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Density Functional Theory and Molecular Modeling Studies of New 4-(Furan-2-yl) Thiazol-2-Amine Derivatives as Cyclooxygenase Inhibitors

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) involve various of pharmacologically active compounds used in treatment of acute and chronic inflammation, relieve pain and fever, but chronic use of NSAIDs associated with gastrointestinal lesions, hemorrhage and nephrotoxicity. In this present research molecular modeling approach was applied on several derivatives of thiazole bearing Schiff base to design safe and effective compounds. These derivatives were docked inside the crystal structure of cyclooxygenase enzyme (COX-1 and COX-2) to evaluate the binding potency of each one with the active site of enzyme. Also, we used density functional theory (DFT) by applying energies evaluation of the highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs) in order to identify the reactivity parameter. Furthermore, root mean square deviation (RMSD) tool was used which shows an important role in the comparison of different conformers of the same ligand and it means a similarity measure vastly utilized in analysis of macromolecular structures and dynamic.

Keywords: Drug Design; HOMO; LUMO; RMSD; Inflammation; DFT.

1. Introduction

Inflammation is known as local response of tissues to injury by any agent. Specifically, it is a series of molecular and cellular responses acquired to get rid of foreign agents and promote repair of affected tissues [1]. It is due to release of chemicals mostly prostaglandin from tissues and migrating cells [2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the main therapeutic agents in the treatment of inflammation and relieve pain. Because of their anti-inflammatory, antipyretic and analgesic activity, they represent the first line of drugs in the treatment of various inflammatory diseases such as arthritis and rheumatism [3]. NSAIDs are inhibitors of cyclooxygenase enzyme (COX) that catalyzes the first step of biosynthesis of prostaglandins (PGG2) from arachidonic acid. COX enzyme has two isoforms: COX-1 enzyme which is formed constitutively (i.e. gastric mucosa) and COX-2 enzyme which is inducible (when inflammation occur) [4].

There is a homology with high degree between COX-1 and COX-2 enzyme: 84% of amino acids are similar and 61% of them are identical. In the upper active site, the homology is >90%. Only a restricted number of sites with the potential for selective exploitation appear. The important one is a substitution at position 523 between isoleucine (in COX-1) and valine (in COX-2). The single methyl group difference is enough to form additional space in the active site and this is defined as the COX-2 pocket [5].

Treatment using NSAIDs associated with drawbacks especially with gastrointestinal tract like dyspepsia, gastric ulcers, and others. In order to avoid these negatives, there is a necessitous need for design and synthesis of new chemical compounds with good anti-inflammatory response and minimum side effect [6]. Thiazole core moiety presents in number of

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natural and synthetic compounds. These compounds are of great importance for their antitumor [7], antimicrobial, anti-HIV [8], anticoagulants [9], anti-inflammatory [10], and antioxidant [11] properties. Thiazole bearing Schiff bases (compounds with carbon nitrogen double bond) show significant role especially in medicinal chemistry due to their flexibility, unlimited efficacy of azomethine group and structural similarities with natural biological substances [12].

In order to overcome time and resources consuming in drug design process, we use computational method that has effective role in drug development, advantage of chemical and biological information about ligands and/or targets to optimize new drugs and design of in silico filters to exclude compounds with unwanted properties such as poor activity and/or poor absorption, distribution, metabolism, excretion and toxicity (ADMET) to select the most promising one [13]. knowledge the reactivity of chemical species is one of the most important questions in chemistry. The evolution of theories to demonstrate factors that affecting reactivities is highly valuable in order to know why a reaction occur and how fast a reaction can be. Likewise, getting quantitative indexes of reactivities is important in rational design because of the role of these indexes in calculation and prediction of the reactions rate. For these causes, many attempts have been done by chemists to evolve quantitative signifiers of reactivities. Obtaining the reactivities (as nucleophilicities and electrophilicities) of molecules is of great role in chemistry. Many theories, such as density functional theory (DFT) which shows that the nucleophilicity of a molecule is linked with the energy of the highest occupied molecular orbital (HOMO) of the nucleophile, while the electrophilicity is linked with the energy of the lowest unoccupied molecular orbital (LUMO) of the electrophile [14]. HOMO and LUMO energies demonstrate that the charge transfer take place within the molecule [15]. The energy of HOMO (E-HOMO) is predominantly related to the ability of a molecule to donate electrons. Therefore, the increase in values of E-HOMO may support the adsorption and thus the efficiency of inhibition by signaling the disposition of the molecule to donate electrons of orbital to a suitable acceptor that has empty molecular orbitals. On the other hand, the energy of LUMO (E-LUMO) is refers to the ability of the molecule to accept electrons. When the value of E-LUMO is low, this means that the molecule is more probable to accept electrons [16] . Other parameter is root mean square deviation (RMSD) which is one of the most generally utilized expression to identify the structural (dis)similarity between two conformations of a molecule [17]. In molecular dynamics (MD) and protein-ligand docking (PLD) techniques, for instance, this tool is important for the analysis and verification of the results [18].

