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Vibrational Spectra of (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone): An Antipsychotic Agent

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Abstract – (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) is an atypical or second-generation antipsychotic of the azapirone family that antagonizes serotonin 5HT2A receptors and dopamine D2 receptors. It also displays affinity towards 5HT1A receptors as a partial agonist. It was introduced in Japan by Dainippon Sumitomo Pharma in 2001 for the treatment of acute and chronic schizophrenia and acute cases of bipolar mania. It is commonly present as the hydrated hydrochloride salt form. Classified as a neuroleptic agent, perospirone is shown to be effective against positive, negative and general symptoms in patients with schizophrenia. It's synonyms are cis-N-(4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl)-1,2-cyclohexanedicarboximide and SM-9018.

Pharmacological and clinical advances in the understanding of the potential use of serotonin 5-HT2 receptor antagonists as treatments for a number of psychiatric disorders, namely anxiety, depression and schizophrenia. A complete assignment of fundamental vibration frequencies has been made, and the spectra have been interpreted in detail. The non-planar frequencies have been calculated with the aid of force constants determined for related molecules.The fundamental vibrational frequencies and intensity of vibrational bands were evaluated using density functional theory (DFT) using standard B3LYP/6-31G methods and basis set combinations. The optimized geometric structure of(3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) has been studied by using Density Functional Theory (DFT). On the basis of ground and excited state geometries, the absorption spectra have been calculated using the DFT method. To understand the Non-Linear Optical properties of(3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone), we computed dipole moment (μ) ,using B3LYP density functional theory method in conjunction with 6-31G basis set.

Keywords: FTIR, DFT, HOMO, LUMO, Vibrational spectra, Antipsychotic.

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INTRODUCTION

(3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) is mainly used for the treatment of schizophrenia and acute cases of bipolar mania. (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) is a serotonin 5-HT2 receptor inverse agonist and dopamine D2 receptor antagonist based on receptor binding experiments that binds to both receptors with high affinity. (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) is also a partial agonist at 5-HT1A receptors which are autoreceptors that stimulate the uptake of 5-HT and inhibit 5-HT release. It also interacts with D4 receptors and α_1-adrenergic receptors as an antagonist, as well as histamine H1 receptor an inverse agonist. Binding to these receptors may explain sedative and hypotensive actions. (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) binds to D1 receptors with low affinity and minimal clinical significance. Antagonism at D2 receptors is believed to relieve the positive symptoms of schizophrenia such as delusions, hallucinations, and thought disorders. (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) targets the mesolimbic patway to reverse the overactivity of the dopaminergic signalling via D2 receptors. 5-HT2A antagonism is thought to allevaite the negative symptoms and cognitive impairments of

schizophrenia. These receptors are Gi/Go coupled receptors that lead to decreased neurotransmitter release and neuronal inhibition when activated, thus play a role in dopamine release regulation. (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) targets these receptors in the nigrostriatal pathway to reduce dopamine release and function. In contrast, 5-HT2A receptor antagonism may improve the negative symptoms by enhancing dopamine and glutamate release in the mesocortical pathway. 5-HT1A receptor activation further inhibits the release of 5-HT into the synaptic cleft. Plasma protein binding ratio is 92% with extensive binding to serum albumin and α1-acid glycoprotein.

(3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) undergoes rapid and extensive first-pass metabolism in the liver; the metabolic pathways involve hydroxylation, N-dealkylation, and S-oxidation, which are catalyzed by CYP1A1, 2C8, 2D6, and 3A4. CYP3A4 is reported to have highest level of contribution in perospirone metabolism. Hydroxyperospirone is formed from hydroxylation of the the cyclohexane-1,2-dicarboximide moiety and retains pharmacological action by mediating antiserotonergic effects, although with lower affinity. (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) using Gauss view program packages at the Becke3-Lee-Yang-Parr (B3LYP) level with standard 6-31G basis set.DFT computational codes are used in practise to investigate the structural, magnetic and electronic properties of molecules, materials and defects. DFT calculations allow the prediction and calculation of material behaviour on the basis of quantum mechanical considerations, without requiring higher order parameters such as fundamental material properties. DFT computational methods are applied for the study of systems to synthesis and processing parameters. In such systems, experimental studies are often encumbered by inconsistent results and non-equilibrium conditions. Examples of contemporary DFT applications include studying the effects of dopants on phase transformation behaviour in oxides, magnetic behaviour in dilute magnetic semiconductor materials.

