UMYU Scientifica, Vol. 4 NO. 1, March 2025, Pp 345 – 353
https://doi.org/10.56919/usci.2541.034
ISSN: 2955 – 1145 (print); 2955 – 1153 (online)
A periodical of the Faculty of Natural and Applied Sciences, UMYU, Katsina

ORIGINAL RESEARCH ARTICLE

Shiff Base Metal Complexes Of Cu (II), Ni(II), and Zn(II) Drived From 2-Hydroxy Acetophenone and O-Phenylenediamine; Synthesis, Characterization, Antimicrobial and Molecular Docking

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ABSTRACT

Conductivity measurements, magnetic measurements, spectroscopic analysis, anti-bacterial, and molecular docking activities have been used to manufacture and analyse Cu(II), Ni(II), and Zn(II) Schiff base metal complexes generated from 2-Hydroxyacetophenone and O-phenylenediamine. The Schiff base's infrared spectra showed an azomethine peak at 1640 cm^{-1}. The complexes' shifting of this band to higher or lower wave numbers suggested that the azomethine nitrogen was involved in coordination (M-N). New bands at 758-762 cm-1 in metal complexes have been attributed to the υ(M-N) mode. New bands at 660–700 cm-1 in metal complexes indicate the presence of the υ(M-O) mode. Metal complexes exhibit new bands at 3300-3200 cm^{-1} that are associated with the υ(OH) mode. Measurements of conductance (1.64 to 30.50 Ohm^{-1} cm^2 mol^{-1}) indicated that none of the complexes were electrolytic. Both the 1.9 B.M. (Cu (II)) and 3.6 B.M. (Ni (II)) magnetic susceptibility values are consistent with square planar geometry, and the metal-ligand ratio was verified as 1:1 using Jobs' method of continuous variation. The antimicrobial activity of the Schiff base and its metal chelates was tested against six pathogenic microorganisms (*Escherichia coli, Candida albican, Mucor indicus, and Staphyloccus aureus*). The complexes exhibited higher antimicrobial activity against the tested microbes, while the Schiff base exhibited moderate activity. The anti-cancer medication Tamoxifen was less effective than the complexes and ligand against human breast cancer cells (HER2-PY1196 4GFV).

ARTICLE HISTORY

Received December 17, 2024
Accepted March 27, 2025
Published March 30, 2025

KEYWORDS

2-hydroxy Acetophenone, o-phenylenediamine, *Staphyloccus aureus*, *Escherichia coli Candida albican*, and *Mucor indicus* and Molecular docking

INTRODUCTION

The first Schiff's base was made by Hugo Schiff in 1864 with a primary amine, aldehyde, or ketone. They are classified as imines because of their overall structure, which is $R_1R_2C{=}NR'$ ($R' \neq H$). In imines known as Schiff bases, R_1 and R_2 may be hydrogen atoms, and R' is an aryl/alkyl group but not hydrogen. Among the many biological properties of Schiff bases are their antiviral, anti-cancer, and anti-bacterial properties (Schiff, 1864).

Because of its benefits, Schiff base complexation development was initially investigated in the nineteenth century. The discovery of Schiff bases made this possible. (Golcu *et al.,* 2005).

Schiff base metal complexes created based on transition metals are frequently discussed and selectively explored due to their unique characteristics, including geometrical configurations, redox states, numerous forms of coordination, and a high chance of complexation. (Mishra, 2014).

