-0.38072	C6	-0.06889
O6	-0.57625	H10	0.195324	O3	-0.39576	C9	-0.10555
C14	0.483187	H12	0.168853	C2	-0.01618	C13	-0.12175
H13	0.177394	H6A	0.399253	N1	-0.78626	C4	0.373305
H3	0.238098	H16C	0.228332	O1	-0.51303	C10	-0.07973
H2A	0.37955	H16B	0.227883	C7	0.487523	C12	-0.10298
H2	0.226649	H16A	0.19415	C3	-0.10877	C5	-0.22161
H11	0.167124	S1	1.130133	O2	-0.56543	C11	-0.14351
H1	0.350077	C1	-0.33908	C8	-0.10925	C16	-0.62144
H6	0.220477	N2	-0.76891	C15	0.570915		

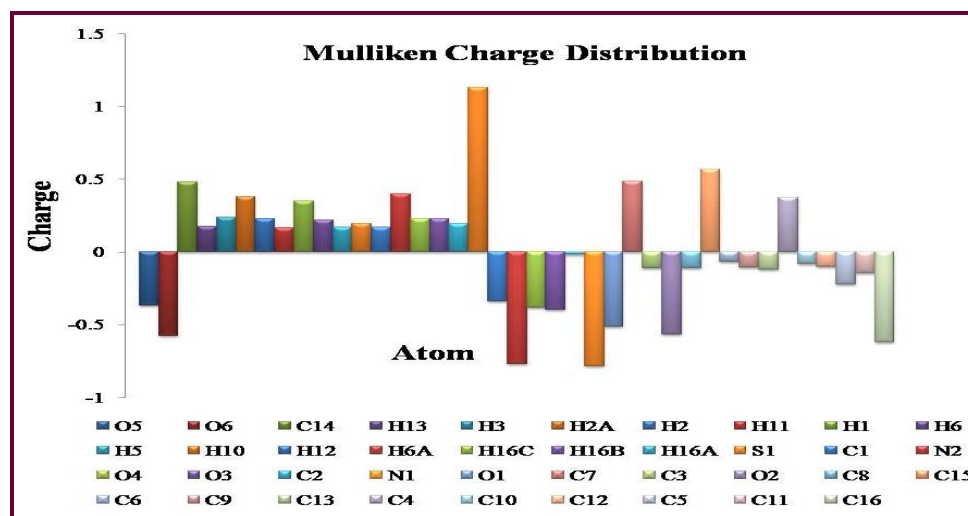


Figure 8.8 Graph sheet of Mulliken atomic charges (e) by B3LYP method

### 8.4.3. HOMO and LUMO Analysis

The HOMO and its orbital play the role of electron donors, and the LUMO and its orbital play the role of electron acceptors. HOMO and LUMO energies for the title molecule have been calculated using B3LYP/ 6-311G method. The calculated energy value of HOMO is -6.9253eV and LUMO is -2.3565eV. The energy gap of HOMO-LUMO (-4.5688eV) explains the charge transfer interaction within the molecule. The value of dipole moment (9.325 Debye) suggests the reactivity and attraction for the interaction with other system.

### 8.5. Lattice Energies

The coulombic, polarization, dispersion and repulsion contributions to the total lattice energies, calculated using PIXELC software, are tabulated in **Table 8.13**. Different molecular pairs involved in intermolecular interactions as obtained from crystal structure data along with their respective interaction energies are presented in **Table 8.14**.

**Table 8.13 Total Lattice energies (kcal mol<sup>-1</sup>) partitioned into coulombic, polarization dispersion and repulsion contribution using CLP for PHSCA**

