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Synthesis, crystal structure, density functional theory, Hirshfeld surface analysis and molecular docking studies of 2-(2-phenylanthracen-9-yl)thiophene derivatives

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Thiophene containing molecules have been distinguished as potential candidates in the largely emergent chemical world of heterocyclic compounds that show likely pharmacological characteristics. The knowledge of a mixture of synthetic pathways and the different physicochemical parameters of such compounds describe the especial interest of medicinal chemists to produce combinatorial collections and carry out in-depth efforts in the search of lead molecules. Among the various group of compounds studied, thiophene moieties stand out as unique in features due to their biological, pharmacological and medicinal properties. Synthesis, crystal structure, conformation and density functional theory of 2-(2-phenylanthracen-9-yl)thiophene derivative have been investigated in detail. Thiophene moiety are in planar conformation and having C-H…O type of hydrogen bonds and Van der Waals forces. Density functional theory has been applied to the thiophene derivative. Thiophene compounds score highly against the targeted protein and can be compared to the co-crystal ligand. Hirshfeld surface studies have been used to confirm and quantify the supramolecular features.

Keywords: Thiophene, heterocyclic, molecular modelling studies, Hirshfeld surface analysis, density functional theory

Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulphur as heteroatom with the formula C_4H_4S. Thiophene and its derivatives exist in petroleum or coal. Thiophene is taken from the word theion, the Greek word for sulfur, and another Greek word phaino which means shining. Thiophene structure can be found in certain items of common use and is likewise found in a few pharmacologically active compounds.

The structure of medicinal compounds offers probably the best examples of application of the thiophene moiety at present. Heterocyclic compounds are broadly dispersed in nature and are of fundamental importance. There are immense quantities of pharmacologically dynamic heterocyclic mixes a considerable lot of which are in ordinary clinical use[1]. Therefore, the design of molecular structure and control of molecular arrangements have attracted the attention of chemists and druggists in recent years.

The presence of pharmacologically active thiophene led us to study the compound, 2-(2-Phenylanthracen-9-yl)thiophene. The crystal structure determination of these compounds has been carried out by X-ray crystallographic methods in order to establish the conformation of the molecules.

Experimental Section

The title compounds reported in the present work were prepared by the following procedure.

To a solution of diketone **8** (0.42 g, 1.11 mmol in THF−ethanol (20 mL; 1:3), sodium borohydride (0.21 g, 5.58 mmol) was added in portions and refluxed for 4 h. The reaction cmixture was then poured into water (200 mL), extracted with ethyl acetate (2 × 20 mL) and dried (anhyd. Na_2SO_4). The removal of solvent gave crude diol. which was dissolved in dry DCM (20 mL). To this, pivaloyl chloride (0.63 g, 5.22 mmol) and triethylamine (2.13 g, 21.04 mmol) in the presence of a catalytic amount of DMAP (10 mg) were added. The reaction mixture was refluxed under nitrogen atmosphere for half an hour, and then hexane (20 mL) was added to the reaction mixture. The triethylamine hydrochloride salt formed was filtered off. The filtrate was concentrated, and the crude product was purified using column chromatography (silica gel; hexane−ethyl acetate

98:2). Pivaloyl ester **9** (0.66 g, 1.20 mmol) was then dissolved in dry DCM (20 mL), a catalytic amount of $ZnBr_2$ (0.02 g, 0.13 mmol) was added, and stirred for 20 min under nitrogen atmosphere. Removal of solvent followed by column chromatographic purification (silica gel; hexane−ethyl acetate, 99:1) led to the isolation of **10** as a green solid (0.33 g, 93%): m.p.206−208°C (Scheme I).

X-ray Crystallography

Data Collection and Reduction

X-ray reflection intensities for the various planes of the crystal of the title compound was collected by Bruker SMART APEXII CCD diffractometer[2] available at in-house GNR X-Ray facility center. The diffractometer is equipped with graphite mono-chromated MoKα (λ= 0.7107Å) radiation and CCD detector. The lattice parameters were calculated from 36 frames (0.5˚ phiscan) measured from three different angle zones using the method of difference vectors. The intensities collected possess an average four-fold redundancy per reflection and optimum resolution (0.75Å). A total number of 11024 reflections were collected for the title compound crystals, out of that 2935 reflections were considered to be unique and used for structure solution. The intensity data collection, frames integration, Lp and decay corrections were done using *SAINT*[2] software. Empirical absorption correction (multi-scan) was performed using *SADABS*[3] program.

