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Computational calculations and molecular docking studies on 2-(2-ethylaminothiazol-5-oyl)benzothiazole

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2-(2-Ethylaminothiazol-5-oyl)benzothiazole has been synthesized and its bond length, bond angle, dihedral angle, HOMO-LUMO and Mulliken charges on the atoms have been calculated by density functional theory (DFT/B3LYP) method with 6-311++G(d,p) basis sets. Biological properties like the target receptor identification and identification of interacting residues, of this compound is identified and analyzed by using Openbabel GUI (C) software.

Keywords: DFT method, marine alkaloids, benzothiazole and molecular docking

Alkaloids have attracted the attention of humans due to their significant bioactivity. The chemical compounds, which are isolated from marine sources usually consists of nitrogen containing heterocyclic rings. Due to these promising biological activities, there has been a rapid growth of interest in the synthesis of this class of compounds and their analogues. Benzothiazole is a privileged heterocyclic scaffold found in a number of biologically important molecules and chemotherapeutic agents, which includes clinically used drugs. Based on this conjecture, we have conceived a tentative, retro synthetic analysis for the synthesis of benzothiazole analogs of alkaloid topsentin[1]. However, so far, no work has been reported on the vibrational analysis and molecular docking of 2-(2-ethylaminothiazol-5-oyl)benzothiazole (Figure 1). Hence, in the present work, a detailed vibrational analysis is carried out and for a proper understanding of the IR spectra a reliableassignment of all vibrational bands is essential. DFT calculations, particularly those based on hybrid functional methodshave evolved to a powerful quantum chemical tool for the determination of the electronic structure of molecules[2-8]. In this framework, the B3LYP hybrid exchange–correlation functional is one of the most used since it proved its ability in reproducing various molecular properties, including vibrational spectra[9-15] (Figure 2). The combined use of B3LYP functional and standard split valence basis set 6-31G(d) has been previously shownto provide an excellent compromise between accuracy and computational efficiency of vibrational spectra for large and medium-size molecules. In addition, molecular docking studies were carried out and, the mechanism of action of this compound on pancreas cancer cell line (PDB ID: BCL2), HIV-1 reverse transcriptase (PDB ID: 1RT2) and cytochrome P450 enzyme 14-alpha-demethylase of *M. tuberculosis* (PDB ID: 1EA1) is found and it is very much useful to develop efficient drugs.

Experimental Section

The title compound was prepared from 1-alkyl-3-(N,N-dimethylimidoyl)thiourea and 2-(2-bromo-acetyl)benzothiazole, which was prepared from 2-(1-hydroxyethyl)benzothiazole in DMF. The reaction mixture was stirred well and triethylamine was added. The reaction mixture was warmed at 80-85°C for 5 minutes. It was then cooled and poured into ice cold water with constant stirring. An orange precipitate thus obtained was filtered, washed with water and dried. The crude product was crystallized from methanol: water (2:1) and then from benzene:

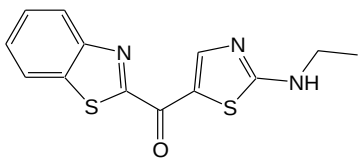

Figure 1 — Structure of 2-(2-ethylaminothiazol-5-oyl) benzothiazole

petroleum ether (1:1) to give orange crystalline solid. The FT-IR spectrum of the compound is recorded by KBr disc method and recorded in the region 4000–400 cm^{-1}, using Nicolet 400D FTIR spectrometer. Yield 55 %, m.p.250-251°C. Elemental analysis report (found): Carbon, 53.41; Hydrogen, 3.90; Nitrogen, 14.55 %.Calc for $C_{13}H_{11}N_3OS_2$ (289.03) Carbon, 53.96; Hydrogen, 3.83; Nitrogen, 14.52 %.IR (KBr) cm^{-1}: 3468, 3284, 3233, 3174, 3069,2973, 2925, 2859, 1624, 1596, 1559, 1452, 1355, 1096, 883,819, 757, 722; ^{1}H NMR (DMSO-d_6 - 300 MHz) :δ 7.55 (triplet,1H), 8.12 (doublet,1H), 8.23(doublet,1H), 8.18 (singlet,1H), 4.0 (singlet,1H), 3.10(quartet,2H),1.00 (triplet,3H).^{13}C NMR (DMSO-d_6 - 75 MHz): δ 15, 44, 122, 123, 125,126, 133,139,153,108,172,187; ESI MS: 290 (MH+).

