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Chapter

Studies on Histamine H2-Receptor Antagonists by Using Density Functional Theory

Kodakkat Parambil Safna Hussan, Indulekha Jayarajan Jithin Raj, Sailaja Urpayil and Mohamed Shahin Thayyil

Abstract

Density functional theory (DFT) is a quantum mechanical approach used to investigate the electronic structure (principally the ground state) of many-body systems, in particular atoms, molecules, and the condensed phases. In this work, we have used DFT/B3LYP/6-31+G(d) level of theory to get insight into the molecular geometry and thermochemical properties of histamine H2-receptor antagonists. Histamine H2-receptor antagonists or H2 blockers are a group of pharmaceutical ingredients that reduce the amount of acid produced by the cells in the lining of the stomach. The potential H2 blockers include cimetidine, famotidine, nizatidine, and ranitidine. The detailed theoretical investigation on the listed H2 blockers in terms of their thermochemical parameters and global descriptive parameters revealed that, though famotidine is the best among them with highest Gibbs free energy, nizatidine showed higher biological activity with high softness, low hardness, and high electrophilicity index. The theoretical vibrational spectra of these four Histamine H2-receptor antagonists were analyzed and the infrared spectra of nizatidine was compared with the experimental IR spectra, and found to be good agreement with the experimental values. Further, frontier molecular orbitals especially the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were determined and the activation energy of the selected samples were calculated. In addition to this, the amorphisation technique were employed to enhance the solubility and bio availability of the best biologically active H2 blocker nizatidine using broadband dielectric spectroscopy.

Keywords: histamine H2-receptor antagonists, density functional theory, molecular orbitals

1. Introduction

The branch of computational chemistry is identified to be one of the nascent applications of technological growth within chemistry. Within this branch, different algorithms are introduced through incorporating aspects of theoretical chemistry for identifying and predicting chemical properties of compounds. Analyzing the results obtained from computational chemistry it was fascinating to note that

the theoretical results provide information with same quality of the data obtained through conducting experiments. With the required level of availability of variables or data, it helps in describing various unobserved chemical phenomena [1]. Computational chemistry is identified to be one of the major components identified to be included in the process of making new chemical products. The use of this technology provides increased efficiency of the drug introduced through analyzing the nature of the particular receptor site. The role of organic chemists is followed by attempting to synthesize the proposed structure of the chemical components, which is occasionally tested by biochemists. This set of actions is iterated by analyzing experimental results after obtaining feedback on the same. The aspect of the feed back provides suggestions for effectively increasing the quality of molecules.

Various tools used by computational chemistry starting from molecular mechanics to higher quantum mechanical calculations including Hartree Fock method, density functional methods & ab initio calculations. The balls and springs model of molecules is identified to be included within molecular mechanics [2]. The element of quantum mechanics is introduced within the ab initio aspect through treating the same with the Schrödinger Equation [3]. Semi-empirical methods are identified to include Hartree-Fock theory in a more simplified version along with empirical corrections resulting in increased performance [4]. DFT or Density Function Theory uses electron density function irrespective of the wave function. The electron density function is also identified as charge density or just merely electron density. Two of the Hohenberg-Kohn theorems which describe that the ground state property of atom or molecule is identified by its electron density function and the energy produced by trial electron density should be either greater than or equal to its true and valid energy, are the main constituents of density functional theory [5]. The Kohn - Sham approach, on the other hand, is identified to analyze the level of variations made by a system through considering an ideal system that is comprised of non-interacting electrons [3]. Through reducing the energy along with Kohn-Sham orbitals, the Kohn-Sham equations can be derived from the energy equation [6, 7].

Experiment and theory are identified to be the major components for the functioning of science and almost all of its disciplines. Hence, one without the other won't be able to effectively assist in the creation of scientific breakthroughs. A theory without experimental data to support it is regarded as a hypothesis, while experiments without theory will not provide a degree of finiteness to it. In the field of science, the advent of the computational facility is identified to provide increased support for such experimental needs. Focusing on the branch of chemistry, computational chemistry is identified to effectively assist in various experimental chores [1]. The major reason for the success of computational chemistry was the chance provided for skipping over the tedious and hazardous chemical experimentation with the help of computer simulation.

