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Molecular docking and in silico ADME prediction of Ticagrelor as an antagonist of the $P2Y_{12}$ receptor

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ABSTRACT

The purpose of the present research work is prediction of electronic and physico-chemical properties of the novel medicinal compound Ticagrelor (AZD6140) using density functional theory (DFT) method. Firstly, its molecular structure was optimized at B3LYP/6-311++G(d,p) basis set of theory at room temperature. The global reactivity indices used to study the reactivity and stability of the title molecule. These indices showed it is a more stable molecule and has low reactivity. On the other hand, the molecular electrostatic potential (MEP) graph indicates the hetero-atoms (N, F, S and O) of the molecule can interact with residues of the receptor. The molecular docking analysis data indicates the $P2Y_{12}$ residues containing Lys 232, Lys 125, Thr 126, Glu 215, Arg 231, Ile 212, Asn 235, Thr 127, Lys 233, Arg 128, Tyr 123 and Lys 237 are the main amino acids which participate in the ligand-receptor complex formation. Evaluation of intramolecular bonds shows that the steric interactions play the main role in the ligand-receptor complex formation.

Keywords: AZD6140; $P2Y_{12}$ receptor; Platelet aggregation inhibition; Ticagrelor; Molecular docking; Molecular simulation

INTRODUCTION

Ticagrelor is a cyclopentyltriazolo-pyrimidine platelet aggregation inhibitor indicated for the prevention of thrombosis in different classifications of disorders. Ticagrelor received its FDA approval under the name of BRILINTA® in 2011 for reduction of heart attack and cardiovascular death in patients suffering from ACS (Acute Coronary Syndrome) [1-8]. ACS is a syndrome (a set of medical signs and symptoms) including unstable angina, myocardial infarction and sudden cardiac death. ACS arises from platelets' aggregation and thrombus formation which

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consequently lead to decreased blood flow in the coronary arteries. The most common symptoms of ACS include chest pain or discomfort, shortness of breath, dizziness, nausea, excessive sweating and feeling of pain or discomfort in arms, back, neck, or the jaw [9-14]. ACS is generally accompanied by several dangerous comorbidities [15] such as, diabetes [16, 17], anemia [18, 19], obesity [20, 21], atrial fibrillation [22] and chronic renal failure [23] making the prognosis for this disease that much worse. Over the years, a variety of therapeutic strategies and interventions have been considered for the treatment of ACS. Dual antiplatelet therapy has become the treatment of choice in management of ACS in recent years, replacing monotherapy with Aspirin which was common place for many years. In this method, 2 drugs with different antiplatelet mechanisms of action are utilized to prevent recurrent thrombotic events [24-30]. Adenosine diphosphate (ADP) is an agent greatly associated with platelet aggregation and thrombin generation. ADP exerts its effects by activating G-protein-coupled receptors, namely, P2Y1 and P2Y12. Additionally, P2Y12 induces growth and stabilization of thrombus and displays a more selective tissue distribution than P2Y1 and therefore is of significant importance in choice of proper intervention for ACS management [31-34]. Ticagrelor specifically and reversibly binds to P2Y12 platelet receptor and induces a conformational alteration in the receptor, rendering it inactive. Consequently, antagonization of P2Y12 by Ticagrelor interferes with platelet activation signaling pathway and inhibits platelet aggregation [35-38]. Furthermore, long-term monotherapy with Ticagrelor has been considered in high risk patients following percutaneous coronary intervention to reduce the risk of bleeding in patients [39]. The previous studies provide detailed information about efficacy and safety of Ticagrelor in management of thromboembolic events in Acute Coronary Syndrome and its interaction with P2Y12 receptor. However, the exact structural and molecular drug-receptor interactions and the amino acids involved remains unstudied. In the present study, we analyzed the exact molecular mechanisms involved in interaction of Ticagrelor with P2Y12 receptor using molecular docking methods and computational chemistry. Moreover, the pharmacokinetic behavior and biological attributes of the titled drug was determined using SwissADME and FAFdrugs4 web tools.

