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Original Research article

In Silico Study of Metoclopramide as A Small Molecule of Dopamine D2 Receptor: a Quantum-Mechanical (QM) Based Molecular Docking Treatment

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ABSTRACT

The present research exploration will contain studying the molecular structure, bonds nature, stability, reactivity and electronic properties of the title molecule.The molecular optimization and all theoretical computations were carried out by density functional theory (DFT) method using the hybrid B3LYP (Becke, three-parameter, Lee-Yang-Parr) exchange-correlation functional employing the 6-31G(d,p) basis set of theory. Quantum-mechanical (QM) computations of the molecular structure geometry of the molecule under study were calculated with scaled quantum mechanics. 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 molecular orbitals (HOMO and LUMO). The calculated global reactivity indices indicated that metoclopramide which was a stable small molecule can bind with the residues of the dopamine D2 receptor (D2R). Molecular docking studies showed that the steric interactions of the ligand with the residues Phe 198, Phe 382, Ala 122, Thr 119, Ser 197, Trp 386, Phe 390, Val 115, Cys 118 and Asp 114 from the protein binding site are the main binding modes between the ligand and the receptor.

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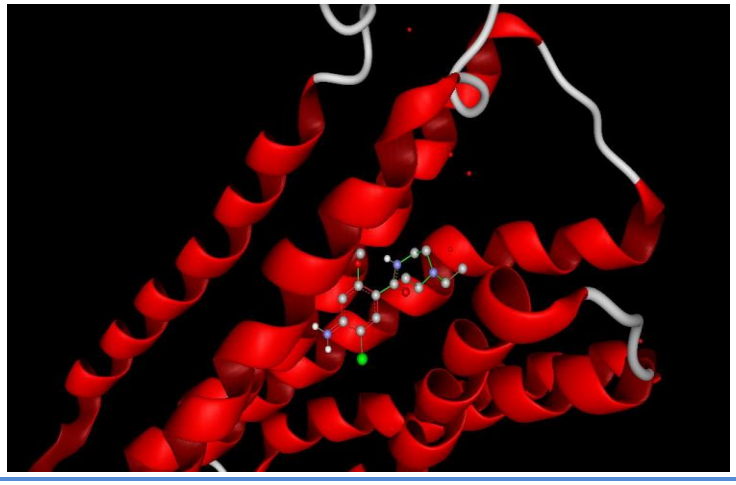
Graphical Abstract



Introduction

Dopamine D2 receptor (D2R) has been constructed from various natural amino acids in humans that is encoded by DRD2 gene [1]. This protein (D2R) is the most important receptor for many antipsychotic medicines. The D2R structure has been known using a radiolabeled antipsychotic compound [2]. The main agonists for dopamine D2 receptor are bromocriptine [3], cabergoline [4], dihydrexidine [5], piribedil [6], pramipexole [7], quinelorane [8], quinpirole [9], ropinirole [10], sumanirole [11] and talipexole [12]. Some drugs like aplindore [13], aripiprazole [14], armodafinil [15], brexpiprazole [16], cariprazine [17], ketamine [18], GSK-789 [19], 2-phenethylamine [20], LSD [21], OSU-6162 [22], roxindole [23], RP5063 [24] and salvinorin A [25] show the partial agonistic activity in interaction with D2R binding sites. In recent years, antagonist drugs have shown better properties than agonist compounds for binding with dopamine D2 receptor. The main antagonist drugs are atypical antipsychotics [26], cinnarizine [27], chloroethylnorapomorphine [28], desmethoxyfallypride [29], domperidone [30], metoclopramide [31], eticlopride [32], fallypride [33], hydroxyzine [34] and itopride [35].

