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Physicochemical properties analysis and dopamine D2 receptor (D2R) docking of zotepine as an atypical antipsychotic antagonist

Mehdi Nabati* and Vida Bodaghi-Namileh

Synthesis and Molecular Simulation Laboratory, Chemistry Department, Pars Isotope Company, P.O. Box: 1437663181, Tehran, Iran

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ABSTRACT

The main purpose of the present investigation is the study of therapeutically effect of Zotepine in schizophrenia disease treatment. In first step, the molecular structure of the said compound is optimized using density functional theory (DFT) technique by B3LYP functional method at 6-311++G(d,p) level of theory. Then the electronic properties of the title molecule are calculated using frontier molecular orbitals (FMOs) theory. The global reactivity indices show the molecule has high stability and can react with both nucleophiles and electrophiles. In overall, Zotepine shows low reactivity against the biomolecules. Finally, the molecular docking studies indicate the Zotepine-D2R complex formation is mainly carried out by the residues Phe 437, His 442, Ser 433, Phe 433 and Leu 441 using steric interactions.

Keywords: Dopamine receptor; Molecular docking; Molecular simulation; Schizophrenia; Zotepine

INTRODUCTION

Schizophrenia is a chronic, critical condition characterized by collective psychotic signs and symptoms, exhibited as alterations in patient's thoughts, perception and behavioral attributes [1]. Schizophrenia is mostly accompanied by symptoms that are generally categorized into two major groups: 1: Positive symptoms including hallucinations (auditory, visual, olfactory, gustatory and tactile), delusions, trouble concentrating and movement disorders and 2: negative symptoms such as lack of pleasure blunting of affect, apathy, loss of motivation and anhedonia [2, 3]. The previous studies demonstrated the prevalence of this disorder to be relatively low with a social and clinical recovery rate of only 13.5% [4,5]. Furthermore, life expectancy in schizophrenic patients is about 15–20 years shorter than a normal person and mortality rate is 2–12 times higher than general population [6]. In addition, schizophrenia is associated with several comorbidities which could result in higher rates of mortality in patients. More observed are chronic diseases including type II diabetes [7], coronary heart disease [8], some cancers [9] and neurological conditions such as major depressive disorder [10], dementia [11] and obsessive compulsive disorder [12]. As a result, schizophrenia is considered a major financial burden on society, health systems and families [13]. The mechanism contributing to cognitive deficits witnessed

*Corresponding author: mnabati@ymail.com

in schizophrenia is multifactorial and could include environmental exposures, genetics and several medications. Schizophrenia is prominently associated with alterations of brain dynamics [14] and the dopamine's role in etiology of this condition has been specifically evaluated [15-17]. Dopamine is an important endogenous chemical belonging to catecholamine family and acts as a neurotransmitter in neuronal tissues. Dopamine is responsible for many regulatory processes relating to CNS function and any disruption in its activity could result in various disorders in CNS namely, schizophrenia. Dopamine exerts its effects by binding to D1 or D2 receptors [18] which belong to G protein-coupled receptor (GPCR) family. These receptors are of great importance in dopamine homeostasis and in diseases associated with dopamine dysregulation [19]. Therefore, the utilization of antipsychotics that target and antagonize D2 receptors in order to manage schizophrenia has been extensively studied [20]. Zotepine is an atypical antipsychotic and D2 receptor antagonist indicated in treatment of schizophrenia. Zotepine is shown to induce dopaminergic neurotransmission at low doses while at higher doses it possesses antagonistic effects on dopamine receptors. Zotepine is determined to ameliorate both negative and positive symptoms of schizophrenia and has a low tendency to induce extrapyramidal side effects [21, 22]. A survey through previous studies has demonstrated that while the efficacy and safety of Zotepine as an atypical antipsychotic and D2 receptor antagonist in treatment of schizophrenia has been thoroughly evaluated, the exact structural and molecular interactions between Zotepine and D2 receptor is yet to be analyzed. The focus of this study was to comprehensively investigate the formation of dug-receptor complex and the molecular mechanism contributing to their interactions. For this purpose, molecular docking methods and computational chemistry were utilized. Furthermore, the prediction of pharmacokinetic attributes and biological behavior of Zotepine was examined using SwissADME web tool.

