ELECTRONIC STRUCTURE AND VIBRATIONAL ANALYSIS OF BLONANSERIN 2-(4-ethylpiperazin-1-yl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine

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Abstract

Blonanserin (Lonasen) is an atypical antipsychotic agent indicated for use in patients with schizophrenia in Japan and Korea. It is effective in the treatment of patients with schizophrenia, providing short- and long-term efficacy against both the positive and negative symptoms of the disorder in several randomized and noncomparative trials. It belongs to a series of 4-phenyl-2-(1-piperazinyl)pyridines and acts as an antagonist at dopamine D2, D3, and serotonin 5-HT2A receptors. Blonanserin has low affinity for 5-HT2C, adrenergic α1, histamine H1, and muscarinic M1 receptors, but displays relatively high affinity for 5-HT6 receptors. In several short-term double-blind clinical trials, blonanserin had equal efficacy as haloperidol and risperidone for positive symptoms in patients with chronic schizophrenia and was also superior to haloperidol for improving negative symptoms. Blonanserin is generally well tolerated and has a low propensity to cause metabolic side effects and prolactin elevation. The structure and the ground state energy of the molecules under investigation has been analyzed employing DFT / B3LYP level. The optimized geometry and their properties such as equilibrium energy, frontier orbital energy, dipole moment and vibrational frequencies have been used to understand the activity of Blonanserin. The calculated highest occupied molecule orbital or HOMO and the lowest un-occupied molecular orbital or LUMO energies shows that charge transfer within the molecule. The vibrational spectra of IR and Raman have been interpreted with the help of B3LYP level of theory with the 6-31G basis set from the Density function theory.

Keywords— *blonanserin, schizophrenia, antipsychotic agent, Vibrational spectra, DFT, HOMO, LOMO*

INTRODUCTION

Schizophrenia is a heterogeneous devastating psychiatric disorder characterized by positive, negative, affective, and cognitive symptoms. It generally presents in late adolescence or early adulthood and is associated with an increased risk of mortality and social or occupational dysfunction. Most patients with the illness usually need life-long treatment, and antipsychotic drugs are the mainstay of the pharmacologic treatment for schizophrenia.

The introduction of second-generation antipsychotics (SGAs) or atypical antipsychotics

represented an important advance in the pharmacologic treatment of the disorder. Accumulating evidence suggests that SGAs have at least equal or superior efficacy as first-generation antipsychotics (FGAs) and may offer some advantages over FGAs such as fewer extrapyramidal symptoms (EPS). SGAs excluding clozapine are currently recommended in many guidelines as first-line agents for acute and maintenance therapy for schizophrenia. However, increased concern has arisen regarding the safety profile of SGAs, as problems such as weight gain, metabolic abnormalities, and/or hyperprolactinemia have been noted. These side effects are associated with potential long-term health risks for patients as well as decreased adherence to treatment regimens. The need for more effective and safer agents has prompted the development of new antipsychotics.

Blonanserin was developed as a novel antipsychotic drug in Japan and was approved in Japan in 2008 and Korea in 2009 for the treatment of schizophrenia. It is currently under clinical investigation in a Phase III trial in the People's Republic of China. This article reviews the available data about the pharmacological profile, clinical efficacy, safety, and tolerability of blonanserin, and discusses its place in the treatment of schizophrenia as well as future perspectives.

The ground state and the excited state properties of the title molecule have been calculated employing DFT/ B3LYP level of theories. As vibrational and electronic spectroscopic study provides very useful information about the structure and conformation of the molecules if used in synergy with quantum chemical calculations, therefore in order to obtain a complete description of molecular dynamics, vibrational wave number calculation has been carried out at the DFT level of theories .The comprehensive investigation of geometrical and electronic structure in ground electronic states, dipole moment, may lead to better understanding of the structural, spectral characteristics of the compound under study.

METHOD, MATERIAL AND THEORY

DFT has been very popular for calculations in solid-state physics since the 1970s. Density functional theory (DFT) is a computational quantum mechanical modelling method used in physics, chemistry and materials science to investigate the electronic structure (principally the ground state) of many-body systems, in particular atoms, molecules, and the condensed phases

In the chemistry community, one popular functional is known as B3LYP (from the name Becke for the exchange part and Lee, Yang and Parr for the correlation part). Even more widely used is B3LYP which is a hybrid functional.