At the end, series of theoretically active compounds designed by our team to generate new anti-inflammatory agents with high binding affinity inside enzyme.

2. Computational Method

Drug discovery and development consider as great challenge in recent years, because of the cost and efforts which required to develop novel compound with suitable pharmacological properties. The failure of many drugs in phase II and III of clinical trial due to their toxicity and lack of activity leading to increase this cost partly [19]. Use of computational techniques is rapidly gaining in popularity and show significant role in discovery and development process of drugs because they help the researchers in avoiding time, cost and efforts consuming. The docking process is one of these techniques by which the conformation and orientation of ligand within binding site of target are predicted. The main goals of docking studies in general are accurate structural modelling and exact knowledge of activity of compounds [20].This process use three-dimensional conformations were achieved by ChemDraw16.0 program of Chem Office package software (Chem Office, 2016). Following step, geometry optimization was carried out by MM+ force field method by applying Hyperchem program version 8.013 and kept as sprite files. Furthermore, an additional geometry optimization by semi-empirical calculation (The semi-empirical method uses the same formalism as mechanical-like employing basis sets involving only the electrons of valence shell of the system [21]) was practiced with RM1 (Recife Model 1). From this stage the lowest energy conformation of molecule is kept as sdf format and improved by utilizing Spartan 14.0 package (Spartan, 2014) with Monte Carlo approach reinforced with 200 optimizations of 1500 interactions [22]. Molecular docking evaluation study and molecular modeling drug design were carried out by Glide software (Maestro 11.4) under Schrodinger software (Schrodinger, 2018) running on Windows 7 operating system on workstation (Intel(R) Core(TM) i7 CPU 895 @ 3.4GHz, 32 GB RAM, 1TB HD). The Desmond

program was used to carry out classical MD simulations for the complex of compounds structures and selected enzyme docked poses. Each complex was solvated in a simple point charge (SPC) model using an orthorhombic box with periodic boundary conditions. The overall charge of each system was neutralized by adding Na^+ or Cl^- ions as appropriate. The NPT ensemble available within the Desmond package was used for minimization and relaxation of system. Each simulation was run for a total of 5 ns with a recording interval of 100 ps. The temperature and pressure were kept constant at 310 K and 1.01325 bar, respectively, throughout the simulations. Data analyses such as root mean square deviations and ligand interaction fingerprints were performed using the simulation interaction diagram (SID) program in Schrödinger. Frontier molecular orbital is evaluated by applying a full geometry optimization via Spartan 14.0. The geometry was optimized at the density functional theory B3LYP (Becke three parameters hybrid Lee-Yang-Parr) and STO-3G basis set. The HOMO energy, LUMO energy and energy gap were computed for optimized geometrical structures. The crystal structure of COX enzyme and ligand were got from protein data bank beneath PDB code: 3LN1 with 2.4. crystallographic resolution. The enzyme preparation steps occurred by using suitable program for optimization and minimization. Ligand structure preparation occurred by utilizing Lig preprogram prior to docking to determine and add of hydrogens in order to obtain the optimal orientation and ionization position with low energy conformations of all ligands by OPLS 2005 force field. The grid box was set at 1.20 Å with 0.27 partial atomic and best docking orientation was kept to form numerous derivatives with several replacement processes application. All thiazole derivatives were saved and used for drug design evaluation.

3. Results and Discussion

The general aim of drug discovery is to identify new active compounds against biological target with improved pharmacological properties [23]. According to the role of COX enzyme in the production of prostaglandins and thus the occurrence of inflammation, efforts have been directed towards designing inhibitors for this enzyme with appropriate efficacy and minimal side effect. In this research, theoretical modeling and approaches of binding affinity were used to design new compounds of thiazole Schiff based moiety as inhibitor with high degree of binding at the active site of COX enzyme. Addition of different aldehydes to 4-(furan-2-yl) thiazol-2-amine product resulting in formation of various compounds with different docking score on both COX-1 and 2 enzymes as shown in the following table.