COMPUTATIONAL METHODS

In silico study in medicines refers to evaluating the mechanisms of their interactions and metabolisms in the living organisms without any experiment. These studies are performed using different chemistry software packages by high computers [40-43]. This type of study helps us to design and discovery novel medicinal molecular structures without the need for expensive lab work and clinical trials [44-46]. In silico study contains various methods and techniques for prediction of the physicochemical properties of the chemical compounds and their biological treatment in the cells [47-49]. Quantum mechanics uses different estimations for solving the wavelet equations about small molecules and it divides to various techniques [50-52]. In the present study, the Ticagrelor molecular structure optimizes using density functional theory (DFT). Firstly, Ticagrelor molecular structure is optimized at B3LYP/6-311++G(d,p) level of theory in isolated form at room temperature using Gaussian 03 software. After molecular geometry optimization, the stability and reactivity properties of the title medicinal compound will be discussed using global

reactivity indices. These parameters are calculated using the energy levels of the frontier molecular orbitals (FMOs) [53]. Finally, the steric and hydrogen bond interactions of Ticagrelor with $P2Y_{12}$ receptor will be analyzed using molecular docking method. The molecular docking analysis is carried out by Molegro Virtual Docker (MVD) program.

RESULTS AND DISCUSSION

Ticagrelor structural properties study

Ticagrelor is a small molecule with antagonistic activity of the $P2Y_{12}$ receptor. This medicinal compound was approved by the food and drug administration (FDA) of the united states on July 20, 2011 [54]. Figure 1 shows the theoretical molecular structure and optimized geometry of the said medicinal compound. Ticagrelor has high similarity to adenosine. Its cyclopentane ring and nitrogen rich aromatic system are similar to the sugar ribose and the nucleobase purine. Optimization of the molecular structure of the Ticagrelor is necessary for further computational studies on the compound. The said molecular structure was optimized using B3LYP density functional method with 6-311++G(d,p) level of theory at room temperature. Figure 2 indicates the dependence between the theoretical and experimental bond lengths of the medicinal compound Ticagrelor. This dependence is shown by the equation y=0.9922x-0.0103. The higher correlation coefficient (R^2=0.9793) for this equation shows 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 title compound.

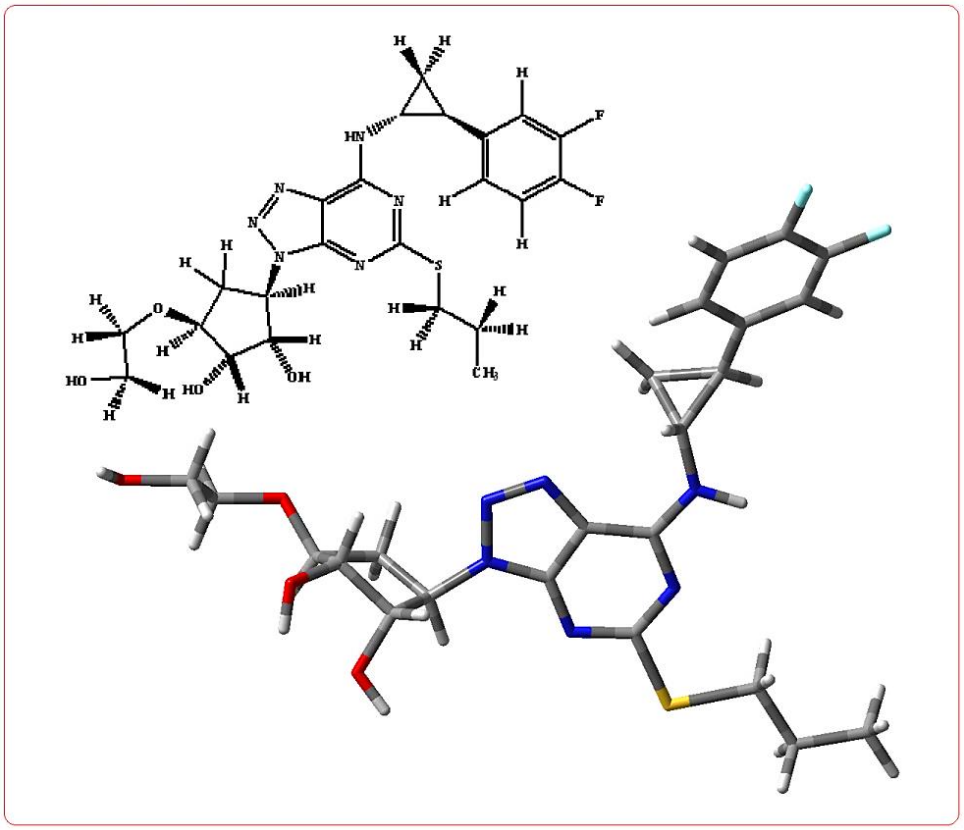

Fig. 1. The theoretical geometric structure of Ticagrelor.

