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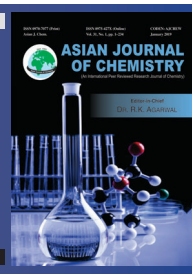

DFT and Molecular Docking Study of 2-[2-(4-Chlorophenylaminothiazol-5-yl]benzothiazole

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The title compound was computed by means of DFT chemical quantum calculations to obtain optimized molecular geometry, harmonic vibrational frequencies and atomic charges. Vibrational bands to the various structural groups and their importance were predicted by analyzing the vibrational spectra. The data showed that B3LYP method provide satisfactory data for assigning vibrational frequencies and structural properties.The HOMO and LUMO energies calculated permit the determination of atomic and molecular parameters and they also represented the transfer of charge in the molecule. Mulliken atomic charge analysis was also done. A comprehensive molecular picture of 2-[2-(4-chlorophenylaminothiazol-5-yl]benzothiazole and its interactions were got from NBO investigations. The molecular docking study indicates that benzothiazole derivative may possess inhibitory activity against BCL2 pancreatic cancer cell lines.

Keywords: DFT, Molecular docking, 2-[2-(4-Chlorophenylaminothiazol-5-yl]benzothiazole.

INTRODUCTION

Oceans occupy about 70 % of the earth planet and supply a wealth of organisms that develops bioactive substance. The chemical compounds, which are derived from marine origin usually consists of nitrogen containing heterocyclic rings [1-3]. Many of these may be classified as marine alkaloids due to this fact. Alkaloids have attracted the awareness of humans due to their potent bioactivity. Numerous alkaloids are isolated from marine species such as coelenterates, symbiotic bacteria, sponges, bryosoans, tunicates and red algae [4-7]. Alkaloids are nitrogen bearing bioactive heterocyclic substance found in nature. Topsentin, a bisindole alkaloid isolated from the marine sponge *Topsentia genitrix*, exhibits significant biological activity. Indole derivatives are quite common among marine alkaloids, which possess potential *in vitro* cancer cell cytotoxicity. In addition, substitution of indole by benzothiazole exhibits several biological activities just like indoles. Benzothiazole is a privileged heterocyclic scaffold found in numerous biologically significant molecules and chemotherapeutic agents, which includes clinically used drugs [8-10].

The benzothiazole nucleus constitute the core structure in numerous synthetic drugs and the search related benzothiazoles derivatives leads to the discovery of large number of drugs which are now accessible in market. 2-[2-(4-Chlorophenylaminothiazol-5-yl]benzothiazole, which is a hybrid structure in cooperating the features of phenylaminothiazole and benzothiazole moieties that displayed remarkable antibacterial and anti-inflammatory activities [11-13]. Because of our interest in the structural and medicinal properties of benzothiazole analogs, we present investigation on the electronic properties, molecular structure, biological activity and vibrational spectra of the title compound. Halogen and methyl substituted compounds and their spectroscopic studies have been reported in the literature. To our best of knowledge vibrational analysis study, quantum chemical calculations and docking study of 2-[2-(4-chlorophenylaminothiazol-5-yl]benzothiazole has not been reported in literature. This paucity seen in the literature inspired us to study this theoretical and experimental vibrational research cited on the structure of molecule to give an accurate assignmentin experimental FT-IR spectrum [14,15].

In the present paper, a well ordered quantum chemical and spectroscopic study of the feasible conformations and their relative stabilities has been performed. The wavenumber, intensity of the vibrational bands and optimized geometry of feasible conformers were obtained by density functional theory

(DFT) utilize B3LYPusing 6-311++G (d,p) basis set. The infrared spectrum calculated is compared with the results of observed Fourier transform FT-IR spectrum. Comprehensive assignments of the vibrational spectra have been compared with the vibrational frequencies predicted theoretically. For a clear understanding of IR spectra, a definitive assignment of all vibrational bands is essential [16-18]. For this reason, DFT methods, mainly hybrid functional methods have been a significant chemical quantum tool for the assessment of the electronic structure of molecules. The combined utility of B3LYP functional and standard valence basis set 6-31G (d) has been shown to provide a perfect agreement between accuracy and computational assignment of vibrational spectra for huge and medium-size molecules [19-22].