In virtual screening (VS), compounds are selected by computer programs to detect their binding affinity with the target receptor [24]. The results of VS to assess the score of binding affinity of whole screening compounds was between -9.788 to -5.271 kcal/mol on COX-1 enzyme while the binding ability of indomethacin was at -8.667 kcal/mol, mofezolac was at -8.62 kcal/mol and aspirin was at -6.68 kcal/mol. The docking score of all listed compounds on COX-2 enzyme was between -9.66 to -1.992 kcal/mol while the binding ability of celecoxib was at -11.557 kcal/mol, valdecoxib was at -10.84 kcal/mol, parecoxib was at -9.154 kcal/mol, rofecoxib was at -9.012 kcal/mol and indomethacin was at -8.589 kcal/mol. Among these listed compounds, compound (1) showed highest binding affinity with COX-1 enzyme while compound (6) had the highest binding affinity with COX-2 enzyme. The reasons for this highest activity is potency in binding affinity and a good orientation of molecules inside the active sites of enzyme surrounded by amino acids which are important for optimal interactions. The orientation of the best molecules from the list inside the active side of COX-1 and COX-2 enzyme surrounded by the most important amino acids are shown in figure 1.

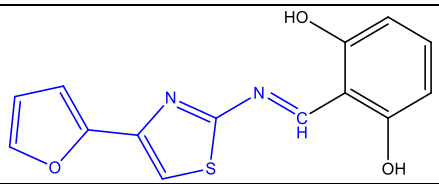
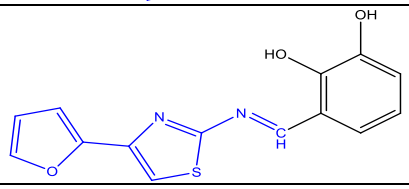
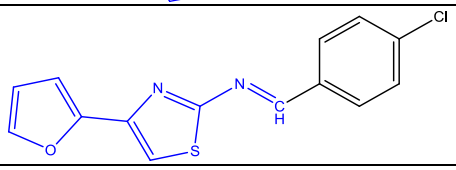
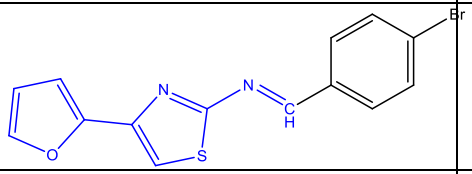
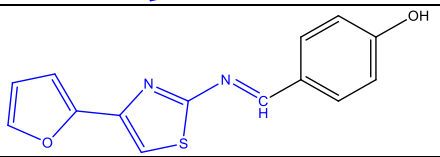
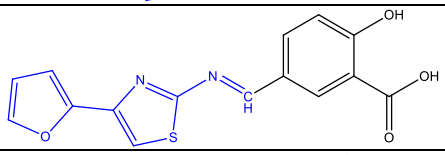
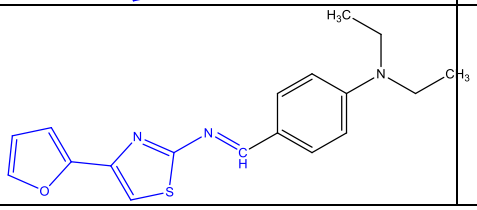
Inside COX-1 enzyme active sites, compound (1) bind by various interactions include: one pi-cation interaction between ARG 120 with thiazole ring, two pi-pi stacking interactions one between TYR 355 with thiazole ring and the other between TYR 385 with benzene ring, one H-bond between MET 522 and one hydroxyl group and also hydrophobic interactions with the surrounding amino acids (TRP 387, LEU 384, PHE 381, PHE 518, ILE 523, GLY 526, ALA 527, SER 530, LEU 531, MET 113, VAL 116, LEU 539, LEU 357, SER 353,TYR 348 and VAL 349).

