Synthesis, DFT, HOMO-LUMO, Vibrational and docking studies of 3-(2-phenylaminothiazol-5-oyl)pyridine

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Abstract : In the present study, Quantum chemical calculations of geometrical structure and vibrational wavenumbers of 3-(2-phenylaminothiazol-5-oyl)pyridine were done by ab initio HF and density functional (DFT/B3LYP) method with 6-31G basis set. The calculated geometric criterion of 3-(2-phenylaminothiazol-5-oyl)pyridine are presented. The exact diagnosis of the infrared spectra of 3-(2-phenylaminothiazol-5-oyl)pyridine are also reported. The molecular orbital picture and theoretical molecular frontier orbital energies of the compound have been calculated using density functional method. The molecular HOMOs and LUMOs generated via HF and B3LYP method have been outlined.

Keywords: DFT,HOMO,LUMO,Docking

Introduction

Marine algae is one of the substantial sources of novel bioactive compounds. Several of these eccentric compounds have revealed pharmacological activities for many of the deadly diseases. Dendrodoine 5-[3-(N,N-dimethylamino-1,2,4-thiadiazolyl]-3-indolylmethanone is an alkaloid and extricated from marine algae dendrodoa grossularia. It enchanted a 1,2,4-thiadiazole unit a anomaly among natural products[1]. Pyridine derivatives are convoluted in bioactivities with implementation in pharmaceutical drugs and agricultural consequence [2-7]. Some of them perform as anesthetic agents, drugs for brain diseases, and prodrugs for curing neuronal damage originated by stroke, to name a few. Pyridines also assist analgesics for acute and chronic pain, treatment for tinnitus, depression, and diabetic neuropathy. The ring nitrogen of pyridines undertakes reactions typical of weak, tertiary organic amines such as protonation, alkylation and acylation [8]. The thiazole ring embrace of both sulphur and nitrogen are accessible in different and manifold molecules and they have boundless applications in agriculture and medicinal chemistry [9,10]. Pyridine has been used simple frequently as a proton acceptor in hydrogen bonded complexes [11,12]. Pyridine derivatives are used as non-linear material [13] and photo chemicals[14–18]. Because of our interest structural and medicinal properties of ketothiazole analogs, detailed investigation on the electronic properties, molecular properties and vibrational spectra of the compound. Halogens and methyl substituted compounds and their spectral studies was reported in the literature. In our present study vibrational analysis and quantum chemical calculations of 3-(2-phenylaminothiazol-5-oyl)pyridine has not been reported. The solid complex was synthesized and identified by means of elemental analysis, H^1 NMR and FTIR spectral data. In order to accessory the experimental and theoretical studies of DFT will be applied using B3LYP/6-31G basis set to compute optimized structures, geometrical parameters, Mulliken atomic properties and computing the distribution of electron density on frontier molecular orbitals of donor, acceptor and the formed complex (HOMO and LUMO). The origin of electronic spectra is calculated using DFT method.

I. EXPERIMENTAL

The compound (m.f. $C_{15}H_{11}N_3O_S$) was prepared through the reaction of phenyl-2-(N,N-dimethylimidoyl)thiourea in DMF and 3-bromoacetylpyridine. The resulted mixture was stirred well and triethylamine was added. Then the reaction mixture was heated to about 80-85ºC. Then it was allowed to cool and purged into ice-cold water. An orange coloured precipitate was obtained and filtered. Washed with distilled water and finally dried. The obtained crude product was crystallized from methanol: water (2:1) mixture produce slightly orange coloured crystalline solid.

II. Computational Studies:

Gaussian '09 package at Becke's three parameter hybrid functional and Lee-Yang-Parr correlation functional with the 6-31G basis set were exploit to achieve DFT calculations of 3-(2-phenylaminothiazol-5-oyl)pyridine. DFT employed the B3LYP, which importune Becke's three-parameter hybrid method [19] using correlation function of Lee *et al*.[20].