METHOD, MATERIAL AND THEORY:

Geometrical Structure

DFT is supported by many quantum chemistry and solid state physics software packages, often along with other methods Optimized geometrical structure of (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione(Perospirone);

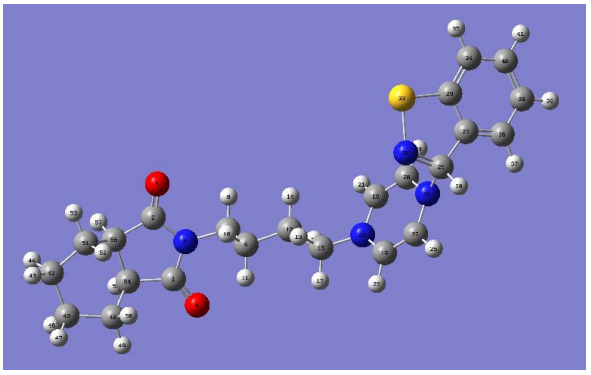

Fig 1

The vibrational frequencies of the solid phase FT-IR and FT-Raman spectra of (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) were recorded in the regions 3500-500 and 3500-100 cm(-1), respectively. The optimized geometry, frequency and intensity of the vibrational bands of (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) were obtained by the Restricted Hartree-Fock (RHF) density functional theory (DFT) with complete relaxation in the potential energy surface using 6-31G basis set. The harmonic vibrational frequencies for (3aR, 7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) were calculated and the scaled values have been compared with experimental values of FTIR and FT-Raman spectra. The observed and the calculated frequencies are found to be in good agreement. The harmonic vibrational wave numbers and intensities of vibrational bands of (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) with its cation and anion were calculated and compared with the neutral Thiothixene. The DFT calculated HOMO and LUMO energies shows that charge transfer occurs within the molecule. DFT calculations allow the prediction and calculation of material behavior on the basis of quantum mechanical considerations, without requiring higher order parameters such as fundamental material properties.

IR and Raman Frequencies

Infrared and Raman spectra of different crystalline forms of the same organic compound can be used to identify a pure crystal form and quantify a mixture of two forms. Many organic compounds have one or more crystalline or polymorphic forms. The observed differences in the spectra of different polymorphs include changes in frequencies, relative intensities, band contours and the number of bands.The IR and Raman spectra of (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) an antipsychotics compound have been computed

performing density functional theory calculations at the B3LYP/6-31G(d) level of theory. In Vibrational spectroscopy the infrared and Raman spectra of optimized geometrical structure of pharmaceutical compound (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) were also evaluate from the calculation of intensities. Then the following figures show the calculated IR and Raman spectra of Optimized geometrical structure (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone).These calculations were done by using B3LYP/6-31G methods.

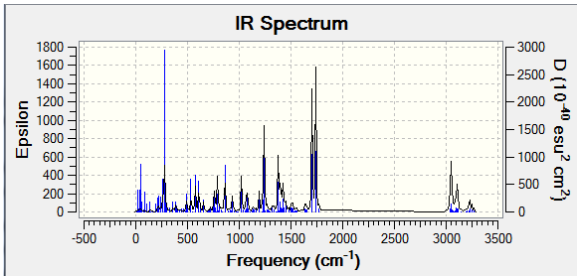

FIG.2Spectrum of IR

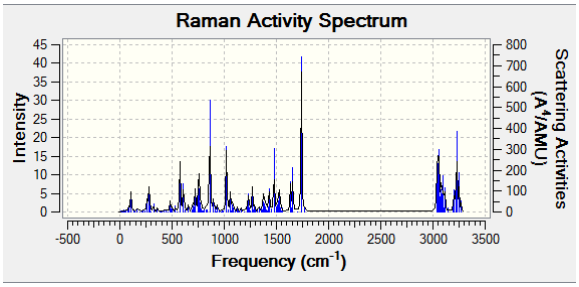

FIG.3 Spectrum of Raman

Energy and Dipole Moment

Dipole moment, the measure of the electrical polarity of a system of chargesThe electric dipole moment is a measure of the separation of positive and negative electrical charges within a system, that is, a measure of the system's overall polarity.Bond dipole moment of Optimized geometrical structural compound is the measurement of polarity of a chemical bond and also known as the mathematical product of the separation of the ends of a dipole and the magnitude of the charges. The dipole moment creates by unequal sharing of electron in optimized geometrical molecules by their atoms.

Dipole moment and energy of the medically active compound (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) is shown in following table:-

Dipole Moment	5.4207 Debye
Total Energy	-1659.89657979a.u.

(1 Debye = 3.34*10^{-30} cm.)

(1 *a.u.* of *energy* = 1hartree = 4.360 × 10^{-18} J. = 27.211*eV* = 2625kJ/mol = 627.5kcal/mol.)

Molecular Orbital Energies

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. The frontier orbital gap helps characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule.

HOMO and LUMO are types of molecular orbitals. The acronyms stand for "highest occupied molecular orbital" and "lowest unoccupied molecular orbital", respectively. The energy difference between the HOMO and LUMO is termed the HOMO**–**LUMOgap. HOMO and LUMO are sometimes called frontier orbitalsin frontier molecular orbital theory. 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.