2-methoxy-4-amino-5-chloro-*N*,*N*-(dimethylaminoethyl)benzamide, also known as metoclopramide, is a dopamine D2 antagonist that is used mostly for esophageal and stomach problems [36]. For the first time in 1964, *Louis Justin-Besancon* introduced metoclopramide. This antagonist drug can bind to dopamine D2 receptor (D2R) with affinity 28.8 nM. Patients with gastroesophageal reflux disease (GERD) use this medicine to relieve heartburn and the esophagus ulcers healing. The other usages of metoclopramide include treatment of vomiting and nausea to help patients with delayed stomach

emptying (DSE). Also, it significantly increases the levodopa absorption and plasma levels in man [36–38]. The injection of metoclopramide is used to treat severe diabetic gastroparesis [39]. On the other hand, the combination of this medicine with aspirin or acetaminophen can be used in the migraine headaches. Metoclopramide has some side effects like feeling restless, depression, diarrhea, movement disorder and feeling tired. Patients containing parkinson's disease (PD), restless legs syndrome (RLS), ADHD and hyperprolactinaemia should be monitored when using this medicine for emesis treatment [36–40].

The present article attempts to study the structural and spectral properties of metoclopramide. Also, the stability and reactivity of this antagonist drug are investigated using frontier molecular orbitals (FMOs) theory. In the following, the interaction of metoclopramide with the binding site of dopamine D2 receptor (D2R) studies by ligand-receptor docking method.

Experimental

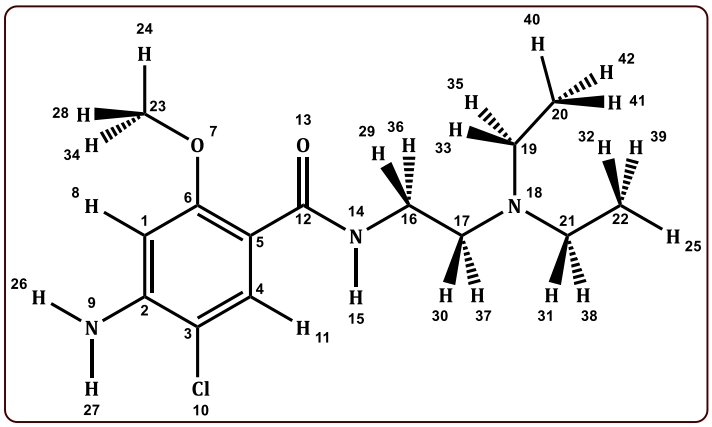
Computational methods

One effective method for quantum-mechanical (QM) computation of organic compounds is the density functional theory (DFT) [41]. In the present work, the molecular structure of metoclopramide is optimized using density functional theory (DFT) computational method by the hybrid B3LYP (Becke, three-parameter, Lee-Yang-Parr) exchange-correlation functional [42] using the 6-31G(d,p) basis set of theory. After molecular structure optimization, the frontier molecular orbitals (FMOs) theory [43–45] is done for calculation the global reactivity indices of the title compound. All theoretical computations are performed by Gaussian 03 program [46]. No imaginary vibrational frequency is observed for the molecule. This shows the accuracy of our computations. The geometry of the molecular structure and the spectral graphs of the molecule under study are obtained using GaussView and GaussSum softwares [47].The binding interactions of the title ligand with dopamine D2 receptor (D2R) is done by Molegro Virtual Docker (MVD) software package [48]. To achieve this, twenty cavities are considered for the D2R protein. To get the best ligand-receptor interaction, the docking process is done one thousand times. Also, the resolution of the cavities is considered about one angstrom due to obtaining the best pose.

