

Density Functional Theory and Docking Studies of Schiff Base Complexes of Thiazole

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ABSTRACT

We optimized and determined frontier orbitals, highest occupied molecular orbital (HOMO), and lowest unoccupied molecular orbital (LUMO) energy of Schiff base of thiazole (L) and its complexes of Cu(II) and Zn(II). Calculations were carried out using density functional theory (DFT) for thiazole (L) and its complexes with 6 to 31G* and LanL2DZ basis sets, respectively. The gap energy between HOMO and LUMO was small for the complexes and higher for Schiff base of thiazole (L). This means the Schiff base of thiazole is more stable than complexes

Since the docking studies on coordination compounds are rare, we studied Schiff base of thiazole ligand and its copper and zinc ions complexes. We used Molegro virtual docker (MVD) software to predict the inhibition activity of thiazole and its complexes against 2MUJ in plasmodium falciparum. These molecules exhibited a MolDock score of (-272.1 to -397.1) kcal/mole and a re-rank score in (-91.4 to -198.1) kcal/mole. All studied molecules exhibit good docking results, but the best one is the copper complex.

Keywords: Discrete fourier transform, Docking, Malaria, Schiff base, Thiazole.

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INTRODUCTION

Schiff base ligands exhibited the ability to coordinate to many metals ions.¹ They are used as dyes, pigments, intermediates inorganic synthesis, catalysts, and polymer stabilizers.² Plenty of Schiff base ligands exhibit biological activities³ including antitumor, anti-bacterial, fungicidal, and anticarcinogenic properties,⁴ candidates for Alzheimer's disease.⁵

Compounds of thiazole have large range of biological activities such as anti-microbial,⁶ anti-inflammatory, antitubercular, anticonvulsant, and anticancer.⁷⁻⁹ There are many drugs with thiazole ring,¹⁰ such as famotidine which is used for the treatment of peptic ulcer and controls gastro-esophageal reflux, Abafungin for the treatment of dermatomycoses Cefdinir for treatment of FDA-approved anti-microbial and a third era wide range cephalosporin.¹¹

The analogues of curcumin were studied by (molegro virtual docker) against the main protease of COVID-19. They can be used as antiviral drug candidates for COVID 19 because of their potential inhibitor of the main protease of COVID-19.¹²⁻¹⁸

The molecular docking is considered good practice to get potential therapeutics via short time and low cost to fill the lack of drugs and vaccines for plenty of diseases such as cancer, viruses, malaria, and bacteria.¹⁹⁻²¹ In this device, we can test the interactions of the ligands and metal coordination complexes in the three-dimensional space with the targets.^{22,23} Molegro virtual docker is an excellent software for successfully docking ligands

and metal-ligands complexes with very reasonable and less time-consuming.²⁴

Molegro virtual docker was used for docking plenty of compounds to predict their anticancer activity, and it exhibited good results.²⁵ Molegro virtual docker was used in many studies to get solutions or notices on the resistance problem for malaria drugs^{26,27} and check the binding interaction of many ligands with malaria proteins to increase *Plasmodium falciparum* inhibition.²⁸⁻³¹ This problem is considered as a big challenge to treat malaria, an endemic particularly in some places of the world like African countries.²⁸

This study aims to optimize geometry for Schiff base ligand of thiazole and its copper and zinc ions complexes prepared and characterized by Abd Elzاهر.³² On the other hand, the study aims to investigate the inhibitor ability of these molecules against 2MUJ in plasmodium falciparum which causes malaria in humans.

MATERIALS AND METHODS

The geometry optimization of Schiff base ligand (L) of thiazole and its complexes was achieved using DFT with B3LYP/6-31G* level for the ligand and B3LYP functional under LanL2DZ basis set for copper(II) and zinc(II) complexes using Gaussian 09 package. On the other hand, we calculated gap- energy and the shapes of HOMO and LUMO orbitals of these compounds.

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The docking examinations were performed for these molecules via employing molegro software program according to the literature information. We downloaded the 2MUJ protein form location of the data bank website in PDP format; simultaneously, the ligand and its complexes in the MOL2 format were imported from Gauss View 6. We selected the lowest (high number with negative signal) of MolDock re-rank scores to rank the inhibitor poses.