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

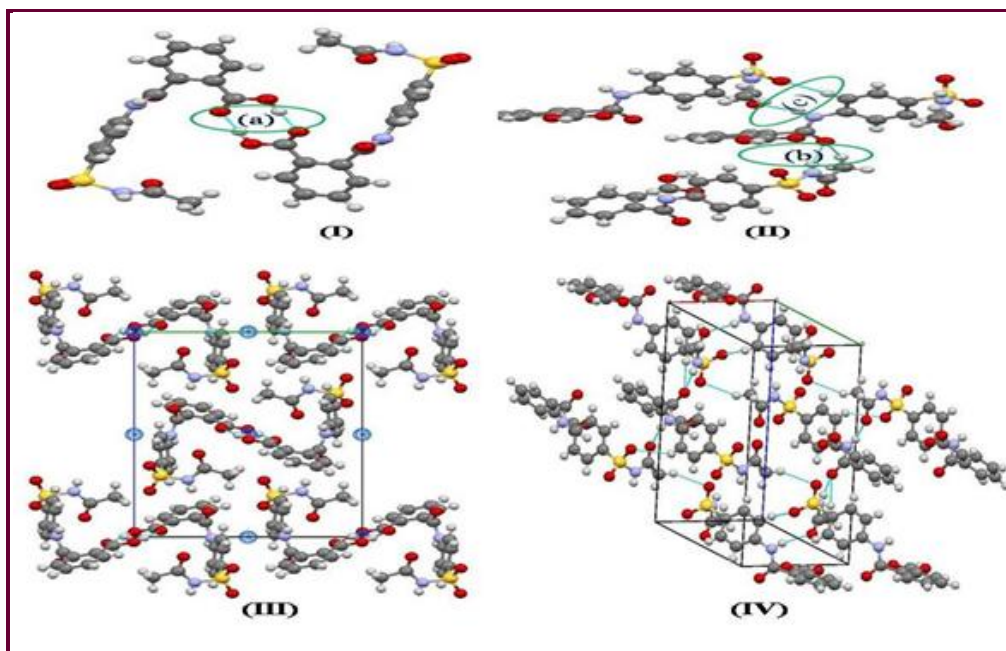
**Table 8.14 PIXEL interaction energies (kcal mol<sup>-1</sup>) between molecular pairs related by a symmetry operation and the associated intermolecular interactions**

Mol. Pair	Centroids distance	E <sub>Coul</sub>	E <sub>Pol</sub>	E <sub>Disp</sub>	E <sub>Rep</sub>	E <sub>Tot</sub>	Symmetry	Important interactions
<b>I</b>	7.672	-33.75	-18.23	-10.95	45.08	-17.88	-x-1, -y+2, -z+2	O6–H6A...O5
<b>II</b>	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
<b>III</b>	7.984	-9.98	-4.18	-12.73	11.9	-14.98	x+1, y, z	Cg(2)–Cg(1)
<b>IV</b>	6.451	-5.05	-1.58	-10.75	4.65	-12.73	-x-1, -y+1, -z+2	C12–H12...O1
<b>V</b>	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-C6)  
Cg(2) represents centroid of phenyl ring (C8-C13).

The calculated interaction energy for O6–H6A...O5 interaction (**Figure 8.9: motif I** marked with circular region a) is -17.88 kcal mol<sup>-1</sup> (with major contribution from coulombic) being the lowest among all. The O6–H6A...O5 interaction is observed at each center of inversion point as seen in **Figure 8.9: motif III**. The next minimum lattice energy is -14.98 kcal mol<sup>-1</sup> (with major contribution from dispersion), as calculated from PIXEL— is due to the joined contributions from N1–H1...O3, C5–H5...O1 and N1–H1...O1 interactions (**Figure 8.9: motif II** marked with circular region c) at x-1, y, z and from planar stacking interaction at x+1, y, z. The next minimum stabilization energy (-12.73 kcal mol<sup>-1</sup>) is due to C12–H12...O1. The least contributed molecular pair involves N2–H2A...O4, C16–H16A...O4 and C6–H6...Cg (2) with interaction energy of -12.65 kcal mol<sup>-1</sup> (**Figure 8.9: motif II** denoted by circular region b). The molecular packing view for molecular pair II to V are shown in **Figure 8.9: IV** down the ab plane.