Structure Solution and Refinement

The reduced data from the collected intensities happened to be the potential information used to elucidate the three dimensional structures of thiophene molecule. Direct methods strategy available in the software package SHELXS-97[4] is used to solve the structures. A total of 256 phase sets were generated for both the molecules and the best set with the Combined Figure of Merit (CFOM) revealed the structural model.

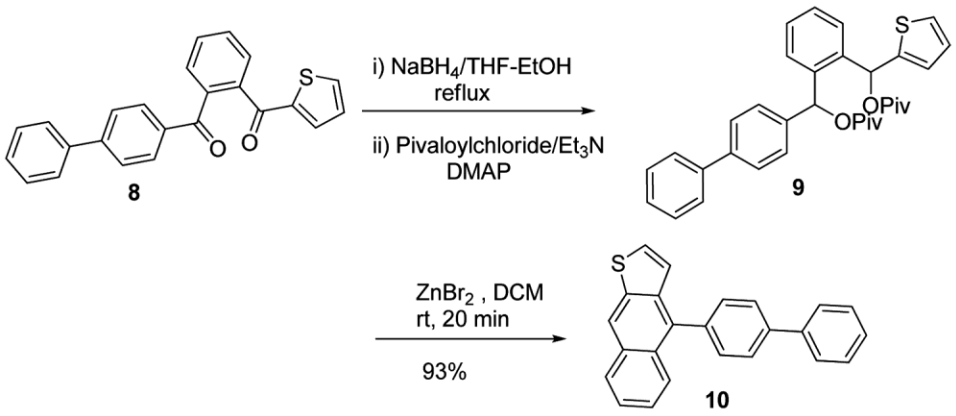
By this method, the positions of all non-hydrogen atoms were refined anisotropically and the hydrogen atoms in both the structures were constrained to ride on their respective parent atoms. The final cycle of refinement converged to R1 = 0.1045. The maximum and minimum heights in the final difference Fourier map were found to be 1.271 and −0.927 e.Å^{-3}, respectively. Least-squares planes, puckering and asymmetry parameters calculations were done using the program PARST97[4]. The thermal ellipsoid plots and packing of the crystal structures were done using ORTEP[5] and PLATON[6] plots. Non-bonded interactions and graphics were carried out using the program PLATON[6]. The crystal data, data collection, and refinement parameters for the structure of the compounds are given in Table I.

Density Functional Theory (DFT)

For the past 30 years density functional theory has been the predominant method for the quantum mechanical simulation of periodic frameworks. In recent years it has also been adopted by quantum chemists and is currently broadly utilized for the simulation of energy surfaces in molecules. Right now present the essential ideas underlying density functional theory and outline the features that have lead to its wide spread area. Recent developments in exchange correlation functionals are presented and the performance of groups of functionals reviewed.

Docking method

Docking was carried out using Autodock programminge which depends on genetic algorithm



Scheme I

(GA). This strategy permits the partial flexibility of protein and full flexibility of ligand. The selected compounds are docked to the active site of the AmpC beta-lactamase enzyme[7] (**PDB:** 2HDQ). The interaction of these ligands with the active site residues are thoroughly studied using molecular computational calculations. Default cutoff estimations of 3.0 Å (dH-X) for hydrogen bonds and 6.0 Å for Van der waals interactions were employed. The number of docked poses for each inhibitor was set 100, and early termination was allowed if the top three bound conformations of a ligand were within 1.5 Å RMSD. After docking process, the individual binding poses of each ligand were observed and measure their hydrogen bond interactions with the targeted protein molecule were studied.