RESULTS AND DISCUSSION

The DFT is used to predict and interpret the behavior and structures of molecules. We optimized the geometries of Schiff base of thiazole (L) and its complexes of Cu and Zn ions as shown in (Figure 1) by using Gaussian 09 package.³³

The term HOMO refers to the highest occupied molecular orbit that works as an electron donor, while LUMO refers to the lowest unoccupied molecular orbit that works as electron acceptor. Both terms refer as frontier molecular orbits, which consider great parameters in quantum chemistry.

HOMO and LUMO view the possibility of electronic transitions that are allowed to use in medicine, solar cell, and other applications.

$$E_{\text{gap}} = (E^{\text{LUMO}} - E^{\text{HOMO}}) \approx \text{IP} - \text{EA}, (\text{IP})$$

refers to the ionization potential, and (EA) is electron affinity

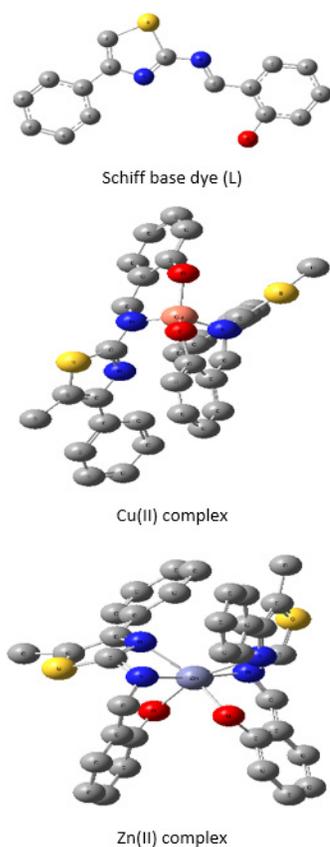


Figure 1: Optimized structures of Schiff base dye of thiazole (L) and its Cu(II) and Zn(II) complexes

Electronic density on HOMO orbitals of (L) dye and its complexes is more spread than in LUMO orbitals, especially with copper complex (Figure 2).

HOMO, LUMO data, and the gap energies are put in Table 1. Small gap informs about the reactivity of molecules, more polarizable with low kinetic stability, which means soft molecule.³⁴ The energy gap is small for the ligand and complexes (0.47-2.49 eV), which means the compounds are high polarizable with low kinetic stability.^{33,34}

Molegro virtual docker (MVD) results are of high quality because they depend on a new optimization technique combined with a user interface experience focused on usability and productivity. The docking process of MVD provides important parameters of energy like MolDock Score and re-rank Score. A re-ranking scoring work is presented to encourage move forward docking precision, which distinguishes the foremost promising docking arrangement from the arrangements gotten by the docking calculation. The re-rank Score is a good parameter providing from MVD to show the forte of drug-receptor binding. The results of docking study molecules were listed in Table 2, which indicates that MolDock Score and re-rank Score for complexes are lower than the starting material (thiazole ligand).

MolDockscore and re-rank Score calculated for Cu complex is less than Zn complex and thiazole ligand. Cu complex

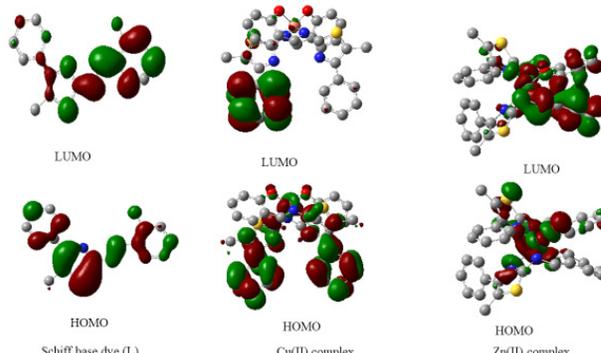


Figure 2: HOMO and LUMO orbitals of Schiff base dye of thiazole and its complexes of Cu(II) and Zn(II)

Table 1: HOMO, LUMO, and the gap energies (eV) for the molecules studied

Compound	E^{HOMO}	E^{LUMO}	$\Delta E^{\text{(LUMO-HOMO)}}$
Ligand of thiazole	-7.91	-5.42	2.49
Cu(II) complex	-5.03	-4.56	0.47
Zn(II) complex	-7.14	-5.63	1.51

