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Modeling and interactions analysis of the novel antagonist agent flibanserin with 5-hydroxytryptamine 2A (5-HT_{2A}) serotonin receptor as a HSDD treatment in premenopausal women

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Abstract

Flibanserin is a novel antagonist small molecule to treat the hypoactive sexual desire disorder (HSDD) in the premenopausal women. The present article is related to the structural and electronic properties and docking analysis of the title compound with 5-hydroxytryptamine 2A (5-HT_{2A}) serotonin receptor. To access these aims, the molecular structure of the compound was optimized using density functional theory (DFT) computational method (B3LYP) with 6-31+G(d,p) basis set at room temperature. Accordingly, the frontier molecular orbitals (FMOs) theory was used to investigate the stability and reactivity of flibanserin. The mentioned studies showed that the molecule under investigation is a compound with high stability. The docking analysis was used to understand the nature of receptor-ligand interactions. Our study indicated that the steric interactions play the main role in ligand-receptor complex formation.

Keywords: Flibanserin; HSDD; molecular docking; molecular simulation; premenopausal women.

Introduction

The sexual dysfunction in premenopausal women due to an absence or lack of sexual fantasies and desire for sexual activity is called inhibited sexual desire (ISD) or hypoactive sexual desire disorder (HSDD). The premenopausal women with this dysfunction can't respond to their partner's desire for sexual activity. The hypoactive sexual desire disorder is classified as general and situational dysfunctions. The general HSDD is called to general lack of sexual desire, while in the situational HSDD; women still have sexual desire but lack sexual desire for their current partner. This dysfunction will be shown in two types: the acquired form and or lifelong. In the acquired type, ISD start after a normal sexual functioning period. On the other hand, a woman has always no or low sexual desire in the lifelong type [1-3].

To treat this dysfunction (HSDD) in women, the flibanserin medicine is used. Flibanserin is sold under the trade name addyi. This drug is not used in men or children. Addyi is a FDA (U.S. food and drug administration) approved medicine for treatment of this disorder.

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The flibanserin effectiveness was evaluated in three phase 3 clinical trials. All these clinical trials indicated that the said medicine produced the satisfying sexual events (SSEs) number increasing and distress decreasing related to the sexual desire. This novel chemical compound is an antagonist for 5-hydroxytryptamine 2A (5-HT_{2A}) serotonin receptor. The mammalian 5-HT_{2A} serotonin receptor is a G protein coupled receptor (GPCR). This receptor is expressed widely throughout the central nervous system (CNS) and also near most of the serotoninergic terminal rich areas including the olfactory tubercle and the neocortex (mainly parietal, prefrontal, and somatosensory cortex). These receptors are coded by the HTR2A gene on chromosome 13 in humans [2-5]. The title receptors can be imaged with positron emission tomography (PET) scanners using fluorine-18 radiopharmaceuticals.

From literature survey, it was found that the electronic properties identification of the flibanserin molecular structure has been carried out previously in the light of theoretical chemistry [5-7] and hence the study was undertaken. The main goal of the present study is to give a comprehensive description of the electronic properties of the novel compound flibanserin as an antagonist for 5-hydroxytryptamine 2A (5-HT_{2A}) serotonin receptor in premenopausal women with HSDD by quantum-mechanical (QM) and molecular docking methods. It is believed that the outputs of this investigation will provide a deep and accurate understanding of the possible biological activities of the medicine under study.