The geometries of molecule were optimized using the Gaussian 09 suite of programs . The ground state geometry of Blonanserin were optimized using DFT. The basis set used for all atoms was 6-31G. Optimized geometrical structure of Blonanserin is shown below.

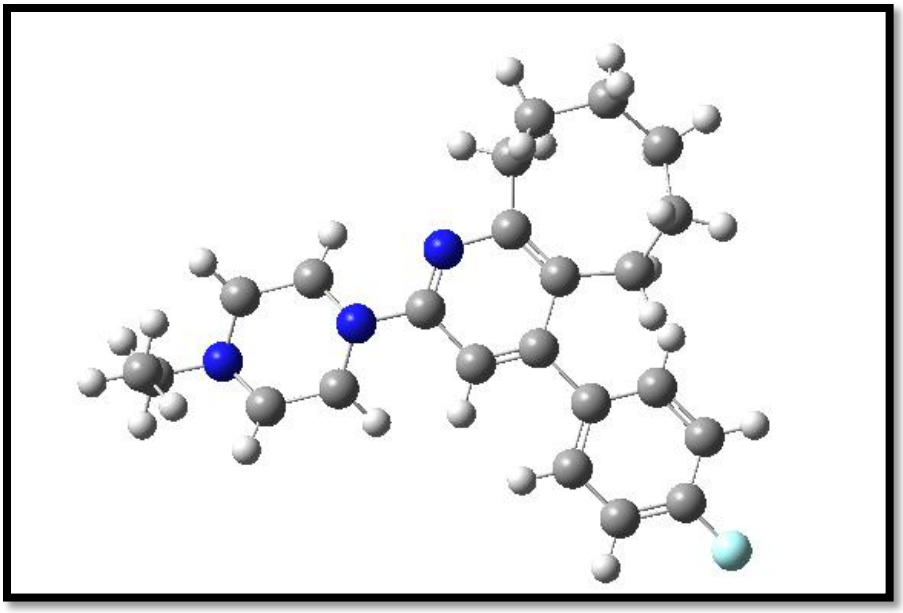


FIG 1

IR AND RAMAN FREQUENCY

Vibrational spectroscopic methods use infrared or near infrared (the low energy end of the visible spectrum) to create vibrations (bond stretching or bending) in chemical species. Like visible spectroscopy, the radiation causing the vibration is absorbed and a corresponding peak is created on an Infrared or Raman spectrum. The excitation in Raman spectroscopy results in a transition between electronic states; in IR spectroscopy only a change in vibrational states occurs.

Fig 2 and 3 show the calculated IR and Raman spectra of Blonanserin. These calculations were done by using DFT/6-31G.