Table 2: MVD data for studied molecules towards 2MUJ

	MolDock score (kcal/mole)	Rerank score kcal/mole	Number of interactions
L	-272.1	-197.3	36
Cu	-397.1	-198.1	104
Zn	-342.3	-91.4	154

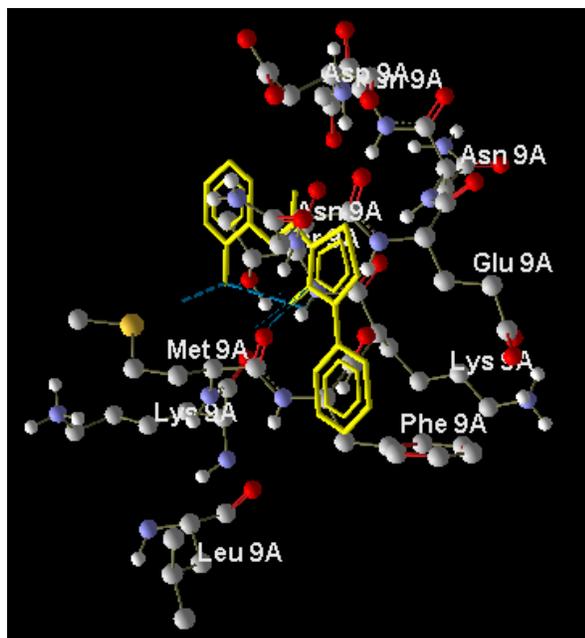


Figure 3: Interaction of thiazole dye with receptor 2MUJ [9A]

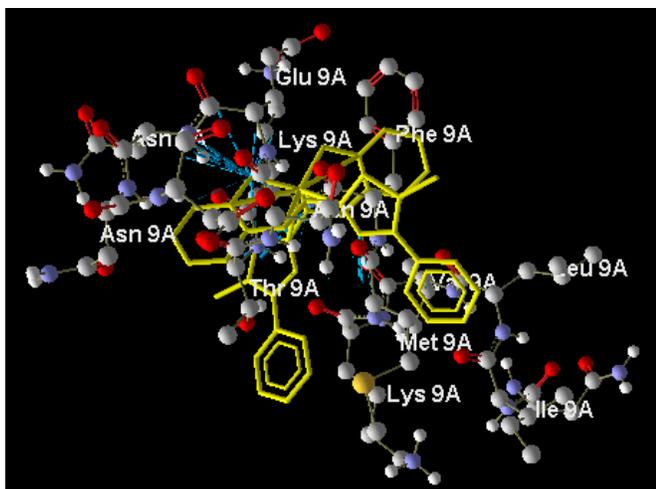


Figure 4: Interaction of Cu(II) complex of thiazole ligand with receptor 2MUJ [9A]

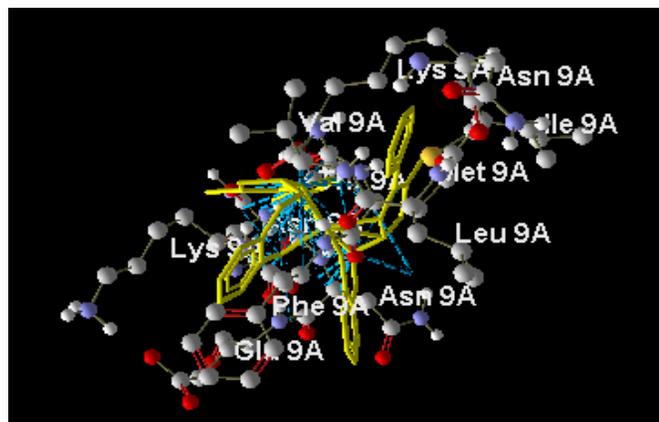


Figure 5: Interaction of Zn(II) complex of thiazole ligand with receptor 2MUJ [9A]

is suggested to be an interesting candidate against malaria. The least energy leads to be the more stable molecule with binding affinities. The Figures 3–5 show the interactions of study molecules with 2MUJ.

CONCLUSION

A very interesting approach in drug discovery research is to check biological activities by docking process. This allows knowing the potential activity of the molecule before starting to work in the laboratory, meaning an optimization in time and money. The complexes and the ligand have good binding potency with high interaction towards 2MUJ. Therefore these compounds have the potential to be interesting for researchers to be used in clinical trials as a potential anti-plasmodium falciparum agent.

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