Here in this work structural properties along with the reactivity, energy, vibrational properties and frontier molecular orbitals of histamine H2-receptor antagonists (cimetidine, famotidine, nizatidine and ranitidine), are investigated using Density functional theory [4]. H2 blockers are a group of medicines that reduce the amount of acid produced by the cells in the lining of the stomach and are used to treat duodenal ulcers, gastric ulcers and Zollinger-Ellison disease [8]. They are also called 'histamine H2-receptor antagonists' but are commonly called H2 blockers. The H2 blockers compete with histamine for H2 receptors on the stomach's parietal cells and thereby depress the production of hydrochloric acid. They are rapidly absorbed and will reach peak blood levels in 1 to 3 hours. Acid-suppression lasts several hours thereafter and permits peptic ulcers to heal over a few weeks. It also counteracts the corrosive effects of acid, which refluxes into the esophagus

(food pipe) and causes heartburn. Though histamine H2 blockers inhibit the action of histamine on gastric H2 receptors thereby decreasing gastric acidity, they were considered a breakthrough in the treatment of peptic ulcer disease but it is used as non-NSAID ulcers, and control severe esophagitis. There are four H2 blockers available by prescription: cimetidine, ranitidine, nizatidine and famotidine [9]. But we are unaware about the chemical and biological activities of these H2 blockers and information are less to claim best among the four. This work is an attempt to get an insight to the structural and thermochemical properties and parameters such as Gibbs free energy, enthalpy and entropy, and stability of the four selected H2 blockers and to find out which molecule is comparatively active; chemically as well as biologically. Further we have included the molecular dynamics of the best one among the four H2 blockers to enhance its solubility by amorphosizing the sample by quench cooling technique, though such study is out of focus of this chapter.

2. Materials and method

2.1 Materials

The input structures the drugs; cimetidine (PubChem: 3033637); famotidine (PubChem: 2756); nizatidine (PubChem: 5702160); ranitidine (PubChem: 3001055) were taken from the PubChem database [10], which are in sdf (Standard Data File) format and were converted to GJF (Gaussian Job File) input files using the application Open Babel [11].

2.2 Computational methodology

All the quantum calculations have been performed by density functional theory using a Gaussian 09 software package [12]. The initial geometries chosen for calculation was taken from the PubChem database and optimized with DFT/B3LYP/6-31 + G(d) level of the theory [6]. The B3LYP is Becke's three-parameter practical hybrid methods that add the exchange and electronic correlation terms in DFT, including the Lee, Yang Parr (LYP) functional. The optimized geometry was used for the calculations of harmonic vibrational frequencies at the DFT/B3LYP/6-31 + G(d) method, it also helps to ensure the systems to be local minimum number imaginary vibration frequencies. The thermochemical properties [13–15] like, hardness (η), softness (S), chemical potential (μ), electronegativity (χ) and electrophilicity index (ω), were calculated using Koopman's theorem for closed-shell compounds. Electrostatic potential analysis has also been made to identify the mapping surface of drugs. The thermo chemical properties of the selected molecules were calculated from electronic energy, the equilibrium geometry and the vibrational frequencies.

3. Results and discussion

3.1 Molecular geometry

All four histamine H2 receptor antagonists: cimetidine, famotidine, nizatidine, and ranitidine were optimized using DFT method using B3LYP/6-31 + G(d) level of theory. Optimized geometry parameters of the four samples were listed out in the supplementary material for reference. The optimized structure of four H2 blockers were depicted in **Figure 1** [16–18].