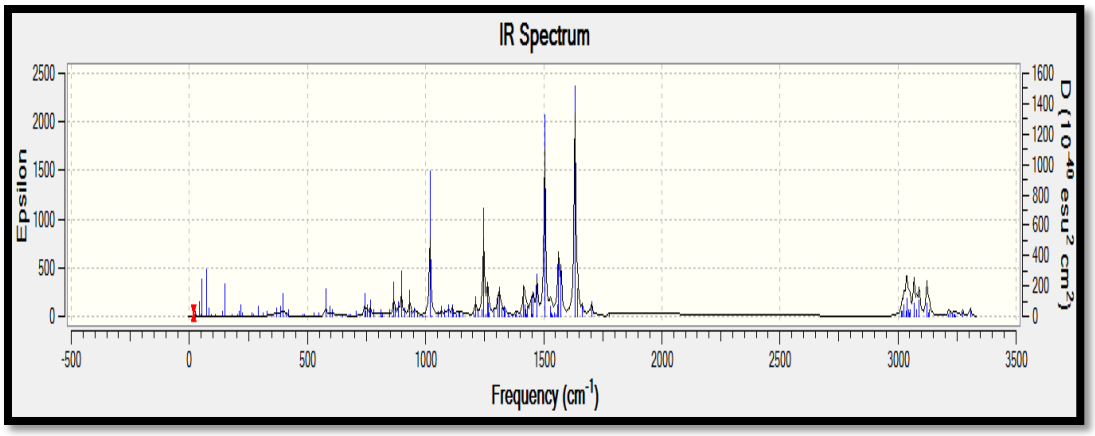


FIG 2

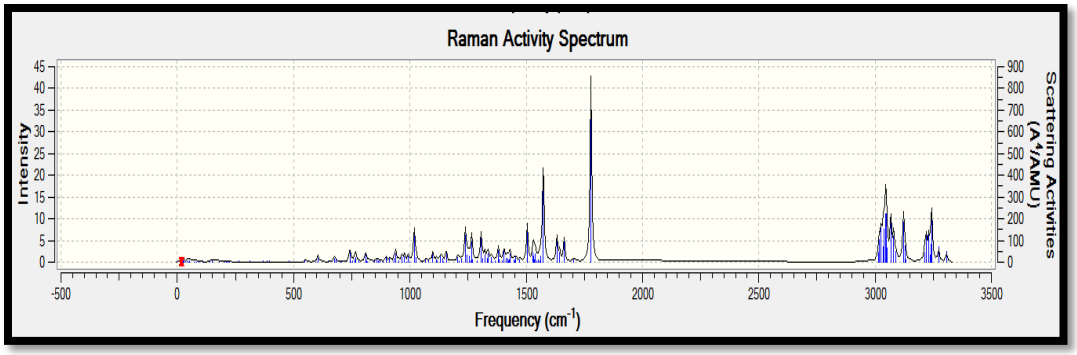


FIG 3

DEPOLARIZATION SPECTRA

In Raman spectroscopy, the depolarization ratio is the intensity ratio between the perpendicular component and the parallel component of Raman scattered light. The Raman scattered light is emitted by the stimulation of the electric field of the incident light. Therefore, the direction of the vibration of the electric field, or polarization direction, of the scattered light might be expected to be the same as that of the incident light. The optimised spectra of p-depolarization and u-depolarization is shown in the fig-4 and fig-5

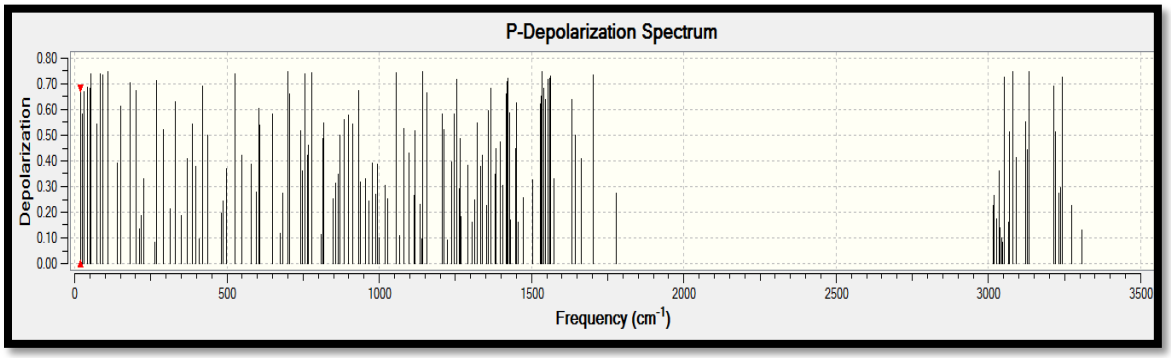


FIG 4

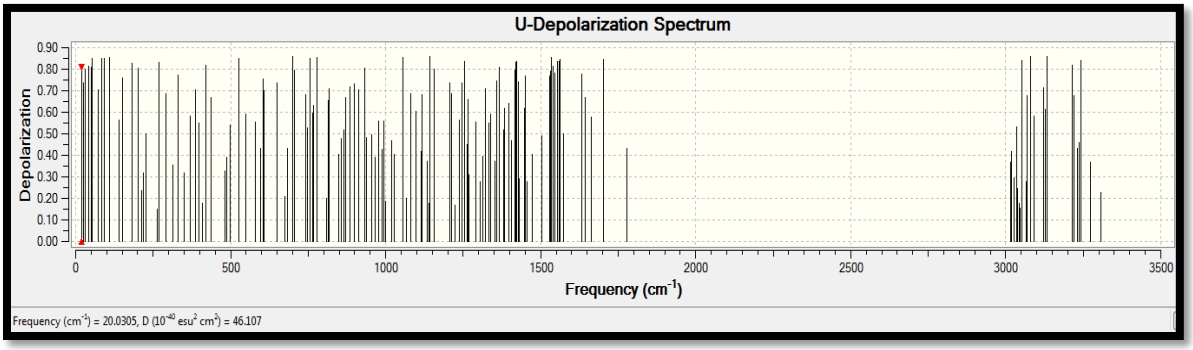


FIG 5

THEORETICALLY COMPUTED GROUND STATE OPTIMIZED PARAMETERS

Parameters	Blonanserin (B3LYP/6-31G)
Energy	-1155.86757029 a.u.
Dipole moment (in Debye)	2.8013

ELECTRONIC PROPERTIES

The most important orbitals in a molecule are the frontier molecular orbitals, called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).These orbitals determine the way the molecule interacts with other species. HOMO-LUMO orbitals are also called frontier orbitals as they lie at the outermost boundaries of the electrons of the molecules. The frontier orbital gap helps the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule. The difference in energy between these two frontier orbitals can be used to predict the strength and stability of transition metal complexes, as well as the colors they produce in solution.