Results and discussion

Metoclopramide structural study

Metoclopramide, although chemically related to procainamide, is a medicine with formula $C_{14}H_{22}ClN_3O_2$ and molar mass 299.80 g/mol. As can be seen from the Scheme 1, metoclopramide is a benzamide structure with amine, chloro and methoxy substituents. In the first part, we optimized the



Scheme 1. The molecular structure of metoclopramide

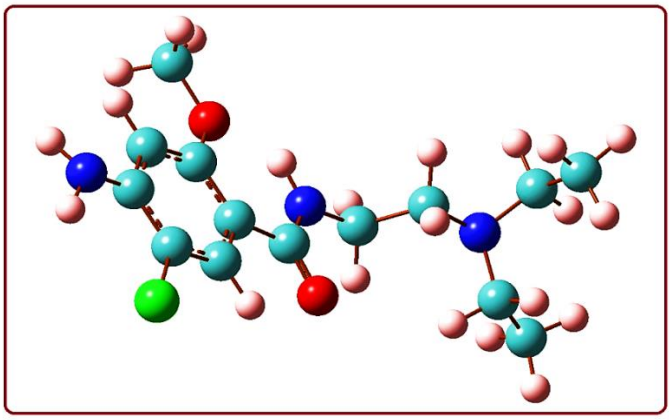


Figure 1. The theoretical geometric structure of metoclopramide

Table 1. Bond lengths and bond orders data of metoclopramide

Bonds	Bond Length (Å)	Bond Order (B.O.)
C1-C2	1.407	1.323
C2-C3	1.407	1.297
C3-C4	1.383	1.435
C4-C5	1.400	1.371
C5-C6	1.415	1.303
C1-C6	1.395	1.411

C1-H8	1.083	0.909
C2-N9	1.379	1.165
C3-Cl10	1.766	1.030
C4-H11	1.084	0.877
C5-C12	1.508	1.007
C6-O7	1.373	0.991
O7-C23	1.422	0.897
C12-O13	1.234	1.601
C12-N14	1.362	1.203
N14-C16	1.454	0.964
C16-C17	1.540	0.991
C17-N18	1.464	0.974
N18-C19	1.465	0.980
C19-C20	1.539	1.012
N18-C21	1.468	0.968
C21-C22	1.530	1.024

molecular structure of this small molecule antagonist using B3LYP/6-31G(d,p) basis set of theory by Gaussian 03 software package in the gas phase at room temperature. Analysis of its vibrational frequencies confirms the molecular structure assignment to energy minima and contributions to Gibbs (G) free energies.

Figure 1 indicates the theoretical geometric structure of metoclopramide. The bond lengths and bond orders (B.O.) data of the optimized structure of metoclopramide are listed in Table 1. At first glance, it can be seen that the C–C bonds of the benzene ring are not similar. The range of aromatic C–C bond lengths is 1.38-1.42 angstrom. The Wiberg bond order (B.O.) analysis shows this too. This difference in aromatic C–C bond lengths happens due to the electronic effect of various electron-donating and electron-withdrawing substituents on the benzene ring. On the other hand, the comparison between C2-N9 (1.379 Å), C12-N14 (1.362 Å) and C17-N18 (1.464 Å) shows the C–N bond length of the amide group is smaller than the others. This is due to the resonance effect between lone pair electrons of nitrogen atom and electron cavity of carbon atom of the amide group. The C2-N9, C12-N14 and C17-N18 bond orders are 1.165, 1.203 and 0.974, respectively. Big amount of the C12-N14 bond order indicates the strength of this bond among all C–N bonds.

Stability and reactivity study of metoclopramide

Frontier molecular orbital (FMO) theory is an application of the molecular orbital (MO) theory describing the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) interactions. The FMO theory helps us to achieve the global reactivity indices of an organic compound. 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 [49]:

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

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

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

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

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

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

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

As can be seen from the Figure 2, the HOMO and LUMO of metoclopramide are on the aliphatic and aromatic segments, respectively. So, the nucleophiles and electrophiles like to react with aromatic and aliphatic segments, respectively. Figure 3 shows the density of states (DOS) graph of metoclopramide. The DOS graph indicates that the unoccupied orbitals have more density than the occupied molecular orbitals. This shows the title molecule likes more to react with nucleophile agents. The global reactivity indices are reported in Table 2. The electrophilicity index 1.82 eV shows the low affinity of metoclopramide for reaction with electrophiles. The HOMO/LUMO energies gap 4.69 eV indicates the high stability of metoclopramide at room temperature.On the other hand, the low chemical hardness (2.345 eV) and high amount of chemical softness index