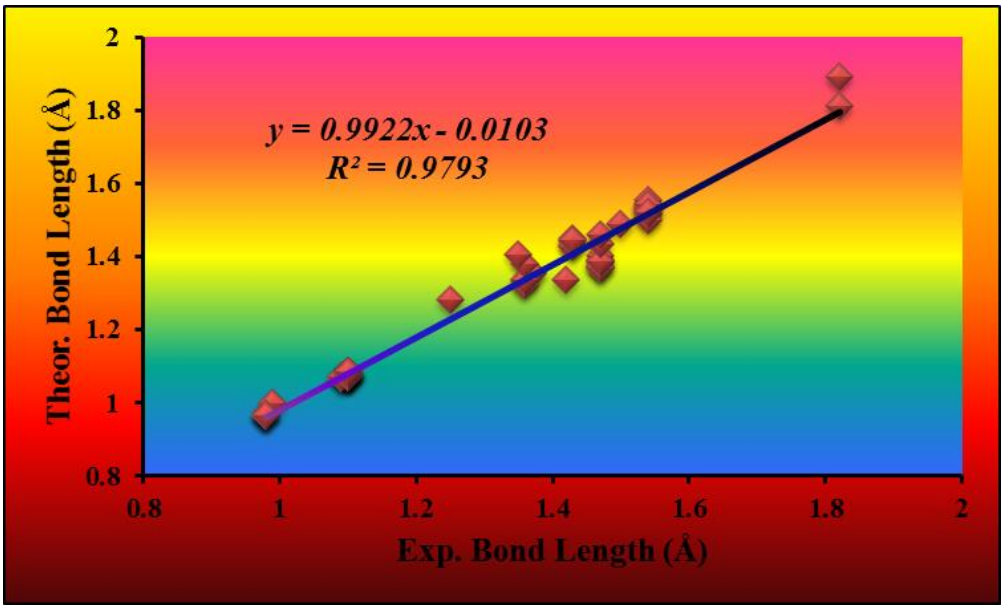

Fig. 2. The experimental and theoretical bond lengths relationship of Ticagrelor.

Stability and reactivity study of the medicinal compound Ticagrelor

Efficiency of a medicinal compound relies on two parameters: 1) its potency in interaction with biomolecules, 2) its potential stability against unwanted reactions like hydrolysis and oxidation. So, Stability and reactivity are two main parameters to describe a medicinal molecule [55]. The frontier molecular orbitals (FMOs) theory helps us in accessing the global reactivity indices which they state the stability and reactivity parameters of the molecules. FMOs divide to two molecular orbitals (MO). The highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) are the FMOs of the chemical compounds. The HOMO is filled with electrons and in contrast the LUMO is empty of electron [56-58]. 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 [59]:

$$E_g = E_{LUMO} - E_{HOMO}$$
$$IP = -E_{HOMO}$$
$$EA = -E_{LUMO}$$
$$\eta = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2}$$
$$\chi = \frac{-(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$
$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$
$$\omega = \frac{\mu^2}{2\eta}$$
$$S = \frac{1}{\eta}$$

The frontier molecular orbitals (HOMO and LUMO) of the said medicinal compound are shown in Figure 3. We can see both HOMO and LUMO are made by elements of the nitrogen rich aromatic system and cyclopropane ring. So, these rings are more reactive than other atoms of the compound. It can be seen from the data of the Table 1, the HOMO and LUMO energy levels are -9.02 eV and 2.32, respectively. The low energy of HOMO

shows the molecule don't like to react with electron poor agents. On the other hand, the big energy of LUMO states the lack of tendency of the molecule to reaction with electron rich agents. The HOMO/LUMO energy levels gap is 11.34 eV. The big energy gap of the FMOs (Figure 4) shows high stability of the title medicinal compound. The electron transfer doesn't happen between frontier molecular orbitals. Also, the density of states graph (DOS) indicates the virtual orbitals have more density than the occupied molecular orbitals. So, it can be said the Ticagrelor prefers to react with electron rich agents or residues. The high chemical hardness (5.67 eV) and the low chemical softness (0.176 eV) indices show the high stability and low reactivity of Ticagrelor. Figure 5 indicates the molecular electrostatic potential (MEP) graph of the molecule under study. The red, green and blue colors in this graph show the regions of the molecule with negative, zero and positive charges, respectively. It seems the charge density of the hetero-atoms (N, F, S and O) are negative. So, these atoms of the molecule can interact with residues of the receptor.