Table I — The crystal data, experimental conditions and structure refinement parameters for the title compound

Parameters	COM1
Empirical formula	C24 H16 S
Formula weight	336.43
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 21/n
Unit cell dimensions	a = 9.7250(4) Å b = 16.0649(6) Å c = 11.1067(4) Å
Volume	1731.63(11) $Å^3$
Z, Calculated density	4, 1.290 Mg/m^3
Absorption coefficient	0.189 mm^{-1}
F(000)	704
Crystal size	0.350 × 0.300 × 0.250 mm
Theta range for data collection	2.232 to 24.741°
Limiting indices	–10<=h<=11, –18<=k<=18, –12<=l<=10
Reflections collected / unique	11024 / 2935 [Rint = 0.0271]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2935 / 2 / 227
Goodness-of-fit on F^2	1.087
Final R indices [I>2sigma(I)]	R1 = 0.1045, wR2 = 0.3221
R indices (all data)	R1 = 0.1376, wR2 = 0.3564
Extinction coefficient	n/a
Largest diff. peak and hole	1.271 and –0.927 $e.Å^{-3}$

Results and Discussion

Crystal Structure Analysis

The ORTEP plot of the title molecule is shown in Figure 1. The fragment C4-C5 planar ring is conjugated with the adjacent thiophene ring is in planar conformation. The thiophen ring (C2-C5\S1) are in planar with the maximum deviation observed for atom C2 [-0.005(6) Å].

The crystallographic study on puckering[8] and asymmetry parameters[9] reveals that the thiophene ring adopts planar conformation. The crystal data and other crystallographic parameters are given in Table I.

The C-S bond lengths 1.6371(1) and 1.8838(1) Å in the present structures are comparable with the corresponding distances of 1.793 (3) and 1.798 (3) Å in methyl 6-benzoyl-3,5-diphenyl-1,4-thiazine-2-carboxylate- 1,1-dioxide[10] and 1.795 (3) and 1.795 (2) Å in thiazine-3-one[11]. The title molecules are stabilized by C–H…O type of intermolecular hydrogen bonds in addition to van der Waals forces as shown in Figure 2[12].