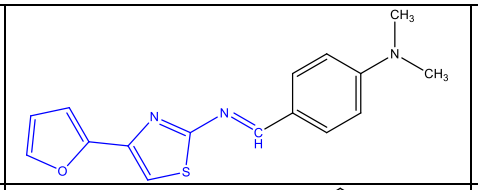
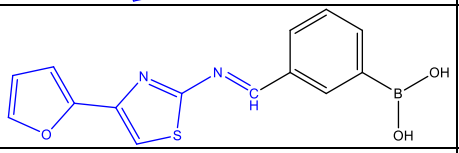
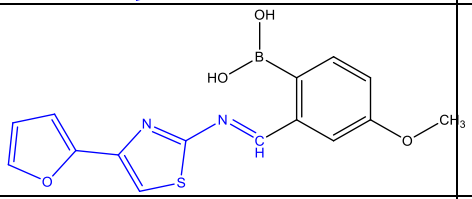
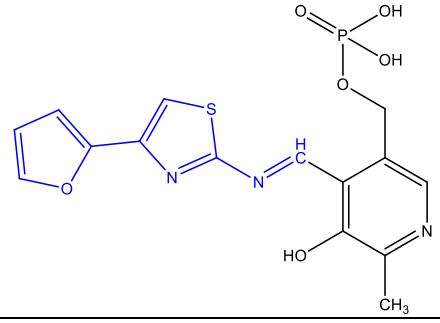
Inside COX-2 enzyme active sites, compound (6) bind by one pi-pi stacking interaction between TRP 373 with thiazole ring and one H-bond interaction between LEU 338 with hydroxyl group of COOH. Furthermore, hydrophobic interactions with the surrounding amino acids (GLN 178, PHE 504, ILE 503, ALA 502, ARG 499, VAL 509, HIE 75, TYR 341, SER 339, VAL 335, TYR 334, PHE 195, TYR 371, LEU 370, PHE 367, VAL 330, PHE 191 and LEU

520). The presence of all these interactions improved the binding affinity with the enzyme leading to increase activity and potency of new generated compounds**.**

The electron donating and receiving ability of a molecule can be determined by considering HOMO and LUMO energy of that molecule. HOMO and LUMO aspect play an important role for predicting the charge transfer within the molecule, chemical reactivity, bioactivity and stability of the compound. The molecule with higher HOMO energy is the stronger electron donor while LUMO energy reflects the ability to accept the electron. The distribution of HOMO electron density in a furan ring may qualitatively indicate the active site to concentrate the electron density.

Table. Docking binding score of new thiazole derivatives inside active site of COX-1 & COX-2 enzymes.

00No.	Chemical structure	Docking score on COX-1 enzyme (kcal/mol)	Docking score on COX-2 enzyme (kcal/mol)	E_{HOMO} (kcal/mol)	E_{LUMO} (kcal/mol)	E gap (E_{HOMO} - E_{LUMO})
1		-9.78	-9.08	-123.03	-46.16	76.87
2		-8.88	-7.72	-125.87	-50.05	75.82
3		-8.43	-8.14	-126.50	-52.15	74.35
4		-8.38	-6.72	-126.71	-52.66	74.05
5		-8.30	-8.19	-121.96	-44.33	77.63
6		-8.05	-9.66	-123.42	-46.83	76.59
7		-6.61	-1.99	-114.44	-37.68	76.76

8		-5.97	-4.82	-114.35	-37.34	77.01
9		-5.76	-9.15	-123.93	-47.49	76.44
10		-5.61	-8.92	-127.40	-55.37	72.03
11		-5.27	-9.43	-123.18	-47.32	75.86