COMPUTATIONAL METHODS

Molecular simulation technique uses powerful computational methods to simulate the molecular structure of the chemical compounds [23]. It can also simulate the interactions between elements to understand the properties of the compounds [24]. The computational methods are classified in two main groups: quantum mechanics (QM) and molecular dynamics (MD) [25]. The quantum mechanical computations are mainly used for small molecules [26]. So, the Zotepine molecular structure will be optimized by density functional theory (DFT) method using B3LYP functional method and 6-311++G(d,p) level of theory in isolated form at room temperature. The stability and reactivity properties of the said active chemical substance are gained using frontier molecular orbitals (FMOs) calculations. Zotepine binding to the dopamine D2 receptor (D2R) is analyzed and studied by Molegro Virtual Docker (MVD) program.

RESULTS AND DISCUSSION

Zotepine structural properties study

2-((8-chlorodibenzo[*b*,*f*]thiepin-10-yl)oxy) -*N*,*N*-dimethylethan-1-amine is called Zotepine in the market. Its molecular structure is shown in Figure 1. Zotepine is a dibenzothiepine and a tertiary amino chemical molecule. For first time, it was designed and prepared by Fujisawa pharmaceutical Company [27]. The optimized molecular structure of Zotepine shows three rings aren't on the plane. So, their pi electrons can't be participated on the same ring current. On the other hand,

the rings and the atoms have no angular pressure. Figure 2 indicates the dependence between the theoretical and experimental bond lengths of the medicinal compound Zotepine. This dependence is shown by the equation y=1.029x-0.0646. The higher correlation coefficient (R^2=0.9107) for this equation indicates a great convergence. So, the B3LYP/6-311++G(d,p) basis set of theory is a good method to compute the electronic properties of the chemical compound under study.

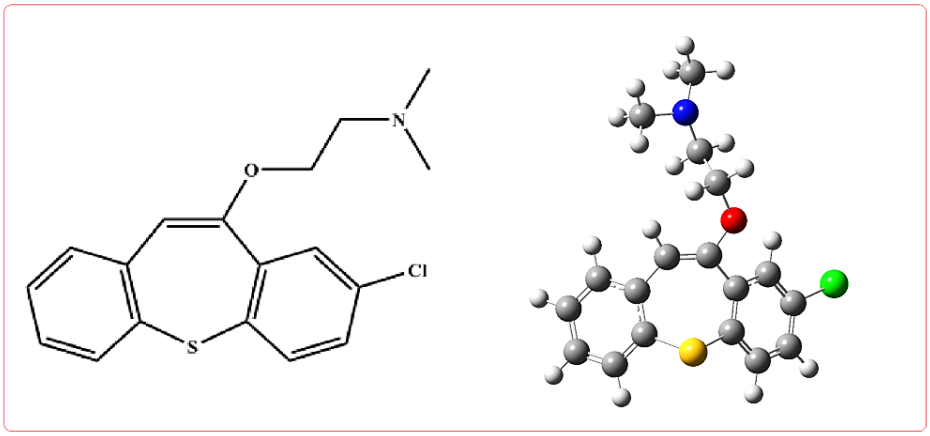

Figure 1. The theoretical geometric structure of Zotepine.

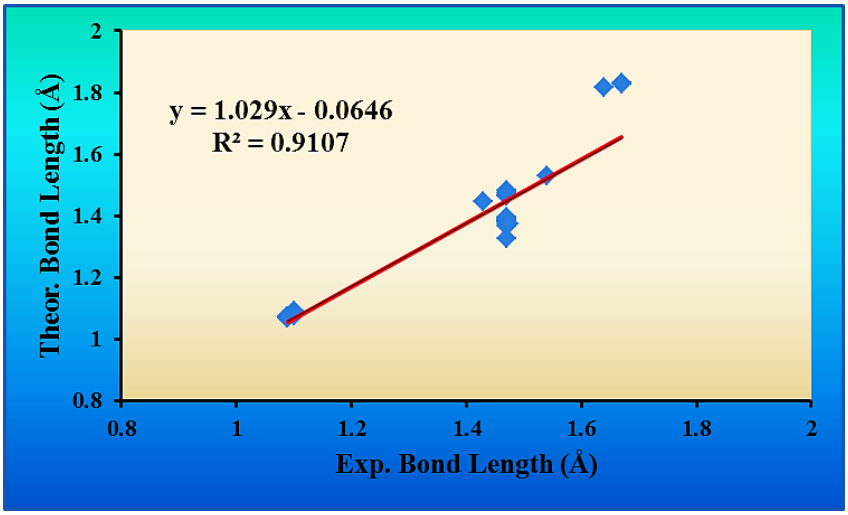

Figure 2. The experimental and theoretical bond lengths relationship of Zotepine.