Cu(II), Co(II), and Ni(II) tetradentate Schiff base (SB) complexes were produced by condensing terepthaldehyde and 2-aminophenol/o-phenylenediamine in an alcohol solution with Cu(II), Co(II), and Ni(II). FTIR, LCMS, and UV-visible analyses were then employed to characterize the complexes. Each complex has been given an octahedral geometry based on analytical, electrical, and magnetic data. *Escherichia coli 4204, Bacillus subtilis 2393, Proteus vulgaris 426, Klebsiella sp., and S. aureus 3160* were the microorganisms that the SB ligands and their complexes were tested against in the anti-bacterial investigations. Four fungus species (*Aspergillus niger, Penicillium chrysogenum, Aspergilus flavus, and Cryptococcus neoformans*) were used to assess its anti-fungal qualities. The findings showed that

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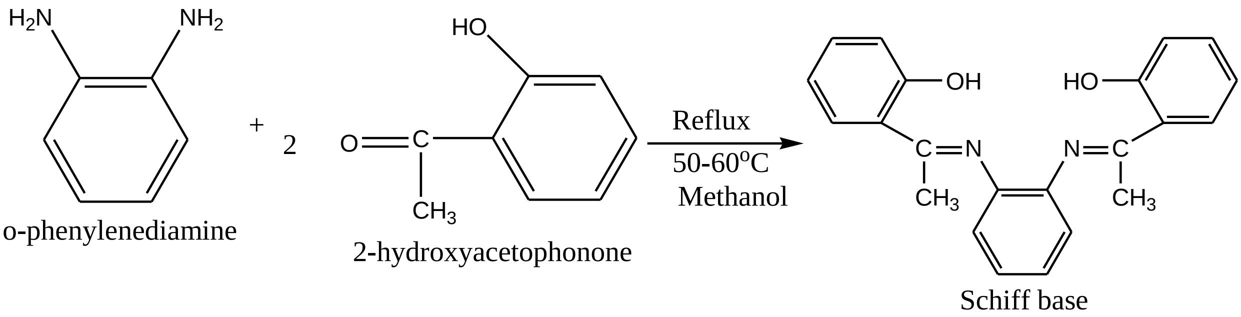
How to cite: Mansur, A. I., Yahaya, I. L., Sule, S. U., & Alhakim, A. A. (2025). Shiff Base Metal Complexes Of Cu (II), Ni(II), and Zn(II) Drived From 2-Hydroxy Acetophenone and O-Phenylenediamine; Synthesis, Characterization, Antimicrobial and Molecular Docking. *UMYU Scientifica*, 4(1), 345 – 353. https://doi.org/10.56919/usci.2541.034

the transition metal complexes have strong anti-bacterial and anti-fungal properties. (Saranya *et al.,* 2020)

EXPERIMENTS

Synthesis of the Schiff base

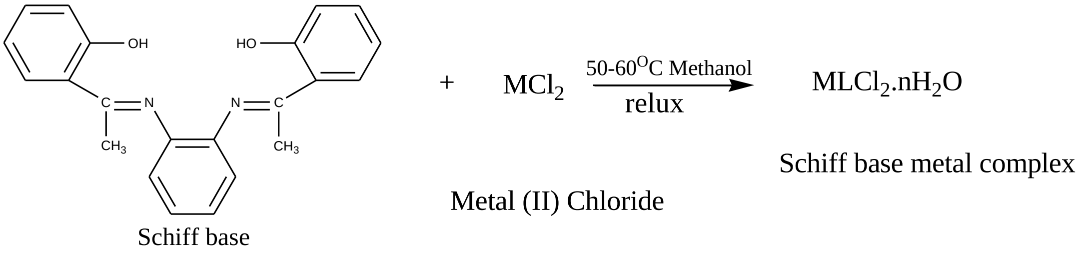
To make the ligand, 0.01 moles of 2-hydroxyacetophenone (1.36 g) and O-phenylenediamine (1.08 g) were mixed together in a methanolic solution. The resulting precipitate was filtered, periodically washed with diethyl ether, and dried over calcium hydroxide in a desiccator following two hours of refluxing the reaction mixture. (Hamil *et al.,*2009).