(0.426 eV) say our antagonist is susceptible to react with the small molecules or macromolecules like a protein. The potential of blue, green and red regions of the molecular electrostatic potential (MEP) graph (Figure 4) of metoclopramide is positive, zero and negative, respectively. So, the amine and carbonyl groups of the title compound have the lowest and the highest electronic potential amounts, respectively due to their electron-donating and electron-withdrawing natures.

The UV-vis spectrum of metoclopramide has been shown in Figure 5. From the data of the Table 3, three groups of electronic transitions are performed between occupied and virtual orbitals of the molecule under study at wavelengths 263 nm, 267 nm and 294 nm. The most important electronic transitionsare related to the peak at wavelength 267 nm with energy 37361 cm^{-1}. These electronic transitions contain HOMO-3→LUMO (16%), HOMO-1→LUMO (48%), HOMO-1→LUMO-1 (21%), HOMO-4→LUMO (2%) and HOMO-3→LUMO+1 (7%).

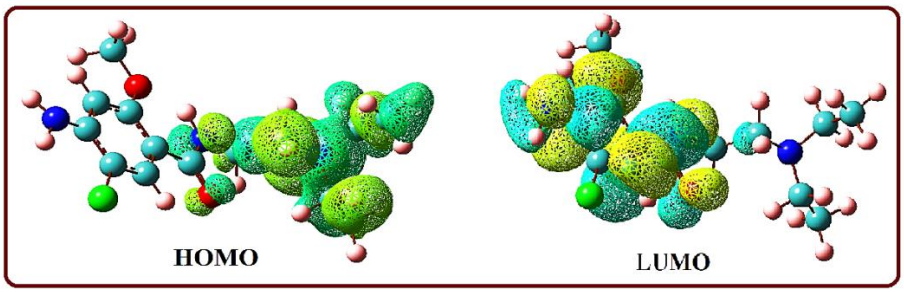


Figure 2. The frontier molecular orbitals of metoclopramide

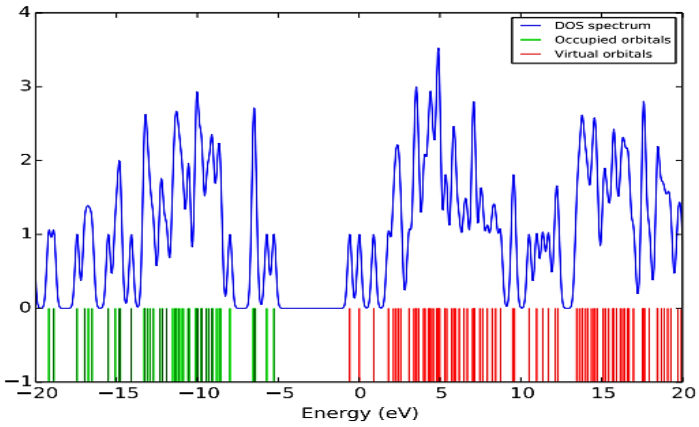


Figure 3. The density of states (DOS) graphof metoclopramide

Table 2. Global reactivity indices of metoclopramide

Parameter	Energy value (eV)
HOMO	-5.267
LUMO	-0.577
Ionization Potential (IP)	5.267
Electron Affinity (EA)	0.577
Energy Gap (Eg)	4.690
Electronegativity (χ)	2.922
Chemical Potential (μ)	-2.922
Chemical Hardness (η)	2.345
Chemical Softness (S)	0.426
Electrophilicity index (ω)	1.820