Results and discussion

Molecular geometry

Intentional geometrical parameters (bond lengths and bond angles) were compared with obtainable experimental data [21]. While the probing values for 3-(2-phenylaminothiazol-5-oyl)pyridine are known, the conceptual values may contribute an plan about the geometry of the molecules and further an scheme of how the geometry of molecule changes from ab initio method of calculation and DFT-B3LYP method of calculation. Hence the optimized structural parameters of 3-(2-phenylaminothiazol-5-oyl)pyridine from the 6-31G(d,p) and B3LYP/6-31G(d,p) calculations were calculated. The B3LYP method shows to geometry parameters, these compounds are convenient to available experimental data [24]. The statistical treatment of data shows that calculations for the bond lengths using B3LYP/6-31G(d,p) is better than the RHF/6-31G(d,p) geometry. The accordance for bond length and bond angles is good for 3-(2-phenylaminothiazol-5-oyl)pyridine.

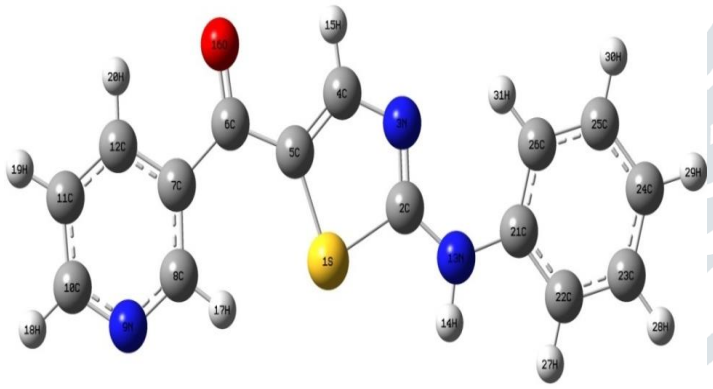

Fig:1 Optimized structure of 3-(2-phenylaminothiazol-5-oyl)pyridine

Bond order analysis

The bond order of 3-(2-phenylaminothiazol-5-oyl)pyridine is presented in Table 1. Bond order is associated to bond strength. Bonds with higher bond order values have short bond length and vice versa. The investigation of bond order may envisage that the weakest bonds may be cleaved better, and they have a relatively low pi bond character. Bond between S1 and C2 possesses higher bond length 1.85652 in B3LYP method

Table 1 : Bond Length data of 3-(2-phenylaminothiazol-5-oyl)pyridine

Bond	Bond Length (Å)	Bond	Bond Length (Å)
S1-C2	1.85652	C11-C12	1.38884
C2-N3	1.31087	C12-H20	1.08224
N3-C4	1.37552	C2-N13	1.35350
C4-H15	1.07857	N13-H14	1.01697
C4-C5	1.37017	N13-C21	1.41881
C5-C6	1.46397	C21-C22	1.40495
C6-O16	1.25204	C22-C23	1.39159
C6-C7	1.49816	C23-C24	1.39712
C7-C8	1.39925	C24-C25	1.39606
C8-N9	1.34928	C25-C26	1.39441
N9-C10	1.34938	C22-H27	1.08556
C10-H18	1.08434	C23-H28	1.08357
C10-H11	1.39665	C24-H29	1.08310
C11-H19	1.08258	C25-H30	1.08383

Electronic properties

Electronic property of 3-(2-phenylaminothiazol-5-oyl)pyridine is discussed by examining the energy gap between the HOMO and LUMO. Many organic molecules containing conjugated pi electrons are characterized by large values of molecular first hyper polarizabilities were analyzed by means of vibrational spectroscopy. The energies of highest occupied molecular orbitals (HOMO) and lowest unoccupied molecular orbitals (LUMO) of 3-(2-phenylaminothiazol-5-oyl)pyridine were calculated. The energy gap allying HOMO and LUMO form the kinetic stability, optical polarizability, chemical reactivity and chemical hardness–softness of a molecule. The positive phase indicates red and the negative phase is green. It is distinct from the figure; the HOMO is localized on phenyl ring while LUMO is localized on thiazole ring. The experimental and theoretical studies of electronic absorption spectrum of 3-(2-phenylaminothiazol-5-oyl)pyridine were made to explained. The energy value of HOMO and LUMO is -0.04372 and -0.25312 respectively. The value of the energy separation between the HOMO and LUMO is 0.29684a.u. The energy gap of HOMO–LUMO explains the consequent charge transfer within the molecule, which impact the biological activity of the molecule.

