Electronic Structure, Geometry Optimization, HOMO-LUMO and IR frequencies of the molecule 2,4-bis[4-(N-cyclobutyldiaminomethyl)phenyl] drug) which is DNA Minor Groove Binder

Maurya D.D.

Assistant Professor of physics
Government Degree College Barakhal
Sant Kabeer Nager U. P.

***Abstract*: DNA minor groove binders have numerous andtherapeutic applications. Crystal structure shows that 2,4-bis[4-(N-cyclobutyldiaminomethyl)phenyl] drug is minor groove binder geometry optimization, HOMO-LUMO, dipole moment and IR assignments using the B3LYP/6-31G** method. Optimized parameters with crystallographic structure there is very slite variations in the conformations of the cyclobutyl groups. Small HOMO-LUMO gap means the high chemical reactivity and inter molecule charge transferability. Several vibrational spectra of the molecule calculated in 400–4000 cm−1 region, reproduce reliable IR spectra bearing in mind the high pharmaceutical significance of minor groove binders and a long numbers of flexible options accessible for lead optimization.**

***Keywords*: Geometry optimization, HOMO-LUMO, IR Spectra**

INTRODUCTION

A large pof the currently used chemotherapeutic anticancer agents are classified into DNA-binding drugs [1]. Due to the application potential of such drugs to cancer and beyond, the development and delineation of such compounds are substantial. Functional intercalators, to disrupt DNA metabolism, bind to DNA duplex in between two base-pairs through a non-covalent stacking interaction that necessitates as a minimum of partial planarity, which is assisted by the realization at least one hydrogen bond [2]. The consequences of intercalation are the decrease of DNA helical twist and enlargement of the DNA duplex [3]. The stability of ligand-DNA complexes is expected to be improved by multiple interactions. Combining covalent-binding with non-covalent recognition signifies an entropic advantage over molecules that do not confine covalently to the DNA. In vigorous cells, most of the DNA is efficiently stored and not reachable to foreign agents. On the other hand, the DNA of briskly dividing cancer cells is continuously being retrieved, modified, and replicated, with concomitant changes in structure, which can be anticipated to DNA duplex in distinct forms, DNA junctions, loops, bulges, etc. DNA recognition by drugs does not seem to be contingent straight on the genetic codes of the four bases but slightly on the mode the construction of the DNA is adapted nation started all over the world. It was pointed out by the crystallographers that the process of intercalation and groove binding can produce deep alterations in the nucleotide secondary structure

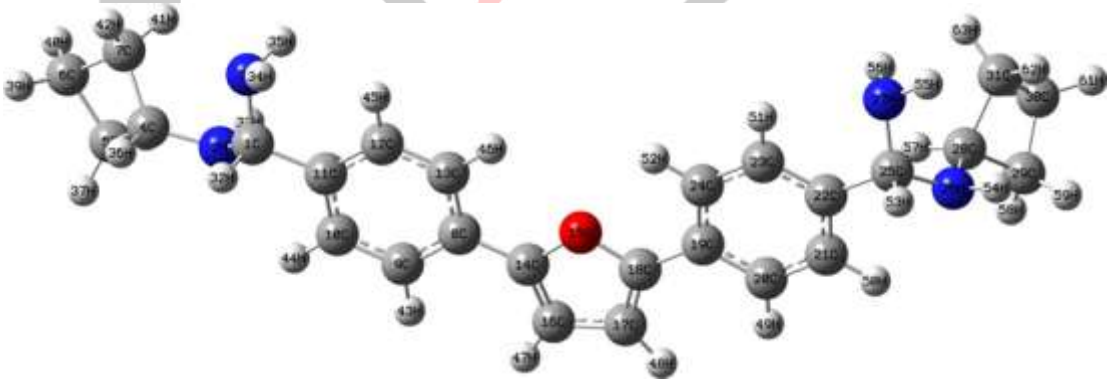

fig1

Environmental conditions [8]. Groove binders are stabilized through intermolecular interactions and naturally have higher association constants than intercalators since a cost in free energies is not required for the creation of binding sites [9]. Minor Groove binders have established as clinical usefulness as anticancer, antiviral, and antibacterial agents.

