Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 194 (2024) 75-87 EISSN 2392-2192

Investigation of biological properties of metal (II) complexes of uracil and biotin against two sources of learning disorders by computational means

Ishola Kayode Taiwo* and **Ajayi Titilope Adewumi**

Department of Chemistry, Federal College of Education (Special) Oyo, P.M.B. 1089, Oyo, Oyo State, Nigeria

*E-mail address: Isholatk@gmail.com

ABSTRACT

Learning disorders in children have been linked to sezrious causes such as oxidative stress and malaria. Numerous medications have been used to address the variables, but the majority of them have been shown to be less successful. Because the metal complexes have been reported to have greater antioxidant and therapeutic effects, chelation between biologically active ligands and transition metals has garnered a lot of attention in recent years. Still, not enough research has been done on the theoretical analysis of the biological efficacy of uracil and biotin mixed-ligand complexes. In order to explore the nature of interaction and the potential applications of the ligands and their metal complexes as antioxidants and antimalarial drugs, mixed-ligand complexes of uracil and biotin with Cu^{2+} and Zn^{2+} are theoretically studied in this work using molecular docking and the density functional theory method (Dmol3). Following geometry optimization, the metal complexes were found to adopt a tetrahedral geometry. Based on the results of the Lowest Unoccupied Molecular Orbital (LUMO) and Highest Occupied Molecular Orbital (HOMO), the Cu(II) complex was found to be the most reactive with the least value of ionization potential and more stable than the Zn(II) complex. Cu(II) complex has the lowest value of ionization potential (IP) according to the results of the antioxidant activity in the neutral state, indicating that it is a superior antioxidant candidate than Zn(II) complexes. The Cu(II) complex demonstrates the maximum binding affinity with the receptor protein, as evidenced by its lowest negative score. Consequently, it may be said that Cu(II) complex has the potential to be an antioxidant and an antimalarial medication.

(Received 07 May 2024; Accepted 31 May 2024; Date of Publication 02 June 2024)

***Keywords*:** Learning disability, Malaria, Metal complex, Ligand, Oxidative stress

1. INTRODUCTION

Academic performance can be negatively impacted by learning disorders, which are characterized by an inability to acquire, retain, or apply particular skills or information. These disorders can be caused by deficits in attention, memory, or reasoning (Sulkes, 2022). Persistent difficulty in reading, writing, math, or mathematical reasoning skills during the school years are indicative of learning impairments (Ramirez et al., 2020). Learning difficulties are known to be caused by a variety of conditions, including oxidative stress and malaria (Cavendish, 2013). *Plasmodium falciparum* is one of the plasmodium protozoa that cause malaria, a parasitic disease. According to Shields et al. (2016), the illness is linked to both environmental sanitation and poverty. With significant morbidity and death, it continues to be a public health concern in sub-Saharan Africa. In its most severe forms, the infection can cause death, a coma, and lasting learning deficits if left untreated. According to the World Health Organization (2019), malaria threatens world prosperity and takes more than 655,000 lives annually. It kills a kid every 60 seconds and is the biggest cause of death for children under five in sub-Saharan Africa. It also poses a serious risk to pregnant women (Okpok et al., 2014; Macarayan et al., 2020; Laia et al., 2022; Johns, 2023).

The condition known as "oxidative stress" occurs when antioxidant activity is insufficient to prevent oxidizing agents from activating within the body. Radical oxygen species (ROS) and other oxidizing species are overproduced, which is mostly to blame. Low ROS concentrations may also be the cause of it. ROS facilitate a multitude of beneficial tasks, such as controlling cardiovascular function and protein activation or eliminating pathogens during inflammatory responses. However, ROS can lead to tissue damage and organ failure if they are not properly controlled by cellular antioxidants. H_2O_2, hydroxyl (OH^-), and superoxide (O^{2-}) are examples of reactive oxygen species (ROS). Out of which the other two are derived, O_2 is the most stable and fundamental ROS. Since OH^-can harm proteins, lipids, carbohydrates, and DNA, it is the most harmful ROS (Thomas, 2022). Oxidative stress has been linked to the pathophysiology of neurodegenerative and neurodevelopmental illnesses, including vascular cognitive impairment, which impairs adult memory and learning. It has been observed that executive skills and oxidative stress are inversely correlated in healthy people (Pesce et al., 2016; Nishimura et al., 2021). According to Alzyoud et al. (2021) oxidative stress has an impact on students' academic performance as well as their capacity to learn and retain newly acquired knowledge.

Stress has an impact on memory and learning because it triggers psychophysiological reactions. Stress does not always have the same impact on learning and working memory. Impaired memory performance has been linked to oxidative stress (Shields et al., 2016). Odera (2018) examined how malaria affected students' performance in terms of extracurricular activities, exams, assignments, private study, and attendance in class. Descriptive survey design was used in the study. The overall research results showed that many students with malaria are associated with symptoms include headaches, upset stomachs, and high fevers, which can impair focus and academic performance. Prospects for using metal complexes as medicinal agents have improved due to developments in inorganic chemistry. Utilizing the special qualities of metal ions, medicinal inorganic chemistry creates novel pharmaceuticals. More

researchers are turning to transition metal complexes as medicinal substances. In addition to their anti-cancer capabilities, these complexes have also been employed as anti-inflammatory, anti-infective, and anti-diabetic agents. This shows how diverse their modes of action are. Medicine and pharmacy are two areas where transition metal complexes are "gaining ground" (Todorov & Kostova, 2024). The two major causes of learning impairments in children have been identified as oxidative stress and malaria. Though most of the medications are less effective, many have been used to prevent the causes. Consequently, because metal complexes have been found to give stronger antioxidant and therapeutic properties, chelation between physiologically active ligands and transition metals has garnered a lot of attention recently. Still lacking, nevertheless, is a thorough theoretical analysis of the biological efficacy of uracil and biotin mixed-ligand complexes. In this study, the nature of the interaction and the potential use of the ligands and their3 metal complexes as antioxidants and antimalarial medications are investigated theoretically through the use of molecular docking and the density functional theory method (Dmol3) for mixed-ligand complexes of uracil and biotin with Cu^{2+} and Zn^{2+}.