Energy levels of the frontier molecular orbital's especially HOMO, LUMO as well as their spatial distributions are important parameters for determining the optoelectronic properties. The density plot of the HOMO and LUMO of (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) is calculated at B3LYP/6-31G level of theory and are shown in Figure;

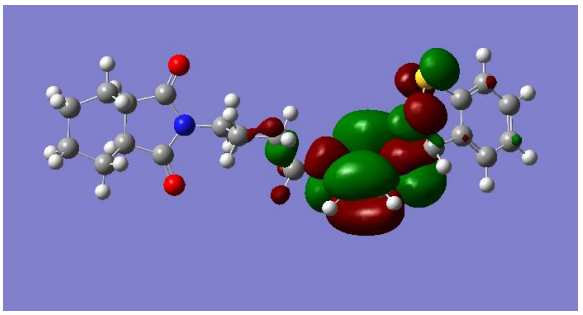

FIG.4HOMO

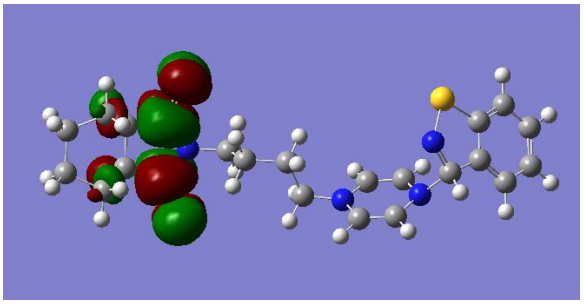

FIG. 5LUMO

The energy gap between HOMO and LUMO has been used to prove the bioactivity from intermolecular charge transfer. The energy gap measures the kinetic stability of the molecules. The HOMO and LUMO energy gap show the charge transfer interaction taking place within the molecule.

The HOMO and LUMO energy calculated by B3LYP /6-31G method as shown below in table:-

HOMO Energy	-0.14685 au
LUMO Energy	-0.03543 au
ENERGY GAP (LUMO-HOMO)	0.11142 au

Bond Length and Bond Angle

In molecular geometry, bond length or bond distance is the average distance between nuclei of two bonded atoms in a molecule. It is a transferable property of a bond between atoms of fixed types, relatively independent of the rest of the molecule. Molecular geometries can be specified in terms of bondlengths, bond angles and torsional angles. The bond length is defined to be the average distance between the nuclei of two atoms bonded together in any given molecule. A bond angleis the angle formed between three atoms across at least two bonds. The such as bond lengths, bond angle are the optimized structural parameters , so these parameters were determined at B3LYP level theory with 6-31G basis set and they are presented in a table, which is given below –

ATOMS	BOND LENGTH
C45-C42	1.56536
H49-C48	1.07000
H55-C54	1.07000
C55-C51	1.56031
O4-C1	1.25841
C1-N5	1.49067
C56-C2	1.52953
C2-O3	1.25840
N5-C6	1.47000
H7-C6	1.07001
C6-C9	1.54002
C9-C12	1.53995
H16-C15	1.07000
C15-N30	1.46993
C18-C20	1.53992
N30-C19	1.47001
C22-N31	1.47001
N31-C26	1.46993
N32-S33	1.72836
C26-C27	1.55612
C36-C38	1.54922
C40-C34	1.54541
C29-S33	1.74069

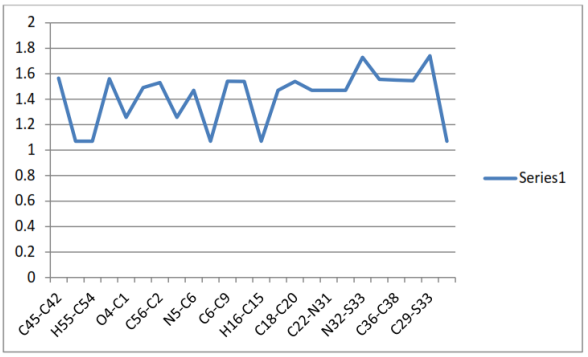

Fig.6. Graph of Bond Length

ATOMS	BOND ANGLE
H41-C40-C34	120.038
S33-C29-C34	129.445
H39-C38-C40	119.870
H37-C36-C27	120.898
N32-S33-C29	94.374
N31-C26-N32	110.109
H23-C19-C22	120.652
N30-C18-C20	118.879
C15-N30-C18	109.996
H13-C12-H14	109.472
H11-C9-C6	109.474
C2-N5-C6	109.226
O3-C2-N5	125.787
O4-C1-C54	124.263
C56-C54-H55	115.496
H52-C51-H53	77.124
C42-C45-C48	109.546
H47-C45-H46	109.642

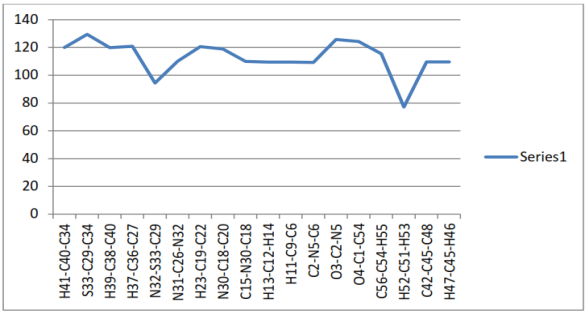

Fig. 7 Graph of Bond Angle

CONCLUSION:

Thus, the Simulation report of (3aR,7aS)-2-{4-[4-(1,2-benzothiazol-3-yl)piperazin-1-yl]butyl}-octahydro-1H-isoindole-1,3-dione (Perospirone) is on progress. It will be reported very soon.

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