Compounds with the ability of binding within the minor groove can obstruct chromosome condensation in mitosis along with the outcome change in gene expression. Plausibly, the most illustrious anti-microbial DNA minor groove binding agent is pentamidine which demonstrates activity against an assortment of protozoa, for instance, Pneumocystis jiroveci. Though, like other antimicrobial minor groove binding drugs, penta amidines have notable toxicity including nephrotoxicity, cardiotoxicity, and hepatotoxicity that

have provoked research for harmless agents to delicate Pneumocystis pneumonia. Pentamidine is also known to inhibit oncogenic PRL phosphatases [11], which play important roles in many cancers and clinically usable in ailments, for example, pancreatic cancer. Footprinting experiments and molecular modeling studies have demonstrated that pentamidines bind selectively within the minor groove of the AT-rich DNA duplex [12, 13]. Experiments also show that the cis conformations of pentamidines are the most favored conformation for binding with the duplex [14]. Pentamidine compounds are obtained by the substitution of amidino-nitrogens by hydrophobic alkyl groups of the furamidine, which increases the binding affinity with DNA against pneumocystis carinii pneumonia [14]. Though the detection of DNA binding and the effects on biological functions are well studied, a complete understanding of the mechanism of binding or the causes of affinity, etc are yet to be accomplished.

In the present effort, the electronic structure and the molecular properties of a having cyclobutyl substituent namely, 2,5-bis{[4-(N-)phenyl]furan have done and the assignment of normal modes of vibration have out within the 400–4000 cm−1 wavenumber range, using GAUSSIAN03 program.

Methodology

The crystallographic geometry of this molecule has been taken from the PBD ID: 1FMQ. The optimization of the geometry of the molecule without any constraint, in vacuum, has been carried out through the B3LYP/6-31G** DFT as implemented in GAUSSIAN03 software [15]. With the help of optimized coordinates of the molecule various parameters are calculated such as Mullikan's charge dipole moment HOMO LUMO IR spectra and thermodynamic properties has been done.

5. Results and discussion

6. Geometry optimization

The molecular geometry of 2,4-bis[4-(n-cyclobutyl-aminomethyl)phenyl] drug, isoptimized by B3LYP/6- 31G** method, true minima indicate negative IR wavenumber. The comparisons of geometrical parameters indicate that the core rings have robust conformations while substituents conformations have slight variation in Bond lengths of the optimized geometry of the molecule is rather elongated to that of the

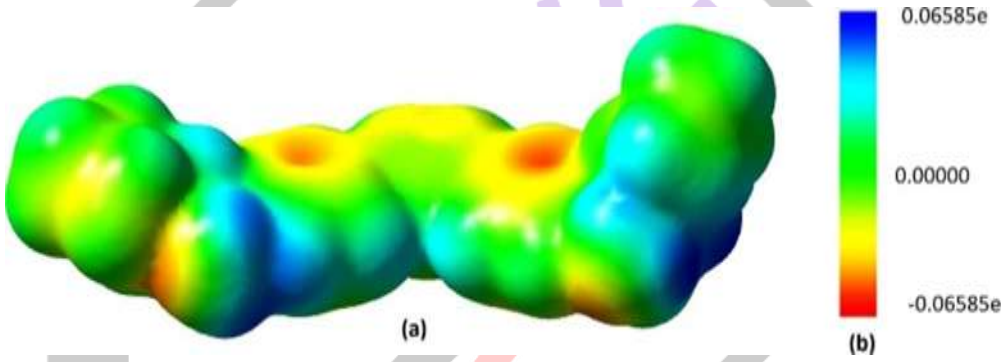

Fig 2

Crystallographic structure, the most change being for C–N bonds. Changes in bond angles have been observed at both terminal carbon atoms where the cyclobutyl group is attached. The dihedral angles of cyclobutyl rings show change i.e. the conformation of cyclobutyl rings is slitely change in crystallographic and gas- phase states.

