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Structural Properties Study and Spectroscopic (FT-IR and UV-Vis) Profiling of the Novel Antagonist LY2157299 as a Transforming Growth Factor-β (TGF-β) Receptor I Kinase Inhibitor by Quantum-mechanical (QM) and Molecular Docking Techniques

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ABSTRACT

During the present study, the structural, vibrational, electronic and biological properties of the novel antagonist LY2157299 as a transforming growth factor-β (TGF-β) receptor I kinase inhibitor are explored by quantum-mechanical (QM) and molecular docking methods. The characterization of the title compound is done using FT-IR and UV-Vis spectroscopy methods. The above computations were carried out using density functional theory (B3LYP) method with 6-31+G(d,p) basis set. The frontier molecular orbitals (HOMO and LUMO) energies were used to calculate the global reactivity indices of the said compound. The results explored the stability, reactivity and bioactivity of the compound under study. To identify the nucleophilic and electrophilic sites in the said compound, the molecular electrostatic potential (MEP), electron localization function (ELF) and Mulliken charge distribution graphs were generated. The present paper further explains the ligand-protein interactions through molecular docking investigations. The results of the molecular docking studies indicate that the most important interactions between the ligand and protein are related to the residues His 285, Val 341, Lys 342, His 283 and Glu 284.

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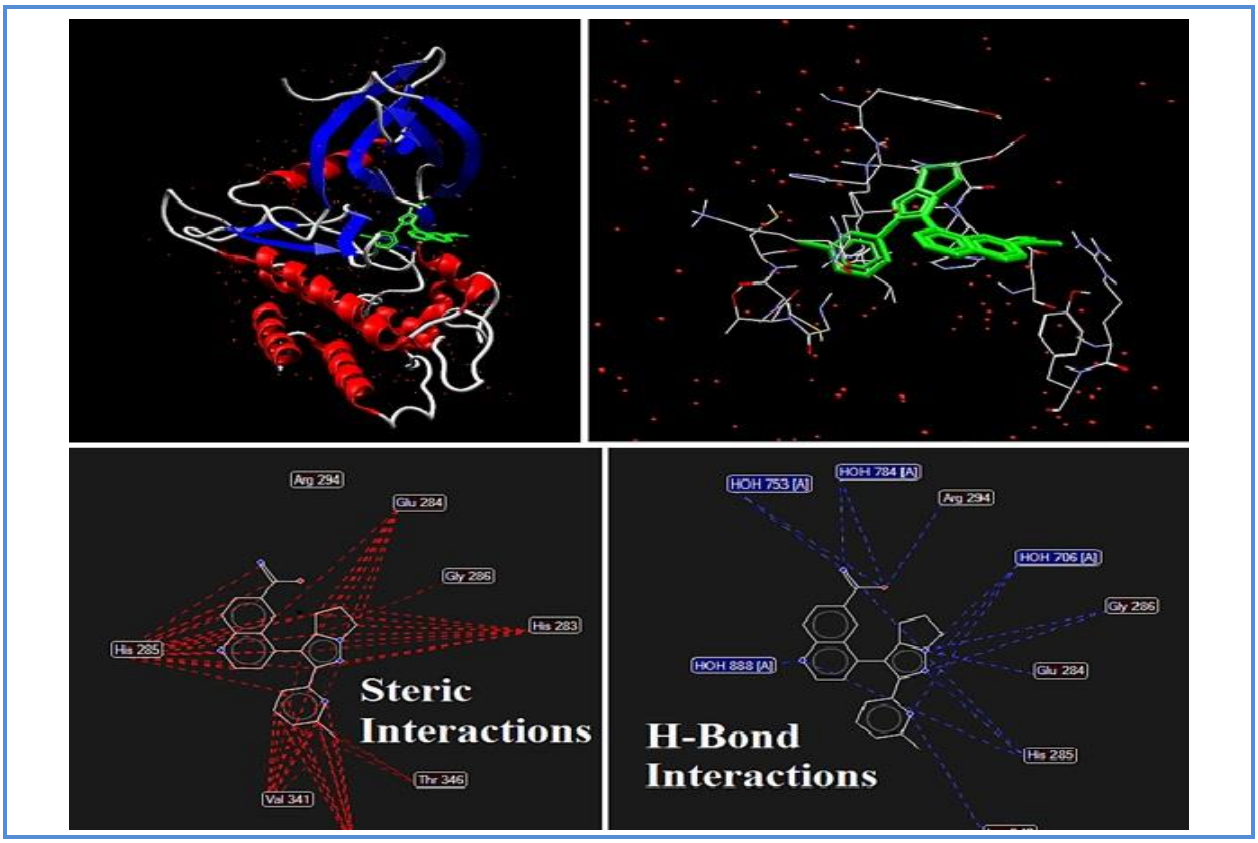
Graphical Abstract