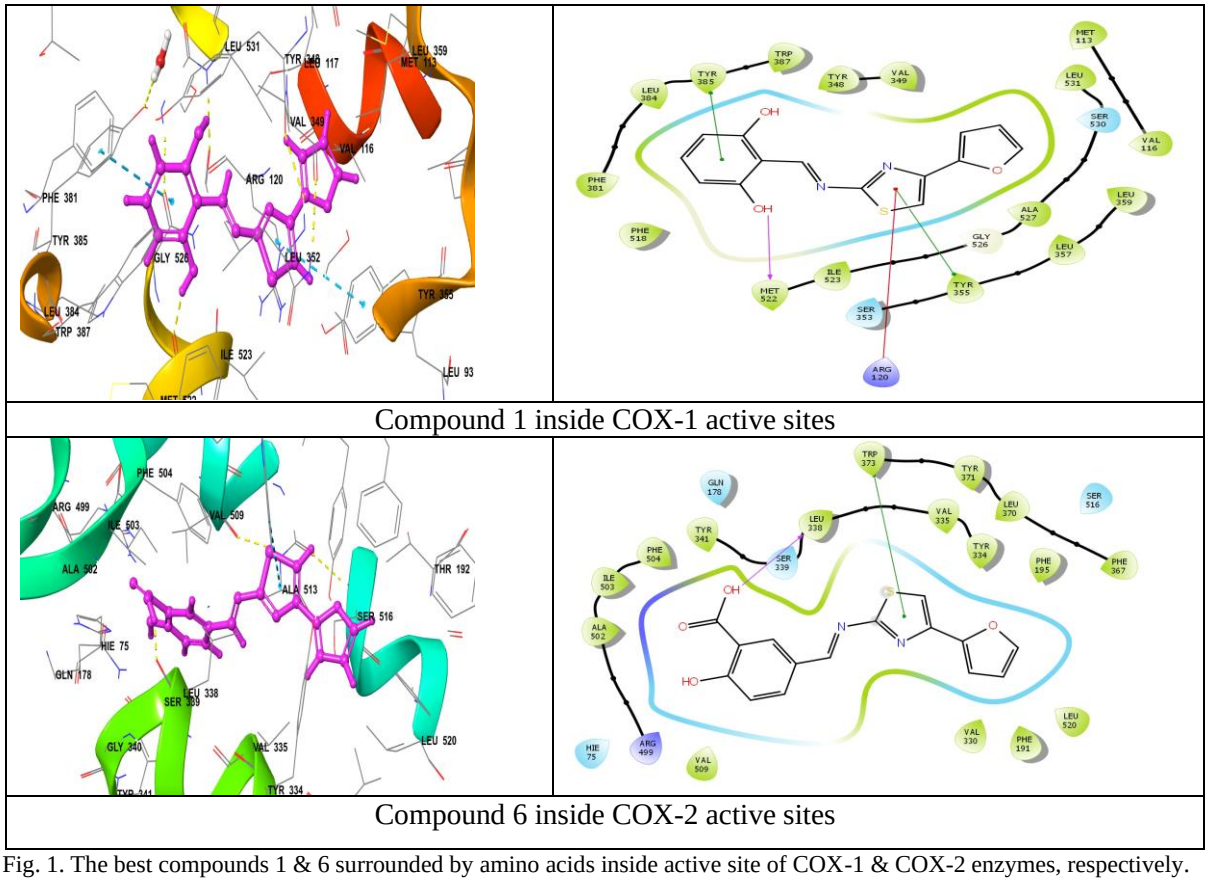


Fig. 1. The best compounds 1 & 6 surrounded by amino acids inside active site of COX-1 & COX-2 enzymes, respectively.

0

In LUMO, the electron density is distributed over thiazole and aromatic rings. This is beneficial for electron scattering and has clear effects on activity of furan ring as electron donor to stabilizes electron density over thiazole and aromatic rings. This action of furan ring is approved by the limitation of energy gap average (E_{HOMO}-E_{LUMO}) between 77.01-72.03.

The RMSD plots of compound 1 & 6 show the evaluation binding ability within simulation time of the COX-1 & COX-2 enzymes, respectively. This process can indicate the equilibrium state of fluctuations fragment at the end of simulation time based on selected ligand structure. The result shows a very good fluctuations states during simulation time within acceptable limits around 1-3 Å. Moreover, the RMSD values appears stable after 2.5 nanosecond around fixed value of receptor-ligand alignment fluctuations until the end of simulation time as shown in figure 3.