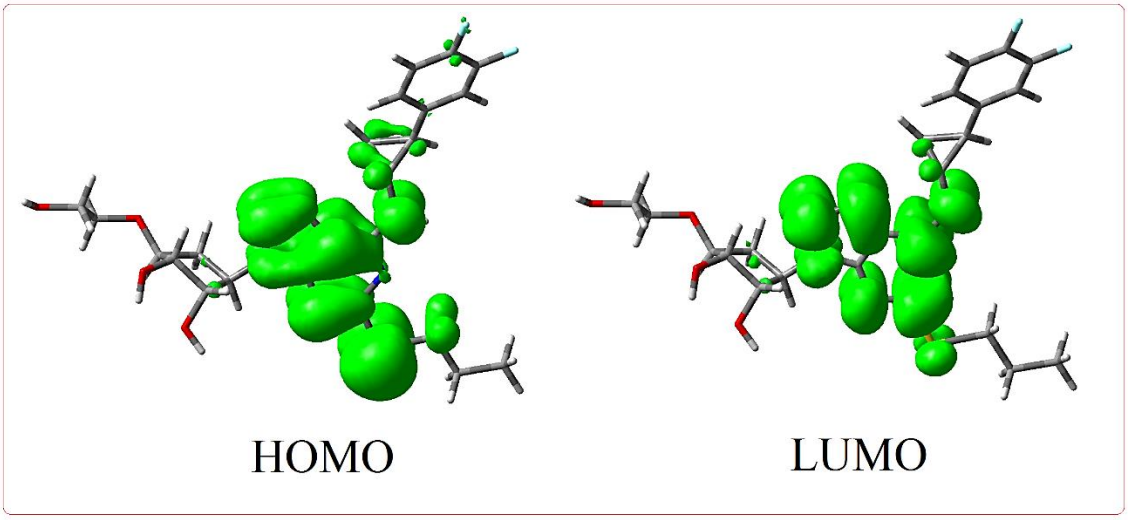

Fig. 3. The frontier molecular orbitals of Ticagrelor.

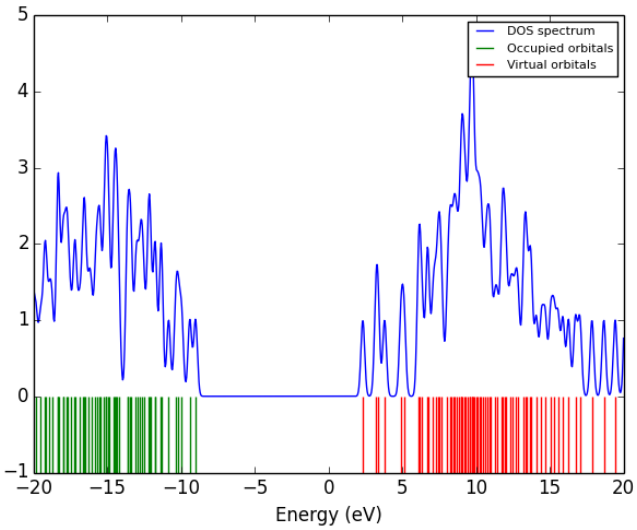

Fig. 4. The density of states (DOS) graph of Ticagrelor.

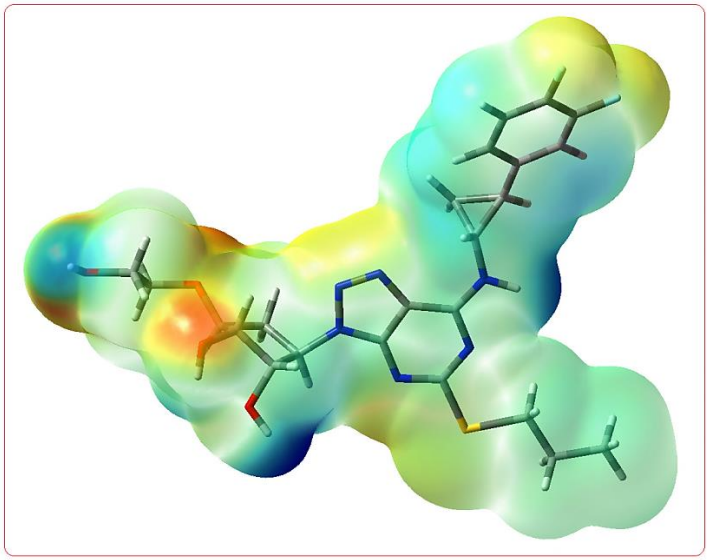

Fig. 5. The molecular electrostatic potential (MEP) graph of Ticagrelor.