2. MATERIALS AND METHODS

2. 1. Computational Methodology

Chemdoodle and Chemdraw were used to prepare the ligands (biotin and uracil) and their metal complexes. Material Studio 2020 was used to compute the electronic structures of the ligands, Cu(II), and Zn(II) complexes. The Dmol3-based method and the PBE basis set were applied for full optimization. The effect of molecular orbitals on HOMO and LUMO was determined.

2. 2. Molecular Docking

A 32GB RAM-equipped XPS 15 laptop was used to conduct the molecular docking study. The docking software used in the MOE (Molecular Operating Environment) was called MOE-Dock (MOE, 2019). The Chemical Computing Group created MOE, a software platform that can be used to create new applications based on SVL (Scientific Vector Language) that supports Chemoinformatics, Molecular Modeling, Bioinformatics, Virtual Screening, and Structure-based Design. The interaction of *Plasmodium falciparum* and ligands (Biotin, Uracil, and their metal complexes) was shown using LigPlot, which was implemented in MOE. By computing binding energies, the docking technique was used to look into the inhibitory potentials.

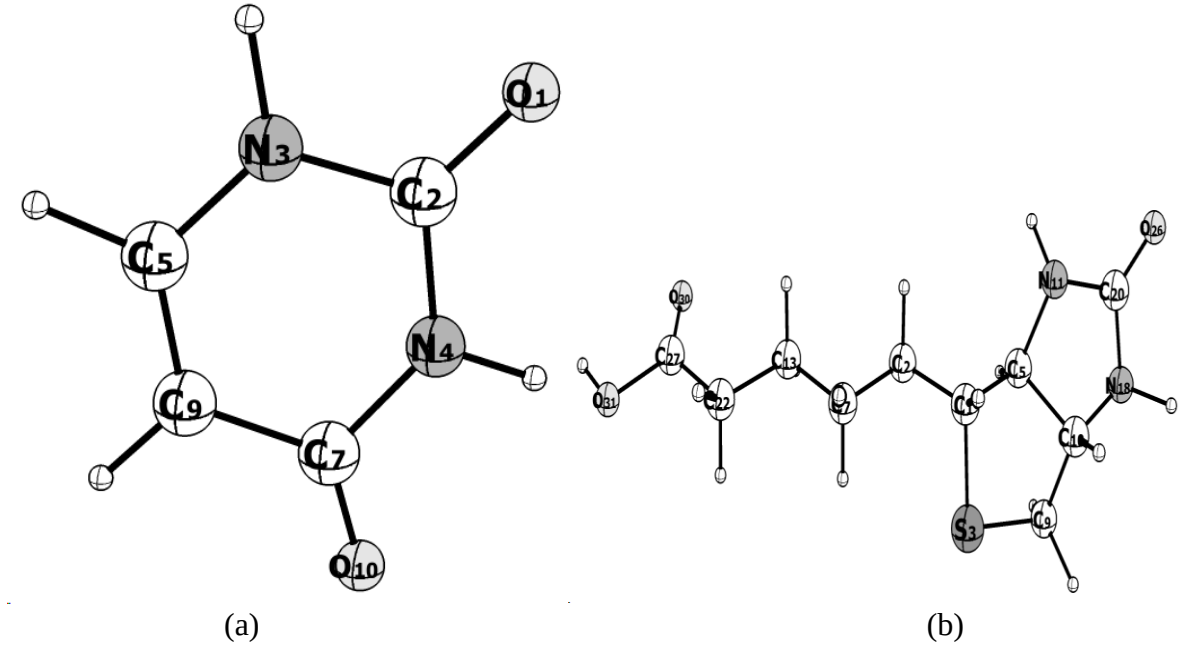
2. 3. Protein Preparation

From the Protein Data Bank, the *Plasmodium falciparum* protein structure was obtained. In MOE 2019, the receptor's energy was minimized in order to prepare it for docking, and it was then 3D protonated. After the protein had been stripped of all water molecules and binding ligands, 3D protonation and energy minimization were carried out. As a result, only inhibitors or ligands might now interact with the chosen receptor.

