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Electronic structure, vibrational spectroscopic assignment antioxidant, anticancer activity and DFT study of some novel (1-benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole

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The quantum mechanical calculation of optimized parameters and energies of (1-benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole have been done by using Density Functional Theory (DFT) with 6-31G(d,p) basis set. The optimized geometrical parameters acquired by DFT are in better agreement with analogues single experimental data. Electrical dipole moment values have been computed by using *ab initio* and DFT quantum mechanical calculations. The total energy, dipole moment and energy difference are calculated for the derived compounds. The HOMO-LUMO energies have been calculated. Energy gap of HOMO-LUMO strongly supports the presence of intramolecular energy transfer within the molecule. The compound **1a** shows highest activity against Hep-C cell line. The antioxidant study has also evaluated excellent IC50 value. It shows the best inhibitory concentration against breast cancer. The compound (1-benzyl)-2-(2-ethylaminothiazol-4-yl)benzimidazole is found to be highly active on the MDA-MB-231 breast cancer cell line.

Keywords: DFT, Dipole moment, HOMO, LUMO, DPPH, Docking

Benzimidazole moieties are a very important class of heterocyclic compounds that have many applications in pharmaceutical chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. In 1991 benzimidazole derivatives were synthesized by derivatization at N-H of benzimidazole by electron donating group and substitution with long chain of propyl, acetamido, thio, thiazole-amino, tetramethyl piperidine on pyridine resulting in good antiulcer activity[1,2]. Based on their broad biological functions, they are used in clinical medicine as anti-ulcer, antitumor and anti-viral agents. Nowadays Infectious microbial diseases are causing problems world-wide, because of resistance to number of antimicrobial agents (βlactam antibiotics, macrolides, quinolones, and vancomycin). A variety of clinically significant species of microorganisms has become an important health problem globally. One way to fight with this challenge is the appropriate usage of the available marketed antibiotics the other is the development of novel antimicrobial agents[3]. Hence, there will always be a vital need to discover new chemotherapeutic agents to overcome the emergence of resistance and ideally shorten the duration of therapy.

The antibacterial ability of benzimidazoles is explained by the structural similarity, and hence, their competition with purines resulting in inhibition of the synthesis of bacterial nucleic acids and proteins. The present work describes the studies on geometrical and electronic parameters of (1-benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole supported by density functional theory (DFT) calculations. DFT calculations have been carried out using Gaussian 09W package. The optimized geometry of the molecule was found by optimizing all geometrical variables such as bond length, bond angle, *etc*. The electronic properties like frontier molecular orbital energy, ionisation potential, hardness, electronegativity, softness and dipole moment were calculated.

Experimental Section

Computational details

All the theoretical calculations were studied with Gaussian 09 program package and the calculated

results were visualized by means of GaussView 5.0. Electronic parameters and the optimized geometries of the benzimidazole derivatives were carried out using the DFT (B3LYP) methods with the 6-31G (d,p) basis sets[4,5].

Molecular Docking

Molecular docking was accomplished by using Auto Dock Vina. Auto Dock tools (ADT) were used to assigned polar hydrogen atoms. Each and every compound (**1a-d**) were found to have minimum binding energy ranging from –7.1 to –7.4 kJ/mol.

Results and Discussion

Optimized geometry

Optimizations of the derived compounds have been carried out using the DFT/B3LYP methods with the 6-31G(d,p) basis sets. Optimized geometric structure in theoretical is shown in (Fig. 1.)

All the calculated geometric parameters are obtained in (Table 1). The C-C bond lengths of benzimidazole ring were obtained at about ~1.39 Å for 6-31G (d,p) basis set. The above datas shows that there is conjugation of electrons in benzimidazole ring like in benzene ring that means it has no distinction of single bond or double among these bonds[6]. On the size of atom increases bond length also increases. Example for the derived compound (1-benzyl)-2-(2-alkylaminothiazol-4-yl) benzimidazole containing, C-N, C-C and C-S bonds. The size of sulphur atom is bigger than all other atoms carbon and nitrogen hence the bond length is greater for sulphur in this compound[7]. The order of bond length is C-S > C-N > C-C. On the basis of these results, it may be finalized that the B3LYP/6-31G (d,p) method well reproduce the geometry of the derived benzimidazole derivatives.