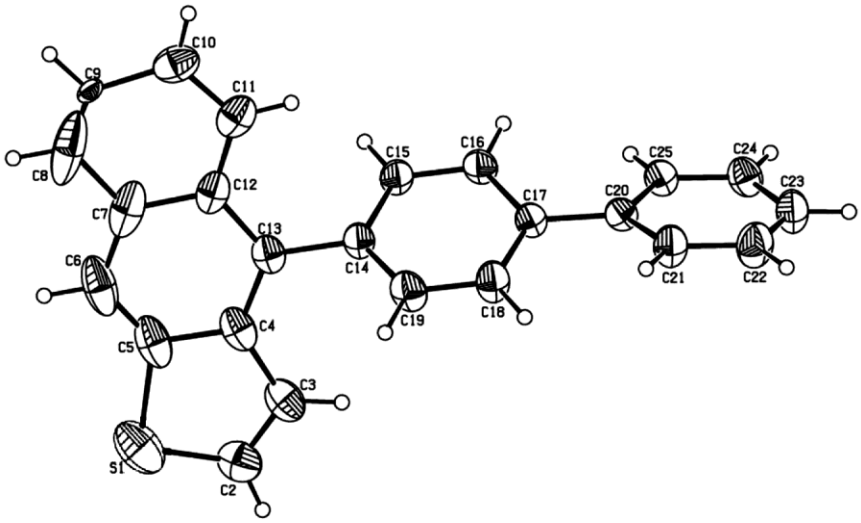


Figure 1 — ORTEP plot of the **COM1**

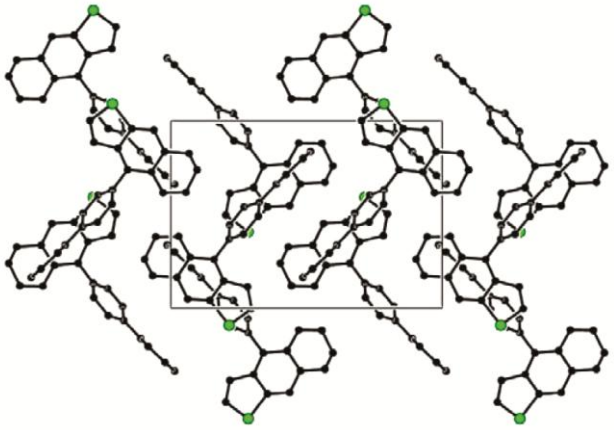


Figure 2 — Packing of the molecules for **COM1**

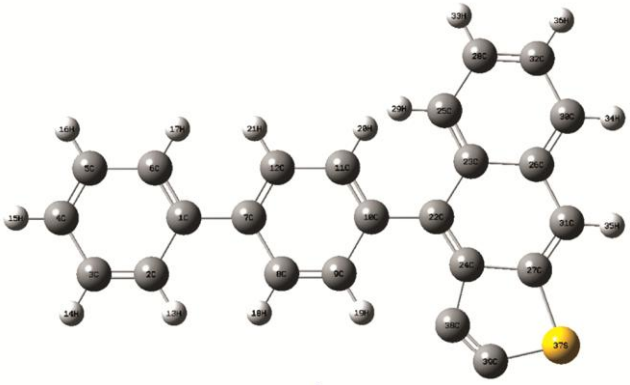


Figure 3 — The HF//3-21G optimized geometry of **COM1**

HOMO–LUMO Analysis

The optimized molecular structure of thiophene as shown in Figure 3 with atomic numbering scheme. The HOMO and LUMO are important quantum chemical parameters to determine the molecular interaction with other species and to characterize the chemical reactivity, global hardness, softness and kinetic stability of the molecule[13]. HOMO and LUMO energies determine the ability to donate an electron and accept an electron, respectively. The energy gap measure the excitability of the molecule, smaller the energy implies more easily to get excited.

Physico-Chemical Properties

The frontier molecular orbitals (FMO's) plot of thiophene molecule is shown in Figure 4. Based on the optimized structure, the HOMO and LUMO energy level was calculated at DFT/B3LYP/6-311++G(d,p) method. The contributions of HOMO orbitals located at entire molecule except hydrogen atoms. But, the LUMO occupied at thiophene ring. The energy gap value is measured at 2.299 eV in gas phase medium. The small energy gap explains the eventual charge transfer taking place occur within the stabilization of the molecule.

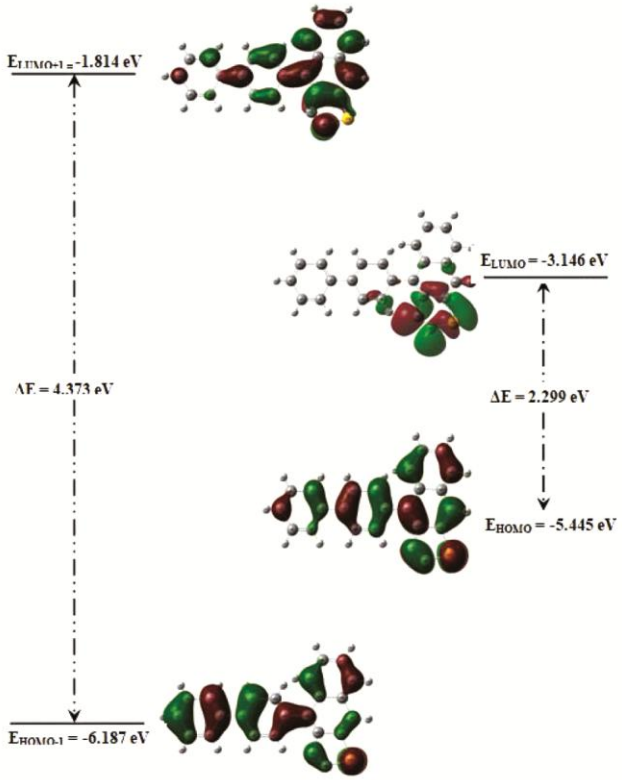


Figure 4 — Molecular orbital HOMO-LUMO diagram of **COM1**

Table II — The Physico-Chemical properties of **COM1**

Parameters	Values
HOMO	–5.445 eV
LUMO	–3.146 eV
Energy gap	2.299 eV
HOMO-1	–6.187 eV
LUMO+1	–1.814 eV
(H-1 to L+) Energy gap	4.373 eV
Ionization potential (IP)	5.445 eV
Electron affinity (EA)	3.146 eV
Electrophilicity Index (ω)	4.011
Chemical Potential (μ)	4.295
Electro negativity (χ)	–4.295
Softness (η)	–2.299

In addition, the physico-chemical properties such as Ionization potential (IP), Electron affinity (EA), electro negativity (χ), softness (η) and Electrophilicity index (ω) values are listed in Table II.