Table 1. Global reactivity indices of Ticagrelor

Parameter	Energy value (eV)
HOMO	-9.02
LUMO	2.32
Ionization Potential (IP)	9.02
Electron Affinity (EA)	-2.32
Energy Gap (Eg)	11.34
Electronegativity (χ)	3.35
Chemical Potential (μ)	-3.35
Chemical Hardness (η)	5.67
Chemical Softness (S)	0.176
Electrophilicity index (ω)	0.990

Physicochemical descriptors and ADME parameters of the compound Ticagrelor

Evaluation of absorption, distribution, metabolism and excretion (ADME) has long been considered an important step in the process of drug discovery and drug development [60]. Assessment of physicochemical and pharmacokinetic attributes of the lead compound is now performed at early stages of drug discovery to lower the chance of failure in later stages. ADME prediction and computational analysis of the compound Ticagrelor was performed using SwissADME and FAFdrugs4 web tools. The predicted physicochemical graph of the investigated compound is presented in Figure 6. The evaluation of the compound's *physiochemical properties* in the first section showed a molecular weight of 522.57 g/mol, 36 heavy atoms, 15 aromatic heavy atoms, the fraction Csp3 of 0.57, 10 rotatable bonds, 10 hydrogen bond acceptors and 4 hydrogen bond donors. Moreover, the calculated topological polar surface area (TPSA) is 128.22 $Å^2$ and the molar refractivity is 163.74. The next factor examined is *lipophilicity*. Lipophilicity plays a major role in determining the lead compound's solubility, permeability through biological membranes, toxicological profile,

selectivity, potency and metabolism. Lipophilicity values are determined by measurement of the partition coefficient between n-octanol and water (log PO/W). ADME utilizes five predictive models regarding lipophilicity of the compounds (iLOGP, XLOGP, WLOGP, MLOGP and SILICOS-IT). Based on calculations, iLog P of the compound is 3.81, XLog P3 is 2.03, WLog P is 2.66, MLog P is 2.12, SILICOS-IT is 1.79 and the consensus log PO/W is 2.48. *Water solubility* significantly influences the drug's bioavailability and absorption from gastrointestinal tract (GIT) and therefore is of great importance in drug discovery and design, specifically in oral dosage forms. Water solubility of the title compound was determined using ESOL model, a topical method to evaluate Log S. In this regard, the compounds are placed into six categories: 1) Insoluble (Log S < -10), 2) Poorly soluble (-10< Log S< -6), 3) Moderately soluble (-6< Log S< -4), 4) Soluble (-4< Log S< -2), 5) Very soluble (-2< Log S< 0) and 6) Highly soluble (Log S > 0). The measured Log S is -4.01, determining the compound moderately soluble. Individual ADME behaviors of the molecule is predicted in *pharmacokinetics* section. The investigated compound has a low gastrointestinal (GI) absorption, does not permeate blood-brain barrier (BBB) and is a P-gp efflux pump substrate. Identifying CYP 450 inhibitory potential of the compound is important in predicting any drug-drug interactions and adverse effects since drug biotransformation is heavily dependent on CYP 450 isoenzyme family. The compound shows an inhibitory effect on CYP3A4 isoform. The skin permeation index (Log Kp) is calculated using lipophilicity and molecular weight of the compound and the more negative values are indicative of lower skin permeability. The calculated Log Kp for this molecule is -8.05 cm/s. The compound's drug likeness was determined based on its compliance with Lipinski's rule of five (MLOGP ≤4.15, relative MW ≤ 500, N or O ≤ 10, NH or OH≤ 5) and bioavailability score. The investigated molecule shows one violation from Lipinski's rule as its molecular weight exceeds 500 and has a bioavailability score of 0.55. The molecular structure was further analyzed using FAFdrugs4 web tool. The results are presented in Figures 7. Section a in the Figure is *Physchem Filter Positioning* which provides a radar plot, incorporating all predicted physiochemical descriptors. The compound's values (blue line) should reside in the drug-like filter area (pale blue and red). As observed in Figure 6, the compound falls within the designated ranges. Section b visualizes *Compound Complexity*. It involves the number of system rings, stereo centers, rotatable and rigid bonds, the flexibility (ration between rotatable and rigid bonds), the carbon saturation (fsp3 ratio) and the maximum size of system rings. The compound's value (blue line) is superimposed outside of the oral library min and max ranges (determined by red and pink areas). Section c analyses Golden Triangle Rule which is a visualization tool used to optimize clearance and oral absorption of drug candidates. The compounds located in the triangle are likely to have an optimal permeability (low clearance) and a good metabolic stability. As presented in Figure 6, the compound is positioned outside of the golden triangle. Section d represents Oral Property Space, which is obtained by applying the PCA (Principal Component Analysis) of the 15 main physico-chemical descriptors of the chosen compounds (red), compared with two oral libraries extracted from eDrugs (blue) and DrugBank (orange). The compound is located within the specified range. Oral Absorption Estimation is presented in section e. The compounds