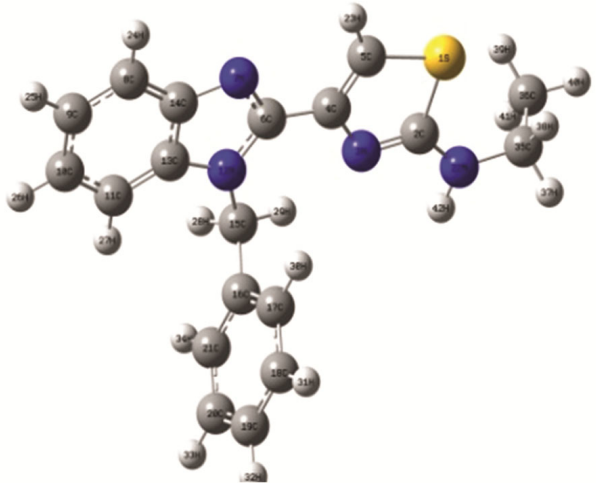

Fig. 1 — The optimized structure of (1-benzyl)-2-(2-ethylaminothiazol-4-yl)benzimidazole

Atomic charge distribution

Atomic charge calculation plays an important aspect of vibrational spectra and the application of quantum mechanical calculations to molecular systems. Effective atomic charges are calculated by determining the electron population of each atom as defined in the basis functions. The solvent effect for the atomic charge distributions of derived compounds, based on the B3LYP/6−31G (d,p) model. The most of the carbon and nitrogen atoms have negative charges while sulphur and hydrogen atoms have positive charges. Negatively charged species are electron acceptor and positively charged atoms are electron donating group[8,9]. Most obviously, S1 having high positive charge (S1 0.534) and nitrogen N3 having high negative charge (-0.847). The Mullliken population analysis compute charges by dividing orbital overlap evenly between the two atoms involved. Increasing or decreasing of bond length between the atoms is based on the sharing of positive and negative charges[10]. Literature reveals that Mulliken charge calculations highlight the application of chemical calculation to molecular system because of charges, dipole moment, molecular polarizability, electronic structure, acidity–basicity behaviour and many more properties of the molecular system (Fig. 2).

HOMO-LUMO interaction

The highest occupied molecular orbital (HOMO) and lowest unoccupied orbital (LUMO) are the two

Table 1 — Geometrical parameters of (1-benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole

Position	Parameter	**1a**	**1b**	**1c**	**1d**
Thiazole	C-N	1.3535	1.3562	1.3569	1.3560
Thiazole	C=N	1.3108	1.3098	1.3198	1.3192
Thiazole	C-S	1.8565	1.8526	1.8462	1.8468
Benzimidazole	C-N	1.0785	1.0782	1.0860	1.0806
Benzimidazole	C-H	1.4049	1.4043	1.4074	1.4072
Benzimidazoe	C-C	1.0843	1.0842	1.0843	1.0848
Chain	C-N	1.4048	1.4056	1.4049	1.0431
Chain	C-C	–	1.0848	1.0855	1.0876
Chain	N-H	1.0456	–	1.0789	1.0872

1a-(1-benzyl)-2-(2-ethylaminothiazol-4-yl)benzimidazole,
1b-(benzyl)-2-(2-propylaminothiazol-4-yl)benzimidazole,
1c-(1-benzyl)-2-(2-isopropylaminothiazol-4-yl)benzimidazole,
1d- (1-benzyl)-2-(2-butylaminothiazol-4-yl)benzimidazole

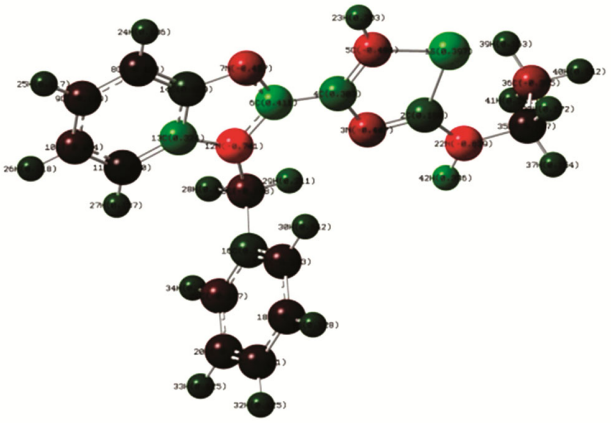

Fig. 2 — Mulliken charge of -(1-benzyl)-2-(2-ethylaminothiazol-4-yl)benzimidazole