Introduction

The transforming growth factor-*β* (TGF-*β*) superfamily was identified as an important group of signaling receptors caused by a family of ligands (TGF-*β* 1, TGF-*β* 2, TGF-*β* 3) that are critical for tissue homeostasis [1]. TGF-*β* signaling pathway also plays important roles in cancer initiation, development, metastasis and the interaction between stromal and cancer cells, making the pathway a potential therapeutic target [2, 3]. All three ligands can first engage the specific receptor TGF-*β*RI/ALK5, which then heterodimerize with TGF-*β* receptor type II (TGF-*β*RII) [4]. Rang of strategies to target the TGF-*β* pathway have been developed, including TGF-*β* pathway inhibition at the translational level using antisense oligonucleotides carried directly into tumors, inhibiting TGF-*β* binding to the type II receptor *via* monoclonal antibodies, and inhibiting the receptor-mediated signaling cascade using inhibitors of TGF-*β* receptor kinases [5]. Among the TGF-*β* inhibitors, small molecule inhibitors (SMIs) denoted a large and various group of chemical compounds that are aimed to block the activation of the signaling cascade downstream of the TGF-*β* receptor type I kinase (TGF-*β*RI or ALK5) [6-9]. Inhibitors such as LY580276 [10], LY364947 [11], and LY2109761 [12] have been developed which three are currently in clinical development. TGF-*β* receptors

inhibitors are based on a dihydropyrrolopyrazole, imidazole, pyrazolopyridine, pyrazole, imidazopyridine, triazole, pyridopyrimidine, and isothiazole skeleton. Galunisertib (LY2157299), a potent and selective ATP mimetic inhibitor of TGF-βRI/ALK5 has been identified using structure activity relationships as the dihydropyrrolopyrazole class [13]. LY2157299 has reported as an attractive target for developing cancer therapeutics because of its multitude of critical roles in progression and metastasis in advanced cancers. Inhibitor LY2157299 monohydrate (galunisertib, LY) inhibited tumor metastasis in colorectal cancer xenograft models in the tumor microenvironment. Galunisertib has confirmed less toxicity and powerful activity against pancreatic and lung cancer in phase I clinical trials. Compared with other SMIs, galunisertib (LY2157299) monohydrate had less cardiovascular toxicity in animals and demonstrated to be less potent in inhibiting pSmad2 levels in *vitro* [10, 14-16]. It is currently being evaluated that LY can to inhibit the growth and/or engraftment in ovarian cancer in *vivo*.

From literature survey, it was found that the identification of the structural properties of the molecule under study had not been performed previously in the light of computational chemistry and hence the study was undertaken. The main goal of the present article is to give a comprehensive description of the molecular geometry, reactivity, stability and spectroscopic (FT-IR and UV-Vis) profiles of the novel antagonist LY2157299 as a transforming growth factor-β (TGF-β) receptor I kinase inhibitor by quantum-mechanical (QM) and molecular docking methods. It is believed that the outputs of this study will provide a deep and accurate understanding of the possible biological activities of the title compound.

Experimental

Computational methods

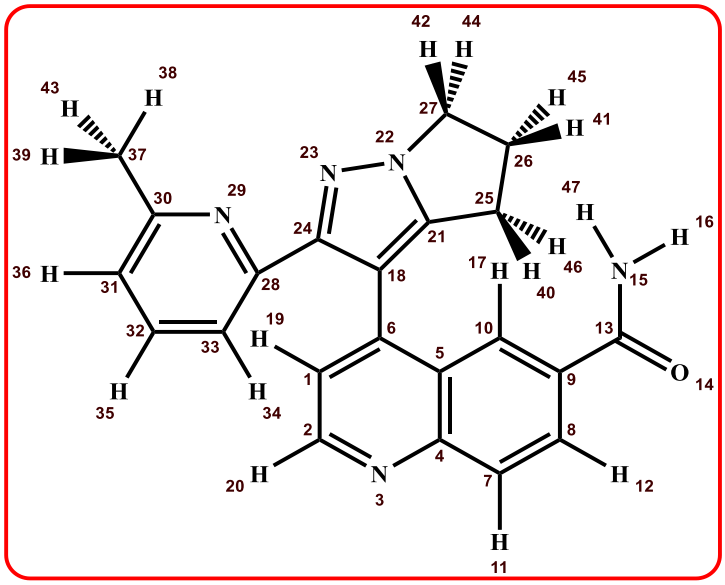
All computations have been carried out with the Gaussian 03 package [17]. The density functional theory (DFT) computational method has gained utmost importance in quantum-mechanical (QM) computation. Geometry optimization at the B3LYP/6-31+G(d,p) level of theory is used to obtain the geometry of the compound under study. The harmonic vibration frequencies are also obtained at the corresponding computational method. No imaginary frequency was found for this compound. This shows the accuracy of our computations. In order to obtain the stability and reactivity of the title compound, frontier molecular orbitals (FMOs) calculations [18] were performed. The molecular electrostatic potential (MEP) computation was examined in order to spot the electrophilic and nucleophilic regions of the said compound [19]. Molegro Virtual Docker (MVD) software package is used to obtain the binding interactions of the compound LY2157299 with