Computational methods

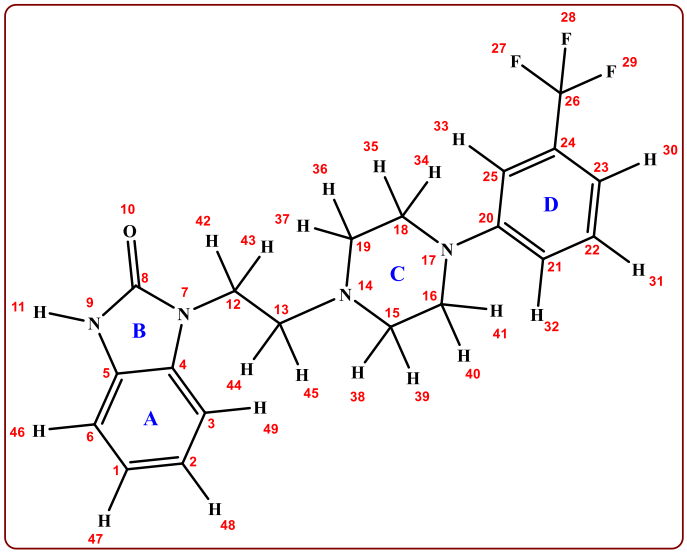
In the present study, the molecular structure of the novel antagonist compound flibanserin was drawn using ChemBioDraw Ultra 13.0 and GaussView 6.0 softwares. Subsequently, all molecular modeling and quantum chemical calculations were carried out using Gaussian 03 software package. Firstly, the molecular structure of the title compound was optimized by density functional theory (DFT) method with B3LYP exchange functional and 6-31+G(d,p) level of theory at room temperature in gas phase. The frequency vibrational calculations didn't show any imaginary frequency for this molecular structure. This indicates our computations have been performed in ground state of the molecule under study. In continues, the molecular electrostatic potential (MEP) graph and the frontier molecular orbitals (FMOs) calculations were used to study the electronic properties of flibanserin molecular structure. Finally, the interactions between flibanserin molecule and 5-hydroxytryptamine 2A (5-HT_{2A}) serotonin receptor were analyzed and studied using Molegro Virtual Docker (MVD) software. After ligand-protein docking process, the graphs of the hydrogen bond (HB) and steric interactions between the said medicine and 5-HT_{2A} receptor were analyzed using Molegro Molecular Viewer (MMV) software.

Results and discussion

Flibanserin structural properties study

Flibanserin with IUPAC name 1-(2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one is sold under the trade name addyi in the universal markets. Scheme 1 indicates its molecular structure. As can be seen from the Scheme 1, flibanserin molecule has been constructed from four saturated and unsaturated rings. Due to the various rings and elements, it is expected that we observe different electron distribution on the various

segments on the molecular structure of flibanserin. To access this important structural property, optimization of the title molecular structure is necessary. So, the molecular structure of flibanserin was optimized using DFT method by B3LYP/6-31+G(d,p) level of theory. Figure 1 shows the optimized molecular structure of this small molecule. As can be shown in Figure 1, the A and D rings are planar and aromatic. On the other hand, the ring B is planar due to the participating of nonbonding electrons of nitrogen-7 and nitrogen-9 elements in resonance with carbonyl functional group and phenyl ring (A). The N7-C8 and N9-C8 bond lengths are 1.397° A and 1.391 Å, respectively. While the N14-N19 bond length is 1.461 Å. So, we can see that the N7-C8 and N9-C8 bond lengths are shorter than the N14-N19 bond due to the resonance formation. Figure 2 indicates the dependence between the theoretical and experimental bond lengths of the title molecular structure. This dependence is shown by the equation y=0.9409x+0.0702. The higher correlation coefficient (R^2=0.9902) for this equation shows a great convergence. So, the B3LYP/6-31+G(d,p) basis set of theory is a good method to compute the electronic properties of the molecule under study.