3. RESULTS

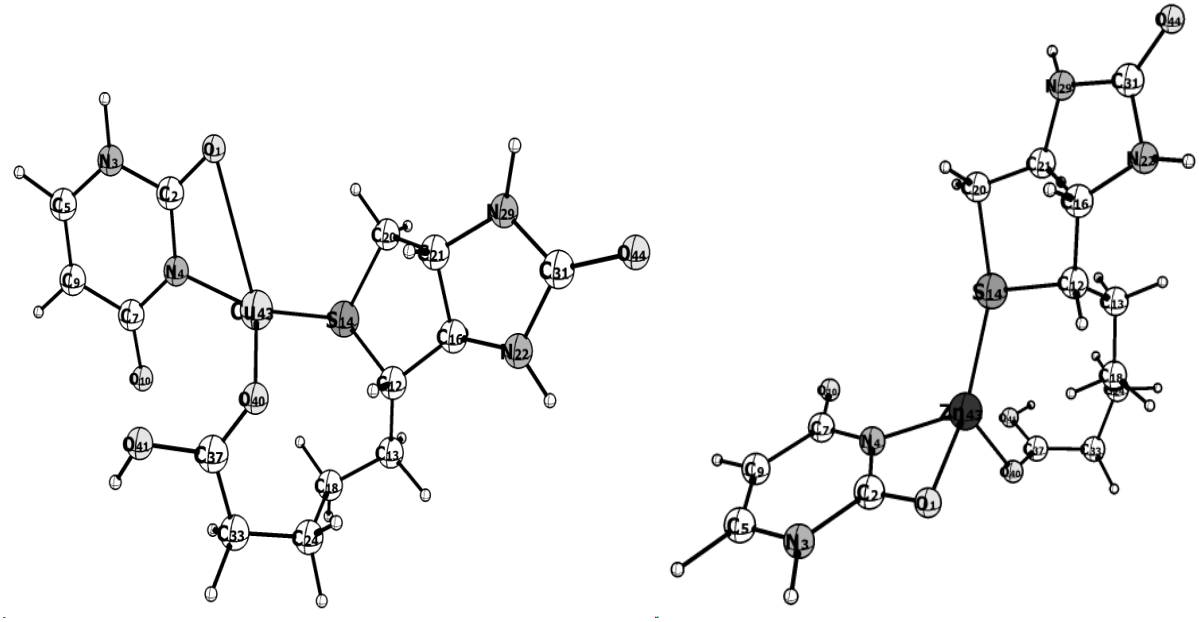
3. 1. Molecular Modeling Study

Figure 1 displays the optimized molecular structures for biotin and uracil that were obtained from Dmol3, whereas Figure 2 displays the molecular structures for the complexes of Cu(II) and Zn(II). The molecular orbitals of the biotin, uracil, and Cu(II) and Zn(II) complexes are shown in Figures 3 and 4, respectively. The ligands' and their metal (II) complexes' molecular properties, such as frontier eigenvalues, were computed with Dmol3 using the GGA function and the PBE basis set (Table 1).



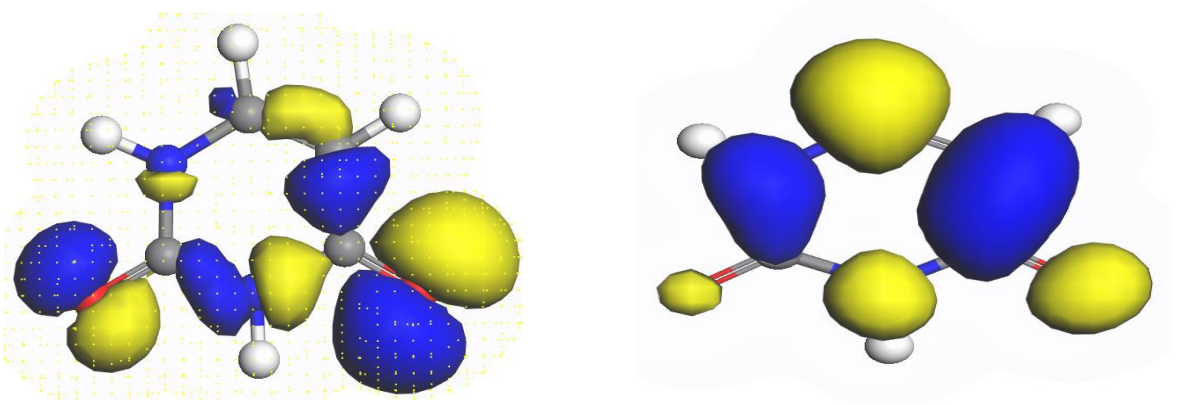
(a) (b)

Figure 1. Structures of uracil (a) and biotin (b)



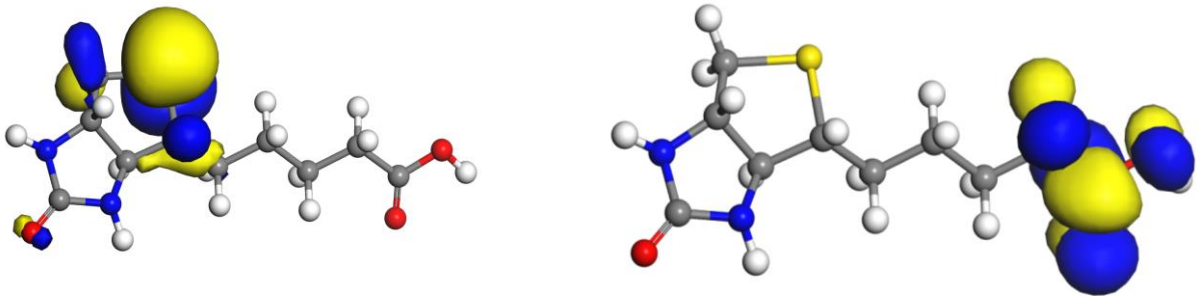
(a) (b)

Figure 2. Structures of Cu(II) complex (a) and Zn(II) complex (b)