transforming growth factor-β (TGF-β) receptor I kinase inhibitor. To achieve this, twenty cavities are considered for the TGF-βRI inhibitor. 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

LY2157299 structural study

The molecular structure representation of galunisertib (LY2157299) molecule with its labeling and atomic numbering is shown in Scheme 1. As can be mentioned above, the B3LYP/6-31+G(d,p) computational method was used to optimize the molecular structure under investigation. Figure 1. shows the optimized molecular structure of the title compound. The optimized geometric parameters (bond lengths and dihedral angles) and bond orders (B.O.) for the molecule under study are tabulated in Table 1. This molecule comes under C1 point group. All the unsaturated rings of the said compound are planar. The dihedral angles indicate that the rings of the molecule have been twisted to each other. From the data of the Table 1, the lengths of the C-N bonds are in range 1.3-1.4 angstrom but the bond orders data indicates that the strength of these bonds is different. So, the electron distribution in the unsaturated rings of the molecule is not monotonic. This lack of uniformity in the electron distribution can give specific structural properties to the molecule.The comparison between the bond lengths and bond orders of the C21-N22 and C27-N22 bonds show the lone pair electrons of the nitrogen-22 atom participates in the ring current of pyrazole. This is the reason of the short length of the C21-N22 bond to the C27-N22 bond.



Scheme 1. The molecular structure of LY2157299

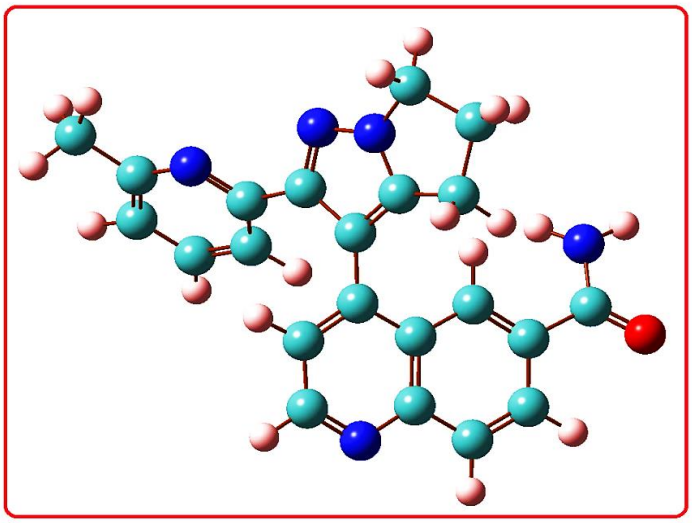


Figure 1. The theoretical geometric structure of LY2157299

Table 1. Bond lengths, bond orders and dihedral angles data of LY2157299

Bonds	Bond length (Å)	Bond order (B.O.)	Dihedral angles (degree)
C2-N3	1.319	1.526	-
C4-N3	1.364	1.279	-
C9-C13	1.502	1.000	-
C13-O14	1.225	1.674	-
C13-N15	1.377	1.167	-
C21-N22	1.352	1.218	-
C27-N22	1.457	0.938	-
N22-N23	1.339	1.215	-
N23-C24	1.343	1.478	-
C28-N29	1.347	1.370	-
N29-C30	1.339	1.379	-
C1-C6-C18-C24	-	-	52.216
C6-C18-C24-C28	-	-	8.141
C18-C24-C28-C33	-	-	35.469

Stability and reactivity study of the compound LY2157299

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 [20]. Figure 2. shows the frontier molecular orbitals (HOMO and LUMO) of the compound LY2157299. It can be seen from the Figure 2, LUMO is mainly on the quinolone segment while the HOMO has been made by the atoms of the quinolone, pyridine and pyrazole rings. The FMO theory helps us to achieve the global reactivity indices of an organic compound [21]. 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 [22]:

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

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

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

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

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

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

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

The global reactivity indices of the said compound are listed in Table 2. The small HOMO/LUMO energy gap (Eg) shows that the molecule is more reactive, polarizable and comes under soft compound. In addition, the HOMO and LUMO energy values indicate the molecule under investigation prefers to participate in reaction with the chemical reagents by its lowest unoccupied molecular orbitals. Also, the small chemical hardness value (2.147 eV) shows that the compound LY2157299 is a soft molecule and can be chemically reactive. Likewise, the high amount of the electrophilicity index (3.557 eV) indicates the title compound can be biologically active. The capacity of the molecule in accepting and donating of electrons from the neighboring species can be deduced by the electron affinity and ionization potential values. In addition, the chemical softness was found to be low indicating the molecule can has non-toxic nature theoretically. Figure 3. indicates the density of states (DOS) graph of the said molecule. The energies of the occupied and virtual molecular orbitals have been shown with green and red colors, respectively. It clearly shows that the virtual molecular orbitals have high density and the energy gap between HOMO and LUMO is low. So, the title compound is generally reactive and prefers to react with nucleophilic agents. On the other hand, density of highest occupied molecular orbital is more than the lowest unoccupied molecular orbital. So, the HOMO electrons of the molecule can be reacting with electrophilic agents. The molecular electrostatic potential (MEP) graph (Figure 4) clears that the nitrogen atoms have

more electron density due to their more electronegativity property. It can be deduced that the nitrogen atoms of the molecule can play the hydrogen bond acceptor (HBA) role in reaction with the hydrogen bond donors (HBD) of the biomolecules such as receptors, proteins and enzymes.

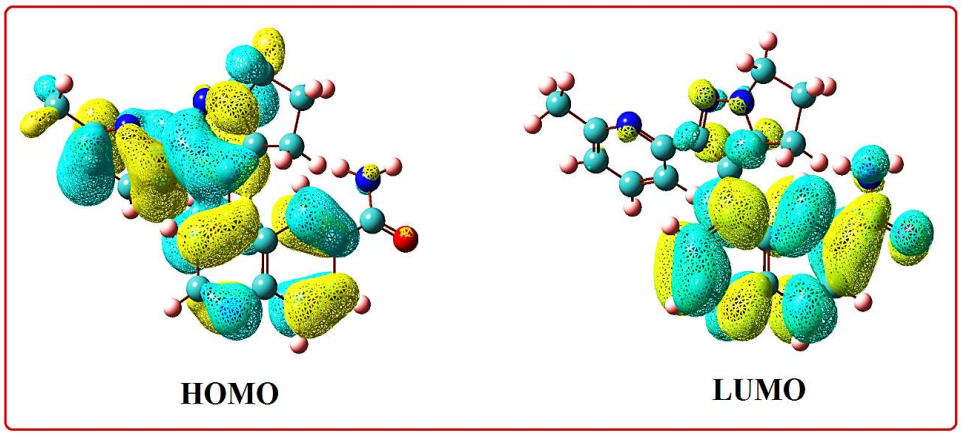


Figure 2. The frontier molecular orbitals of LY2157299

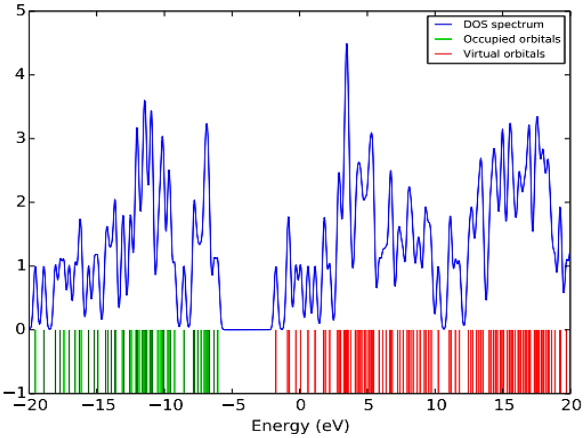


Figure 3. The density of states (DOS) graph of LY2157299

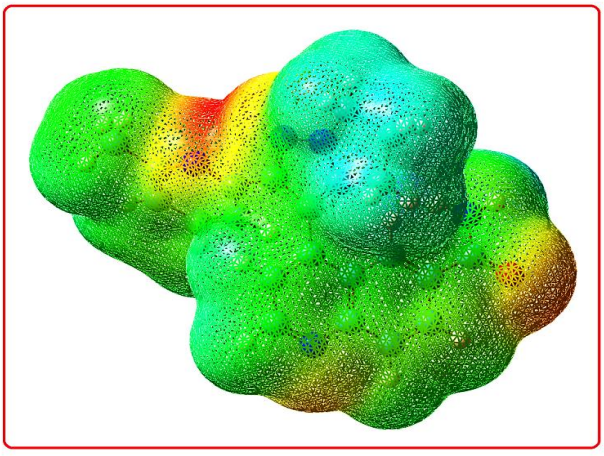


Figure 4. The molecular electrostatic potential (MEP) graph of LY2157299

Table 2. Global reactivity indices of LY2157299

Parameter	Energy value (eV)
HOMO	-6.055
LUMO	-1.761
Ionization potential (IP)	6.055
Electron affinity (EA)	1.761
Energy gap (Eg)	4.294
Electronegativity (χ)	3.908
Chemical Potential (μ)	-3.908
Chemical hardness (η)	2.147
Chemical softness (S)	0.466
Electrophilicity index (ω)	3.557