Scheme 1. Flibanserin molecular structure

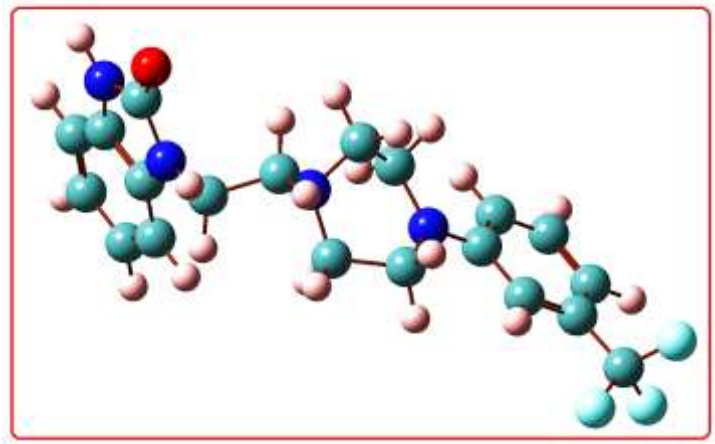


Figure 1. The theoretical geometric structure of flibanserin

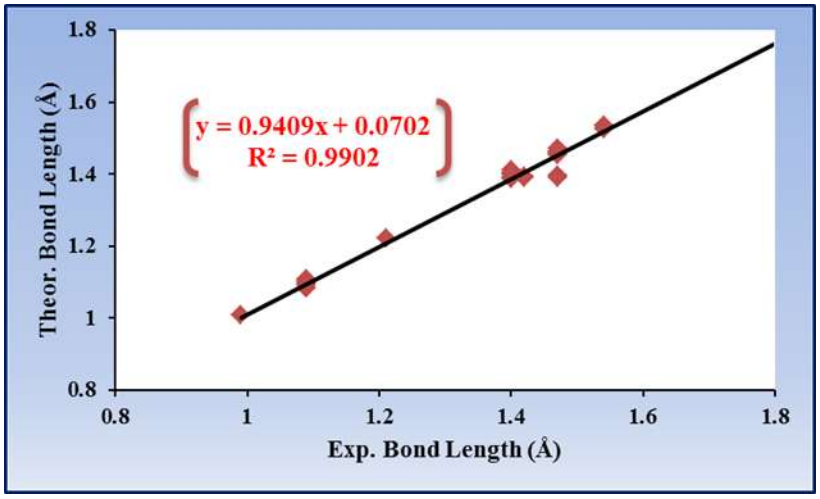


Figure 2. The experimental and theoretical bond lengths relationship of flibanserin

Stability and reactivity study of the compound flibanserin

The frontier molecular orbitals (FMOs) of a molecule contain the highest-energy occupied molecular orbital (HOMO) and the lowest-energy unoccupied molecular orbital (LUMO). The HOMO is generally described as electron donating or nucleophilic, while the LUMO is logically viewed as electron accepting or electrophilic. Due to this, all chemical reactions can be explained by HOMO/LUMO interactions. In organic chemistry, this theory is used to understand the structural and electronic properties, stability and reactivity of a compound [8-10]. Figure 3 shows the frontier molecular orbitals (HOMO and LUMO) of the molecule under study (flibanserin). These graphs indicate that the LUMO is constructed by the orbitals of the elements of the D ring, while the HOMO has been made by the atoms of the C and D rings. So, it can be concluded that the atoms of the ring D mainly participate in HOMO/LUMO interactions. The most important application of the FMO theory is predicting the reactivity nature of a molecule [11]. From this point of view, the stability and global reactivity indices of an organic molecule can be computed using the FMO theory [12]. The global reactivity descriptors like energy gap (Eg), ionization potential (IP), electron affinity (EA), chemical hardness (η), chemical softness (S), electronegativity (χ), electronic chemical potential (μ) and electrophilicity index (ω) can be obtained from the energies of the frontier orbitals. These reactivity indices are achieved by following formulas [13]:

$$\boldsymbol{E_g = E_{LUMO} - E_{HOMO}}$$

$$\boldsymbol{IP = -E_{HOMO}}$$

$$\boldsymbol{EA = -E_{LUMO}}$$

$$\eta = \frac{(\boldsymbol{\varepsilon_{LUMO} - \varepsilon_{HOMO}})}{\mathbf{2}}$$

$$\boldsymbol{\chi} = \frac{-(\boldsymbol{\varepsilon_{LUMO} + \varepsilon_{HOMO}})}{\mathbf{2}}$$

$$\mu = \frac{(\boldsymbol{\varepsilon_{LUMO} + \varepsilon_{HOMO}})}{\mathbf{2}}$$

$$\boldsymbol{\omega} = \frac{\mu^2}{2\eta}$$

$$\boldsymbol{S} = \frac{\mathbf{1}}{\eta}$$

The energies of the frontier molecular orbitals and the global reactivity indices of the title compound have been listed in Table 1. As can be seen from the data, the energies of HOMO and LUMO are -5.376 eV and -