Hirshfeld surface analysis

A Hirshfeld surface analysis[14,15] of the thiophene compound was carried out to investigate the location

of atoms with potential to form of hydrogen bonds and the quantitative ratio of these inter actions. Crystal Explorer software was used to produce the Hirshfeld surface analysis and 2-D fingerprint plots[16,17], using the atomic coordinates of the atoms (Figure 5 and Figure 6). The electrostatic potentials were mapped on Hirshfeld surfaces utilizing the STO-3G basis set at the Hartree–Fock level of theory.

Hirshfeld surfaces analysis and 2-D fingerprint plots was performed to study the intercontacts and their quantitative contributions towards the crystal packing[15,18]. The Hirshfeld surface volume and area calculated were 425.07 Å^3 and 372.12 Å^3, respectively. The Hirshfeld surface for the title compound is shown in Figure 5 and has been mapped over dnorm range from -0.0304-1.2457 Å. The normalized contact distance (dnorm) is based on both di and de. In Figure 6, the negative value indicates red color for intermolecular contacts shorter than rvdW (van der Waals (vdW) radii), positive value indicated blue color when intermolecular contacts are longer than rvdW and the white regions corresponded to the distances of contacts with exact vdW separation having dnorm value of zero.

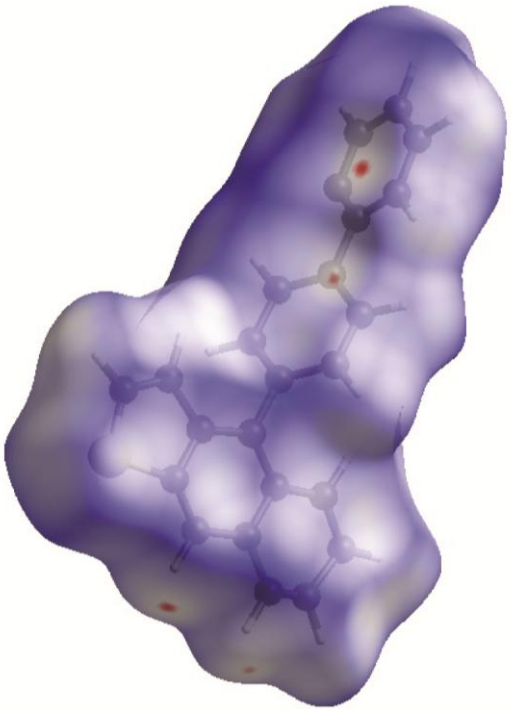


Figure 5 — The Hirshfeld surface of **COM1** mapped over d_{norm}

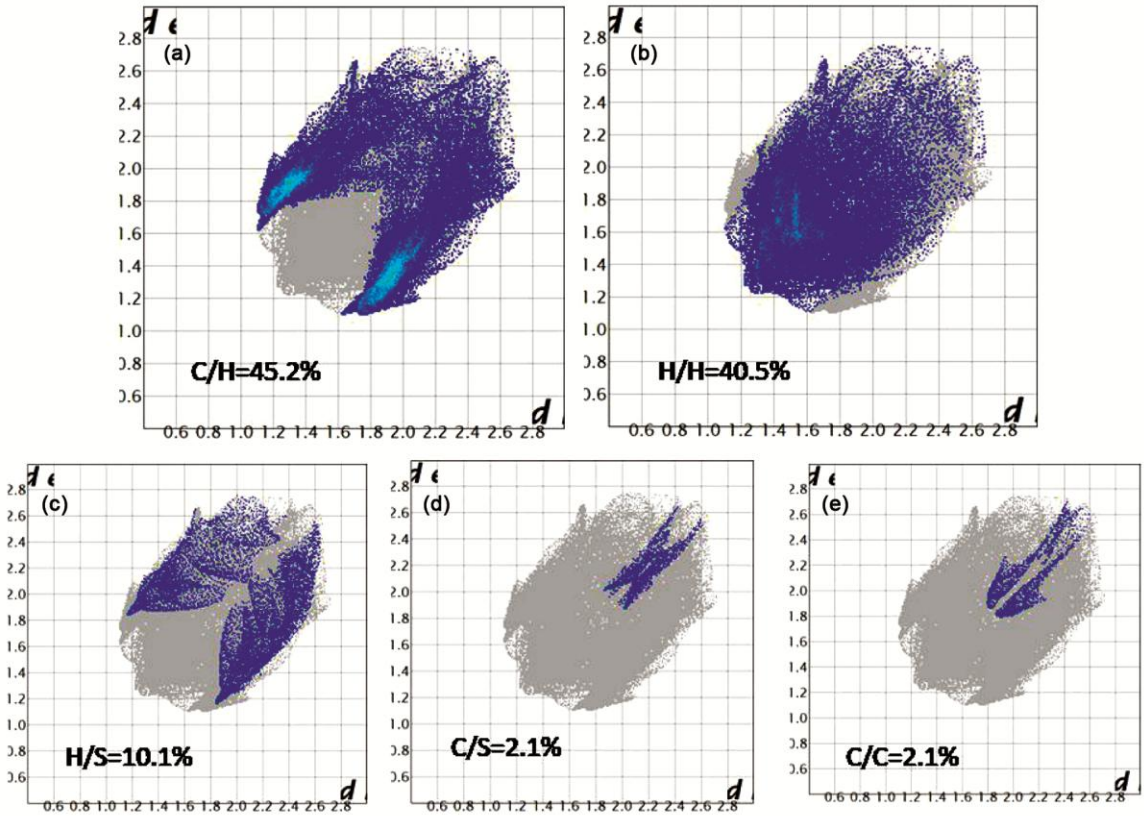