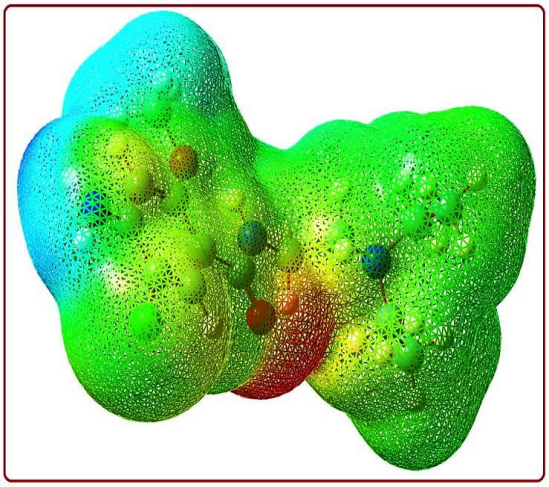


Figure 4. The molecular electrostatic potential (MEP) graph ofmetoclopramide

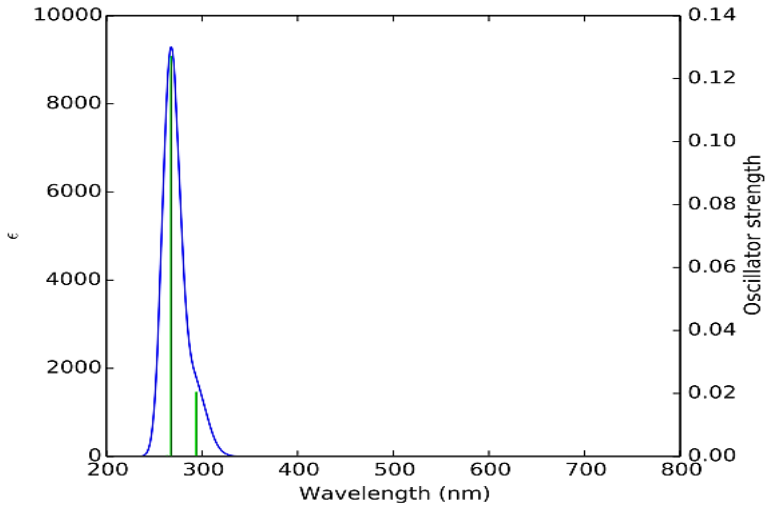


Figure 5. The UV-vis spectrumof metoclopramide

Table 3. Electronic transitions of metoclopramide in UV-vis region

Energy (cm^{-1})	Wavelength (nm)	Osc. strength	Electronic transition (possibility)
34007.796	294.050	0.0205	HOMO→LUMO (99%)
37361.472	267.655	0.1272	HOMO-3→LUMO (16%), HOMO-1→LUMO (48%), HOMO-1→LUMO-1 (21%), HOMO-4→LUMO (2%), HOMO-3→LUMO+1 (7%)
37984.137	263.268	0.0004	HOMO-4→LUMO (50%), HOMO-2→LUMO (37%), HOMO-3→LUMO (6%)

Charge distribution and molecular docking

The natural population analysis (NPA) of the molecule under study is obtained by Mulliken population analysis (MPA) using DFT method by B3LYP/6-31G(d,p) level of theory. MPA can help us in understanding the ionization potential and the chemical potential [50]. Figure 6 shows the charge distribution on the molecular structure. The green, black and red loops indicate the electron-poor, natural and electron-rich regions of the molecule. The electron-rich and electron-poor regions of the molecule can bind to the dopamine D2 receptor by hydrogen bond, but the natural regions of the title compound can bind with the receptor by the steric interactions. The two-dimensional electron localization graph of metoclopramide (Figure 7) indicates more electron distributions on the chloro, amide and ethyl groups of the molecular structure. So, the most important steric interactions will be happened from these regions.