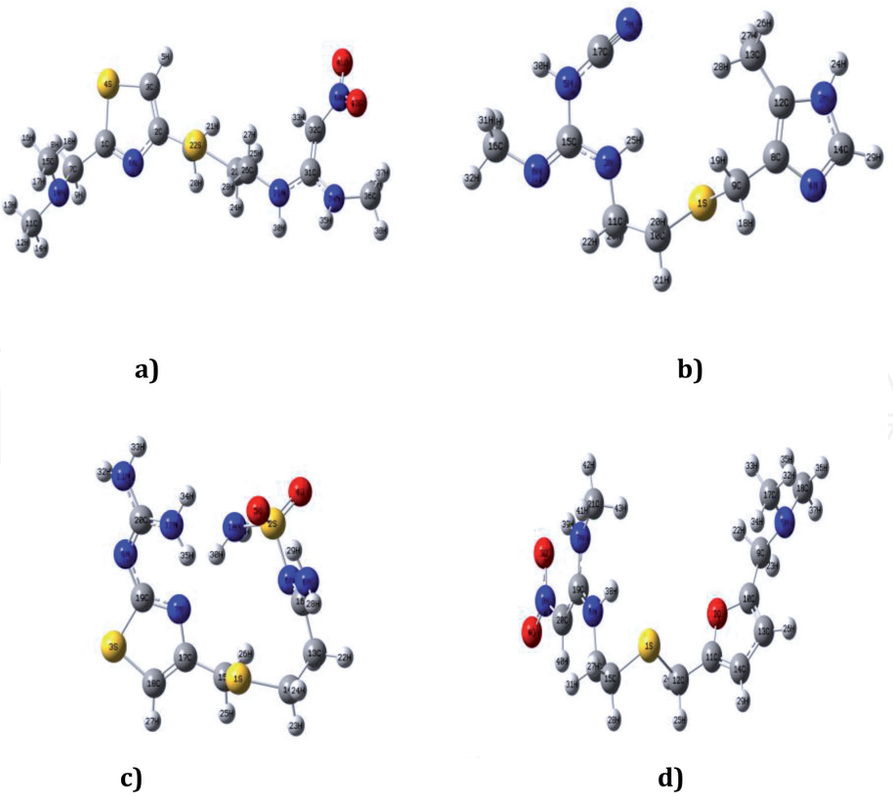


Figure 1.
Optimized molecular structures of Histamine H2 receptor antagonist using the B3LYP/6-31 + G (d) basis set. (a) nizatidine, (b) cimetidine, (c) famotidine and (d) ranitidine.

3.2 Vibrational analysis

Infrared (IR) spectroscopy refers the analysis of interaction of infrared radiation with a molecule. IR spectra of nizatidine obtained from DFT method using B3LYP/6-31 + G(d) level of theory (in **Figure 2(a)**) is compared with the experimental IR spectra (in **Figure 2(b)**) and their assignments were tabulated in **Table 1**.

From the comparison of IR spectra of nizatidine it is clear that, the computed vibrational results were in good agreement with the experimental spectra. IR spectra of cimetidine, famotidine and ranitidine are also generated using DFT method using B3LYP/6-31 + G(d) level of theory and shown in **Figures 3–5.**

The vibration at 3109 cm^{-1} shows the presence of N-H bond. The C-H band is present at 1741 for bending mode of vibration. The vibration band around 1435 and 1462 cm^{-1} are due to C-H scissor vibration. The bands due to C-N stretching are appeared at 1300 and 1255 cm^{-1}. The band due to C-C skeleton vibration are appeared at 544 and 508 cm^{-1}.

The band due to asymmetric NH_2 stretching vibration appears at 3336 cm^{-1} in the vibrational spectra of famotidine. The vibration band around 1696 and 1664 cm^{-1} are due to C=N stretching. The vibration at 1088 cm^{-1} shows the presence of C-N bond. The N-H band is present at 832 cm^{-1} for out of plain bending mode of vibration.

Spectral analysis of ranitidine shows a vibration at 3442 cm^{-1} and it is due to the presence of N-H bond. The C=C band is present at 1660 and 1588 cm^{-1} for stretching mode of vibration. The band due to NO_2 stretching is appeared at 1390 cm^{-1}. The vibration band around 1264 and 1174 cm^{-1} are due to C-N stretching.

3.3 Thermo-chemical properties

The reaction parameters of the four Histamine H2-receptor antagonists were calculated and tabulated below in **Table 2**.

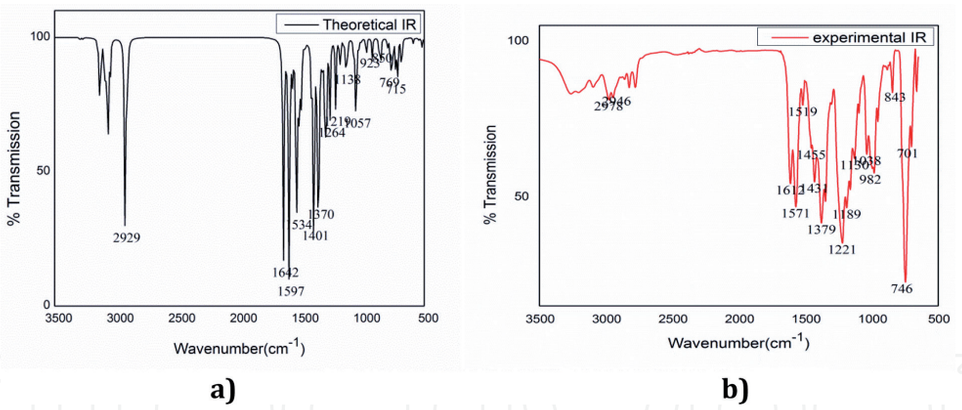


Figure 2.
Theoretical (DFT generated) IR spectra (a); experimental IR spectra (b) of nizatidine.