Figure 6 — The two-dimensional fingerprint plots of **COM1**, showing (a) C…H (b) H…H, (c) H…S, (d) C…S and (e) C…C inter-actions. The outline of the full fingerprint plots is shown in grey. di is the closest internal distance from a given point on the Hirshfeld surface and de is the closest external contact

Molecular Docking

Molecular binding affinity of thiophene ligand and its co-crystal ligand with target protein have been studied by molecular docking study. In the targeted binding pocket, Hydrogen-bonding interactions and Van Der Waals interactions were formed between all docked compounds and the active site residues TYR150, SER64, LYS315 and THR316 interact with the ligands.

In order to explain the binding affinity of these selected compounds, the H-bonding interactions with the other surrounding residues in the hydrophobic binding pocket were also investigated. In Figure 7 and Figure 8, strong H-bonding interactions between the methoxy oxygen (O) of compounds with the hydrogen atom of targeted protein. The surface diagram of the title compound and cocrystal ligand bind with the targeted protein of AmpC beta-lactamase as shown in Figure 9 (Table III).

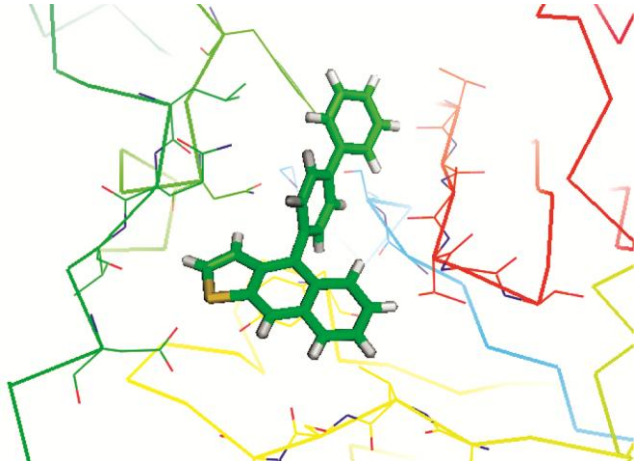


Figure 7 — Molecular docking interactions for compound **COM 1** within the binding pocket of **AmpC beta-lactamase**

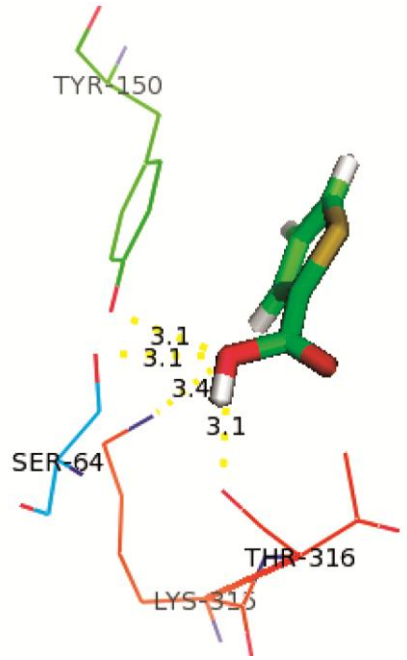


Figure 8 — Molecular docking interactions for **Co-Crystal** Ligand within the binding pocket of **AmpC beta-lactamase**