HOMO-LUMO

Higher the gap between LUMO and HOMO showes greater hardness as well as a higher stability of the molecule. It is not always HOMO and/or LUMO involved in chemical reactivity but symmetry also plays a role. The total electronic energy of the molecule is −1304.2450 Hartree whereas HOMO and LUMO energies of the molecule are −0.1903 and −0.0351 Hartree, respectively. The high chemical reactivity of the molecule is indicated by the small value of the HOMO-LUMO gap. The HOMO lobes are highly concentrated on carbon atoms of the phenyl rings and less intense on nitrogen and oxygen atoms while virtual orbitals, delocalized in LUMO, are highly concentrated around single bonds of the molecule in the central region (figure 3). These results clearly suggest

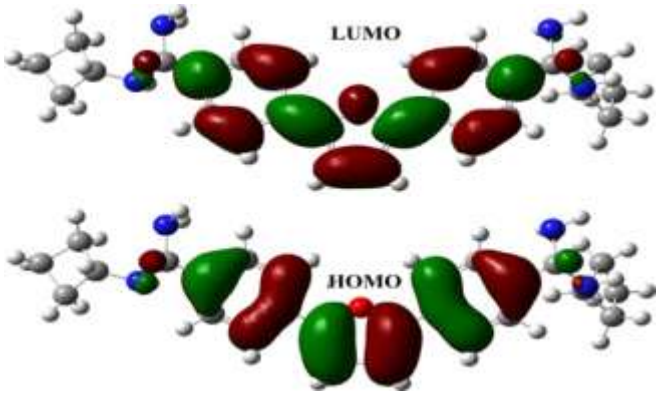

Fig 3

That the molecule is bioactive and intermolecular charge transfer can take place easily. Thermodynamical parameters of the molecule are also calculated using the same functional and basis set (table 1). The zero-point vibrational energy of the molecule is 339.578 cal mol−1.