Vibrational and electronic spectral analyses of the compound LY2157299

In current section, a detailed analysis of the title molecule has been performed through FT-IR and UV-Vis spectroscopy methods. The FT-IR spectrum of the molecule is shown in Figure 5. It can be seen from the title spectrum, the vibrational frequencies in ranges 3500-3700 cm^{-1}, 3000-3200 cm^{-1}, 1600-1650 cm^{-1}, 1500-1600 cm^{-1} and 1300-1500 cm^{-1} are related to the N-H, C-H, C=N, C=O and C-H (bending) vibrations, respectively. The detailed vibrational modes of the compound under study are: 17.510, 28.542, 41.956, 54.164, 61.465, 68.633, 85.344, 94.071, 129.025, 146.387, 166.276, 190.902, 200.678, 204.954, 208.624, 220.923, 274.261, 300.032, 314.459, 321.384, 342.865, 364.934, 419.826, 427.828, 438.089, 445.787, 455.868, 486.542, 520.387, 539.546, 554.349, 567.349, 567.418, 577.325, 588.215, 601.081, 613.645, 643.611, 655.329, 665.867, 684.287, 693.650, 708.838, 744.286, 748.155, 765.747, 773.691, 792.274, 814.077, 823.904, 834.350, 861.079, 867.479, 885.569, 897.151, 902.155, 907.182, 918.351, 932.306, 939.921, 981.179, 987.696, 1000.398, 1004.366, 1006.617, 1008.975, 1013.096, 1061.575, 1082.631, 1091.614, 1096.219, 1100.602, 1120.928, 1129.712, 1151.710, 1166.572, 1187.630, 1192.314, 1213.144, 1229.705, 1235.158, 1252.215, 1265.757, 1283.844, 1299.969, 1304.984, 1311.696, 1324.691, 1336.054, 1340.823, 1359.588, 1365.041, 1386.777, 1397.892, 1409.849, 1415.844, 1441.631, 1468.222, 1470.628, 1487.691, 1494.861, 1499.870, 1501.354, 1509.169, 1515.342, 1523.744, 1541.336, 1545.213, 1585.551, 1613.639, 1623.678, 1632.621, 1635.810, 163.567, 1669040, 1783.984, 3043.477, 3047.615, 3055.733, 3081.055, 3098.868, 3112.145, 3119.201, 3138.545, 3154.858, 3158.847, 3183.882, 3199.931, 3209.108, 3210.402, 3212.643, 3220.926, 3226.563, 3588.790 and 3718.811 cm^{-1}.

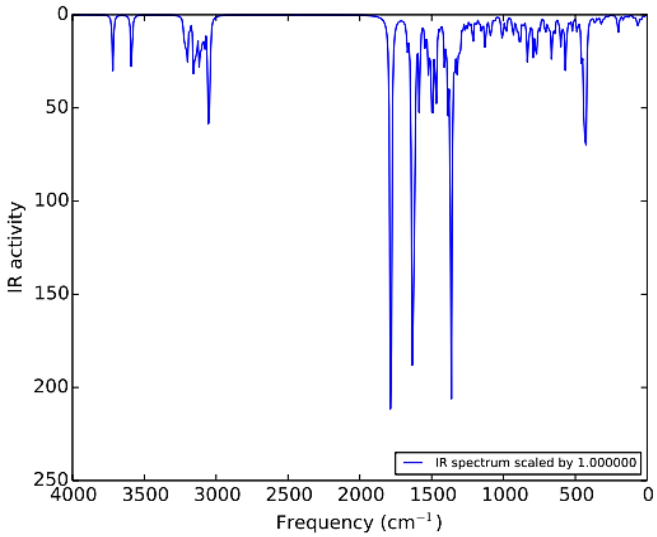


Figure 5. The FT-IR spectrum of LY2157299

The organic molecular structures can absorb visible (Vis) or ultraviolet (UV) lights. Different molecular structures absorb radiation of different wavelengths. An absorption spectrum will indicate the absorption bands corresponding to the structural groups within the molecule [23]. The UV-Vis spectrum of the title compound is seen in Figure 6. The electronic transitions of antagonist LY2157299 in UV-Vis region have been tabulated in Table 3. The electronic transitions of the title compound are happened in wavelengths 332 nm, 310 nm and 300 nm with energies 30142 cm^{-1}, 32267 cm^{-1} and 33349 cm^{-1}, respectively. The electronic transition from HOMO to LUMO is seen in wavelength 331.763 nm.