Experimental IR	DFT IR	Assignments
2978	2929	Asymmetric C-H stretching vibration
2946		
1612	1642	C-H vibration (overtone)
1571	1597	C=C stretching vibration
1519	1534	
1455	1401	Asymmetric C-H deformation vibration
1431		
1379	1370	Symmetric C-H deformation vibration
1221	1264	C-N stretching vibrations
1189	1219	
1130	1138	C-H sym. Deformation vibration
1038	1057	C-N stretching vibration
982	923	
843	850	C-H out-of-plane deformation vibration
746	769	C-C skeleton vibration (rocking)
701	715	CH3-metal groups due to CH2 rocking vibration

Table 1.
Vibrational analysis of nizatidine by experimental and theoretical obtained from DFT method using B3LYP/6-31 + G(d) level of theory.

By calculating reaction parameters of histamine H2 receptor antagonist it was found that famotidine is having high free energy, zero-point energy, enthalpy and low entropy. If the Gibbs free energy is higher the solubility will be higher i.e. famotidine having higher solubility. Nizatidine exhibits higher entropy value with less energy indicating that it has higher degree of freedom to be active. Cimetidine is less potent and having low solubility. If nizatidine get a small perturbation in terms of thermal energy it will be in full mode to be active for its specified task.

3.4 Frontier molecular orbital analysis

Both the energies of HOMO (Highest Occupied Molecular Orbitals) and LUMO (Lowest Unoccupied Molecular Orbitals) are identified. The chemical reactivity of

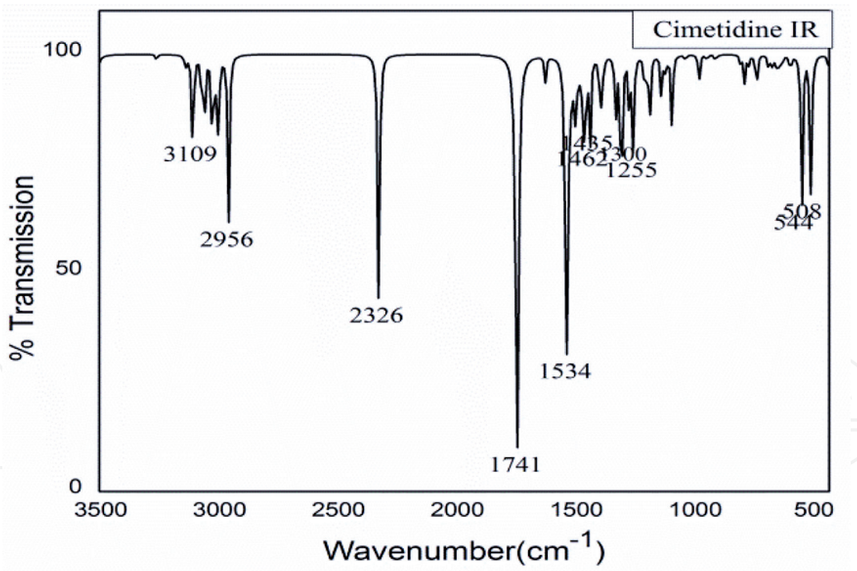


Figure 3.
Theoretical IR spectra of cimetidine using DFT/B3LYP/6-31 + G(d) level of theory.

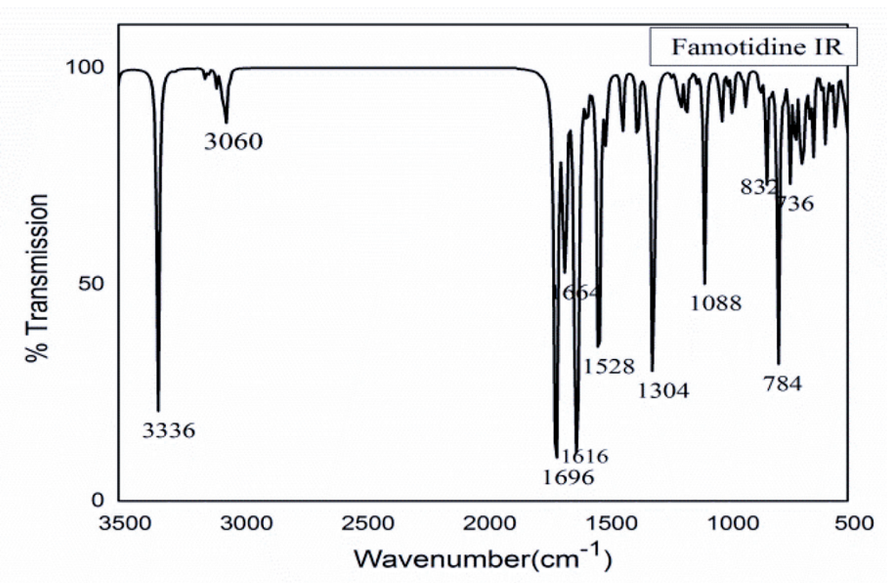


Figure 4.
Theoretical IR spectra of famotidine DFT/B3LYP/6-31 + G(d) level of theory.