8. IR SPECTRA

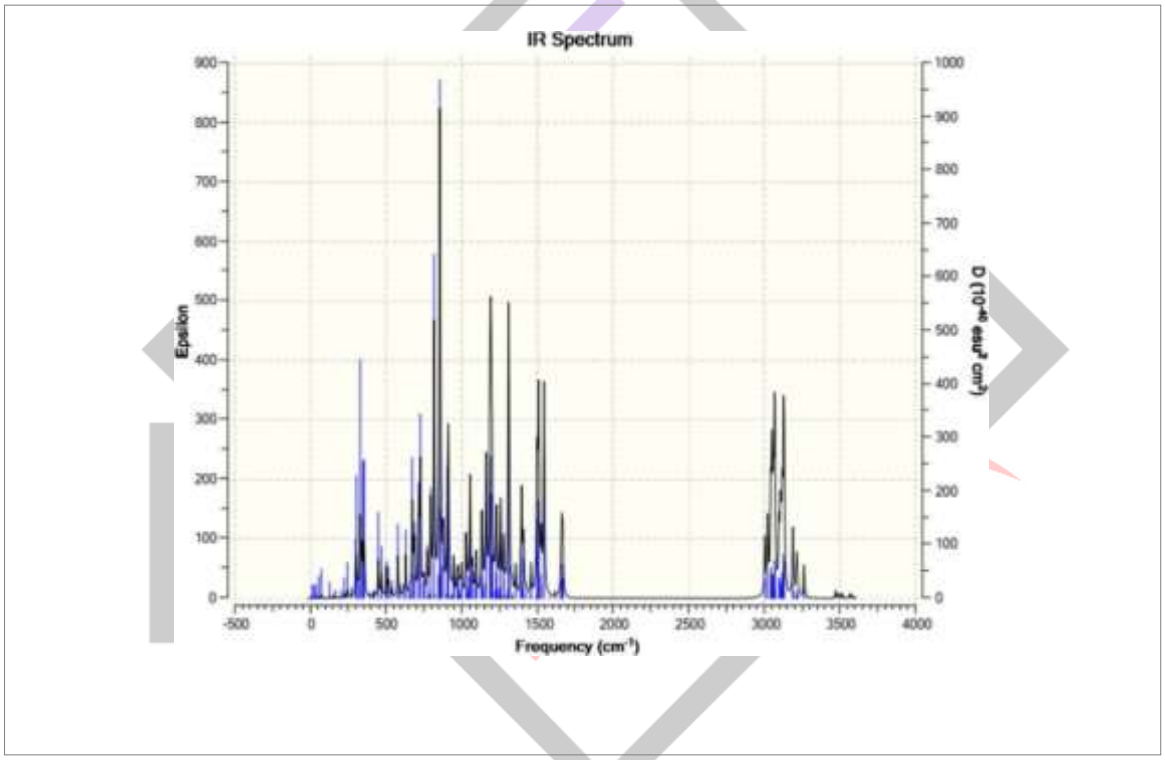

Fig 4

Wavenumbers In large molecules, IRspectra are used to ascertain the specific groups present in the molecules. The absorption peaks of the molecule in the wavenumber range 400 to 4000 cm−1 calculated at B3LYP/6-31G** level have been a done. Molecule is structurally symmetric which show syn conformation with no imaginary wavenumbers exhibiting very small difference wavenumbers at the two sides of the molecule. Peaks observed in the IR spectrum ring deformation, is symmetric and asymmetric stretching. NH2 twisting is observed at 347.92 and 356.86 cm−1 while the molecule as a whole shows vibration at 394.87 cm−1. The ring out of plane deformations has been observed at 417.30 and 419.41 cm−1 wavenumbers though. the experimental value, average value is 412 cm−1 C–H out-of-plane bending vibrational value from experimental value around 474 cm−1 , in contrast, to theoretically observed values at 577.89 and 589.45 cm−1. The oxygen atom of the central furan ring show out of plane deformation at 687.07 cm−1. C–C–C and C–H out of plane distortions are observed at a small bit more wavenumbers than experimentally reported tenets. Aromatic C–Cstretching modes have been found in the range 996 to 1034 cm−1 whereas furan ring C–H twisting at 972.39 cm−1. The normal modes at 1053.04, 1058.00, 1246.12, and 1336.89 cm−1 are done as C–H scissoring and rocking, C–N stretching, and C–H wagging. In- plane H–C–Cbending is displaying by the molecule at 1096.82 and 1098.21 cm−1 while ring –CH–C–C stretching is observed in the range 13005 to 1317 cm−1. CH2 scissoring modes are detected at 1355.61, 1388.56, 1488.52, and 1489.62 cm−1. Asymmetric and symmetric C–H stretching vibration modes of CH2-groups of the molecule are exhibited in the range 3042 to 3067 and 3069 to 3120 cm−1 while asymmetric and symmetric aromatic C–H stretching vibrations in the range 3189 to 3208 and 3214 to 3224 cm−1 respectively. NH2 groups in the molecule exhibit three types of vibrational

modes: symmetric NH2 stretching at 3472.26 and 3492.66 cm−1, asymmetric NH2 stretching at 567.78 and 3582.82 cm−1 and N–H stretching at 3506.63 and 3515.98 cm−1 respectively.

Conclusion

The geometrical parameters of 2,4-bis[4-(N-cyclobutyldiaminomethyl)phenyl]drug has been calculated using the B3LYP/ 6-31G** method have been compared with the crystallographic structure which is slightly different. The conformation of core rings is robust enough while the conformation of cyclobutyl rings has significant deviations. HOMO-LUMO energy calculations obviously is that the molecule is bioactive with easy intermolecular charge transference. Good correlation is also observed with the infrared (IR) assignments of the normal vibrational modes of the computed and experimental wavenumbers with a scale factor of 0.96 as reported by molecule. It has been proven that the molecule had both strands of the duplex binding within the minor groove. In view of the high pharmaceutical significance of the molecule and also the range of flexible options of the molecule for lead optimization, these computations will be a productive ground for the development of drugs targeting minor grooves.

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