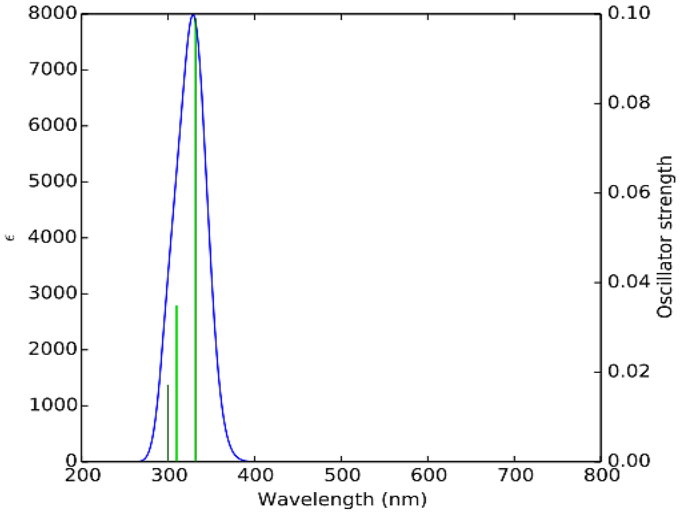


Figure 6. The UV-Vis spectrum of LY2157299

Table 3. Electronic transitions of LY2157299 in UV-Vis region

Energy (cm^{-1})	Wavelength (nm)	Osc. strength	Electronic transition (possibility)
30141.954	331.763	0.0991	HOMO→LUMO (90%)
32267.239	309.912	0.0349	HOMO-1→LUMO (80%), HOMO-5→LUMO (4%), HOMO-4→LUMO (4%), HOMO-3→LUMO (4%)
33348.836	299.861	0.0172	HOMO-5→LUMO (60%), HOMO-1→LUMO (10%), HOMO-6→LUMO (9%), HOMO-4→LUMO (6%), HOMO-3→LUMO (6%)

Charge distribution and molecular docking

Figure 7. shows the Mulliken charge distribution on atoms of antagonist LY2157299. We can see that more electron density distribute on the oxygen and nitrogen atoms. So, these atoms probably participate as hydrogen bond acceptors in the binding regions of the acceptor. In contrast, the electron-deficient regions of the title compound are related to the carbon atoms of the carbonyl group and pyrazole ring. So, these regions prefer to react as electron acceptors in binding site of the inhibitor. Other regions of the said compound have charge zero. So, these regions can react with binding regions of the inhibitor by steric interactions. The two-dimensional electron localization graph (Figure 8) of antagonist LY2157299 indicates same electron charge distribution on the atoms of the title compound.