Scheme 1.1: Schiff Base Ligand Synthesis

Schiff base metal (II) complex synthesis:

50 mL of a methanolic solution containing 0.002 mole (0.96g) of the synthesized Schiff base was mixed with a few drops of ammonia solution of $CuCl_2.5H_2O$, $CuCl_2.2H_2O$, or $ZnCl_2.2H_2O$ salts of 12.32g, 1.71 g, and 1.36g, respectively, to produce compounds of Cu(II), Ni(II), and Zn(II) and to modify the pH. The reaction mixtures were refluxed for three hours and then allowed to cool before being suction-filtered. The precipitates were washed many times with diethyl ether. Desiccators were used to dry the complexes over anhydrous calcium chloride. (Hamil *et al.,* 2009).



Scheme 1.2: Schiff Base Metal Complex Synthesis

Melting Point/ Decomposition Temperature Test

A very small amount was placed in a capillary tube to determine the complex's melting point. After that, the tube was put into a Gallen Kamp melting point device to determine its melting point. Three times, this was done. A similar process was used to determine the temperature at which metal complexes decompose.

Solubility test

The solubility of the complex's constituent parts varied depending on the solvent. In a test tube, a small quantity of the complex was dissolved in several solvents. Distilled water, ethanol, acetone, benzene, dichloromethane, dimethyl sulfoxide, and chloroform were the solvents used in the tests. The molecular complexes' solubility was noted in each instance.

Conductivity Measurement

The molar conductance of 0.003M solutions of the metal complexes in DMSO was measured using the Janway 4010 conductivity meter. The molar conductance value was derived from the relation, and all measurements were performed at room temperature.

$$\text{Molar conductance} = \frac{1000}{C} X K$$

Where C = Molar concentrations

K = specific conductance

Calculating the Complexes' Water of Crystallization Percentage

An oven heated to 110^{0}C was used to maintain a constant weight in a known-weight watch glass that contained around 0.2g of each metal complex. The formula below was used to get the complex's water content as a percentage.

$$\text{Percentage water of crystallization} = \frac{Weight\ lost}{Weight\ of\ the\ complex\ taken} X\ 100$$

Ligand to Metal (II) Ion Ratio Calculation Using the Continuous Variation Method

Job's methods" were employed to quantify the ligand-to-metal ratio in the complex compounds by making a one millimolar solution of the Schiff base and a metal (II) chloride.

Mixtures with a total volume of 16 cm3 were created by combining these solutions, and the

Mole fraction of the Schiff base, X, was 0.063, 0.188, 0.313, 0.437, 0.563, 0.688, 0.813, and 0.938. The absorbance of each solution was measured at the wavelength where the metal (II) ion solution absorbs the most, known as the wavelength for a metal salt at maximum absorbance (λmax). Plotting the absorbance versus the ligand mole fractions allowed for the calculation of the amount of coordinated Schiff bases per metal ion, or n. Next, the combination of M2+ and ligand stoichiometric quantities was measured to determine the mole fraction (X) at maximum absorbance. (Angelici 1977). In a plot of absorbance against the ligand's mole fraction, the number of coordinated ligands was determined using the following relation:

$$n = \frac{Xi}{1-Xi}$$

Where: n = highest absorbance of the coordinated ligand number

X_i = mole fraction at the highest absorption level

Magnetic susceptibility

The first step was to zero the magnetic susceptibility equipment. A capillary tube that was empty was weighted as w_1. After placing the empty capillary tube into the machine, the magnetic value was measured and recorded as Ro. The capillary tube was carefully filled with a small amount of the complex. W_2 was the weight of the sample and capillary tube. L represents the sample's length in the capillary. After inserting the capillary tube into the device, the complex's magnetic value (R) was noted. The formula was used to extrapolate the magnetic susceptibility value.

$$X_g = \frac{CL\ (R - R_\circ)}{10^9\,M}$$

Where

w_1= weight of the capillary tube when empty

w_2= capillary tube weight when empty and complex

R= magnetic value of complex

Ro= magnetic value of capillary tube

L= sample length in the capillary tube

M= mass of complex (w_2-w_1)