a particular molecule can be determined from their energy gap and eigen values. In addition to being called the frontier orbitals, both HOMO and LUMO are identified to be effectively included within the study regarding charge transfer complex formation reactions [13]. HOMO is identified to represent the ability to be an electron donor through giving an electron, while LUMO, on the other hand, and focuses on the method of gaining electron through being an electron acceptor [14]. The wave function is identified to describe the process of electron absorption as the transition from the ground state to the next excited state. This process is further understood as the excitation of one electron from the highest occupied molecular orbital to the lowest level of an unoccupied molecular orbital. The element of energy gap within both HOMO and LUMO is identified as the parameter describing molecular transport properties [15]. The aspect of electron conductivity also can be understood through the measure of HOMO – LUMO gap along with molecular stability with a large gap denoting higher stability. Hence, the molecular orbitals of all four selected H2 blockers were generated and visualized using DFT, and these molecular orbitals

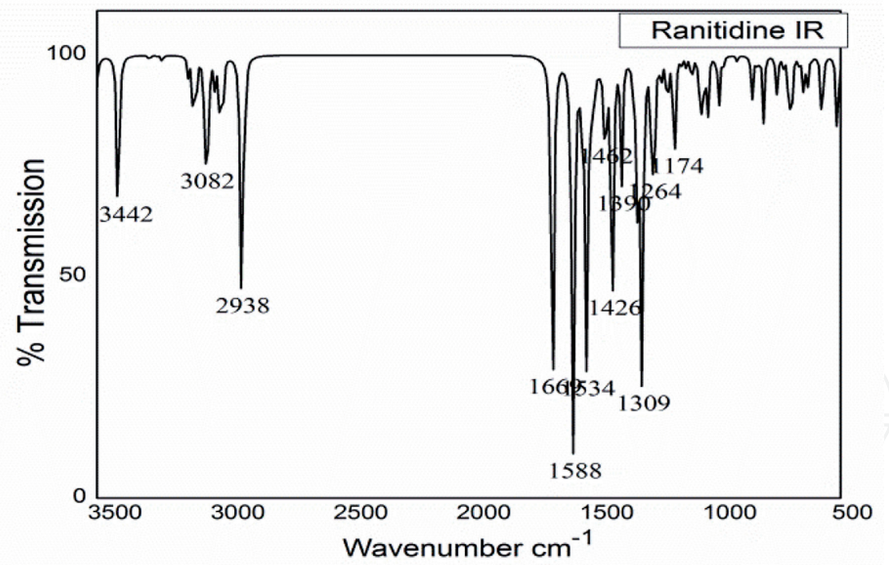


Figure 5.
Theoretical IR spectra of ranitidine DFT/B3LYP/6-31 + G(d) level of theory.

Sample	Molecular Mass (amu)	Zero point Energy (10^9 kJ/mol)	Enthalpy (10^9 kJ/mol)	Entropy (Cal/mol)	Gibbs Free Energy (10^9 kJ/mol)
Nizatidine	331.114	−4.43	−4.43	177.061	−4.43
Cimetidine	252.116	−2.93	−2.93	151.938	−2.93
Famotidine	337.045	−5.36	−5.36	153.901	−5.36
Ranitidine	314.141	−3.54	−3.54	172.629	−3.54

Table 2.
The reaction parameters of Histamine H2 receptor antagonist.

were shown in **Figure 6** (the positive phase is represented in red and the negative one in green).

The possible transitions exhibited by nizatidine and famotidine is π to $\pi*$ transition while cimetidine showed π to π transition and ranitidine exhibited a $\pi*$ to π transition. The least energy required must be for π to $\pi*$ transition and this may be the reason for high reactivity of nizatidine.

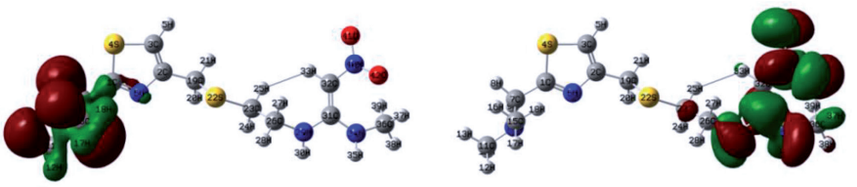
The HOMO, LUMO energies of the selected samples were calculated and tabulated below in **Table 3**.