The HOMO and LUMO energy calculated by B3LYP /6-31G method –.

HOMO Energy	-0.13928a.u.
LUMO Energy	- 0.01958a.u.
ENERGY GAP	0.1197 a.u.

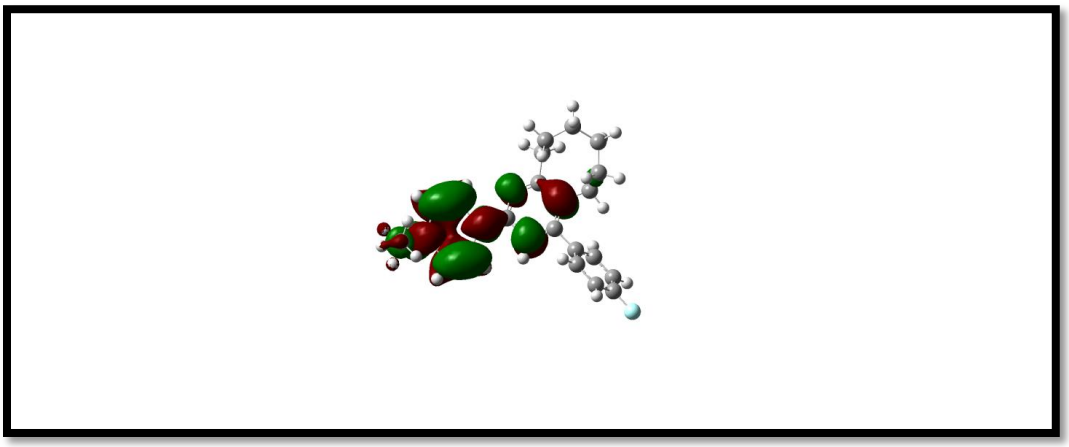


FIG 6

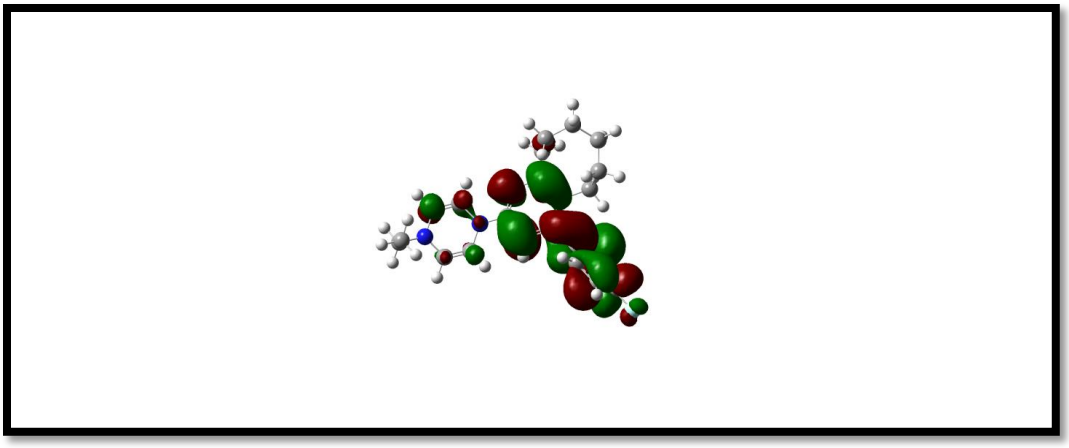
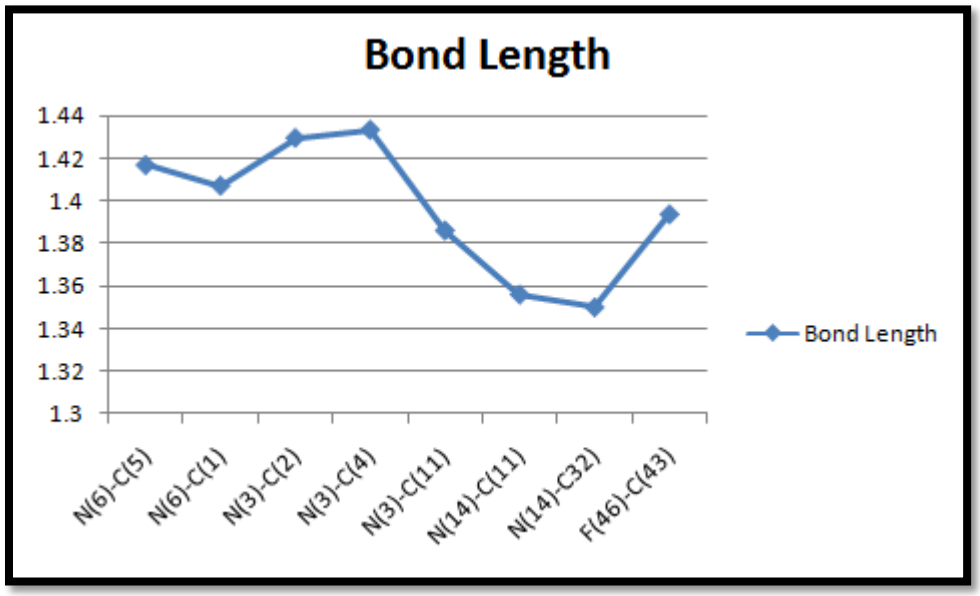