0.437 eV, respectively. The electron transition energy between the frontier molecular orbitals can be used to describe the molecular stability. From the data of the Table 1, the energies gap (Eg) of the said orbitals is 4.939 eV. This big energy gap indicates the high stability of the molecular structure of the antagonist flibanserin. On the other hand, this high stability of the said compound can be viewed by the high amount of ionization potential (5.376 eV) and the low amounts of electron affinity (0.437 eV). These indices show that the molecule doesn't like to lose easily its electrons or easily accept electron from other reagents. So, this molecule is really stable under biological conditions of cells. Also, the low amount of chemical hardness (2.469 eV) and high amount of the chemical softness (0.405 eV) indicate the high tendency of the said compound to interact with residues of the proteins like receptors by steric interactions. This compound won't react with nucleophile reagents into the cell due to its low amount of electrophilicity index. The density of states (DOS) graph of the title compound can be viewed in Figure 4. This graph shows that the density of the virtual orbitals and the occupied orbitals are almost equal together. So, the possibility of any ligand-receptor interaction only relates to the strength of electron-accepting and or electron-donating properties of the residues of the receptor. The molecular electrostatic potential (MEP) graph of flibanserin is shown in Figure 5. In this graph, the regions with blue, green and red colors are related to the molecular segments with positive, zero and negative electrostatic potentials, respectively. The Figure 5 shows that the ring B has negative potential. In contrast, the electrostatic potential of A and D rings are zero. On the other hand, ring C has positive electrostatic potential. So, it can be concluded that the B and C rings may play main role in receptor-ligand interactions by steric interactions.