The difference between HOMO and LUMO energy levels directly gives the band gap or energy gap of the compound. The higher the energy gap lower will be the reactivity of the molecule. Comparing the orbital energy parameters of histamine H2 receptor antagonist, nizatidine is found to be having lower energy gap, which shows that nizatidine is more chemically reactive than others. At the same time cimetidine has high energy gap indicating its less reactivity. So, we can infer that nizatidine is the most biologically active API while cimetidine is the least among the H2 blockers.

3.5 Global descriptive parameters

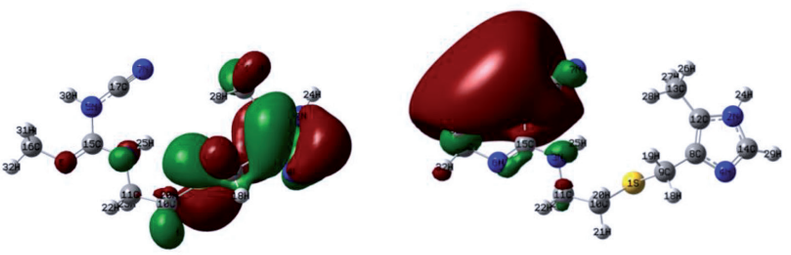
The global parameters are identified to have a larger role to play within the comparison of the behaviors of different compounds and their level of reactivity. A global descriptive parameter is identified to provide the description of the

1) Nizatidine



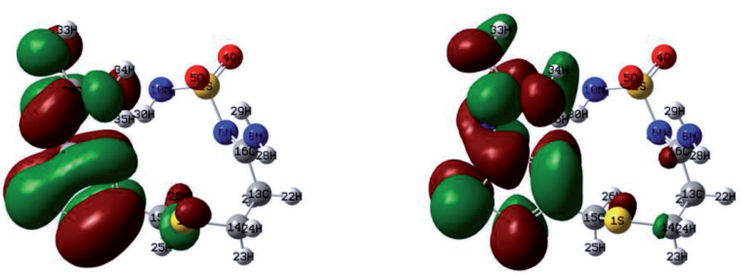
a. b.

2) Cimetidine



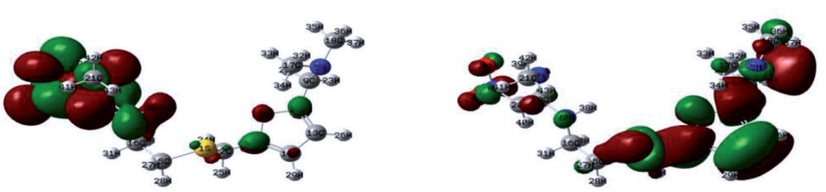
a. b.

3) Famotidine



a. b.

4) Ranitidine



a. b.

Figure 6.
Molecular orbitals of Histamine H2 receptor antagonist using the B3LYP/6-31 + G (d) basis set. (1) a. HOMO Energy =- 6.209 eV, b. LUMO Energy = - 1.650 eV; (2) a. HOMO Energy = -6.052 eV, b. LUMO Energy = -0.475 eV; (3) a. HOMO Energy =- 5.755 eV, b. LUMO Energy = - 0.957 eV; (4) a. HOMO Energy = -6.114 eV, b. LUMO Energy = -1.439 eV.

connection between the chemical reactivity of the molecule along with the range of sensitiveness exhibited to the various external conditions. Various aspects such as chemical potential, chemical hardness, electro negativity, electrophilicity, and

Sample	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)
Nizatidine	−6.209	−1.650	4.559
Cimetidine	−6.052	−0.475	5.577
Famotidine	−5.755	−0.957	4.798
Ranitidine	−6.114	−1.439	4.675

Table 3.
Orbital energy parameters of studied compounds using DFT/B3LYP/6-31 + G (d) level of theory.

softness are contained within the global descriptive parameters. These quantities correspond to the linear responses of the electron density with respect to the changes in the external potential and number of electrons [13]. The aspect of chemical hardness (η) can be understood as the resistance introduced by elements towards deformation or even polarization of the electron cloud of the element which is introduced through following chemical reactions conducted upon the same. Chemical softness (s), on the contrary to the chemical hardness, is identified to provide a measure of the capacity of the molecule for receiving electrons [14]. Through analyzing this case by considering the aspect of the HOMO – LUMO gap, a hard element is identified to have a larger HOMO – LUMO gap compared to a softer element. As the aspect of electro negativity (χ) describes the ability of the molecule for attracting electrons and reaching equalization much more quickly, it is identified to introduce low reactivity. The tendency for an electron to escape from an equilibrium state is referred to as chemical potential while the strength of electrophilies of elements is identified through electrophilicity indices.