values are represented by the blue line, which should fall within the optimal green area (Rule of 5 and Verber rule area). The white area is the extreme maximum zone and the red one is the extreme minimum zone. These zones are determined by the following descriptors ranges: LOGP (-2 to 5), MW (150 to 500), tPSA (20 to 150), Rotatable Bonds (0 to 10), H-Bonds Acceptors (0 to 10) and Donors (0 to 5). The title compound is mostly located within acceptable ranges. Lastly, Pfizer 3/75 rule is exhibited in section f. Molecules located in red square are more likely to cause toxicity. The compound under investigation is placed in the green square predicting it to be non-toxic.

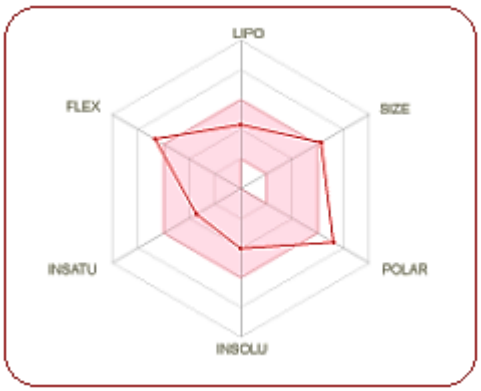

Fig. 6. ADME properties of the compound Ticagrelor.

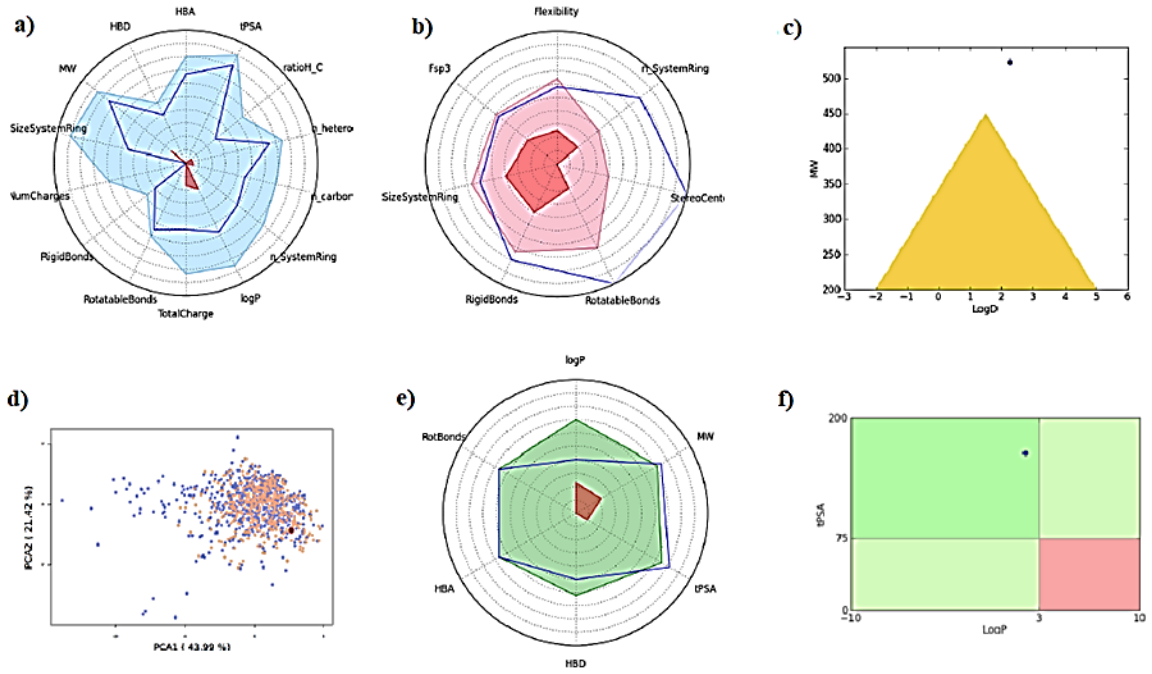

Fig. 7. FAFdrugs4 ADME results of the compound Ticagrelor.