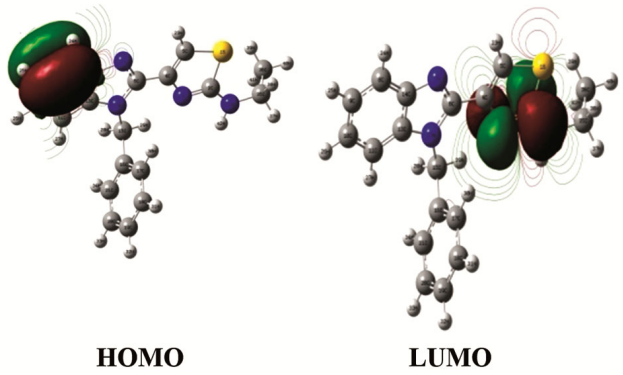

Fig. 3 — HOMO and LUMO image of -(1-benzyl)-2-(2-ethylaminothiazol-4-yl)benzimidazole

most important molecular orbitals. In chemical reactions HOMO and the LUMO are very important parameters[11,12]. Primarily acting orbital HOMO is simply known as electron donor and the LUMO is commonly acts as the electron acceptor. The molecular chemical stability can be characterized by the energy gap between HOMO and LUMO orbitals. Determining the molecular electrical transport properties the energy gap between the HOMO and the LUMO molecular orbitals is a critical parameter because it is a measure of electron conductivity. HOMO–LUMO energies and energy gap were calculated. HOMO orbitals are localized at benzimidazole ring[13]. The LUMO orbitals are localized in the thiazole substitution (Fig. 3). Dipole moment is the most obvious quantity to describe the polarity of a molecule. The negative of the partial derivative of energy E of a molecular system with respect to the number of electrons N with a constant external potential V (r) is called electronegativity.

Table 2 — C-C stretching vibration data

Mode	Calculated IR frequency (cm^{-1})	Intensity	Assignment	Type
81	3220	22.66	Benzimidazole ring	C-H str (asym)
78	3190	20.38	Benzimidazole ring	C-H Str (asym)
75	1642	46.96	Thiazole ring	C-H Str (sym)
74	1634	87.67	Thiazole ring	N-HBend (inplane)
70	1631	33.40	C10-C11, C8-C9	C-C str (asymm)

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-(1-benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole 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[14]. 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 2). 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 benzimidazole 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 thiazole ring while the C-S bending vibration was seen around 1631 cm^{-1} (mode:74, Table 2).

Docking Studies

(1-Benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole 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. Hydrogen atoms were added to the structure allowing for appropriate ionization at physiological *p*H (Ref. 15,16) (Fig. 4). 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. (1-Benzyl)-2-(2ethylaminothiazol-4-yl)benzimidazole 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 benzimidazolethiozole core.

Antioxidant Activity

The simple, quick, and inexpensive method to assess the antioxidant extent of food involves the use of 2,2-Diphenyl-1-picrylhydrazyl (DPPH) which is commonly used to test the ability of compounds to act as hydrogen donors and free radical scavengers and to estimate antioxidant activity. Hence, the DPPH radicals are broadly used to analyze the radical scavenging activity of compounds[17]. Thus, the assessment of antioxidant ability was executed *in vitro* by DPPH scavenging assay (Fig. 5). The free radical DPPH and the odd electron provide maximum absorption at 517 nm (purple colour). The radical is scavenged by the antioxidants, the absorbance decreases resulting in colour change from purple to pale yellow. The absorbance of DPPH at 517 nm was determined using ultraviolet spectra after 30 min. The DPPH concentration in the reaction solution was calculated from the calibration curve plotted at 517 nm at different concentrations and inhibition percentages[18]. Butylated hydroxyanisole (BHA) was used as a standard in our study. Antioxidant study using effective free scavenging activity of the phycocynin as concentration dependent manner. The antioxidant activity of (1-benzyl)-2-(2alkylaminothiazol-4-yl)benzimidazole shows good antioxidant activities (Table 3). The compound **1a** (1-benzyl)-2-(2ethylaminothiazol-4-yl)benzimidazole shows excellent antioxidant activity