Koopmans' theorem states that in closed-shell Hartree–Fock theory, the first ionization energy of a molecular system is equal to the negative of the orbital energy of the highest occupied molecular orbital (HOMO) i.e., Koopmans' theorem equates the energy of the HOMO with the negative of the ionization potential [19]. The global properties were calculated by using equations [12, 13, 20].

$$\text{Ionization potential}\left(\text{IP}\right) \approx -\text{E}_{\text{HOMO}} \tag{1}$$

$$\text{Electron affinity}\left(\text{EA}\right) \approx -\text{E}_{\text{LUMO}} \tag{2}$$

where E_{HOMO} is the energy of HOMO and E_{LUMO} is the energy of LUMO.

$$\text{Hardness}\left(\eta\right) \approx \frac{IP - EA}{2.} \tag{3}$$

$$\text{Electronegativity}\left(\chi\right) \approx \frac{IP + EA}{2} \tag{4}$$

$$\text{Softness}\left(\text{S}\right) \approx \frac{1}{2\eta} \tag{5}$$

$$\text{Chemical potential}\left(\mu\right) \approx -\chi \tag{6}$$

$$\text{Electrophilicity index}\left(\omega\right) \approx \frac{\mu^2}{2\eta} \tag{7}$$

The Global descriptive parameters of the four histamine H2 receptor antagonists were calculated and tabulated below in **Table 4**.

Sample	IP (Ionization potential)	EA (Electron affinity)	χ (Electronegativity)	μ (Chemical potential)	ω (Electrophilicity index)	η (Hardness)	S (Softness)
Nizatidine	6.209	1.65	3.929	−3.929	3.387	2.279	0.219
Cimetidine	6.052	0.475	3.264	−3.264	1.91	2.789	0.179
Famotidine	5.755	0.957	3.356	−3.356	2.348	2.399	0.208
Ranitidine	6.114	1.439	3.776	−3.776	3.051	2.338	0.214

Table 4.
Global descriptors of studied compounds using DFT/B3LYP/6-31 + G (d) level of theory.

Comparing the global descriptive parameters of histamine H2 receptor antagonist, nizatidine is found to be having higher softness, ionization potential, electron affinity, chemical potential and lower hardness, which shows that nizatidine is less stable and chemically more reactive. A higher value of electrophilicity index indicates its high biological activity. In case of stability reactivity and biological activity, ranitidine comes next to nizatidine and among them, cimetidine is more stable and having lower biological activity.

3.6 Molecular dynamics

The theoretical studies revealed that nizatidine is highly stable and biological active molecule among the four histamine H2 receptor antagonists. But the value of Gibbs free energy emphasis that the solubility of nizatidine is less. The possible solution to enhance the solubility and bioavailability of the pharmaceutical drug is amorphisation of its crystalline counterpart. We have already reported the molecular dynamics of nizatidine in its glassy and supercooled liquid state using broadband dielectric spectroscopy [21]. The dielectric measurements of nizatidine were performed from 123.15 K to 373.15 K by quench cooling the sample. However, the sample does not crystallize during cooling from the melting temperature. Then the measured dielectric loss spectra (i.e., imaginary part of dielectric permittivity ε" plotted as a function of frequency f) are shown **Figure** 7.

The dielectric measurements revealed that the sample nizatidine is a good glass former with glass transition temperature Tg around 282.09 K with steepness index 91 without showing any recrystalisation tendency during heating and cooling. The steepness index is the measure of the non-Arrhenius character of the temperature dependence of the α-relaxation times. In contrast to strong liquids (m = 16), fragile glass-forming materials (m = 200) show a fast change in its viscosity (relaxation time) as it approaches the glass transition temperature. The knowledge whether a glass former is strong or fragile seems to be essential in case of choosing the best temperature condition for storing an amorphous pharmaceutical where the structural relaxation