Molecular docking analysis of Ticagrelor-P2Y$_{12}$ complex

The survey through previous studies determines the therapeutically effects of Ticagrelor in prevention of thrombosis in different classifications of disorders [7]. It is the first reversibly binding oral P2Y$_{12}$ receptor antagonist that blocks ADP-induced platelet aggregation [61]. Here, making complex between Ticagrelor and the said receptor has been studied by molecular docking technique. The docking analysis was done using Molegro Virtual Docker (MVD) program. Figure 8 indicates embedding the title medicinal molecule in the active site of the P2Y$_{12}$

receptor. As can be seen from the data of the Table 2, the MolDock score is -160.198 for docking the molecule in the biomolecule. Making ligand-receptor complex is done using steric and hydrogen bond interactions with scores -146.886 and -7.536, respectively. So, the steric interactions play main role in ligand-receptor complex formation. The receptor residues Ile 212, Lys 233, Thr 126, Leu 211, Thr 127, Arg 218, Glu 215, Lys 232, Tyr 123, Asp 1050, Pro 129, Arg 128, Lys 125, Lys 237, Arg 231, Arg 122, Asn 235 and Val 234 participated in steric interactions. In contrast, only the residues Thr 126, Asn 235, Lys 237 and Arg 231 can make interaction with the molecule using hydrogen bond formation. From the data of the Table 3, the residues Lys 232, Lys 125, Thr 126, Glu 215, Arg 231, Ile 212, Asn 235, Thr 127, Lys 233, Arg 128, Tyr 123 and Lys 237 made the strongest interactions with the Ticagrelor.

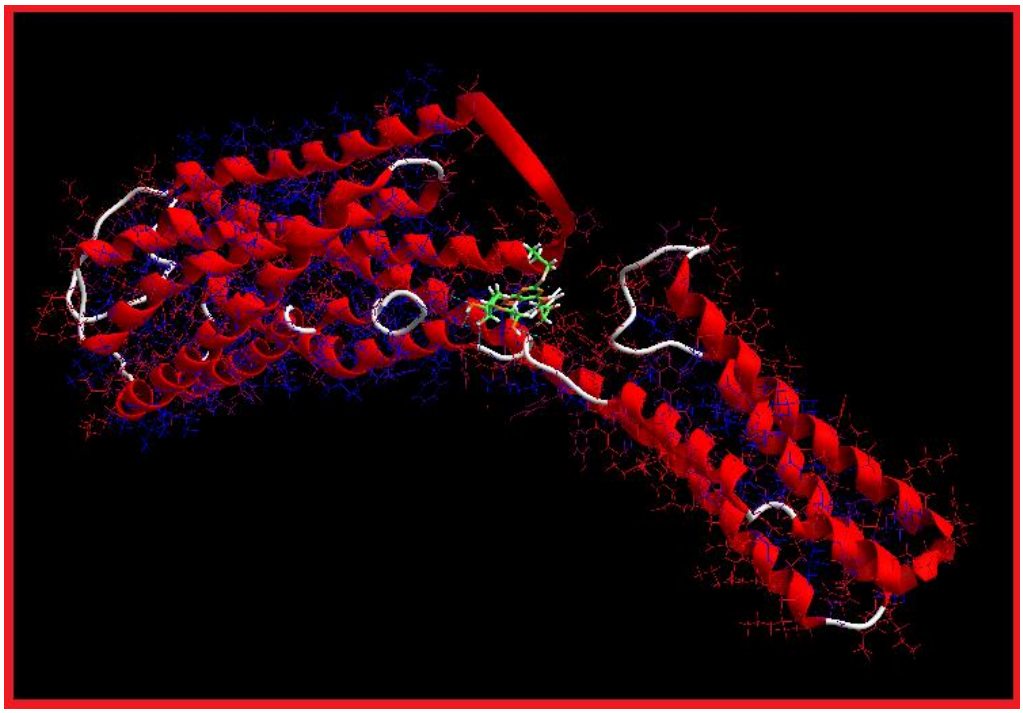

Fig. 8. Ligand Ticagrelor embedded in the active site of the $P2Y_{12}$ receptor.