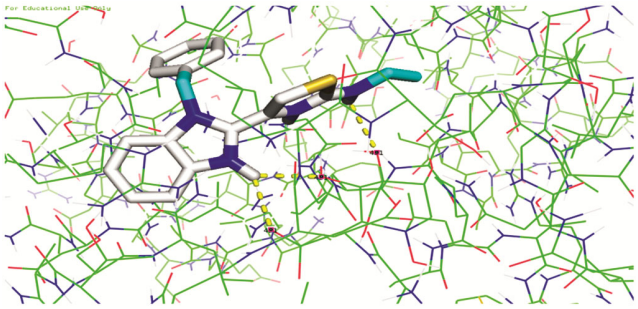

Fig. 4 — Docking image of (1-benzyl)-2-(2ethylaminothiazol-4-yl) benzimidazole

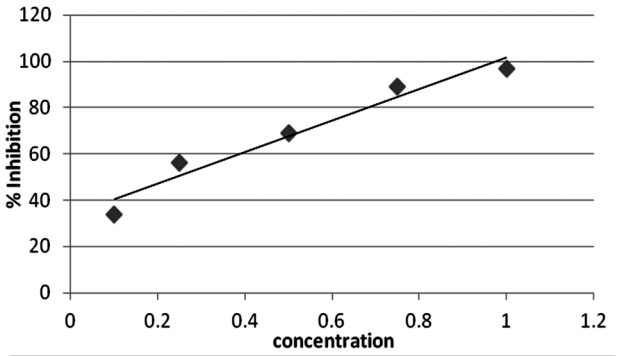

Fig. 5 — Plot of % inhibition *vs* concentration of (1-benzyl)-2-(2-ethylaminothiazol-4-yl)benzimidazole

Anticancer Activity

Cancer is a group of cells that show uncontrolled cell growth, incursion, and occasionally metastasis. Cancer is the world's second leading cause of death and a major health problem in developed countries[19]. Advancement in treatment and awareness of the disease has led to a reduction in cancer deaths, but the number of new diagnoses continues to rise. Several anticancer drugs such as doxorubicin have been identified, which act by binding to DNA and DNA enzymes18. In advances, chemotherapy is one of the terms for cancer, which involves the use of one or more anti-cancer drugs, which can specifically kill cancer cells without making a significant impact on normal cells[20]. Benzimidazole derivatives are used for the study of anticancer activity (Table 4, Fig. 6). The synthesized compounds with high antioxidant

Table 3 — Antioxidant activities of (1-benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole

Compd	IC_{50} (μM)
1a	58
1b	137
1c	111
1d	217

Table 4 — Anticancer activity of (1-benzyl)-2-(2-ethylaminothiazol-4-yl)benzimidazole

Sample Concentration (μg/mL)	Percentage Viability
6.25	92.58
12.5	81.17
25	63.52
50	42.35
100	22.35
IC50	42.23

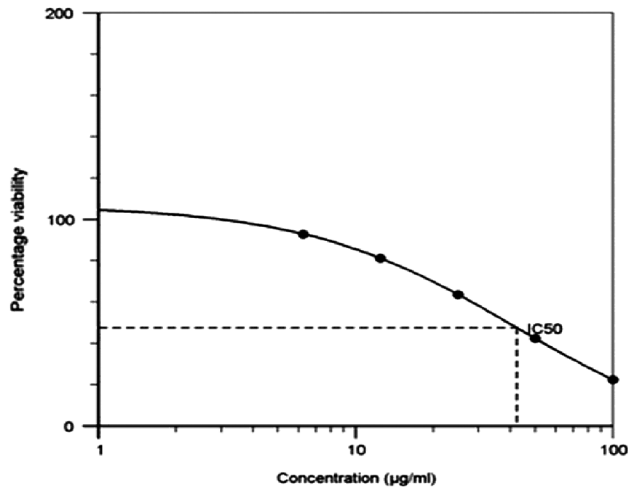

Fig. 6 — Plot of % viability *vs* concentration of (1-benzyl)-2-(2-ethylaminothiazol-4-yl)benzimidazole

activities were examined for their anticancer activity against MDA-MB-231 cell line *in vitro* by MTT assay method.

Conclusion

The complete vibrational analysis of (1-benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole is implemented by DFT-B3LYP methods with 6-31G(d,p), basis sets. The impact of carbon- nitrogen bond and benzimidazole ring to the vibrational frequencies of the compound was discussed. The observed and simulated spectral data are in good agreement when DFT/B3LYP/6-31G(d,p) method 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 (1-benzyl)-2-(2-alkylaminothiazol-4-yl)benzimidazole have been assigned, analyzed and theoretical results were compared to the experimental vibrations. HOMO–LUMO studies the intra molecular charge transfer along conjugated system.. On the basis of docking result, all the compounds **1a** were highly active so we conclude that it possess high agreements with the liver cancer cell line. The compound **1a** possess excellent antioxidant activity, it also proved the compound possess very good anticancer activity against breast cancer cell line MDA-MB-231.

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