HOMO LUMO

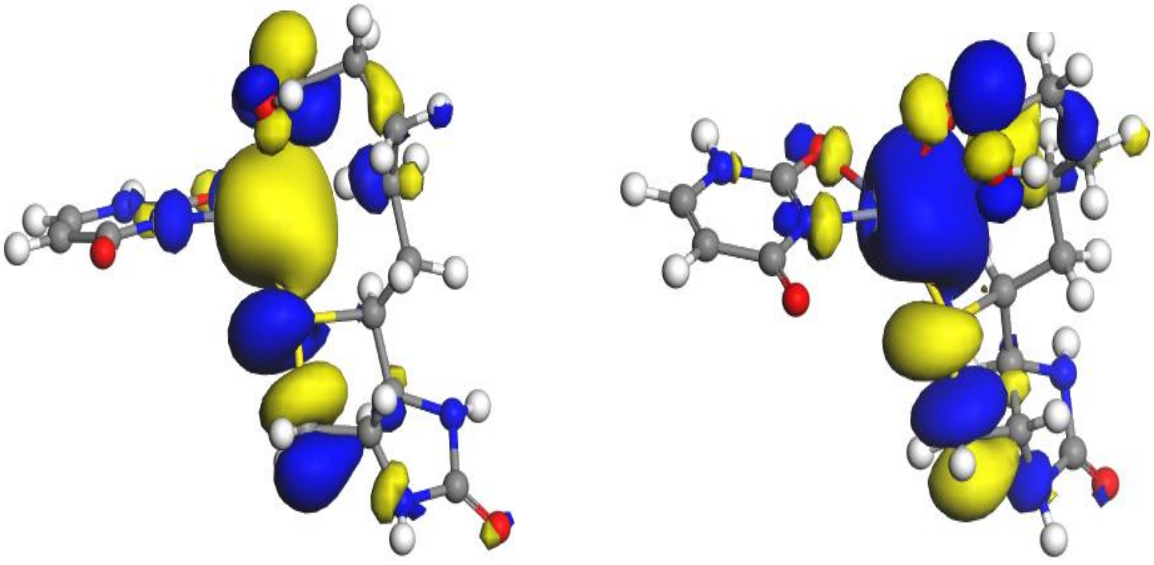
(a)



HOMO LUMO

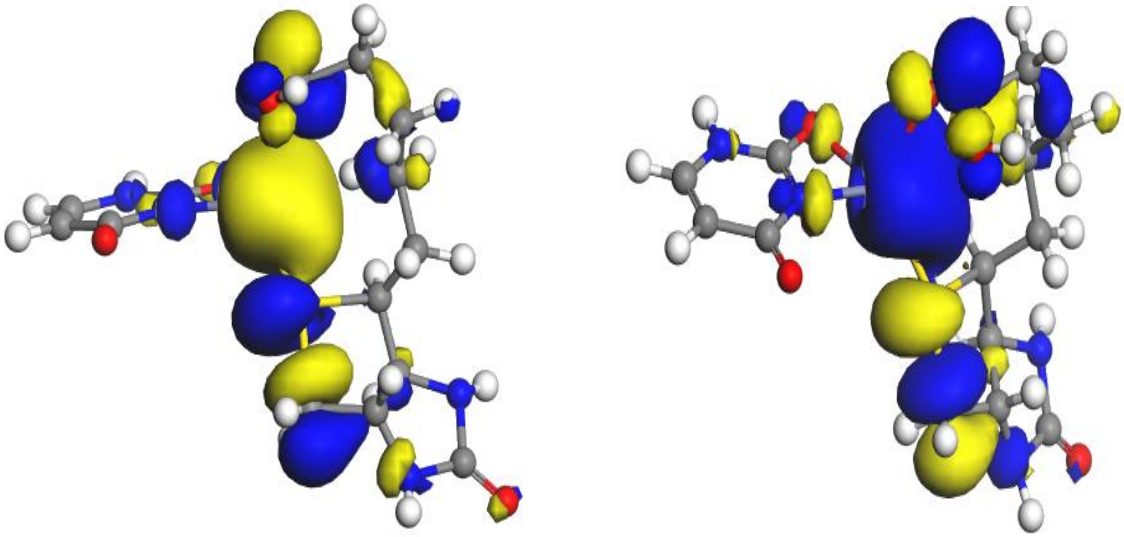
(b)

Figure 3. Molecular orbitals of uracil (a) and biotin (b)



HOMO LUMO

(a)



HOMO LUMO

(b)

Figure 4. Molecular orbitals of Cu(II) complex (a) and Zn(II) complex (b)

Table 1. The metal complexes' and ligands' molecular properties as determined by the Dmol3-GGA/PBE technique

Compound	E_T (Ha)	$E_{Binding}$ (Ha)	E_{HOMO} (Ha)	E_{LUMO} (Ha)	ΔE (Ha)	IP
Uracil	-414.532	-2.2912	-0.2274	-0.0855	0.1419	0.2274
Biotin	-1124.173	-5.4656	-0.2011	-0.0438	0.1573	0.2011
Cu(II) complex	-3177.717	-7.8093	-0.1689	-0.0525	0.1164	0.1689
Zn(II) complex	-3316.477	-7.6615	-0.1183	-0.0962	0.0221	0.1183

3. 2. Molecular Docking

The *Plasmodium falciparum protein* was subjected to in silico docking using MOE against all predicted active sites for the ligands and their metal complex inhibitors; the interaction results were assessed using the S score. The 2D diagrams of the ligands' interaction with the receptor (Plasmodium falciparum) are depicted in Figures 5, 6, 7, and 8. Different inhibitor scores are displayed depending on the interaction with Plasmodium falciparum on different active sites. The docking scores for all metal complexes and free ligands are displayed in Table 2.