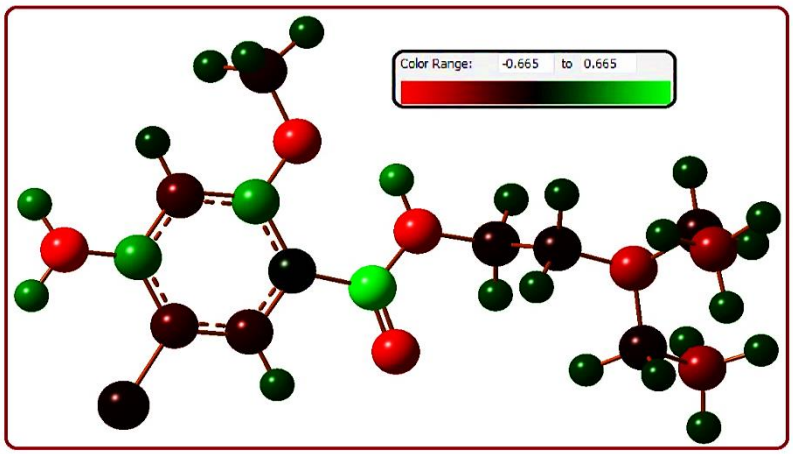


Figure 6. The charge distributionof metoclopramide

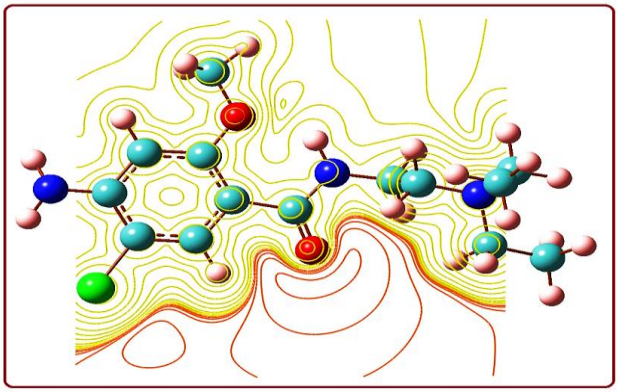


Figure 7. The two-dimensional electron localization graph of metoclopramide

The prediction of the ideal binding orientation, affinity and activity of a ligand (Drug molecules) and its receptor (Protein target) is performed using the molecular docking. The binding interactions of the title ligand (Metoclopramide) with dopamine D2 receptor (D2R) is carried out by Molegro Virtual Docker (MVD) software package. Figure 8 shows the best insertion of the ligand metoclopramide in the active site of dopamine D2 receptor (D2R). The molecule under study was docked in the functional sites of the dopamine D2 receptor (D2R) and minimum docking energy value was examined. It can be seen from the data of the Table 4, the most important protein-ligand interactions are related to the steric interactions. Metoclopramide binds to the residues Cys 118, Val 115, Trp 386, Thr 119, Ser 197, Phe 390, Phe 198, Asp 114, Ser 193, Phe 189, Phe 389, Tyr 416, Phe 382, Ala 122, His 393, Thr 412 and Ser 194 from the dopamine D2 receptor (Table 5). From the Figure 9, the steric interactions of the ligand with the protein are done with the residues Phe 198, Phe 382, Ala 122, Thr 119, Ser 197, Trp 386, Phe 390, Val 115, Cys 118, Asp 114, Phe 189, Phe 389, His 393, Ser 194, Ser 193, Thr 412 and Tyr 416. Also, metoclopramide can bind to the receptor by hydrogen bond interactions with the residues Thr 119, Ser 197 and Cys 118 from dopamine D2 proteine and one water molecule HOH 11.