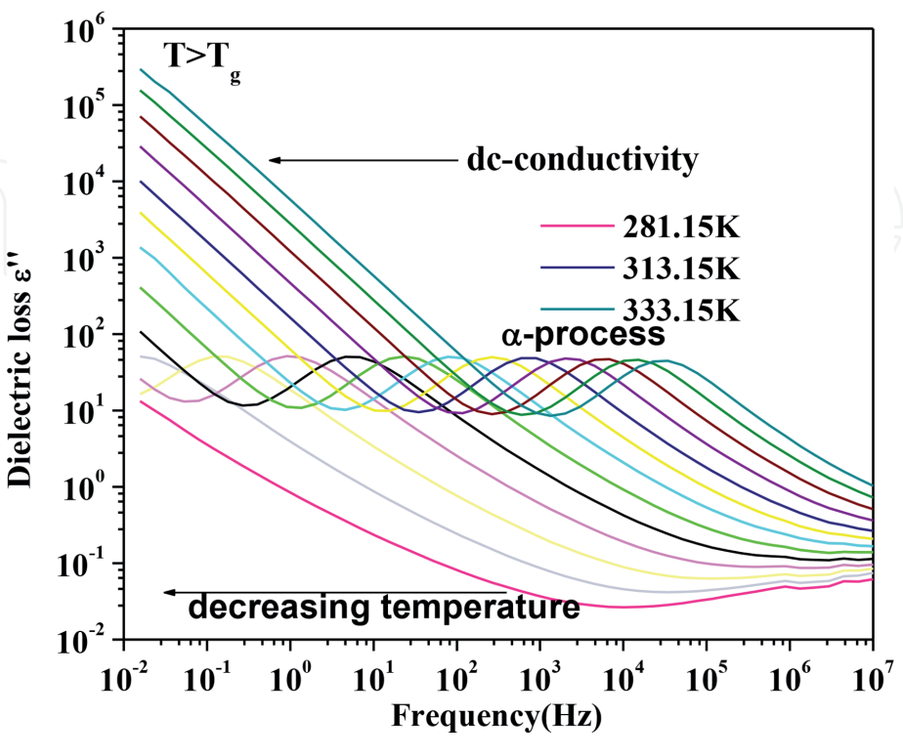


Figure 7.
Dielectric loss curves obtained for nizatidine in the supercooled liquid state [21].

is closely connected to crystallization process [22]. And it is found that nizatidine is stable over the measured temperature range up to 307.15 K. Of course, the dielectric studies is only giving an indication on the molecular mobility, for detailed information regarding the molecular mobility of nizatidine in glassy and supercooled liquid state refer paper published by Sailaja et al. [21].

4. Conclusions

Density functional theory calculation using DFT/B3LYP/6-31 + G (d) level of theory has been performed for four histamine H2 receptor antagonists, cimetidine, famotidine, nizatidine, and ranitidine with the help of Gaussian software. Vibrational analysis (IR) of four histamine H2 receptor antagonists has been generated by using DFT. Generated vibrational results of nizatidine were compared with the experimental result and the computed vibrational results found to be in good agreement with the experimental result. From thermochemical parameters of histamine H2 receptor antagonist, it was found that famotidine is having superior thermodynamics parameters among the four with high free energy, zero-point energy, enthalpy and low entropy. Comparing the global descriptive parameters of histamine H2 receptor antagonist, nizatidine is found to be having higher softness, ionization potential, electron affinity, chemical potential and lower hardness, which shows that it is more stable and chemically reactive. Higher value of electrophilicity index indicates its high biological activity. Nizatidine is found to be having lower energy gap, which shows that nizatidine is more chemically reactive. In case of stability, reactivity and biological activity ranitidine comes next to nizatidine and among them, cimetidine is less stable and having lower biological activity. At the same time, the Gibb's free energy revealed that the solubility of nizatidine is not sufficient to have adequate bioavailability. Finally, we could amorphousize nizatidine by quench cooling technique and found that it stable in amorphous state without showing any recrystallization tendency during super cooling and the subsequent heating in the metastable state. Nizatidine has a glass transition temperature around 282.1 K and was found to be stable over the measured temperature range up to 307 K.

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Conflict of interest

The authors declare no conflict of interest.

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Author details

Kodakkat Parambil Safna Hussan[1*], Indulekha Jayarajan Jithin Raj[2], Sailaja Urpayil[3,4] and Mohamed Shahin Thayyil[1]

1 Department of Physics, University of Calicut, Malappuram, India

2 Department of Physics, Kottakkal Farook Arts and Science College, Kottakkal, Kerala, India

3 Department of Physics, M E S Keveeyam College, Valanchery, Kerala, India

4 Department of Physics, MES Ponnani College, Ponnani, Malappuram, Kerala, India

*Address all correspondence to: safnahussain2@gmail.com

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