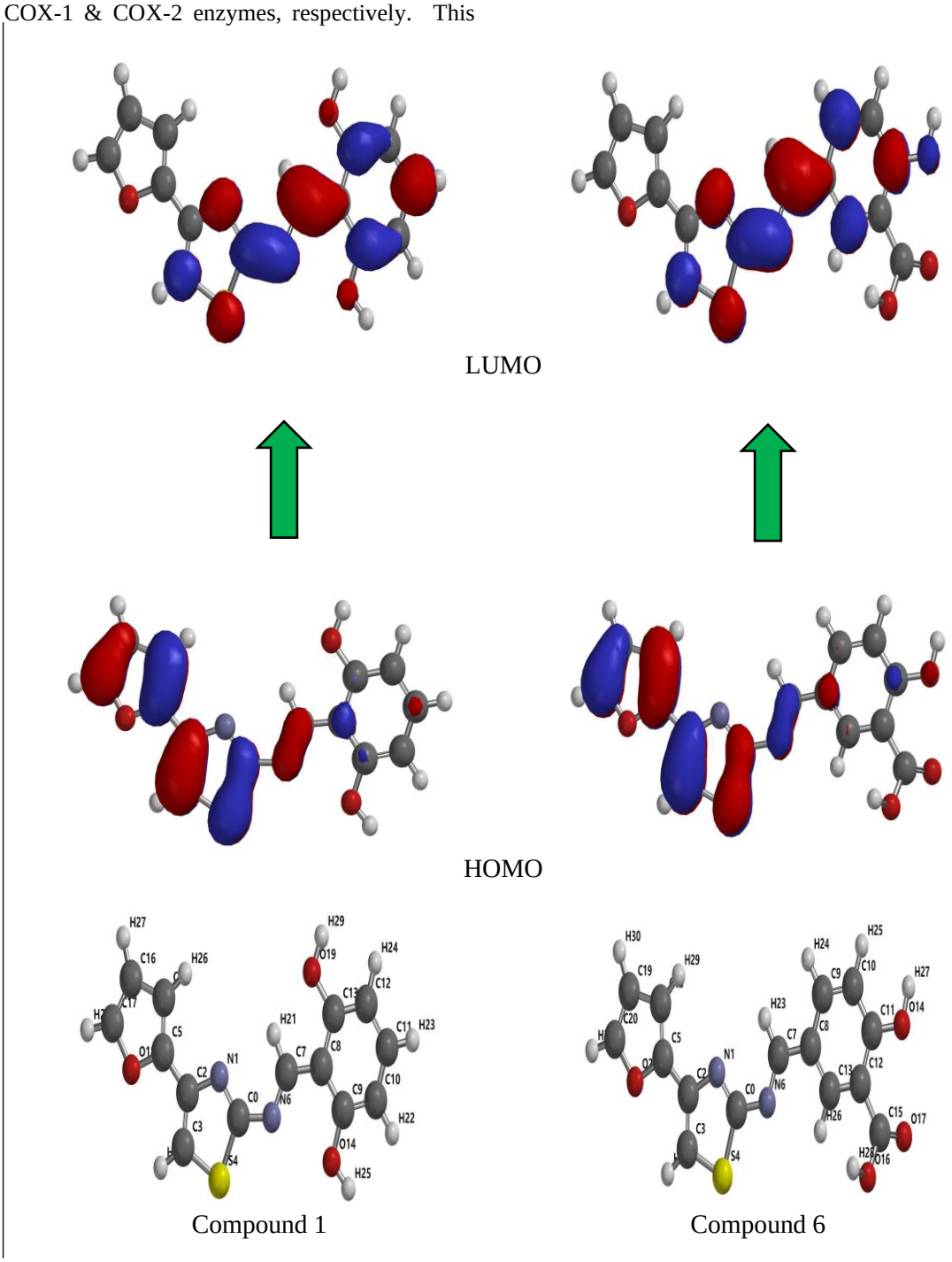


Fig. 2. The HOMO/LUMO electron densities of studied thiazole derivatives compound 1 & 6.

Figure 4 illustrate various percentage ratio of interaction of amino acids inside the active pocket during simulation. These resulst show a clear similarity with docking result by the appearance of specified amino acids kept bound to the pocket throughout simulation. For example, ARG 120, MET 522 and SER 530 show high binding by hydrogen bound interaction while VAL 116, LEU 352, TYR 359, TYR 385, TRP 387 and ALA 527 show good hydrophobic interaction inside COX-1 active pocket. For COX-2 enzyme, ARG 106, TYR 431, TYR 371 and SER 516 show hydrogen bond interaction while a clear water bridges kept connected between enzyme and ARG 106, LEU 338, SER 339 and ARG 499. For COX-1 enzyme, the main interactions inside active pocket were hydrogen bond and hydrophobic while in the same time it was various inside COX-2 active pocket.