EXPERIMENTAL

The title compound (m.f. $C_{17}H_{10}N_3OS_2Cl$) was prepared in good yield through the reaction of 1-chlorophenyl-3-(N,N-dimethylimidoyl)thiourea in DMF and 2-(2-bromoacetyl) benzothiazole which in turn synthesized from hydroxyethylbenzothiazole using DMF as solvent. The resulted reaction mixture was stirred properly and finally triethylamine was added. For 5 min, the reaction mixture was heated to about 80-85 ºC. It was allowed to cool and with constant stirring purged into ice-cold water. An orange coloured precipitate thus obtained was filtered washed with water and finally dried. The finally obtained crude product was crystallized from benzene:petroleum ether mixture (1:1) and then using methanol:water (2:1) mixture to produce orange coloured crystalline solid. DR/JASCO FT-IR 6300 spectrometer using KBr pellets was used to record FT-IR spectrum.

Computational details: Gaussian 09 package at Becke three parameter hybrid exchanges functional and Lee Yang-Parr correlation functional with the 6-31G basis set were utilized to perform DFT calculations of 2-[2-(4-chlorophenylaminothiazol-5-yl]benzothiazole. Optimization of molecular geometries was completed using redundant internal coordinates by Berny′s optimization algorithm. The optimum geometry was determined by energy minimization based on all geometrical parameters without taking molecular symmetry constraints. To correct the over estimations formed from some negative factors such as anharmoniety characters, basis set truncation effect and neglecting electron correlations belongs to the vibration modes, the calculated wave numbers using a single scaling factor of 0.962 were scaled and thus matched to the corresponding experimental wavenumbers. In GAUSSVIEW program, the animation option which shows visual presentation of vibrational modes assisted the assignments of the calculated wavenumbers. Analytic second derivatives were used to secure harmonic vibrational wavenumbers to verify convergence minima seen on the potential surface. Then calculations of frequency were utilized to confirm the structure based on minimum points in energy.

RESULTS AND DISCUSSION

Structure and geometrical properties: To understand the vibrational frequencies, it is important to study the compound′s geometry as structure based properties. With respect to all the geometrical parameters, the structural properties of compound (stable conformer) are optimized by minimization of energy. The optimized structure of compound with numbering of the atoms are depicted in Fig. 1 and its bond lengths are given in Table-1. The molecule contains three rings (benzothiazole, thiazole and NH-Ar rings) connected by a keto group.

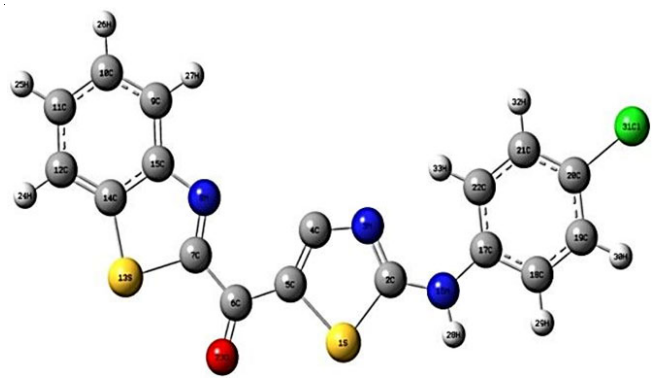

Fig. 1. Optimized structure of 2-[2-(4-chlorophenylaminothiazol-5-yl]-benzothiazole

TABLE-1
OPTIMIZED BOND LENGTH OF 2-[2-(4-CHLOROPHENYLAMINOTHIAZOL-5-YL]BENZOTHIAZOLE

Bond length (Å)		Bond length (Å)	
S1-C2	1.84238	C9-H27	1.08356
C2-N3	1.33212	C9-C15	1.40428
N3-C4	1.33672	C2-N16	1.35561
C4-C5	1.35976	N16-H28	1.01092
C5-C6	1.43965	N16-C17	1.41878
C6-O23	1.25656	C17-C18	1.40754
C6-C7	1.47800	C18-H29	1.08661
C7-N8	1.29903	C18-C19	1.39450
N8-C15	1.39535	C19-H30	1.08282
C15-C14	1.41941	C20-C19	1.39365
C14-S13	1.81388	C20-C31	1.82490
C14-C12	1.39641	C21-C20	1.39196
C12-H24	1.08386	C21-H32	1.08301
C12-C11	1.39733	C21-C22	1.39855
C11-H25	1.08501	C22-C17	1.40514
C11-C10	1.41047	C22-H33	1.08043
C10-H26	1.08356	C20-Cl31	1.6325
C10-C9	1.39173	–	–