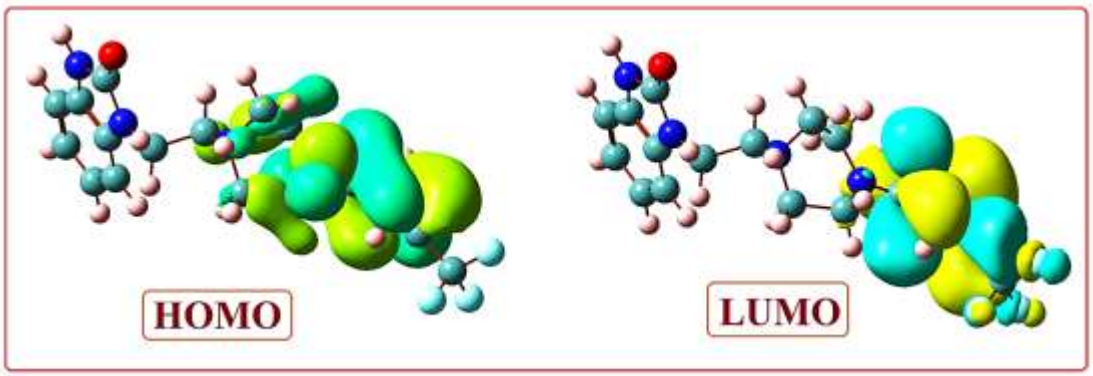


Figure 3. The frontier molecular orbitals of flibanserin

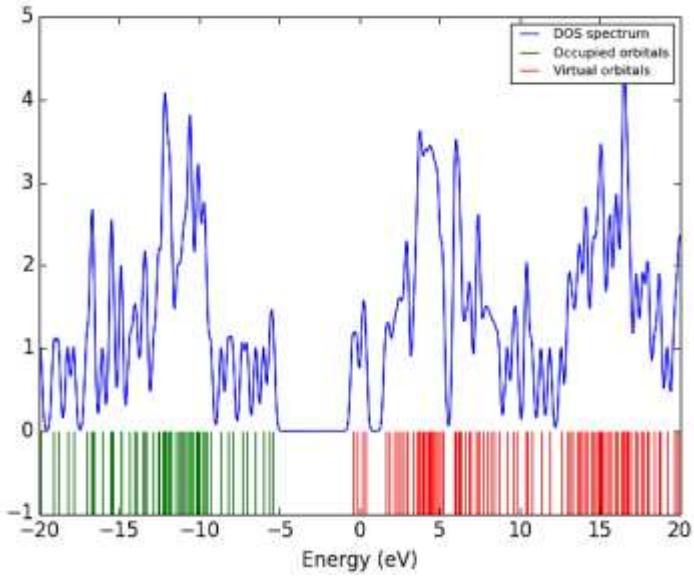


Figure 4. The density of states (DOS) graph of flibanserin

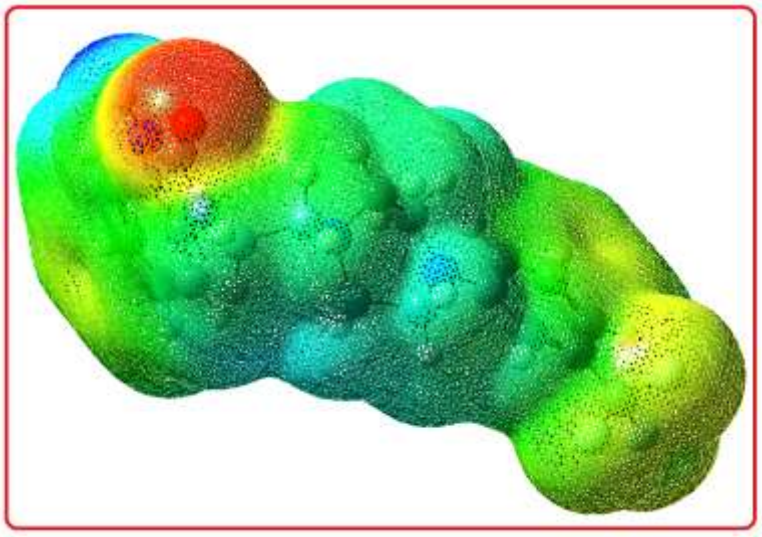


Figure 5. The molecular electrostatic potential (MEP) graph of flibanserin

Table 1. Global reactivity indices of flibanserin

Parameter	Energy value (eV)
HOMO	-5.376
LUMO	-0.437
Ionization Potential (IP)	5.376
Electron Affinity (EA)	0.437
Energy Gap (Eg)	4.939
Electronegativity (χ)	2.907
Chemical Potential (μ)	-2.907
Chemical Hardness (η)	2.469
Chemical Softness (S)	0.405
Electrophilicity index (ω)	1.711

Charge distribution and molecular docking

The Mulliken charge distribution on atoms of the antagonist compound flibanserin is shown in Figure 6. The hydrogen-11 element shows more positive charge than other hydrogen atoms. It is due to its connecting to the electronegative atom nitrogen-11. So, it can be deduced that the hydrogen-11 atom has acidity property. On the other hand, the atoms with positive charges (C4, C5, C8, C20 and C26) can play electron-accepting role in the steric interactions between flibanserin and 5-HT_{2A} receptor. In contrast, the atoms N7, N9, O10, N14, N17, F27, F28 and F29 can play the aelectron-donating role in these interactions. Figure 7 indicates the two-dimensional electron localization graph of flibanserin. This graph shows electron current on all rings of the molecular structure. So, all rings can be participated by steric interactions. The most important point of this graph is high density of electron current on the phenyl rings (A and D). These rings indicate more tendencies to electronic interactions with the residues of the said receptor.