Anti-bacterial Studies

The Schiff base ligand and its metal complexes were tested for anti-bacterial activity against Escherichia coli and Staphylococcus aureus bacterial strain*s*. After the solidified Muller-Hinton Agar (MHA) had been placed in Petri dishes, the surface was coated with each microbe's suspension. After being serially diluted to achieve three different concentrations (250 µg/disc, 125 µg/disc, and 62.5 µg/disc), the Schiff base and the metal complexes were added to the culture media after being individually dissolved in DMSO. After that, they were incubated at 37 °C for 24 hours. Activities were determined and compared to those of a common drug (tetracyclin) by measuring the diameter of the zone of inhibition in millimetres (mm). (Khan *et al.,* 2014).

Anti-fungal Studies

The anti-fungal activity of the Schiff base ligand and its metal complexes was assessed against two dangerous fungus, (*Aspergillus fumigatus and Candida albicans*), using the disc diffusion method. Ketoconazole was used as the traditional fungicide, while DMSO was used as a negative control. The fungal solution was added after the Potato Dextrose Agar (PDA) had solidified and placed in petri plates. By dissolving the Schiff base and metal complexes independently in DMSO, three different concentrations (250µg/disc, 125µg/disc, and 62.5µg/disc) were achieved for each well. They were placed on top of the culture media and let to stand at room temperature for a full 48 hours. To calculate the activities and compare them to the standard, the diameter of the zone of inhibition was measured in millimeters (mm). (Khan *et al.,* 2014).

Molecular Docking Study

The geometry of L and metal complexes was optimized using DFT with the B3LYP functional in Gaussian 09, and the results were converted to PDB format. The HER2-PY1196 4GFV crystal structure was obtained from the Protein Data Bank (www.rcsb.org/pdb). The "receptor" (DNA) and "ligand" (complexes) files were made with Auto Dock Tools. After the heteroatoms, like water molecules, were removed, polar hydrogen atoms and Kollman charges were introduced to the receptor molecule. For all other bonds, rotatable bonds were allowed. Docking studies were carried out using Auto Dock Vina. (Neelakantan *et al.,* 2018).

Due to the rapid increase in breast cancer HER2-PY1196 4GFV receptor was chosen which is responsible for breast cancer.

RESULTS AND DISCUSSION

O-phenylenediamine and 2-hydroxyacetophenone combined to form a brown Schiff base ligand with a 63% yield and a sharp melting point of 160°C. An intensely colorful complex with yields of 85.4%, 65.2%, and 80.1% is produced when the ligand interacts further with Cu (II), Ni (II), and Zn (II) ions. The metal complexes' decomposition temperatures vary from 200 to 250 degrees Celsius, demonstrating that complexation has occurred when the metal (II) complexes' decomposition temperature exceeds the ligand's melting point. Furthermore, the fact that the ligand has a lower melting point than its complexes indicates that complexation strengthens the intra-atomic bonding effect of these compounds' particles. (Daniel, 2009; Kiremire, 2009). The result is shown in Table 1 below.

Test of solubility

Table 2 shows the solubility of the Schiff base and its compounds. Because the Schiff base ligand was soluble in ethanol and benzene but insoluble in water, petroleum ether, chloroform, and diethyl ether, it was found to have low polarity.

Measurement Results for Conductivity of 10-3 M Metal (II) Complexes in DMSO

Each metal (II) complex's molar conductance, as measured in DMSO, is displayed in Table 3. The measured values fell between 7.80 and 15.20 ohm^{-1}cm^{2}mol^{-1} which means a low value, suggesting that the metal complexes are not electrolytic. (Grace *et al.,* 2015). Non-electrolyte metal complexes in DMSO have molar conductance ranges of 1–50 ohms^{-1}cm^{2}mol^{-1}. (Imran *et al.*, 2013).