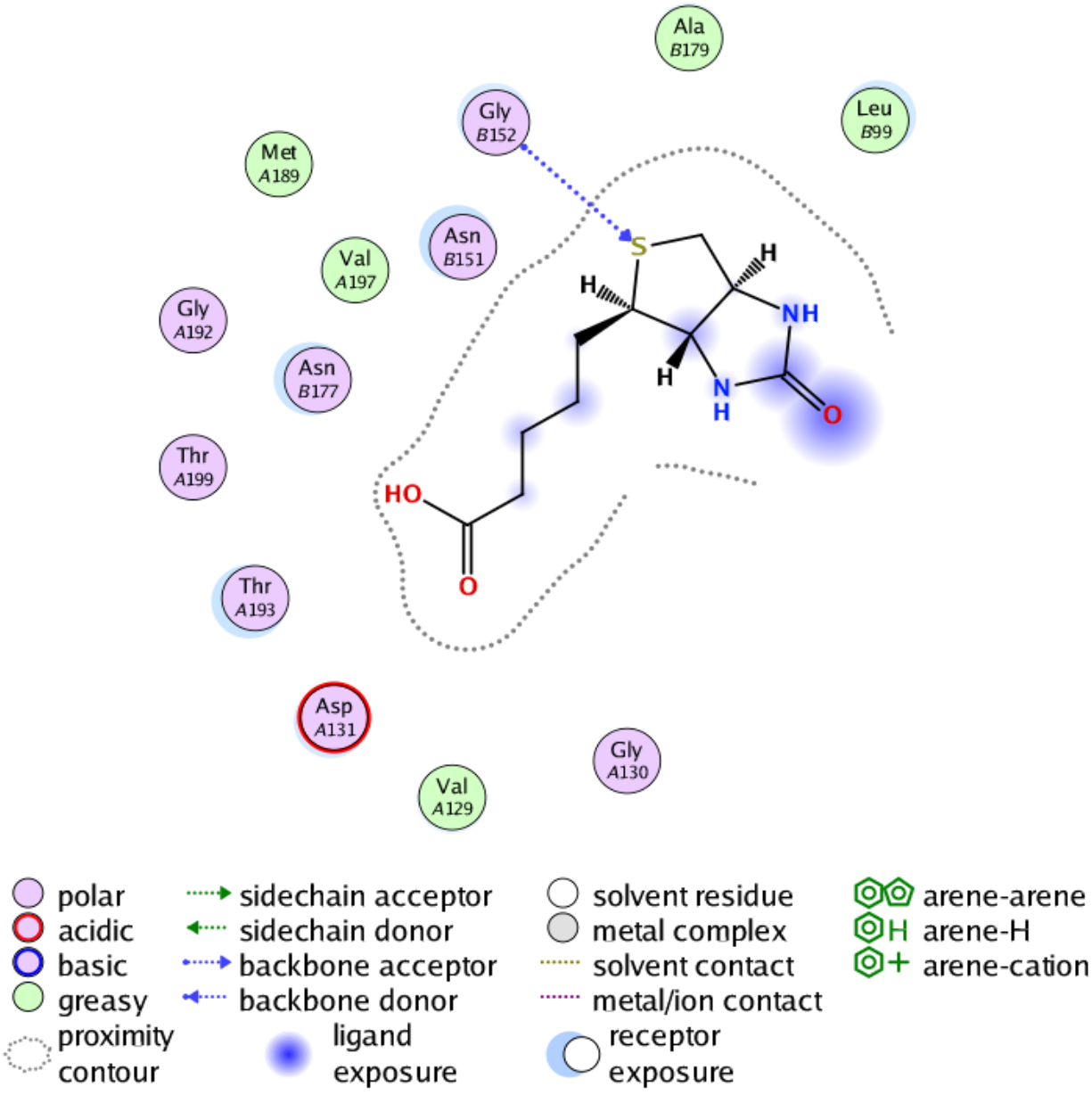


Figure 5. 2D docking interaction of biotin with *Plasmodium falciparum* protein

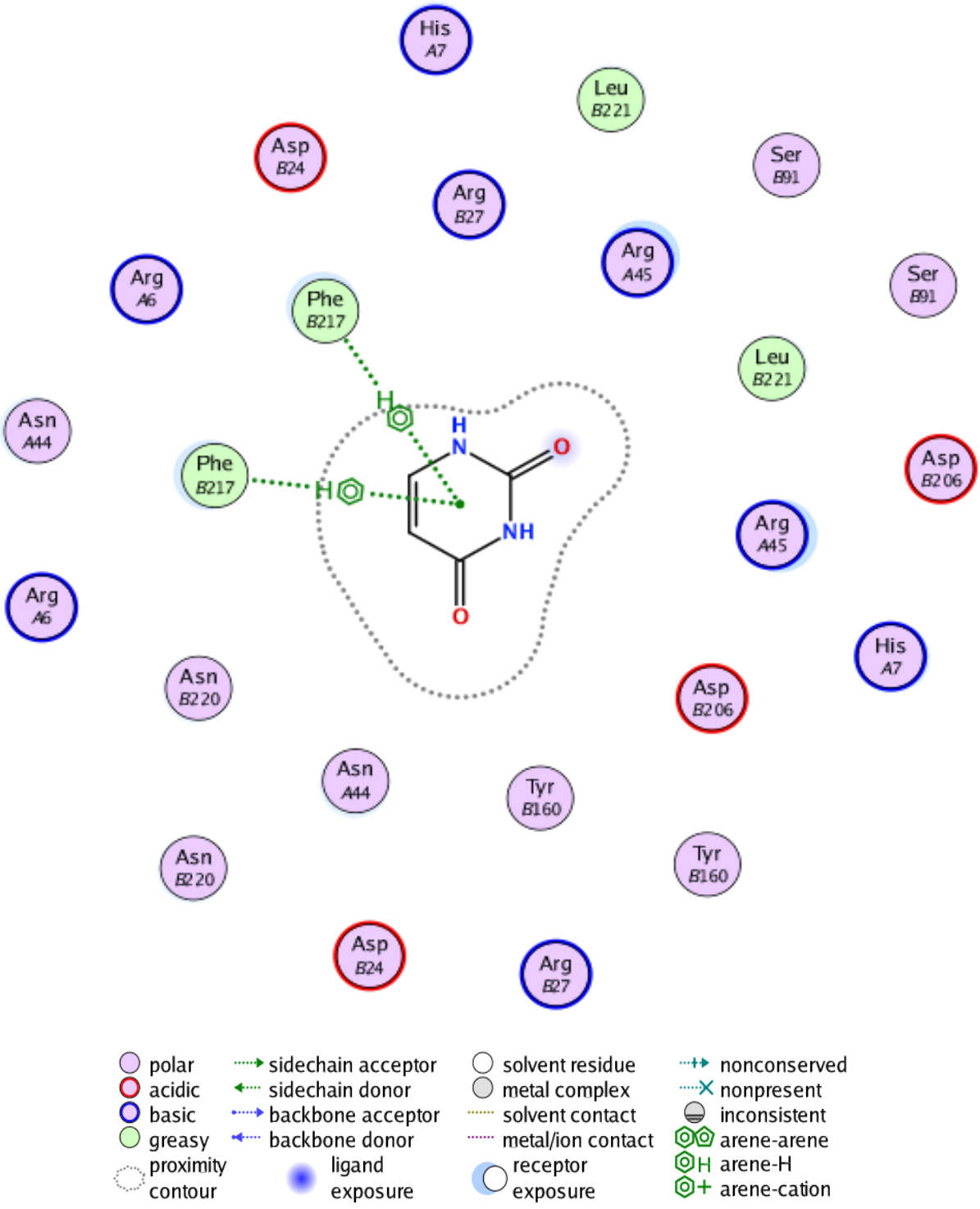