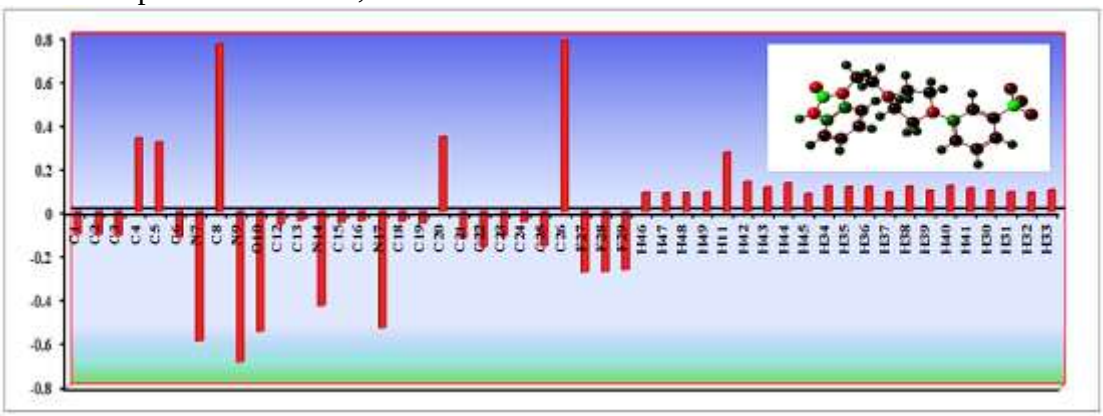


Figure 6. The charge distribution of flibanserin

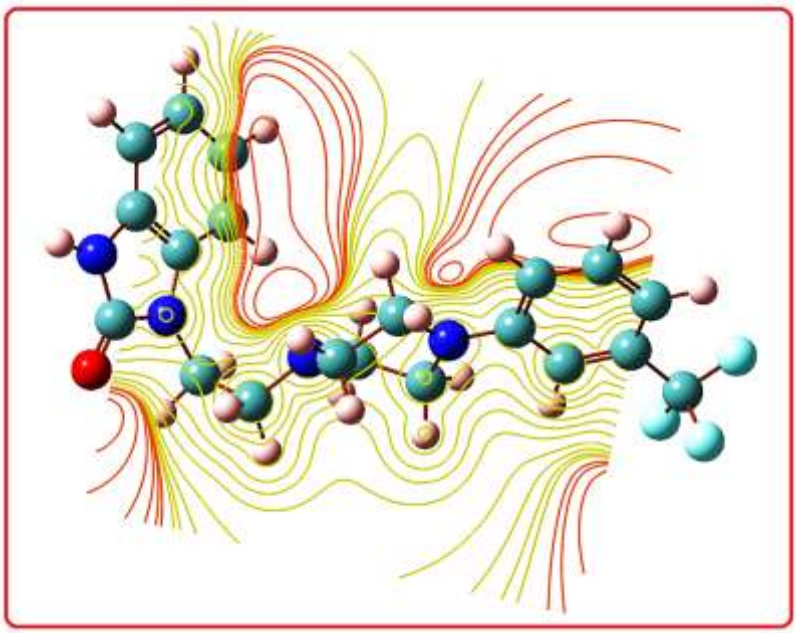


Figure 7. The two-dimensional electron localization graph of flibanserin

Literature review clearly shows that the antagonist compound flibanserin can be used as a treatment for hypoactive sexual desire disorder (HSDD) [14]. The studies indicate that this molecular structure can make complex with 5-HT_{2A} receptor. The docking process was done to clear the interactions of flibanserin-5HT_{2A} complex. The said docking analysis was carried out using Molegro Virtual Docker (MVD) program. Figure 8 shows the second structure, pose state and docking surface of the ligand-receptor interaction. The second structure indicates the folding of receptor residues after making ligand-receptor complex. The pose state shows the residues that they have been interacted with the title compound. Finally, the docking surface graph indicates embedding flibanserin in the active site of the 5-HT_{2A} receptor. Figure 9 shows the hydrophobic areas of the receptor residues in receptor-ligand complex. The intensity order of hydrophobicity in graph is red areas > purple areas > blue areas. Table 2 has been collected the ligand-receptor interactions. The molecule flibanserin make complex with 5-HT_{2A} receptor by steric and H-bond interactions. From the data of the Table 2, the steric interactions play main role in ligand-receptor complex formation. The Moldock scores for steric, H-bond and water-ligand interactions are -148, -4 and -2, respectively. It can be seen from the data of the Table 3 that the residues Leu 329, Phe 331, Gly 328, Lys 327, Leu 391, Lys 392, Gly 330, Gly 357 and Ile 333 are important amino acids in formation of flibanserin-receptor complex. Figure 10 indicates H-bond interactions of antagonist compound flibanserin embedded in the active site of 5-HT_{2A} receptor. The title graphs show that the residues Gly 330 and Leu 329 participate in hydrogen bond formation between ligand and receptor. It can be seen from the Figure 11 that the residues Ile 333, Lys 392, Leu 371, Leu 329, Leu 391, Phe 331, Lys 324, Ser 332, Gly 330, Glu 355, Gly 325, Ile 354, Gly 357, Pro 326, Ala 358, Lys 327, Gly 356 and Gly 328 from the 5-HT_{2A} receptor make steric bonds with the compound flibanserin.