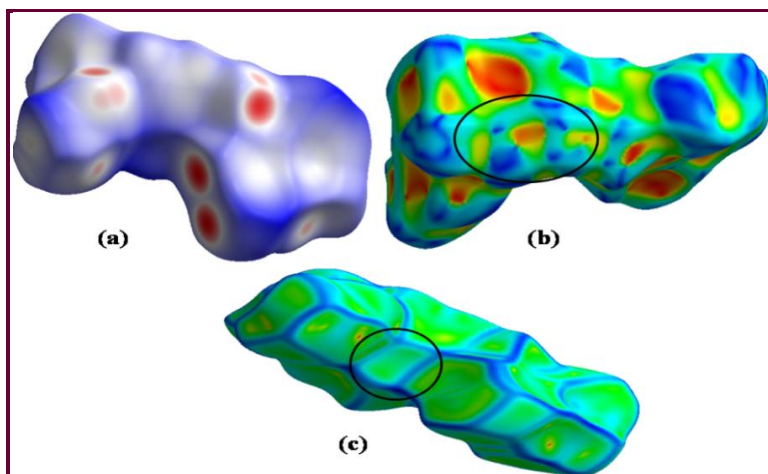




**Figure 8.9** Selected molecular pairs from Table 8.13 (I) O6–H6A...O5 (denoted by circular region a) (II) N–H...O and C–H...O intermolecular interactions (III) Packing of molecular dimer O6–H6A...O5 along a axis (IV) Packing of molecules down the ab plane via N–H...O, C–H...O hydrogen bonds

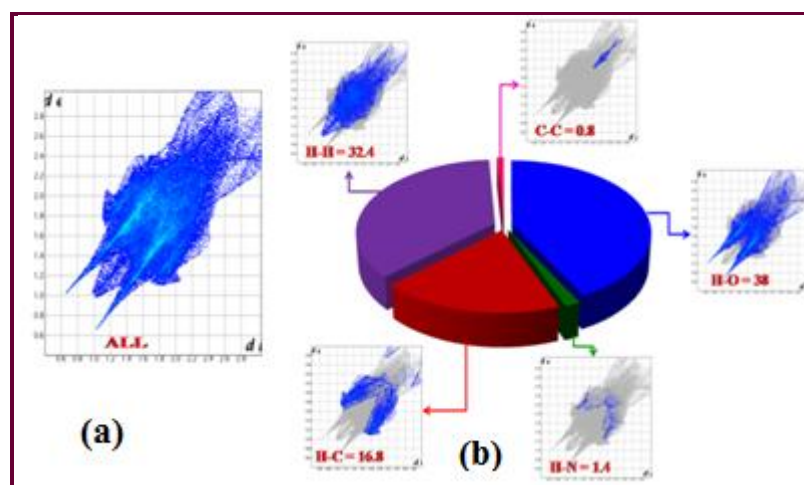
## 8.6. Hirshfeld Surface Analysis and 2-D Fingerprint Plot

The molecular Hirshfeld surfaces generated using a standard (high) surface resolution. The  $d_{\text{norm}}$  surface is mapped over a fixed color scale of  $-0.738$  (red) to  $1.813 \text{ \AA}$  (blue), shape index mapped in the color range of  $-1.00$  to  $1.00 \text{ \AA}$  and curvedness in the range of  $-4.0$  to  $0.4 \text{ \AA}$ . The molecular Hirshfeld surfaces ( $d_{\text{norm}}$ , curvedness, and shape index) are shown in **Figure 8.10**. The presence of two dark red spots (two of identical type) mapped on the Hirshfeld surface with front view of  $d_{\text{norm}}$  reflects the presence of O–H...O, N–H...O and C–H...O interactions. The rare view of shape index mapped on Hirshfeld surface indicating big red spot with a complimentary blue spot over the front side of the shape index is due to the C–H... $\pi$  interaction. The small flat region observed on curvedness surface reflects the presence of  $\pi$ ... $\pi$  stacking interaction.



**Figure 8.10** Molecular Hirshfeld representing (a) front view of  $d_{\text{norm}}$  surface (b) rare view of shape index surface (c) side view of curvedness surface

The 2-D fingerprint plots, complement the Hirshfeld surfaces, are depicted in **Figure 8.11**. The H–H contacts, which are reflected in the middle of scattered points and cover most area in the 2-D fingerprint plots, have a most significant contribution to the total Hirshfeld surfaces (32.4%). The H–O contacts appear as distinct spikes. The proportion of O–H/H–O contacts comprising 38% of the total Hirshfeld surface for each molecule of the compound. The decomposition of the fingerprint plot shows that C–H/H–C contacts comprise 16.8% of the total Hirshfeld surface area. The proportion of N–H/H–N contacts comprising 1.4% of the total Hirshfeld surface. The C–C contact on the fingerprint plot is presented as characteristic stacking kite, which is mainly assigned to  $\pi$ – $\pi$  interaction. The C–C contact includes only 0.8% of the total Hirshfeld surfaces area.