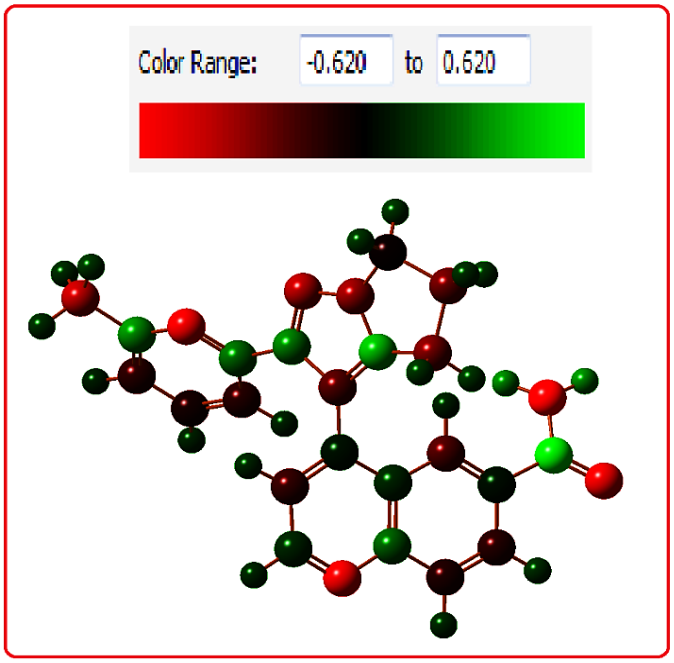


Figure 7. The charge distribution of LY2157299

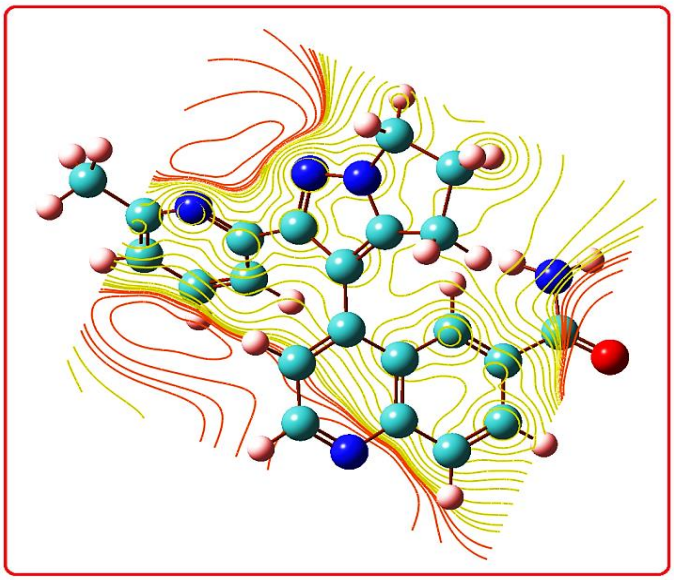


Figure 8. The two-dimensional electron localization graph of LY2157299

Literature review clearly shows that the compound under study can be used as a transforming growth factor-β (TGF-β) receptor I kinase inhibitor [1-6, 24-27]. In this section of the present study, the docking analysis has been performed to clear the desired protein-ligand binding site and its binding affinity. The three dimensional crystal structure of the protein was obtained from protein data bank (PDB) and the docking computations was done using Molegro Virtual Docker (MVD) software package. As can be seen from the Figure 9, the title antagonist compound formed a stable complex with the transforming growth factor-β (TGF-β) receptor I with steric and hydrogen bond (HB) interactions. Importance of the steric (by PLP), steric (by LJ12-6) and HB interactions in the forming complex with binding site of the receptor are valued with scores 932.462, 9542.821 and 7.787, respectively (Table 4). So, the steric interactions have main role in the ligand-protein complex forming. From the data of the Table 4, the value of the water-ligand interaction is about 101. The steric interactions are performed between the electron current of the ligand atoms and the protein residues Arg 294, Glu 284, Gly 286, His 283, Lys 342, Thr 346, Val 341 and His 285 (Figure 10). On the other hand, the protein residues Arg 294, Gly 286, Gly 284, Lys 342 and His 285 participate in making the hydrogen bonds with the title compound. From the data of the Table 5, the most important interactions between the ligand and protein are related to the residues His 285, Val 341, Lys 342, His 283 and Glu 284 with the energy scores of 414.845, 205.525, 147.478, 126.763 and 122.181, respectively.