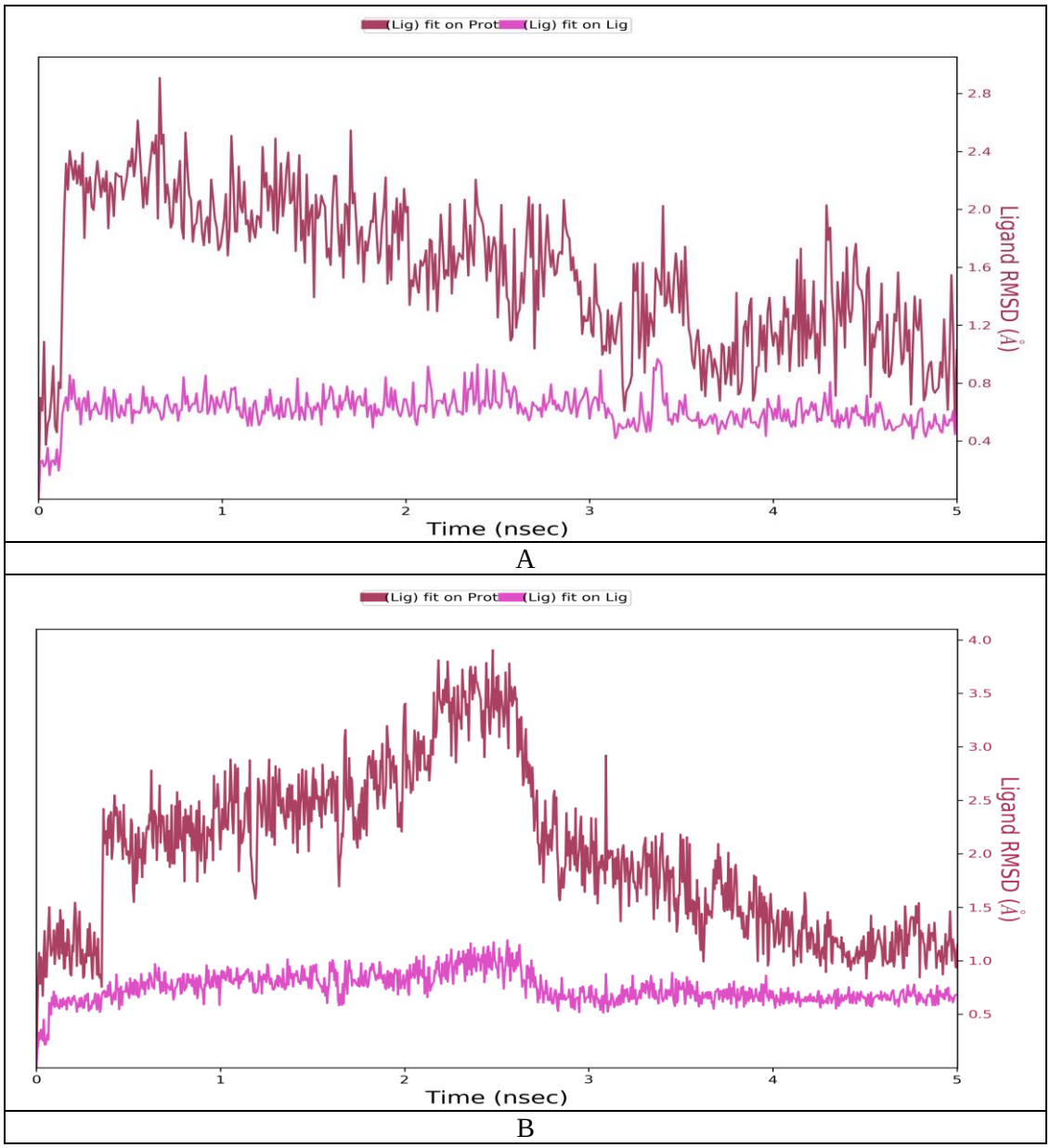
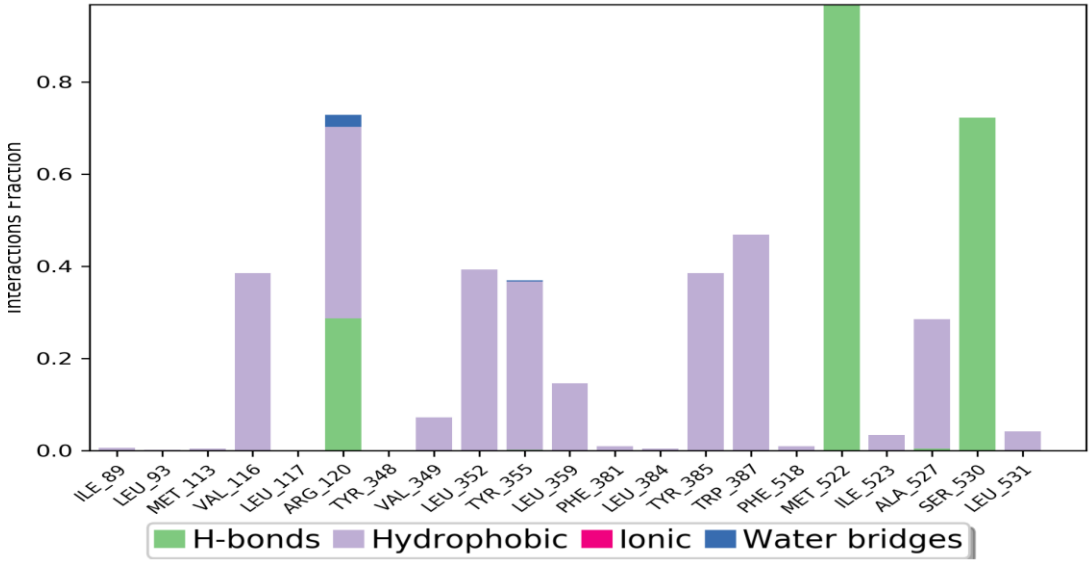
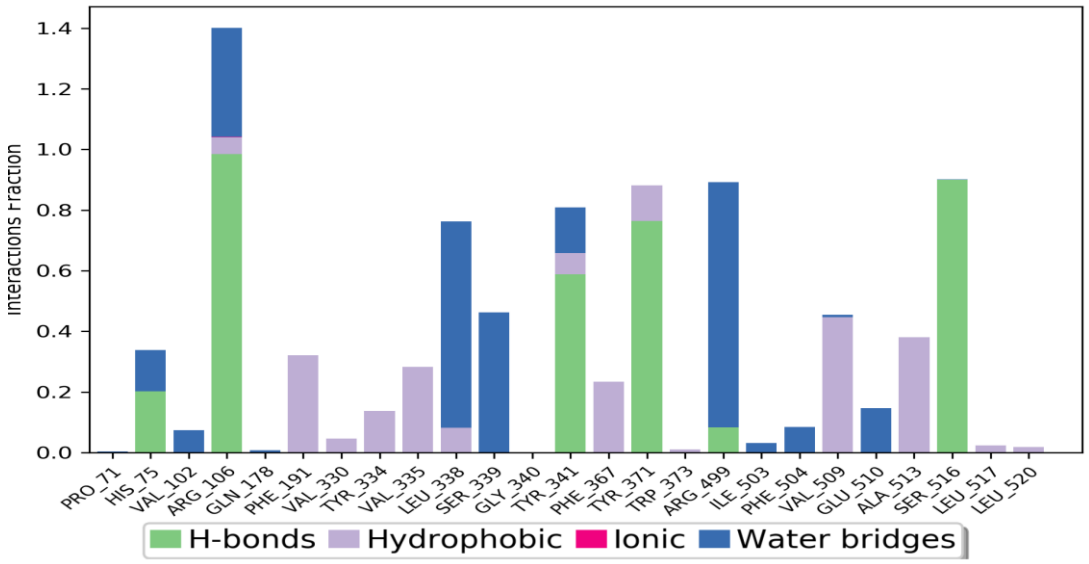


Fig. 3. The RMSD of COX-1 & COX-2 enzyme with compound 1 & 6 as complexes A & B, respectively.



A



B

Fig. 4. Amino acids interactions with COX-1 & COX-2 with compound 1 & 6 as complexes A & B, respectively during simulation time.

4. **Conclusion**

Molecular modeling is becoming a popular method for conducting experiments on computer before applying the research in laboratory. This technique permits the computer-aided generation of molecular structures in addition to computation of molecular properties. By this approach, we knew the active derivatives of thiazole Schiff base which showed higher potency and higher binding affinity with Cox enzyme.

The energies of HOMO and LUMO which estimated by quantum chemistry process are presently of great importance for the finding of new compounds.

RMSD is a similarity measure broadly utilized in analysis of macromolecular structures and dynamics. The analysis is depended on RMSD values between pairs of configurations separated by varying time intervals.

Additionally, biological and pharmacological screening is important to know the side effects and toxicity of all new designed compounds.

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