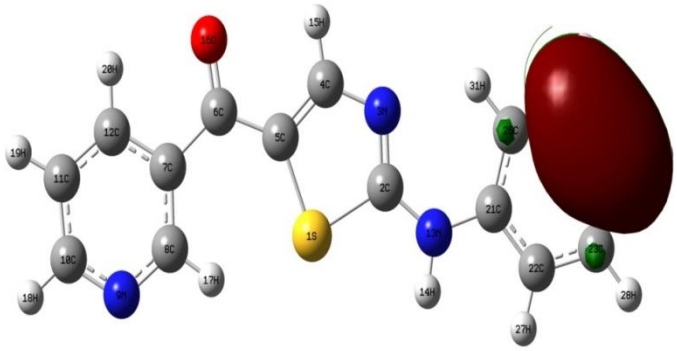

Fig :2 HOMO of 3-(2-phenylaminothiazol-5-oyl)pyridine

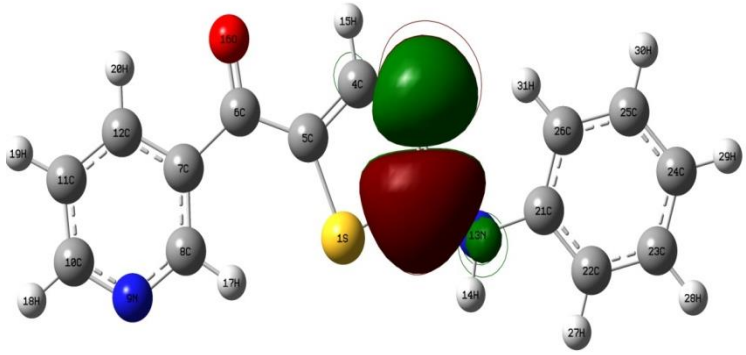

Fig:3 LUMO of 3-(2-phenylaminothiazol-5-oyl)pyridine

Mulliken Atomic Charges:

The bonding structure and molecular conformation was resolved by electronic charge of the atom. Mulliken atomic charge values possess an important part in the implementation of quantum chemical calculation since atomic charges effect dipole moment, electronic structure, molecular polarizability, and more a lot of properties of molecular systems. The Mulliken atomic charges of all hydrogens are positive, oxygen and nitrogen atoms containing negative charge and sulphur atom possess positive charge. The calculated Mulliken charge values of 3-(2-phenylaminothiazol-5-oyl)pyridine are provided in **Table 2**. The charge distribution structures of 3-(2-phenylaminothiazol-5-oyl)pyridine are shown in Fig. 4.

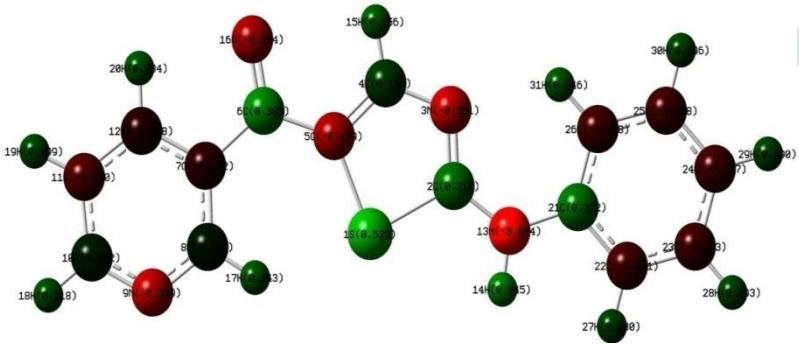

Fig: 4 Mulliken atomic charges of 3-(2-phenylaminothiazol-5-oyl)pyridine

Table : 2

Atom	Atomic Charge	Atom	Atomic Charge
S1	0.523	O16	-0.474
C2	0.31	H17	0.243
N3	-0.561	H18	0.218
C4	0.157	H19	0.189
C5	-0.479	H20	0.234

C6	0.389	C21	0.322
C7	-0.132	C22	-0.201
C8	0.057	C23	-0.183
C9	-0.539	C24	-0.187
C10	0.082	C25	-0.188
C11	-0.240	C26	-0.198
C12	-0.108	H27	0.180
N13	-0.844	H29	0.190
H14	0.345	H30	0.196