Stability and reactivity study of the medicinal compound Zotepine

Frontier molecular orbital (FMO) theory is the most used theory in chemistry to predict the stability and reactivity properties of an organic compound. The frontier molecular orbitals are the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) of a molecule. The energy and type of these orbitals determine the molecular reactivity of the compounds. The global reactivity indices are used to express the said properties of a molecule [28-32]. 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 [33]:

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

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

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

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

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

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

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

Figure 3 shows both frontier molecular orbitals (HOMO and LUMO) are made on atoms of the rings. So, these rings will be participated in nucleophilic and electrophilic reactions. From the data of the Table 1, the energies of the HOMO and LUMO are -8.30 eV and +2.44 eV, respectively. The HOMO-LUMO energies gap (Figure 4) is 10.74 eV. The high energy gap of the frontier molecular shows the high stability of the said compound. The density of states (DOS) graph (Figure 4) indicates the virtual orbitals have more density than the occupied molecular orbitals. So, the nucleophilic reactions will be performed on this compound with high possibility. The low amount of ionization potential parameter and the high electronegativity parameter amount prove the high possibility of the nucleophilic reactions. In overall, the chemical hardness and chemical softness indices show the high stability and low reactivity of the title medicinal compound. Figure 5 indicates the molecular electrostatic potential (MEP) graph of Zotepine. The blue, green and red colors relate to the potentials positive, zero and negative, respectively. The MEP graph shows the rings and amino group have negative potentials. So, these segments of the molecular structure have high reactivity than other atoms of the molecule.

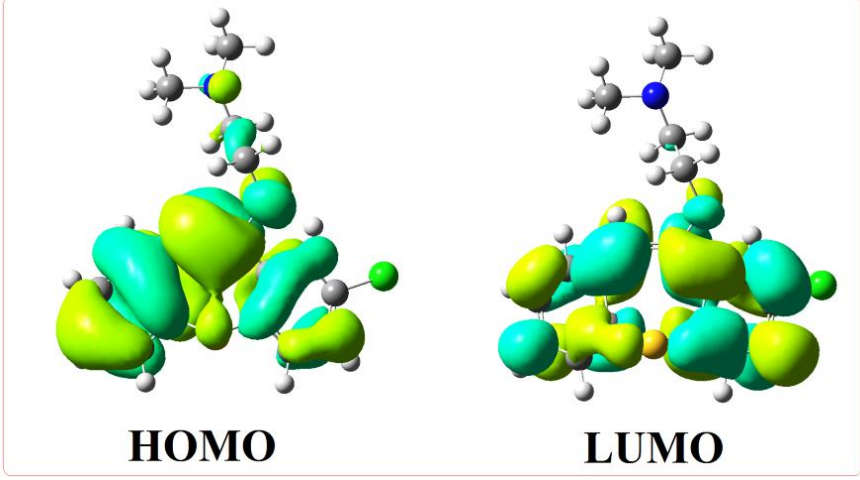

Figure 3. The frontier molecular orbitals of Zotepine.

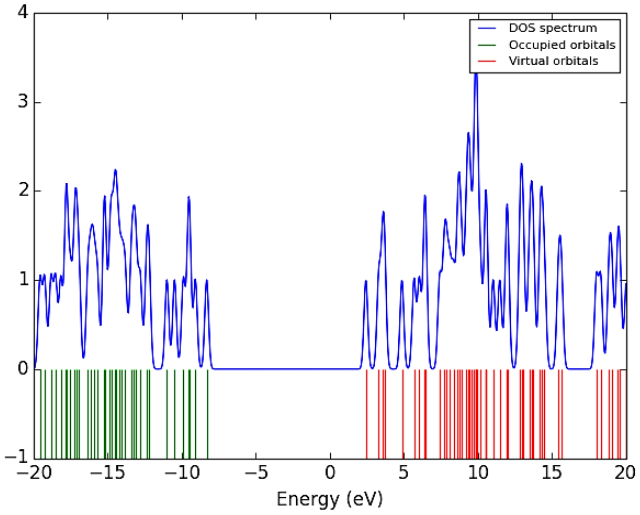

Figure 4. The density of states (DOS) graph of Zotepine.