Figure 6. 2D docking interaction of uracil with *Plasmodium falciparum* protein

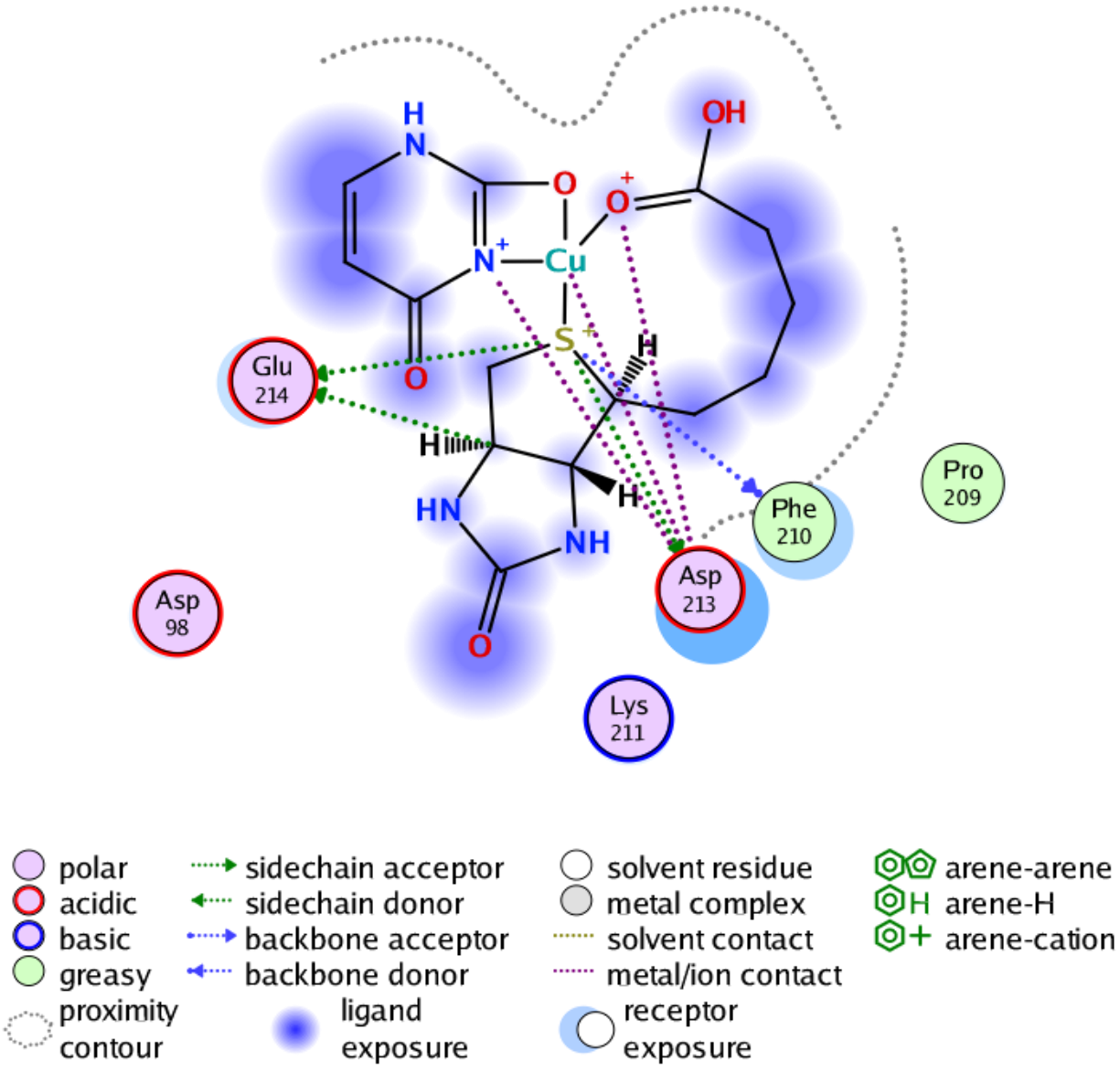


Figure 7. 2D docking interaction of the Cu(II) complex with *Plasmodium falciparum* protein