Vibrational Analysis

Vibrational analysis is the best experimental gadget for the study of hydrogen bonded complex. The exact vibrational modes of the experimental wave numbers are based on normal mode analysis and comparison with theoretically scaled wave numbers by different DFT methods. The spectral data of 3-(2-phenylaminothiazol-5-oyl)pyridine acquire experimentally by expedient of IR spectra and predicted theoretically by density functional theory (DFT) B3LYP/6-31G method. The studied molecule has 31 atoms and 87 normal modes of vibrations. For obtaining theoretical vibrational frequencies scaling factor of 0.903 is used. The vibrational frequencies are numbered from highest to lowest fundamental wave number. The wavenumbers and intensities of normal mode of vibrations and the corresponding vibrational assignments for fundamental modes of vibrations of the compound are shown in Table-3.Stretching vibrations in the region 3100-3500 cm-1 are due to aromatic compounds. Vibrational frequencies in the range of 1634, 1642 cm-1 are due to CH phenyl ring (mode:75,76). At the range of 3190 and 3220 cm-1, the stretching vibration due to CH of pyridine ring (mode: 78,81). The C-C stretching vibration showed bands in the range of 1549 and 1569 cm-1(mode: 69,70) are due to phenyl ring while the C=O bending vibration was seen around 1631 cm-1(mode:74).

Table : 3

Mode	Calculated IR frequency(cm^{-1})	Intensity	Assaignment	Type
81	3220	22.66	Pyridine Ring	C-H Str(asym)
78	3190	20.38	Pyridine Ring	C-H Str(asym)
76	1642	46.96	Phenyl Ring	C-H Str(sym)
75	1634	87.67	Phenyl Ring	C-H Str(sym)
74	1631	33.40	C6-O16	C=O bend(inplane)
70	1569	5.92	C10-C11,C7-C8	C-C Str(Sym)
69	1549	93.61	C21-C22	C-C str(asym)

Docking Studies

3-(2-phenylaminothiazol-5-oyl)pyridine were tested against various cancer cell lines (HepG-2) using a commercially available 3,4,5-dimethylthiazolyl-2,5-diphenyltetrazolium bromide (MTT) assay. PyRx is a valuable device for Computer-aided drug design. For docking purposes, the three-dimensional structure of the Hepg-2 (PDB code: 4mmh) were obtained from RCSB Protein Data Bank [22]. Hydrogen atoms were added to the structure allowing for appropriate ionization at physiological pH. In addition, the protein structure was prepared by deleting the repeated chains, water molecules and any surfactants, hydrogens were also added to the atom of the receptor and the partial charges were calculated.

3-(2-phenylaminothiazol-5-oyl)pyridine showed lowest interaction energy that is -7.1 Kcal/mol for 4mmh. The amino acid residues such ARG-248, VAL-196 and PHE-251 form hydrogen bonding interactions with the pyridinylthiozole core.

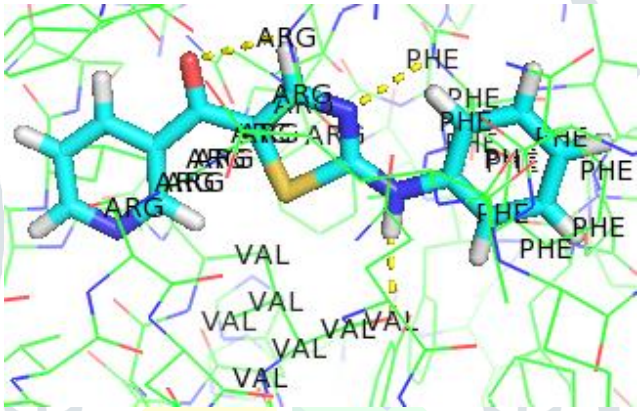

Fig : 5 Docking Image of 3-(2-phenylaminothiazol-5-oyl)pyridine

CONCLUSION

The complete vibrational analysis of 3-(2-phenylaminothiazol-5-oyl)pyridine is implement by DFT-B3LYP methods with 6-31G(d,p), basis sets. The impact of carbon- nitrogen bond and phenyl ring to the vibrational frequencies of the compound was discussed. The observed and simulated spectral datas are good agreement in DFT/B3LYP/6-31G(d,p)method. 3-(3-phenylaminothiazol-5-oyl)pyridine was studied using FT-IR spectra. The wave numbers and molecular geometry were calculated by DFT method. Vibrational frequencies of the fundamental modes of the 3-(2-phenylaminothiazol-5-oyl)pyridine have assigned, analyzed and theoretical results were compared to the experimental vibrations. HOMO–LUMO studies unveil the intra molecular charge transfer along conjugated system. The molecular docking result showed that pyridine derivative may possess inhibitory activity on Hepg-2 liver cancer cell lines.

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