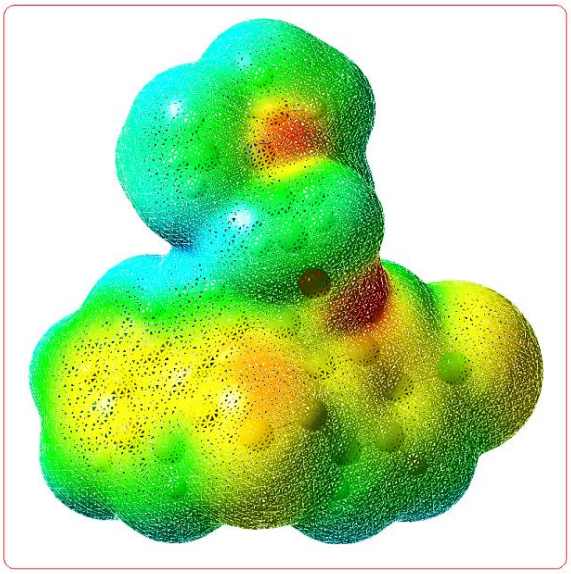

Figure 5. The molecular electrostatic potential (MEP) graph of Zotepine.

Table 1. Global reactivity indices of Zotepine

Parameter	Energy value (eV)
HOMO	-8.30
LUMO	2.44
Ionization Potential (IP)	8.30
Electron Affinity (EA)	-2.44
Energy Gap (Eg)	10.74
Electronegativity (χ)	2.73
Chemical Potential (μ)	-2.73
Chemical Hardness (η)	5.37
Chemical Softness (S)	0.186
Electrophilicity index (ω)	0.694

Physicochemical descriptors and ADME parameters of Zotepine

The pharmacokinetic and biological behavior of the molecule under investigation was assessed utilizing SwissADME web tool which is a convenient source of data used for drug discovery and development. SwissADME web tool provides access to predictive models for physicochemical descriptors, pharmacokinetics, drug-likeness and medicinal chemistry, facilitating prediction of ADME parameters of the molecular structure. Figure 6 indicates the predicted physicochemical graph of the title compound. The colored zone shows the suitable physicochemical space for oral bioavailability. Regarding physiological properties, the title drug has a molecular weight of 331.86 g/mol, 22 heavy atoms, 12 aromatic heavy atoms, 4 rotatable bonds, 2 hydrogen bond acceptors and 0 hydrogen bond donor and the ratio of sp^3 hybridized carbons over the total carbon count of the molecule (Fraction Csp^3) is 0.22. In addition, the investigated drug is observed to have a topological polar surface area (TPSA) of 37.77 A^2 and molar refractivity of 94.15. Lipophilicity is considered an important factor in evaluating the drug's performance pertaining to its membrane permeability [34]. SwissADME analyzes lipophilicity using five predictive models which calculate log $P_{O/W}$. The measured MLog P is 3.96 and XLog P3 is 4.84. Water solubility is another variant which greatly influences absorption in oral formulations and is especially considered in drug development processes [35]. For water solubility prediction SwissADME implements three methods. The first one is based on ESOL model and uses the decimal logarithm of the molar solubility in water values (log S) to predict the compound's water solubility. Based on the calculated values the investigated molecule could be determined insoluble (Log S < -10), poorly soluble (-10< Log S< -6), moderately soluble (-6< Log S< -4), soluble (-4< Log S< -2), very soluble (-4< Log S< -2) and highly soluble (Log S > 0). The measured log S of the investigated compound in ESOL model is -5.09 deeming it moderately soluble. Individual ADME behaviors of the investigated molecule are evaluated in pharmacokinetic properties section. The gastrointestinal (GI) absorption is estimated to be high in this compound. The drug could also permeate through blood-brain barrier (BBB). The CYP P450 isoenzyme family greatly affects drug development since they participate in normal metabolism and influence drug's pharmacokinetics. Therefore, the capacity of the compound in inhibiting CYP 450 enzymes is significantly important in prediction of drug-drug interactions. This drug inhibits the function of CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 isoforms. The skin permeation index (Log Kp) of the compound is -4.89 cm/s. The less negative values indicate higher skin permeability. Drug likeness of the compound is predicted by measuring bioavailability score and evaluating whether the compound obeys Lipinski's rule of five (MW≤ 500 Daltons, NH or OH (hydrogen bond donors) ≤5, N or O (hydrogen bond acceptors) ≤10 and MLog P ≤4.15) [36]. The calculated bioavailability score for the investigated compound is 0.55 and it obeys Lipinski's rule.