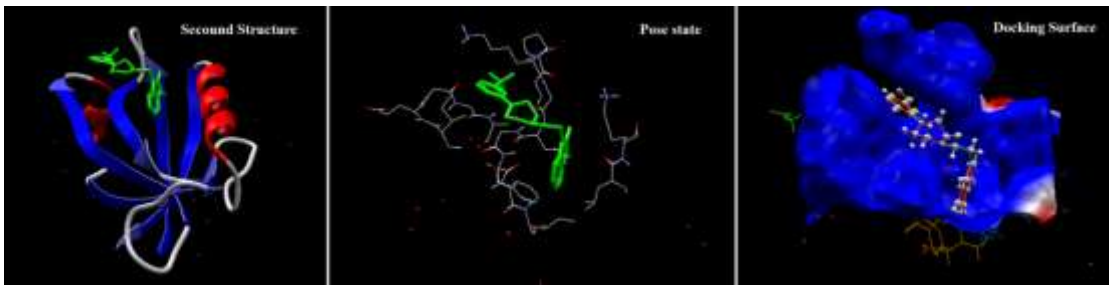


Figure 8. Ligand flibanserin embedded in the active site of the receptor

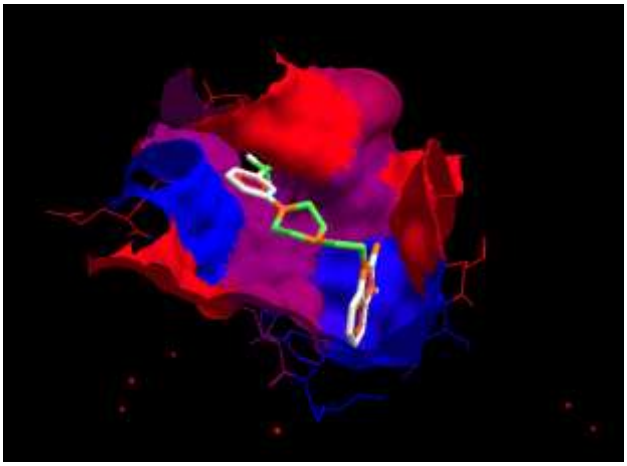


Figure 9. Analysis of hydrophobicity of receptor residues in receptor-ligand complex