Frontier molecular orbital studies: In 2-[2-(4-chlorophenylaminothiazol-5-yl]benzothiazole, the HOMO is delocalized over the benzothiazole ring. By divergence, the LUMO is placed over the thiazole ring. In case of present compound, $E_{HOMO} = -0.25379$, $E_{LUMO} = -0.06007$, energy gap = HOMO-LUMO = 0.31386. For proper understanding of various features of pharmacological sciences inclusive of drug design and the feasible eco-toxicological factors of the drug molecules, some novel chemical reactivity descriptors have been suggested. DFT depended descriptors have make possible in different ways to know the structure of molecules and by calculating the chemical effects to determines their reactivity, electrophilicity and global hardness.

Mulliken population analysis: The bonding capability and molecular conformation was determined by electronic charge on an atom. From the Mulliken population analysis atomic charge values were obtained (Fig. 2). The Mulliken atomic

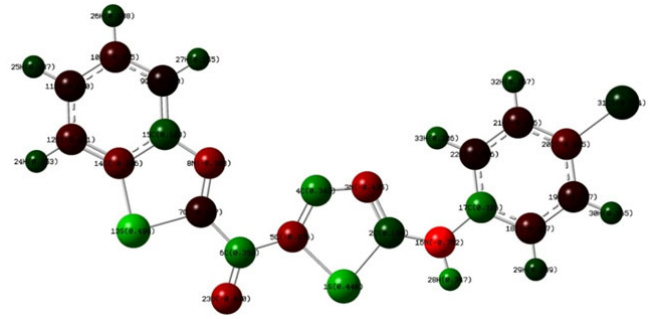

Fig. 2. Mulliken charge distribution of 2-[2-(4-chlorophenylaminothiazol-5-yl]benzothiazole

charges of component atoms of 2-[2-(4-chlorophenylaminothiazol-5-yl]benzothiazole are presented in Table-2. The Mulliken atom charge of all hydrogen atoms are positive, oxygen and nitrogen atoms possess negative charge and sulphur & chlorine atoms carries positive charge.

TABLE-2
MULLIKEN CHARGE DISTRIBUTION OF 2-[2-(4-CHLOROPHENYLAMINOTHIAZOL-5-YL]BENZOTHIAZOLE

Atom	Atomic charges	Atom	Atomic charges
S1	0.440	C18	-0.157
C2	0.160	C19	-0.107
N3	-0.435	C20	-0.225
C4	0.343	C21	-0.125
C5	-0.376	C22	-0.086
C6	0.352	O23	-0.430
C7	-0.117	H24	0.153
N8	-0.398	H25	0.137
C9	-0.060	H26	0.138
C10	-0.155	H27	0.155
C11	-0.100	H28	0.347
C12	-0.171	H29	0.139
S13	0.494	H30	0.165
C14	-0.286	Cl31	0.074
C15	0.193	H32	0.167
N16	-0.752	H33	0.206
C17	0.316	–	–

Vibrational assignments: The spectral data of 2-[2-(4-chlorophenylaminothiazol-5-yl]benzothiazole obtained experimentally by means of IR spectra and predicted theoretically by means of density functional theory (DFT) B3LYP/631G method. There are 33 atoms present in present compound corresponding to 93 fundamental modes of vibrations. For obtaining theoretical vibrational frequencies scaling factor of 0.903 is used. The calculated vibrational frequencies are numbered from highest to lowest fundamental wave number. The calculated wavenumbers and intensities of normal mode of vibrations and the corresponding vibrational assignments for fundamental modes of vibrations of title compound was shown in Table-3. Stretching vibrations in the region 3100-3000 cm^{-1} are due to aromatic compounds. The vibrational frequencies in the range of 3025, 3080 cm^{-1} are due to CH benzothiazole ring (mode: 92,91). At the range of 3100-3000 cm^{-1}, the stretching vibration was due to CH of phenyl ring (mode:89,87). The C-C stretching vibration showed bands in the range of 1503 and 1497 cm^{-1} (mode: 84,83) are due to phenyl ring while the C=O stretching vibration was seen around 1619 and 1595 cm^{-1} (mode:81,79).