Molecular docking analysis of Zotepine-D2R complex

The survey through previous studies determines the therapeutically effects of Zotepine in treatment of schizophrenia disease [37]. Determination of Zotepine effect on schizophrenia disease was carried out by the analyzing of the Zotepine-D2R complex. To access this purpose, the said

molecule was embedded in the active site of the dopamine D2 receptor and their interaction was analyzed using MVD program. Figure 7 indicates the Zotepine-D2R complex. The Zotepine-D2R complex formation shows MolDock score -172.724 (Table 2). The Zotepine binding to the dopamine D2 receptor (D2R) is done by steric interactions (MolDock score: -100.027). Figure 8 indicates the steric interactions of the compound Zotepine embedded in the active site of the D2R. The steric interactions between the molecule and D2R are done using the residues Phe 433, Phe 437, Leu 441, His 442, Ser 443, Arg 434, Leu 433 and 435. From the data of the Table 3, the main interactions between Zotepine and D2R relate to the residues Phe 437, His 442, Ser 433, Phe 433 and Leu 441, respectively.

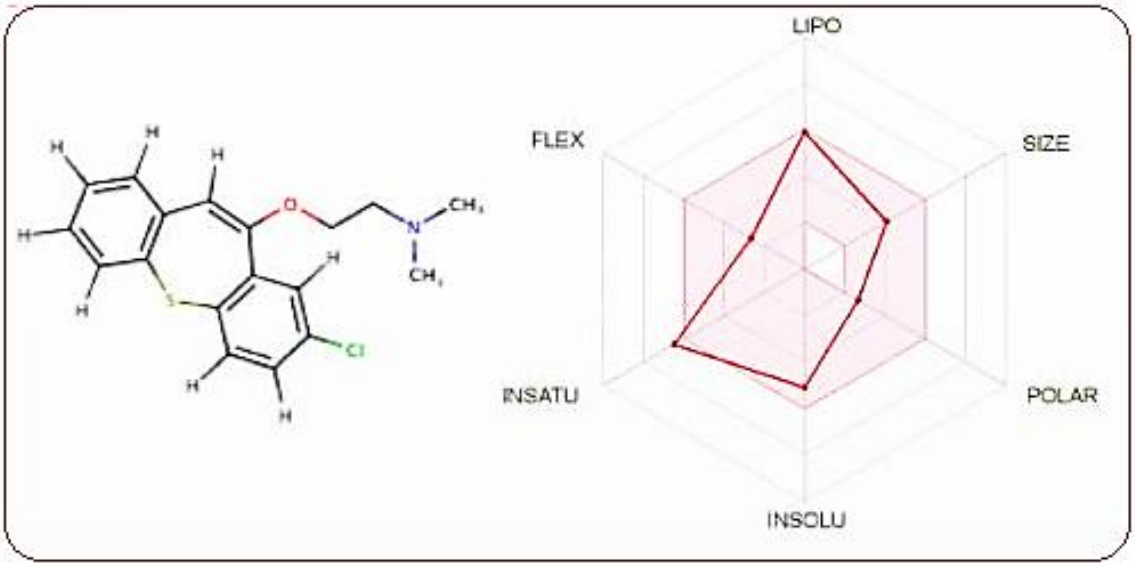

Figure 6. The physicochemical graph of Zotepine.

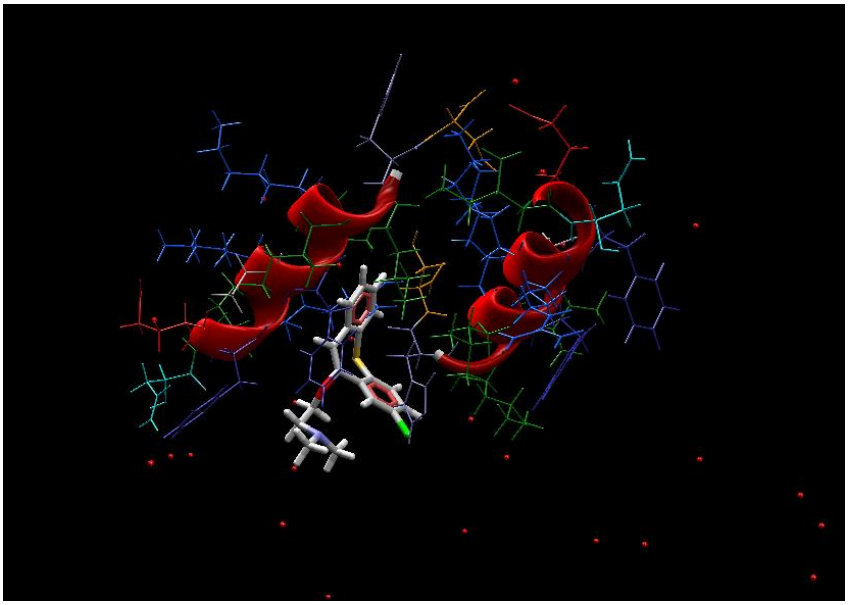

Figure 7. Ligand Zotepine embedded in the active site of the dopamine D2 receptor.