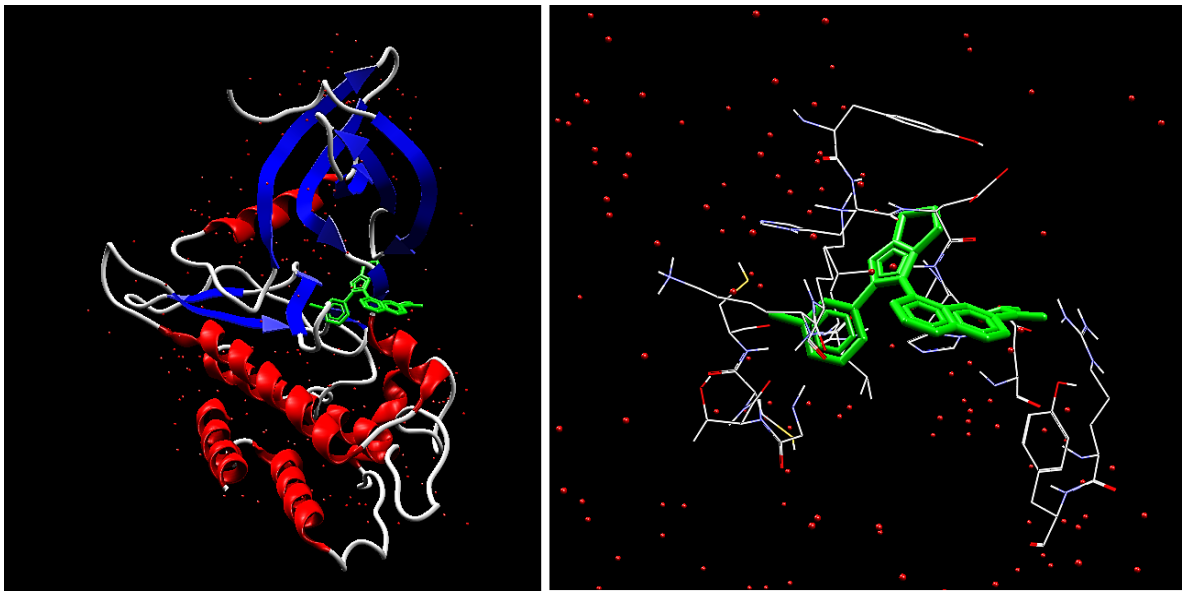


Figure 9. Ligand LY2157299 embedded in the active site of TGF-β receptor

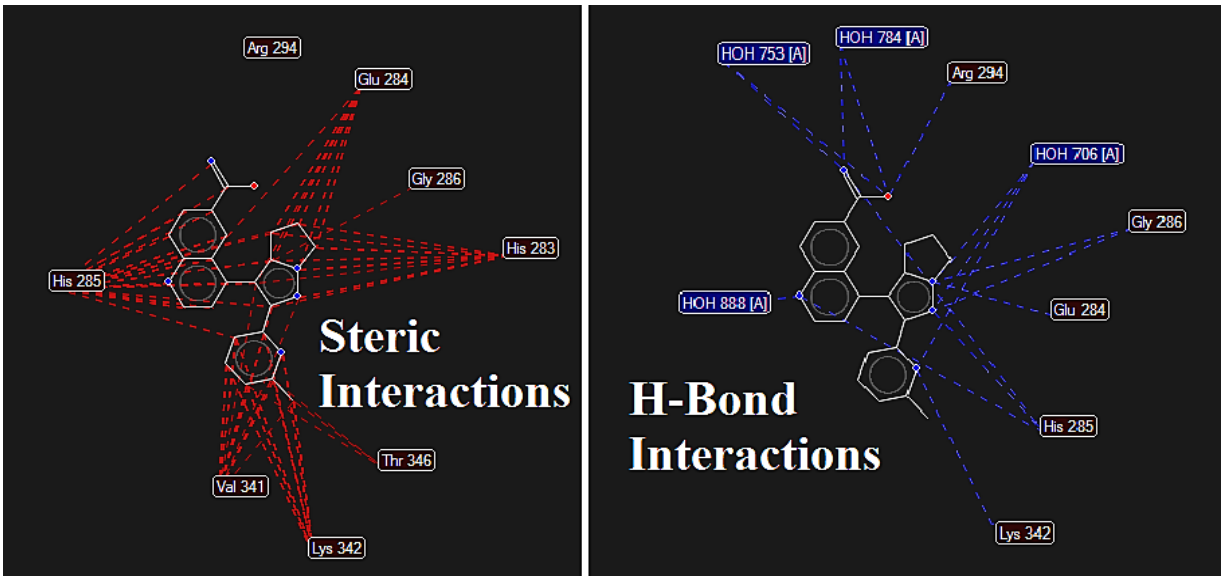


Figure10. H-bond and steric interactions of ligand LY2157299 embedded in the active site of TGF-β receptor

Table 4. The ligand-receptor interactions

Interactions		Energy score
Protein-ligand interactions	Steric (by PLP)	932.462
	Steric (by LJ12-6)	9542.821
	Hydrogen bonds	7.787
	Hydrogen bonds (no directionality)	0.575
Water-ligand interactions		100.944

Table 5. The participated residues of TGF-*β* receptorin ligand-receptor interactions

Residue/HOH	Total energy score
His 285	414.845
Val 341	205.525
Lys 342	147.478
His 283	126.763
Glu 284	122.181
Water 83	45.010
Water 5	34.494
Water 52	15.767
Water 187	11.877
Thr 346	5.543

Conclusion

The main aim of the present research work is a detailed study the structural, vibrational, electronic and biological properties of the novel antagonist LY2157299 as a transforming growth factor-*β* (TGF-*β*) receptor I kinase inhibitor are explored by quantum-mechanical (QM) and molecular docking methods. All above computations were done using B3LYP/6-31+G(d,p) level of theory in gas phase at room temperature by Gaussian 03 software package. The analysis of the frontier molecular orbitals (HOMO and LUMO) energies showed the compound under study is more reactive, non-toxic and biologically active. In addition, the molecular electrostatic potential (MEP) graph clears that the nitrogen atoms of the said compound have more electron density. So, these atoms probably participate as hydrogen bond acceptors in the binding regions of the acceptor. In contrast, the carbon atoms of the carbonyl group and pyrazole ring are the electron-deficient regions of the title compound. So, these regions prefer to react as electron acceptors in binding site of the inhibitor. On the other hand, the molecular docking results show that the most important ligand-protein interactions are related to the residues His 285, Val 341, Lys 342, His 283 and Glu 284.

Conflict of interests

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

Acknowledgments

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