Molecular docking: Molecular docking studies were done to determine the binding effect of ligand with the active site of BCL2 pancreatic cancer cell lines. AutoDock-Vina software was used to carry out calculations. From protein data Bank (PDB ID:1HXW), the 3D crystal structure of stable BCL2 was obtained. For docking, the ligand was prepared by minimizing its energy with B3LYP/6-3111 + G(d) (5D,7F). To calculate Geisteger charges the AutoDock Tools graphical user interface was used and adds the partial charges and polar hydrogen using Kollman united charges. For docking the popular algorithm, Lamarckian Genetic Algorithm (LGA) available in AutoDock was utilized. Docking ritonavir (co-crystallized inhibitor) was used to test the docking protocol by onto the catalytic site of enzyme, which shows good synergy with the co-crystallized ligand with 0.532 Å RMSD value which is within the acceptable limits for docking. The high scored conformation among the docked conformations was predicted by AutoDock scoring function for ligand-enzyme interactions. Fig. 2 shows the ligand-substrate interactions. The molecule binds at enzyme′s catalytic site into the deep and big cylindrical groove. A 68 arg forms a hydrogen bond with benzothiazole derivatives. The above results showed that benzothiazole derivative may possess inhibitory activity on BCL2 pancreatic cancer cell lines.

Conclusion

2-[2-(4-Chlorophenylaminothiazol-5-yl]benzothiazole was studied using FT-IR spectra. The wavenumbers and molecular geometry were calculated by means of DFT method.The transfer of charge within the molecule was analyzed using HOMO and LUMO which is responsible for the bioactive property of molecule. The feasibilities of hydrogen bonding were explained by Mulliken charge analysis. The molecular docking result indicates that benzothiazole derivative may possess inhibitory activity on BCL2 pancreatic cancer cell lines.

TABLE-3
VIBRATIONAL ASSIGNMENTS OF 2-[2-(4-CHLOROPHENYLAMINOTHIAZOL-5-YL]BENZOTHIAZOLE

Mode	Calculated IR frequency (cm^{-1}) scaled	Intensity	Assignment	Type
92	3238	31.43	C22-H32, C19-H30 C9-H27	C-H Str(sym)
91	3231	23.37	C21-32H, C12-24H, C10-H26	C-H Str(asym)
89	3213	9.610	Phenyl ring	C-H Str(asym)
87	3201	1.693	Phenyl ring	C-H Str(asym)
84	1503	49.64	Phenyl ring	C-C Skeletal vibration
83	1497	28.07	Benzothiazole ring, Phenyl ring	C-C Skeletal vibration
81	1619	19.18	C6-O23, N3-C2	C=O, C-N Str
79	1595	590.57	C6-O23	C=O Str

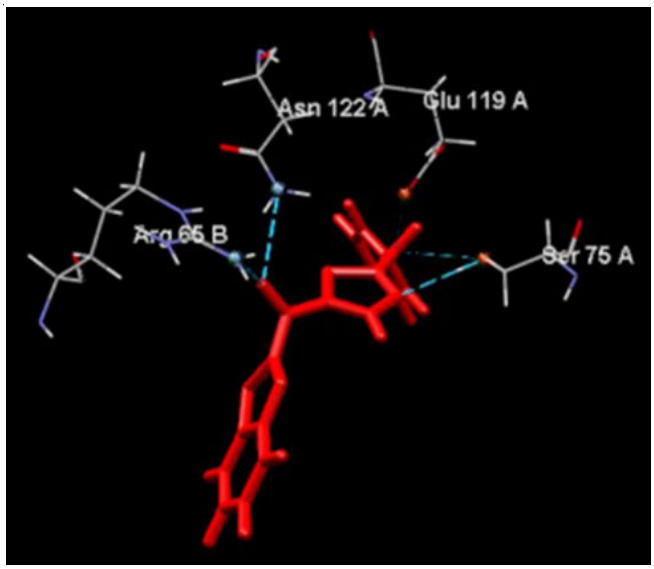

Fig. 2. Ligand interacted into the catalytic site of BCL2 pancreatic cancer cell lines

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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