FIG 7

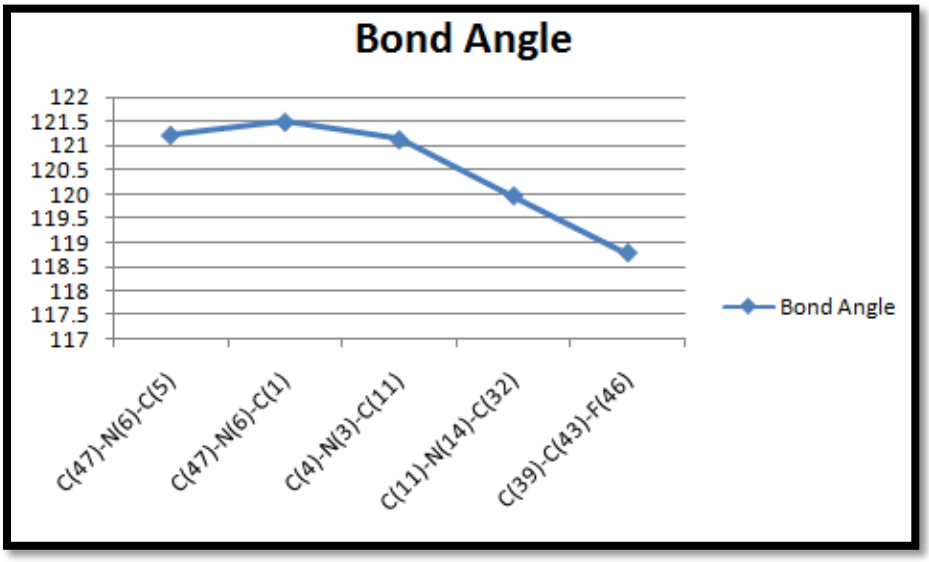
BOND LENGTH AND BOND ANGLE

The optimized structural parameters such as bond length and bond angle were determined at B3LYP level theory with 6-31G basis set and are presented in Table and graph is given below-

Atom	Bond Length
N(6)-C(5)	1.41675
N(6)-C(1)	1.40713
N(3)-C(2)	1.42951
N(3)-C(4)	1.43329
N(3)-C(11)	1.38611
N(14)-C(11)	1.35604
N(14)-C32)	1.35000
F(46)-C(43)	1.39368



Atom	Bond Angle
C(47)-N(6)-C(5)	121.224
C(47)-N(6)-C(1)	121.495
C(4)-N(3)-C(11)	121.130
C(11)-N(14)-C(32)	119.962
C(39)-C(43)-F(46)	118.775



CONCLUSION

Simulation work of Blonanserin is in the process. Simulation report of Blonanserin we will reported very soon.

ACKNOWLEDGMENT

we are very grateful for financial assistance to the UP CST, Lucknow under whose project this work was carried out. *And I would also like to thank my parents for their personal support or attention who inspired me to go own my way and helped me most throughout my project.*

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