Percentage Compositions and Empirical Formula of the Complexes

The complexes' water of crystallization % is displayed in Table 4. With Zn (II) dehydrating, Ni (II) tetrahydrate, and Cu (II) complex being trihydrate, it was discovered that all of the complexes were hydrated. The metal ligand reaction ratio was verified using the Jobs method of continuous variation. The Job's plot was used to determine the number of coordinated ligands exhibiting a 1:1 metal-ligand ratio for the metal complexes.

Magnetic susceptibility

The complexes' measured magnetic susceptibility is displayed in Table 5. The compounds' magnetic susceptibility showed that their effective magnetic moments were 0BM for Zn (II), 3.60BM for Ni (II), and 1.90BM for Cu (II). These values led to the proposal of a square planar geometry.

Table 1 Schiff base physicochemical characterization of its metal (II) complexes

Complex	Molecular weight	Color	%Yield	M.P (^{o}C)	Temperature of Decomposition
Ligand	344.00	Brown	63.00	160	
[CuLCl$_2$]	514.48	Black	85.40	_	245
[NiLCl$_2$]	576.37	Brown	65.20	_	232
[ZnLCl$_2$]	480.00	Brown	80.10	_	210

L = Ligand, $C_{22}H_{20}N_2O_2$ Mol. weight = 344.00

Table 2 Solubility Test of the Schiff base and its Metal (II) Complexes

Ligand/Complex	Distilled water	Di ethyl ether	Benzene	Pet. ether	Chloro form	Ethanol
Ligand	IS	IS	S	IS	IS	S
[CuL]	IS	S	IS	IS	S	S
[NiL]	IS	IS	IS	S	S	S
[ZnL]	IS	IS	IS	IS	S	S

Table 3 Measurement Results for Conductivity of 10-3 M Metal (II) Complexes in DMSO

Complexes	Electrical Conductivity (ohm^{-1} cm^{-1})×10^{-6}	Molar Conductance (ohm^{-1} cm^{2}mol^{-1})
[CuL]	10.50	3.50
[NiL]	15.20	5.00
[ZnL]	11.90	3.56

Table 4 Percentage Compositions and Empirical Formula of the Complexes

Complexes	% of Metal	% of Chlorine	% of ligand	%of Water	M:L ratio	Empirical Formulae
[CuL]	12.01	13.32	64.54	10.13	1:1	[CuLCL$_2$].3H$_2$O
[NiL]	10.81	13.00	63.00	13.19	1:1	[NiLCL$_2$].4H$_2$O
[ZnL]	12.60	13.76	66.67	7.00	1:1	[ZnLCL$_2$].2H$_2$O

Table 5 Values of magnetic susceptibility measurements

Complex	Xg (ergG^{-2}g^{-1})	Xm (ergG^{-2}mol^{-1})	μeff (B.M)
[CuL]	9.20 * 10^{-11}	4.7 * 10^{-8}	1.9
[NiL]	1.10 * 10^{-9}	6.3 * 10^{-7}	3.6
[ZnL]	-	-	
LIGAND	-3.56*10^{-11}	-3.92*10^{-9}	0

FTIR Spectrum

The range (650–4000 cm–1) in Table 6 aids in identifying the absorption vibration locations. Stretching modes for υC=N, υC=C, υOH, υC-N, υM-N, and υM-O are the primary ones. The coordination sites that might be involved in chelation were identified by analysing the IR spectra of the complexes and the free ligands. These peaks' locations and/or intensities are anticipated to alter after the synthesis is complete. The υC=N band has been discovered as the peak between 1640 and 1550 cm^{-1}. In all complexes, the stretching vibrational band of the ligand's (C=N) group changes to a lower frequency, 1588 cm^{-1} in Cu^{2+}, 1573 cm^{-1} in Ni^{2+}, and 1573 in Zn^{2+}, respectively. The band's frequency is 1640 cm^{-1}. The υC-N mode has been ascribed to the bands that show at 1315-1400 cm^{-1}. The presence of υ(M-O) and ν(M-N) is responsible for the new vibrations at 584-748 and 757-862 cm^{-1} that are not present in the free Schiff base. The Schiff base and its related complexes exhibit a notable peak that suggests the presence of water hydration in the compound structure around 3238-3029 cm^{-1}. Variations can influence metal complexes' interactions with microbial cell membranes in M-N and M-O stretching frequencies. FTIR spectroscopy showed that antibiotic-induced metabolic alterations in bacteria produced unique spectral fingerprints that were associated with the drug's mode of action. FTIR may detect conformational changes caused by metal complexes that bind to DNA, disrupting normal DNA functioning and revealing information about the anti-cancer processes of metal-based medications. (Bernardo *et al.,*2020)