Table 2. The Ticagrelor-$P2Y_{12}$ interactions

Interactions		**MolDock Score**
Protein-Ligand Interactions	Steric (by PLP)	-146.886
	Steric (by LJ12-6)	11.679
	Hydrogen bonds	-7.536
	Hydrogen bonds (no directionality)	-9.712
Water-Ligand Interactions		-17.467
Internal Ligand Interactions	Torsional strain	5.573
	Steric (by PLP)	6.118
	Steric (by LJ12-6)	76.822
External and Internal Ligand Interactions	Total Energy	-160.198

Table 3. The participated $P2Y_{12}$ residues in ligand-receptor interactions

Residue/HOH	Total energy score
Lys 232	-29.7663
Lys 125	-19.0824
Thr 126	-17.3650
Glu 215	-12.4610
Arg 231	-10.1185
Ile 212	-9.72142
Asn 235	-9.07780
Thr 127	-8.20541
Lys 233	-7.40074
Water	-6.39978
Arg 128	-6.27955
Water	-5.84412
Tyr 123	-5.82000
Lys 237	-5.47779
Leu 211	-4.96896
Water	-2.85219
Water	-2.37070
Arg 122	-1.64622
Val 234	-1.27535
Asp 1050	-1.15794
Arg 218	-0.415144
Pro 129	-0.367183

CONCLUSIONS

Investigation of the physico-chemical and electronic properties of Ticagrelor was the main objective of the present research work. Electronic properties prediction of the molecule was carried out using the quantum mechanical (QM) computations. The molecular structure was optimized at B3LYP/6-311++G(d,p) level of theory. The frontier molecular orbitals (HOMO and LUMO) energies were used to calculation of the global reactivity indices. The mentioned indices showed the high stability and low reactivity of the compound under study. The molecular electrostatic potential (MEP) graph shows the electronegative elements of the molecule prefer to interact with the residues of the $P2Y_{12}$ receptor. Evaluation of the intramolecular bonds between the molecule and the receptor indicates the main role of the $P2Y_{12}$ residues containing Lys 232, Lys 125, Thr 126, Glu 215, Arg 231, Ile 212, Asn 235, Thr 127, Lys 233, Arg 128, Tyr 123 and Lys 237 in the ligand-receptor complex formation. From the molecular analysis data, formation of the ligand-receptor complex was mainly done by the steric interactions. Finally, the ADME study showed the said compound is non-toxic.

CONFLICT OF INTERESTS

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

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داکینگ مولکولی و پیشبینی خواص فیزیکوشیمیایی محاسباتی داروی تیکاگرلور به عنوان یک ترکیب آنتاگونیستی برای پذیرنده P2Y12

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چکیده

هدف از این کار تحقیقاتی، پیشبینی خواص فیزیکوشیمیایی و الکترونی ترکیب دارویی جدید تیکاگرلور با استفاده از روش نظریه تابع چگالش می‌باشد. در قدم اول، ساختار مولکولی این ترکیب با استفاده از روش محاسباتی B3LYP/6-311++G(d,p) در دمای اتاق بهینه شد. ضرایب واکنش‌پذیری کلی برای بررسی واکنش‌پذیری و پایداری ترکیب مورد مطالعه مورد استفاده قرار گرفت. این ضرایب، پایداری بسیار بالا و واکنش‌پذیری بسیار پایینی را برای مولکول نشان داد. از سوی دیگر، تصویر پتانسیل الکتروستاتیکی مولکولی نشان می‌دهد که اتم‌های نیتروژن، فلوئور، گوگرد و اکسیژن در این مولکول می‌توانند با آمینواسیدهای پذیرنده واکنش دهند. آنالیز محاسبات داکینگ مولکولی نشان می‌دهد که آمینواسیدهای Lys 232, Lys 125, Thr 126, Glu 215, Arg 231, Ile 212, Asn 235, Thr 127, Lys 233, Arg 128, Tyr 123 و Lys 237 مهمترین آمینواسیدهایی از پذیرنده هستند که در تشکیل کمپلکس لیگاند- پذیرنده شرکت می‌کنند. بررسی پیوندهای درون مولکولی نشان می‌دهد که برهمکنش‌های الکترونی- فضایی مهمترین نقش را در تشکیل این کمپلکس ایفا می‌کنند.

کلید واژه‌ها: AZD6140، پذیرنده P2Y12، مهار تجمع پلاکتی، تیکاگرلور، داکینگ مولکولی، شبیه سازی مولکولی

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