**Figure 8.11** (a) 2-D full fingerprint plot (b) decomposition of full fingerprint plot into various contacts

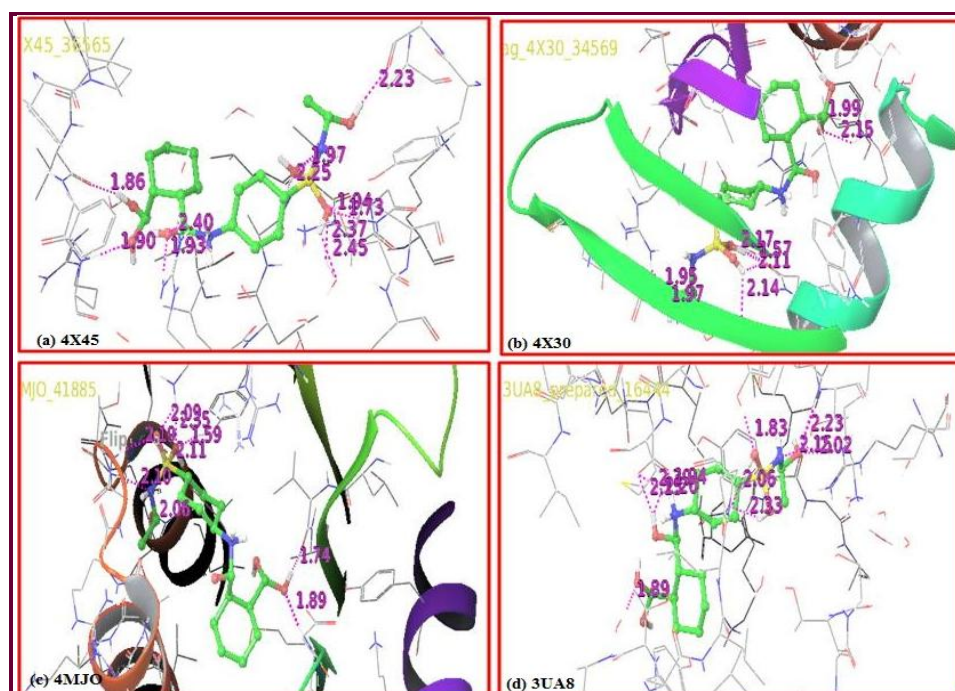
## 8.7. Molecular Docking

GLIDE docking method has been applied to build a binding affinity model for title molecule with different receptors. **Table 8.15** summarizes the glide score and glide energy of title molecule with different receptors.