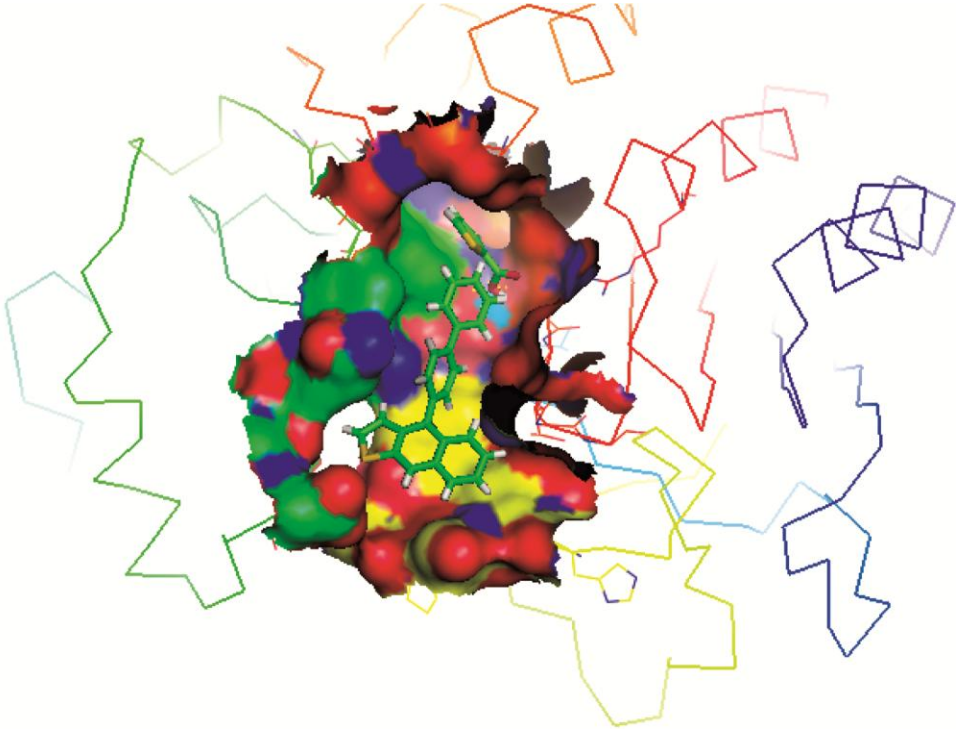


Figure 9 — The docked molecule **COM 1** and **Co-Crystal** ligand at the active site pocket of the targeted protein **AmpC beta-lactamase**

Table III — Docking studies of **COM1** with the AmpC beta-lactamase protein

Ligand	Interaction	Bond Distance(Å)	Docking Score
Co-Crystal	Try150 (O…H-O)	3.1	–2.3260
	Ser64 (O…H-O)	3.1	
	Lys315 (N…H-O)	3.4	
	Thr316 (O…H-O)	3.1	
Com 1	Hydrophobic Interaction		–3.7857

Conclusions

The title compounds were synthesized, crystallized, density functional study, hirshfeld surface analysis and the molecular docking studies have been studied. Thiophene molecule crystallize in monoclinic space group $P2_1/n$. Direct methods strategy is used to solve the molecular structures and full-matrix least-squares procedures adopted to refine the model. The final refinement converged to the R-value of 0.1045 for thiophene molecule. The thiophene ring moiety adopts planar conformation. The structural studies suggest that the formation of intermolecular C-H…O hydrogen bonds interactions are also helpful in stabilizing the crystal structures. Molecular docking studies show that both the compounds having the binding affinity compared with the co-crystal ligand. The docking study reveals that hydrophobic interactions played a major role in ligand receptor interactions.

Acknowledgments

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