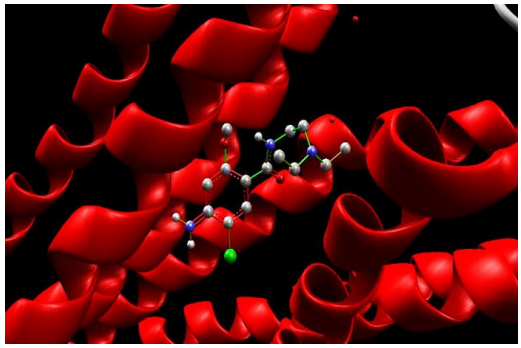


Figure 8. Ligand metoclopramide embedded in the active site of dopamine D2 receptor

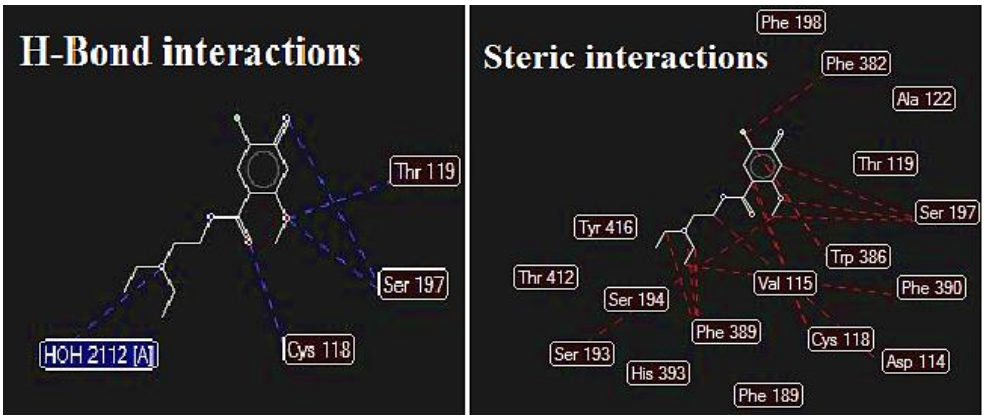


Figure 9. *H*-bond and steric interactions of ligand metoclopramide embedded in the active site of dopamine D2 receptor

Table 4. The ligand-receptor interactions

Interactions		Energy Score
	Steric (by PLP)	-113.908
	Steric (by LJ12-6)	-10.128
Protein-Ligand interactions	Hydrogen bonds	-4.877
	Hydrogen bonds (no directionality)	-6.689
Water-Ligand interactions		-4.366
Internal ligand interactions	Torsional strain	4.128
	Steric (by PLP)	11.832
	Steric (by LJ12-6)	44.320
Total		-79.688

Table 5. The participated residues of dopamine D2 in ligand-receptor interactions

Residue	Total energy score
Cys 118	-17.095
Val 115	-16.280
Trp 386	-11.987
Thr 119	-10.439
Ser 197	-9.949
Phe 390	-9.809
Phe 198	-9.124
Asp 114	-8.411

Ser 193	-5.104
Water (HOH) 11	-4.366
Phe 189	-3.381
Phe 389	-3.352
Tyr 416	-2.980
Phe 382	-2.383
Ala 122	-1.929
His 393	-1.537
Thr 412	-0.790
Ser 194	-0.545

Conclusion

The present research work can be thought of as the silico study of metoclopramide as an antagonist medicine for dopamine D2 receptor (D2R). Firstly, the full optimization and complete vibrational spectral analysis were done for the molecule under study. All theoretically computations were performed using Gaussian 03 software by the density functional theory (DFT) method. The optimized geometric parameters (bond lengths and bond orders) show the resonance effect in C–N and C=O bonds of the amide group of the title compound. The global reactivity descriptors indicate metoclopramide which likes to react with nucleophile agents. The energies gap (Eg) of the frontier molecular orbitals (FMOs) of the title molecule shows the high stability of metoclopramide at room temperature. Also, it can be deduced from the low amount of the chemical hardness index, metoclopramide is susceptible to bind with the residues of the dopamine D2 receptor.Molecular docking studies showed the main binding modes between the ligand and the receptorare related to the steric interactions of the ligand with the residues Phe 198, Phe 382, Ala 122, Thr 119, Ser 197, Trp 386, Phe 390, Val 115, Cys 118 and Asp 114 from the protein binding site.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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