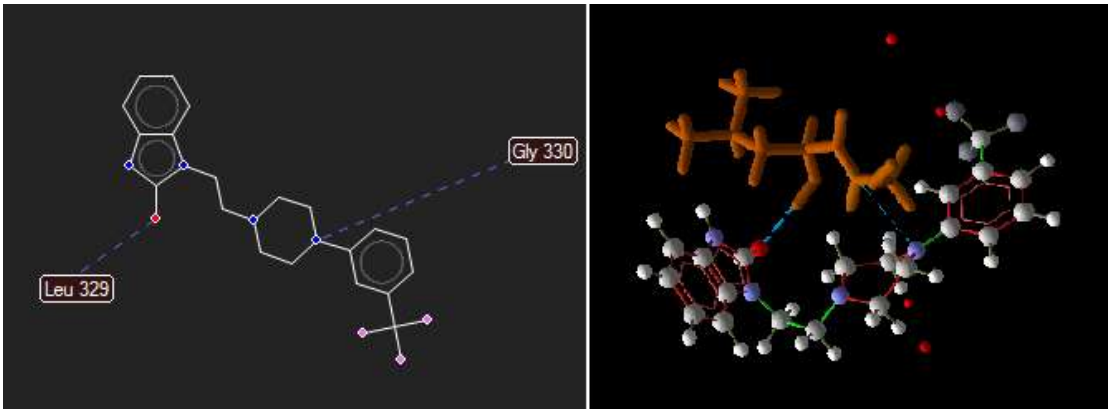


Figure 10. H-bond interactions of ligand flibanserin embedded in the active site of receptor

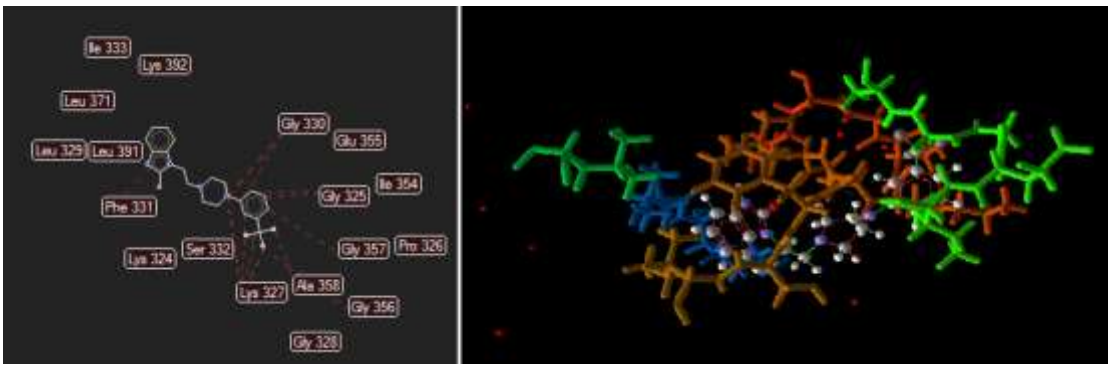


Figure 11. Steric interactions of ligand flibanserin embedded in the active site of receptor

Table 2. The ligand-receptor interactions

Interactions		MolDock Score
Protein-Ligand Interactions	Steric (by PLP)	-148.348
	Steric (by LJ12-6)	-1.367
	Hydrogen bonds	-3.323
	Hydrogen bonds (no directionality)	-4.833
Water-Ligand Interactions		-2.273
Internal Ligand Interactions	Torsional strain	1.588
	Steric (by PLP)	15.728
	Steric (by LJ12-6)	87.624

Table 3. The participated residues of 5-HT_{2A} receptor in ligand-receptor interactions

Residue/HOH	Total energy score
Leu 329	-23.054
Phe 331	-22.298
Gly 328	-16.352
Lys 327	-14.209
Leu 391	-12.019
Lys 392	-9.284
Gly 330	-9.275
Gly 357	-8.357
Ile 333	-6.952
Ser 332	-5.860
Pro 326	-5.390
Gly 325	-5.008
Gly 356	-4.583
Ile 354	-4.122
Water HOH 13	-1.368
Glu 355	-1.365
Water HOH 9	-0.905
Ala 358	-0.900
Leu 371	-0.327
Lys 324	-0.301

Conclusion

The present study is an investigation on the electronic and structural properties of the novel antagonist compound flibanserin. In the first step, the molecular structure of flibanserin was optimized using density functional theory (DFT) by Gaussian 03 software. The molecular structure optimization was performed by B3LYP/6-31+G(d,p) level of theory at room temperature. Then, the global reactivity descriptors were computed to understand the stability and reactivity of the title compound. The high HOMO/LUMO energy gap showed the high stability of the molecular structure of the antagonist flibanserin. From the reactivity indices data, the B and C rings may play main role in receptor-ligand interactions by steric interactions. In final step, the docking analysis was carried out due to understanding the nature of receptor-ligand interactions. The computational data indicated that the ligand-receptor complex formation is done using steric and H-bond interactions.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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