**Table 8.15 Docking results of PHSCA with different receptors**

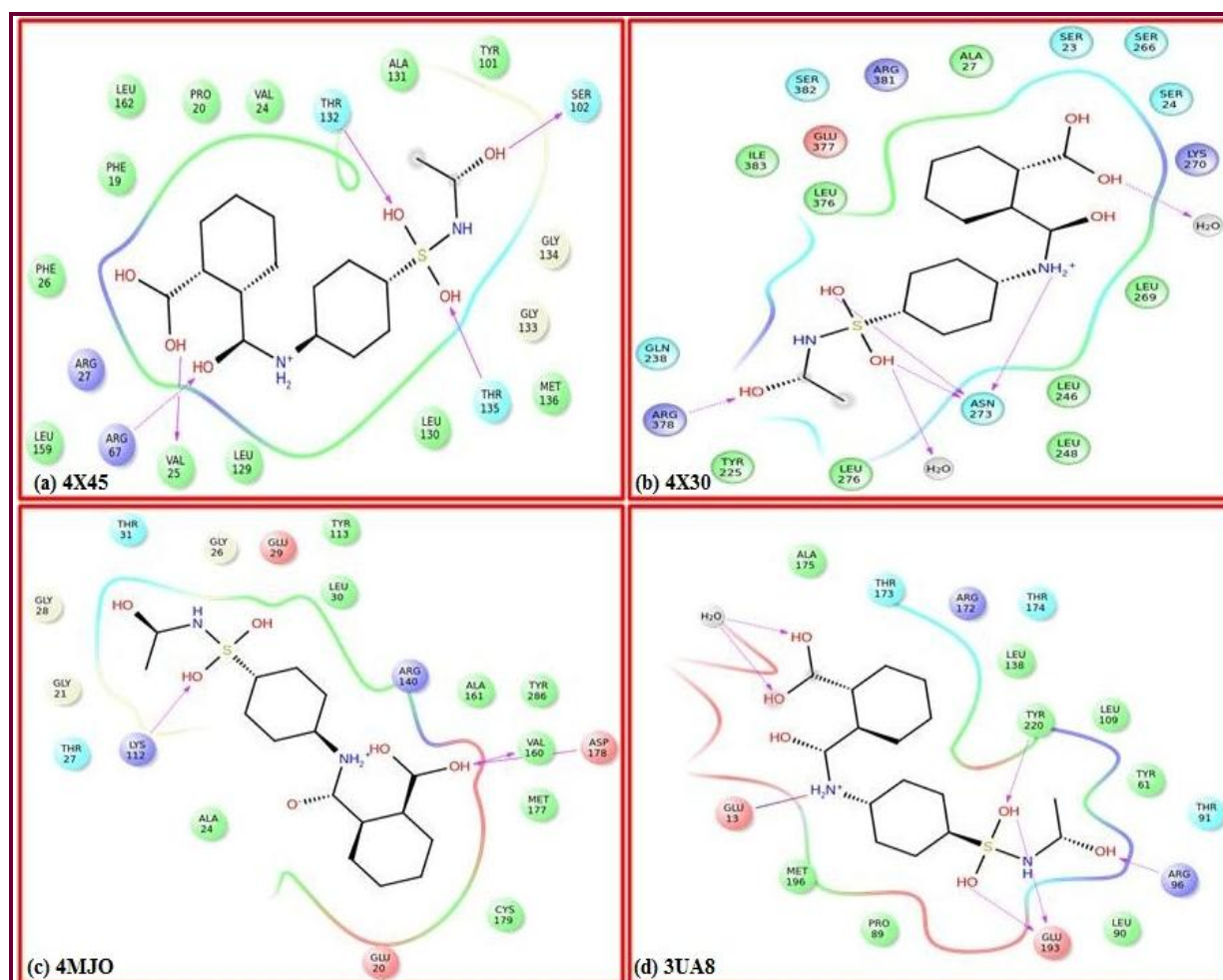
Receptors	4X45	4X30	4MJO	3UA8
Glide Score	-10.19	-9.969	-10.07	-8.917
Glide Energy (kcal/mol)	-55.41	-62.65	-47.26	-71.88

**Figure 8.12** represents hydrogen bond interaction between receptors with title molecule. Out of vast family of receptor four receptors 4X45 [220], 4X30 [221], 4MJO [222] and 3UA8 [223] 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 8.13**. The title molecule is found to have high docking score of -10.19 and energy -55.41 kcal/mol with 4X45 receptor. The title molecule interacts with 4X45 protein at sites: THR135, THR132, SER102, ARG67 and VAL25 (**Figure 8.13(a)**). The 4X30 receptor gives G-score of -9.969 with glide energy -62.65 kcal/mol.



**Figure 8.12 Interaction of PHSCA with (a) 4X45 (b) 4X30 (c) 4MJO and (d) 3UA8 receptors**

Phthalylsulfacetamide interacts with ASN273, ARG378 and H<sub>2</sub>O protein sites of 4X30 (**Figure 8.13(b)**). The 4MJO receptor is hydrolase inhibitor showing G-score of -10.07 with glide energy -47.26 kcal/mol. The protein sites LYS112, VAL160 and ASP178 of 4MJO interacts with title molecule (**Figure 8.13(c)**). 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 via H<sub>2</sub>O, GLU13, GLU193, TYR220 and ARG96 protein sites (**Figure 8.13(d)**).



**Figure 8.13** The binding sites of protein (a) 4X45 (b) 4X30 (c) 4MJO and (d) 3UA8 after GLIDE docking with title molecule