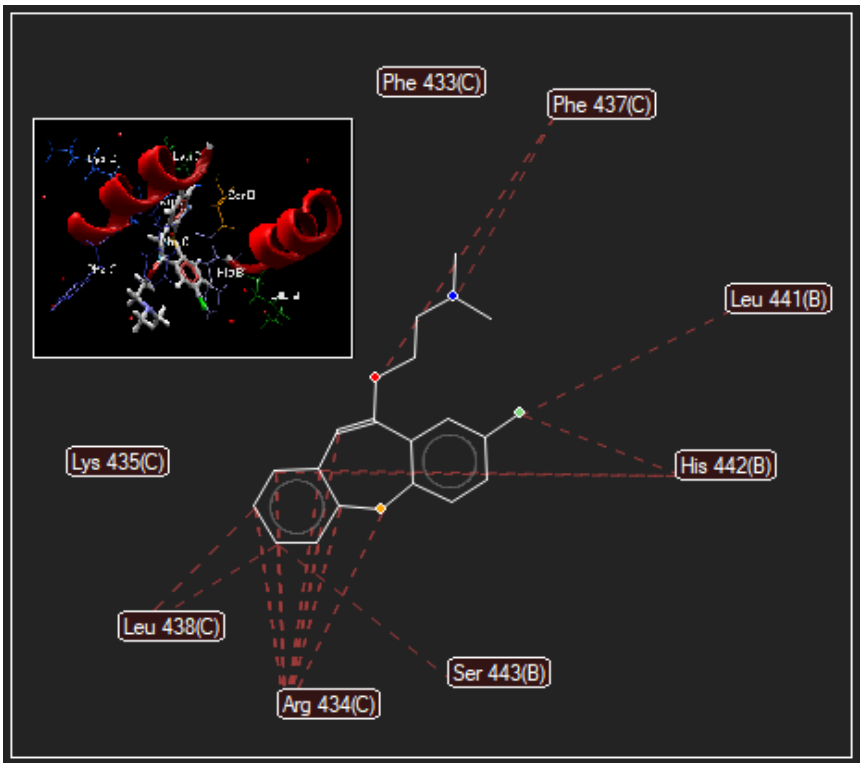

Figure 8. Steric interactions of ligand Zotepine embedded in the active site of the dopamine D2 receptor.

Table 2. The Zotepine-D2R interactions

	Interactions	**MolDock Score**
Protein-Ligand Interactions	Steric (by PLP)	-100.027
	Hydrogen bonds	0.000
	Electrostatic (short range)	0.000
	Electrostatic (long range)	-3.098
Water-Ligand Interactions		-62.953
Internal Ligand Interactions	Torsional strain	-0.782
	Steric (by PLP)	-5.864
	Hydrogen bonds	0.000
External and Internal Ligand Interactions	Total Energy	-172.724

Table 3. The participated D2R residues in ligand-receptor interactions

Residue/HOH	**Total energy score**
Phe [C] 437	-17.2051
His [B] 442	-16.5475
Ser [B] 443	-10.5603
Phe [C] 433	-8.14585
Leu [B] 441	-3.26563
Lys [C] 435	-0.333621
Lys [B] 439	0.310234
Leu [C] 438	1.814070
Arg [C] 434	157.984

CONCLUSIONS

The present research article relates to the molecular simulation and studying the stability and reactivity properties of the medicinal compound Zotepine and its binding modes to the dopamine D2 receptor (D2R). The quantum mechanical (QM) computations show the molecule is a high stable compound and it has low reactivity against the biomolecules like proteins and receptors. On the other hand, the molecular docking studies indicate the Zotepine-D2R complex formation is mainly carried out by the residues Phe 437, His 442, Ser 433, Phe 433 and Leu 441 using steric interactions.

CONFLICT OF INTERESTS

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

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