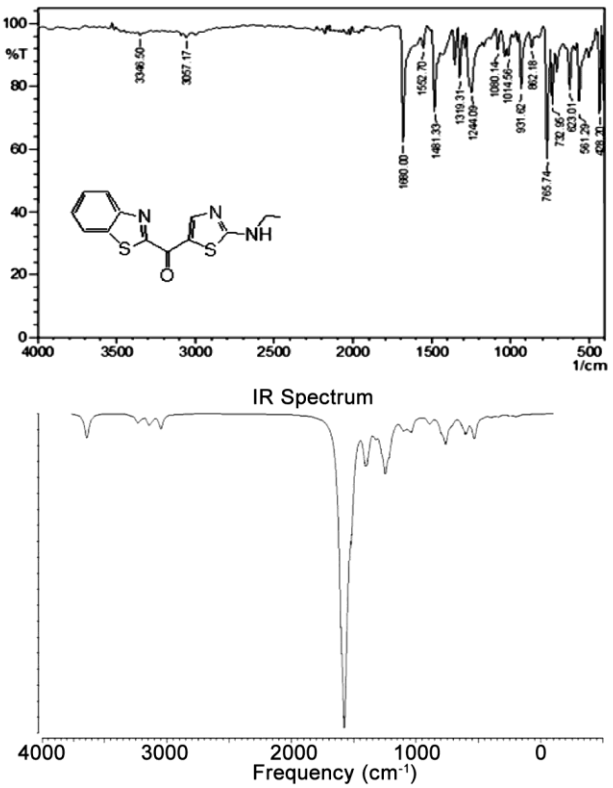

Figure 2 — Experimental and calculated IR spectrum of 2-(2-ethylaminothiazol-5-oyl)benzothiazole

Results and Discussion

Computational Chemistry

Molecular geometry

The structural parameters of the stable conformer of the compound were optimized by minimizing the energy with respect to all the geometrical parameters. The optimized structure of compound is depicted in Figure 3 (a-d) with numbering of the atoms. The molecule contains three rings (benzothiazole, thiazole & NHAr rings) connected by a keto group, the thiazole and aromatic rings are connected by NH group. The bond length of C6-C7 is higher (1.47Å) than the other bonds of benzothiazole due to the electron withdrawing nitrogen and oxygen atoms.

The bond angles C-C-C range from 118.74 to 120.15Å. The C6-C7–O23, C5-C6–O23 bonds have bond angles (119.71, 122.97 º) and this is due to the dominant electron density in oxygen than carbon. If the electro negativity of the central atom is less, the bond angle decreases. Thus the bond angle C14-S13-C7 is very lesser (86.34º) than the bond angle C15-N8-C7 (114.99º) which is due to the fact that electro negativity of nitrogen is greater than sulphur. Dihedral angle of the molecule shows that the three

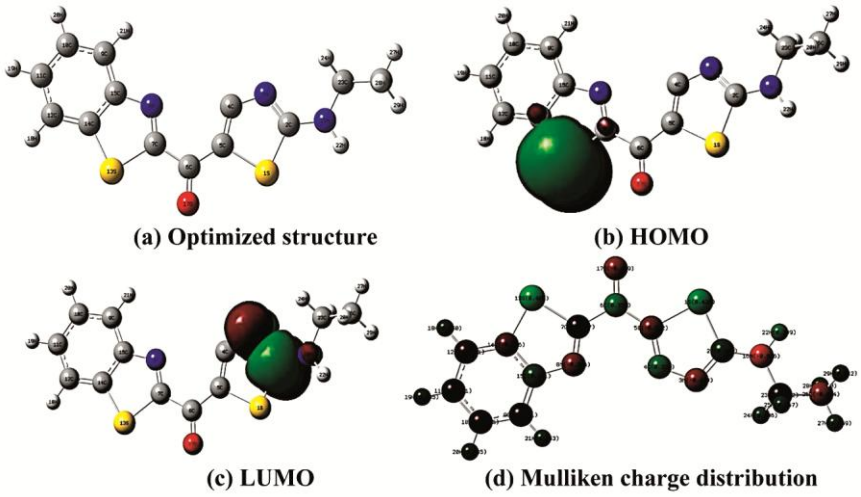

Figure 3 — (a) Optimized Geometry, (b) HOMO, (c) LUMO and (d) Mulliken charge distribution

rings benzothiazole, thiazole and phenyl group attached to NH are in one plane.

Vibrational assignments

In order to obtain the spectroscopic signature of the compound, frequency calculation analysis is performed. The molecule consists of 30 atoms and 81 normal vibrational modes are observed. The scaling factor of 0.962 is used for getting theoretical vibrational frequencies. The selected calculated vibrational frequencies are numbered from largest to smallest fundamental wave number. The NH stretching modes are observed theoretically at 3764 cm^{-1}. Theoretically, CH stretching modes of the phenyl rings are observed at 3248 cm-1. The C–N stretching modes are observed at 1594cm-1 theoretically. The stretching mode of C-O is observed theoretically at 1569 cm^{-1}, 1527cm^{-1}. The C–S stretching modes are observed theoretically at 689 cm^{-1}.