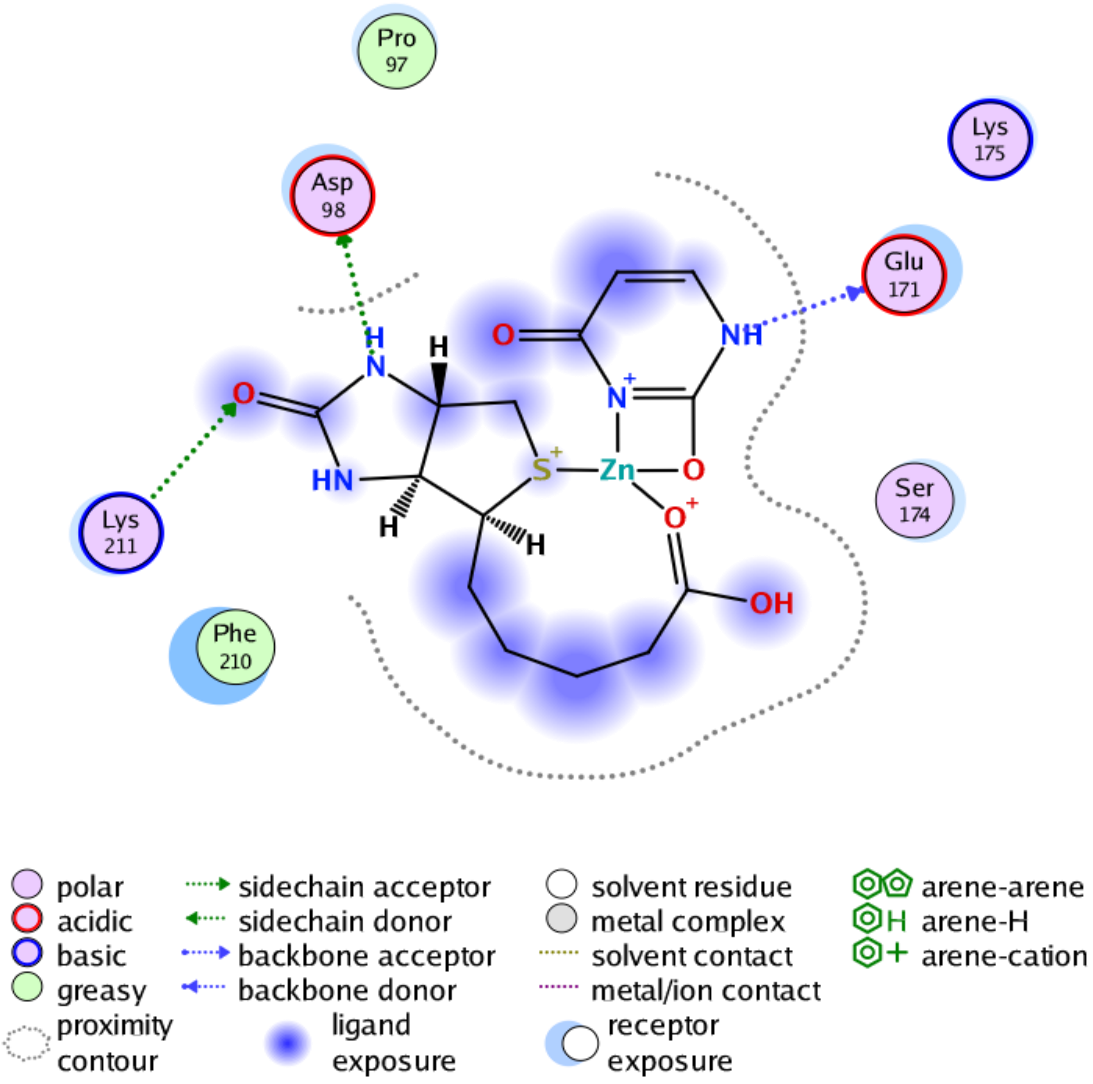


Figure 8. 2D docking interaction of the Zn(II) complex with *Plasmodium falciparum* protein

Table 2. Docking scores and energies of ligands and their metal complexes with *Plasmodium falciparum* protein

Compound	S	rsmd-refine	E-conf	E-places	E-refine
Uracil	-2.4389	0.1171	-137.0889	-18.4004	134.1988
Biotin	-5.0147	1.0197	-78.614	-21.7305	-23.3152
Cu (II) Complex	-5.6167	1.0610	-705.0219	-8.8284	-23.2049
Zn (II) Complex	-4.9617	2.0730	-777.9554	-27.0271	-42.5449

4. DISCUSSION

The energy difference between the corresponding ligand and their metal complexes' high occupied molecular orbitals (HOMO) and low unoccupied molecular orbitals (LUMO) (Figures 3 & 4) is used to estimate the chemical reactivity of the ligands and their metal complexes. Table 1 displays this information. Notably, there is a strong relationship between the ligands' reactivity and structure. In the region of 0.1419–0.1573 eV, the E values for biotin and uracil were almost identical. When compared to the free ligand, the metal complexes exhibit greater stability, as evidenced by their higher negative total energy. Ordered by Cu(II) > Zn(II), the metal complexes are stable.

The ligands' and their metal (II) complexes' antioxidant activity is correlated with their ionization potential (IP). IP is higher for the metal complexes than for the ligands. Table 1 illustrates that the biotin ligand has greater antioxidant activity than uracil. Zn > Cu is the IP order of the metal complexes. The lower value of the ionization potential (IP) indicates a stronger electron-donating reactivity in the Cu-complex, whereas the higher value indicates a less pronounced antioxidant activity in the Co complex with uracil and biotin. Therefore, compared to ligands and the other metal complex, the Cu complex is a better antioxidant candidate. Examining how molecules combine at a receptor's active region is mostly dependent on molecular docking studies. To ascertain how the ligands and their metal (II) complex interact with the protein under investigation, molecular docking research was carried out. Table 2 displays the various binding energy scores that the ligands and metal complexes display following in silico docking. When attaching to the *Plasmodium falciparum* protein, the biotin ligand demonstrated a stronger binding energy compared to uracil, but it also displayed a lower scoring energy.