HOMO–LUMO analysis

The frontier molecular orbitals (HOMO–LUMO) play an important role in the electric and optical properties. Recently, the energy gap between HOMO and LUMO has been used to prove the bioactivity from intra-molecular charge transfer (ICT). The conjugated molecules are characterized by a highest occupied molecular orbital-lowest unoccupied molecular orbital (HOMO–LUMO) separation, which is the result of a significant degree of intermolecular charge transfer (ICT) from the end-capping electron-donor to the efficient electron acceptor group through p conjugated path. The strong charge transfer interaction through p conjugated bridge results in substantial ground state donor–acceptor mixing and the appearance of a charge transfer band in the electronic absorption spectrum. Therefore, an electrondensity (ED) transfer occurs from the more aromatic part of the p conjugated system in the electron-donor side to electron-withdrawing part. The 3D plots of the frontier orbitals, HOMO and LUMO for the title compound in gas phase is shown in Figure 3. As can be seen from Figure 3 HOMO is mainly localized over the benzothiazole ring. However, the LUMO is characterized by a charge distribution over the thiazole ringalone. Energy difference between HOMO and LUMO orbital is called as energy gap which ensures the stability of molecular structure. This view shows that, the lowering of energy gap which reflects the activity of the present compound. The chemical hardness is a good indicator of the chemical stability. The chemical hardness and potential, electro negativity and electrophilicity index are calculated and their values are shown in Table I.

Mulliken charge distribution

The Mulliken atom charge of all hydrogen atoms are positive, all nitrogen and oxygen possess negative charge and all sulphur and chlorine carries positive charge.

Molecular Docking

An attempt to gain a better insight on the molecular structure of our compound ligand and its protein, geometry optimization and conformational analysis has been done.The ligand-protein complex with optimized conformation, possessing lower binding free energy. The predicted binding energy is expressed in terms of hydrogen bonding and hydrophobic interaction between benzothiazoles and DNA. The target protein in required format was obtained from Protein Data Bank (PDB).The target ligand was made in the PDB format using Openbabel GUI (C) 2006. The compounds were optimized using Gaussian 09 software with density functional theory at the B3LYP/631G level of theory. Thepancreas cancer cell line, HIV-1 reverse transcriptase and cytochrome P450 enzyme 14-alpha-demethylase of M. tuberculosis subunits docked our compound using Openbabel GUI (C) 2006 software (Figure 4).

Identification of interacting residues

The interactions shown are mediated by hydrophobic contacts.The residues A26 ARG,B62 ASP, B161 TRY, THR 80, GLU 94, LYS 73 and VAL75 are in hydrophobic contacts with the carbon atom of benzothiazole ringand ethyl group of the ligand2-(2-ethylaminothiazol-5-oyl)benzothiazole. The

Table I — Computed properties of 2-(2-ethylaminothiazol-5-oyl)benzothiazole

Parameters (a.u.)	B3LYP/6-31G ethyl
HOMO	–0.25224
LUMO	–0.0550
HOMO-LUMO	0.30724
I	0.25224
A	0.0550
χ	0.15362
η	0.09862

I-Ionisation potential; A-Electron affinity; χ-Electronegativity; η-Hardness

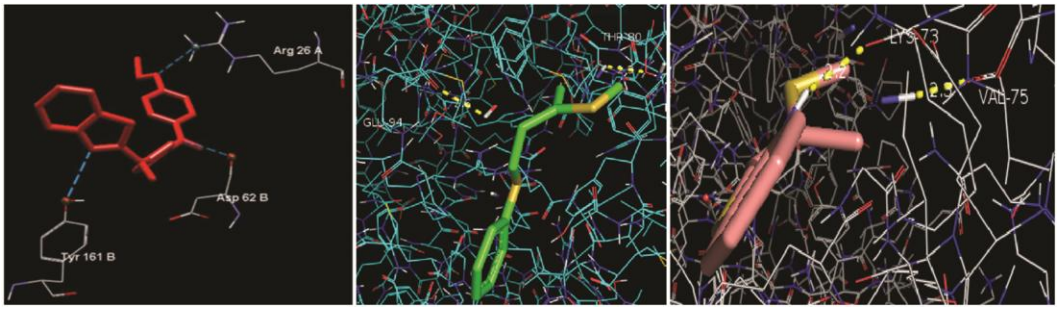

Figure 4 — Docking images of 2-(2-ethylaminothiazol-5-oyl)benzothiazole bound with BCL2, bound with IEA1 and bound with IRT2

Table II — Docking score and hydrogen bond interactions of 2-(2-ethylaminothiazol-5-oyl)benzothiazole

Docking score			Hydrogen bond Interaction		
BCL2	IEA1	IRT2	BCL2	IEA1	IRT2
–7.4	–7.5	− 8.5	A26 ARG, B62 ASP, B161 TRY	THR 80 GLU 94	LYS 73 VAL75

effective substitution ethyl of compound plays a major role in molecular binding similar to the vibrational analysis. The hallucination of identification of interacting residues is shown in Table II.

Conclusion

In the present work, the recorded FT-IR spectrum of the title compound was analyzed. The observed vibrational frequencies are assigned and the computational calculations are carried out by DFT method. A study on the absorption wavelengths and frontier molecular orbital energies, are performed. The calculated HOMO and LUMO energies show that charge transfer occurs within the molecule. Mulliken charges of the compound is also calculated and interpreted. Based on the minimum energy requirement, the suitable target for this compound is identified and residues involved in the interaction also investigated.

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