Simultaneously, the Cu(II) complex demonstrates the strongest binding affinity with the receptor protein, as evidenced by its lowest negative score of -5.6161 KJ mol^{-1} (De et al., 2020; Eno et al., 2023). Moreover, the Cu(II) complex can be utilized to create an effective medication to treat malaria parasites.

5. CONCLUSIONS

Dmol3 was used to optimize the geometry of the Cu(II) and Zn(II) complexes, and molecular docking was used to identify the binding interactions. It was determined how ligands interacted with that *Plasmodium falciparum* protein. After geometry optimization, the metal complexes were seen to take on a tetrahedral geometry. The compounds' activity and docking scores show a strong link, according to the docking results. According to this study, Cu(II) complex has the highest ionization potential and maximal binding affinity for *Plasmodium falciparum*, making it the best antioxidant and inhibitor of the parasite. One potential therapeutic active medication for the treatment of oxidative stress and malaria, two conditions that contribute to learning disorders, could be the metal complex.

Acknowledgement

The work was sponsored by the Tertiary Education Trust Fund (TETFund) in Nigeria, for which the authors are grateful.

References

[1] Abd El-Razek, S. E., El-Gamasy, S. M., Hassan, M., Abdel-Aziz, M. S., & Nasr, S. M. (2020). Transition metal complexes of a multidentate Schiff base ligand containing guanidine moiety: Synthesis, characterization, anti-cancer effect, and anti-microbial activity. *Journal of Molecular Structure*, 1203, 127381

[2] Alzyoud, A., Omar A., Mahmoud, Ma., Fahad, A. & Abdelrahman, R.B. (2021). Learning and memory under Stress: A Review Study with Evaluation Techniques. *Sys Rev Pharm*, 12(1), 1602-1610

[3] Cavendish, W. (2013). Identification of learning disabilities: implications of proposed DSM-5 criteria for schoolbased assessment. *J Learn Disabil.* 46(1), 52–57.

[4] De, A., Ray, H. P., Jain, P., Kaur, H., & Singh, N. (2020). Synthesis, characterization, molecular docking and DNA cleavage study of transition metal complexes of o-vanillin and glycine derived schiff base ligand. *Journal of Molecular Structure*, 1199, 126901

[5] Eno, E.A., Shagal, M.H., Godfrey, O.C., Ngana, O.C., Ekong, J.O., Gber, T.E., Benjamin, I.,Ugi, B.U. & Louis, H. (2023).B Computational study of the interaction of metal ions (Na+, K+, Mg2+, Ca2+, and Al3+) with Quercetin and its antioxidant properties. *Journal of the Indian Chemical Society*, 100 (8), https://doi.org/10.1016/j.jics.2023.101059.

[6] Johns H. B. (2023). Malaria. Retreived from https://www.malariafreefuture.org/malaria Center for Communication Programs

[7] Laia, C., Judit, V. C., Joe, B, Francisco, S. & Elisa, S. (2022).The impact of a malaria elimination initiative on school outcomes: Evidence from Southern Mozambique. *Economic and Human Biology*. 44, 101100. https://doi.org/10.1016/j.ehb.2021.101100

[8] Macarayan, E., Papanicolas, I. & Jha, A. (2020). The quality of malaria care in 25 low-income and middle-income countries. *BMJ global health*, 5(2), 8-20

[9] Molecular operating environment MOE. 2019. C.C.G.I.M, Quebec Canada

[10] Nishimura, Y., Kanda, Y., Sone, H. & Aoyama, H. ((2021). Oxidative stress as a common key event in developmental neurotoxicity. *Oxid Med Cell Longev.* 6685204.

[11] Odera, F. (2018). Effect of malaria on academic performance in secondary schools in south west nyakach ward, kisumu. *International journal of research in education and psychology* 4(1), 49-59

[12] Okpok, E. O., Gboeloh, L.B and Udoh, S.E (2014). Antiplasmodial effects of combined extracts of the leaf of ficus eaxasperata and stem bark of anthocleista vogelii on mice experimentally infected with plasmodium berghei (NK 65). *Research Journal of Medicinal Plant*, 8(3), 99-111

[13] Palanimurugan, A., & Kulandaisamy, A. (2018). DNA, in vitro antimicrobial/anticancer activities and biocidal based statistical analysis of Schiff base metal complexes derived from salicylalidene-4-imino-2, 3-dimethyl-1-phenyl3-pyrazolin-5-one and 2-aminothiazole. *Journal of Organometallic Chemistry*, 861, 263–274

[14] Pesce, M., Rizzuto A. & La Fratta I (2016).Super-oxide anion production and antioxidant enzymatic activities associated with the executive functions in peripheral blood mononuclear cells of healthy adult samples. *Neurosci Res.* 106: 23–28

[15] Ramirez ,O. D., Ovalle, R. P. & Pineda, B. (2020). Kynurenine pathway as a new target of cognitive impairment induced by lead toxicity during the lactation. *Sci Rep.* 10(1), 3184-3190

[16] Shields, G.S., Sazma, M.A. & Yonelinas, A.P. (2016).The effects of acute stress on core executive functions: A metal analysis and comparison with cortisol. *Neurosci Biobehav Rev*. 68, 651-668

[17] Sulkes, S.B. (2022). Learning Disorders. Merck & Co., Inc., USA

[18] Thomas, L. (2022).The role of oxidative stress in congenital syndromes. Retrieved from https://www.news-medical.net/news/20221010/The-role-of-oxidative-stress-in-congenital-syndromes.aspx

[19] Todorov, L.T. & Kostova, I.P. (2024), Coumarintransition metal complexes with biological activity: current trends and perspectives. Front. Chem. 12:1342772. doi: 10.3389/fchem.2024.1342772

[20] World Health Organization (2020). World Malaria Report 2020. Geneva, Switzerland. Retrieved from: https://www.who.int/malaria/publications/world-malaria-report - 2018/en/