Table 6 FTIR Spectrum

	υ(C=N)	υ(C=C)	υ(C-N)	υ(O-M)	υ(N-M)	υ(OH)
LIGAND	1640	1462	1339	-	-	3178
[CuL]	1588	1465	1383	698	762	3197
[NiL]	1573	1573	1354	698	754	3353
[ZnL]	1573	1495	1376	698	754	3231

Schiff Base to Metal (II) Ion Determination Using the Continuous Variation Method

The Jobs technique of continuous variation was applied to ascertain how many coordinated ligands there are for the metal ion. The absorbance was monitored while varying quantities of metal chloride and ligand solution were added to examine complexation. The curve provides the corresponding stoichiometries of metal to ligand for the complexes. (Collumn *et al.,* 2013). The amount of coordinated ligands was determined using the Job's plot, which is displayed in figures IIa, b, and c of the appendix. The findings suggested the formula $[MLCL_2].nH_2O$ and demonstrated that the metal-ligand ratio for each complex was 1:1.

MICROBIAL STUDIES

Anti-bacterial Screening

The results show that the ligand and the metal complexes are both fairly effective against every tested bacterium. But compared to the Schiff base, the metal complexes show stronger anti-bacterial activity, and this activity rises with concentration; this is probably due to chelation in the metal complexes, this chelation results in lessening the polarity of the metal. The complex's lipophilic nature is improved by this decrease, making it easier to pass through microbial cell membranes. In comparison to their free ligands, studies have demonstrated that metal complexes, such as those containing Zn (II), Cu (II), and Ni (II), have higher antimicrobial activity (Hassan *et al.,* 2022). The Cu^{2+} complex showed minimal action against both isolates. The Ni^{2+} complex exhibited greater action against *Escherichia coli* but modest activity against Staphylococcus aureus isolate*s*. The Zn2+ complex demonstrated high activity against both isolates. The standard drug (Tetracycline) has better activity against the selected bacterial isolates than the ligand and the metal complexes.

Anti-fungal Screening

At high concentrations, the Cu^{2+} complex had negligible activity against isolates of *Candida albican*, but at lower concentrations, it exhibited moderate activity against *Mucor species*, with decreasing efficacy. The Ni^{2+} complex had the greatest activity against *Mucor species* and the highest activity against isolates of *Candida albican* at high concentrations while exhibiting negligible action at lower concentrations. With a zone of inhibition of 25 mm, the Zn^{2+} complex has the maximum efficacy against *Candida albican*, however its efficiency decreases with decreasing concentration. It also has significant potency against isolates of *Mucor species*, albeit at lower doses. The ligand and the metal complexes show lower activity than the standard drug (Clotrimazole).

Molecular Docking

The most preferred binding is revealed by the values of the inhibition constant and binding energy; a high negative charge indicates a more stable interaction. A larger negative estimated binding energy value indicates larger efficient binding. Thus, Ni, Zn, Cu, and finally the free ligand are in the optimal order. This indicates that the free ligand and the complexes are more stable than the control anti-cancer medication (Tamoxifen) and some selected standard anti-cancer drugs. Therefore, it is conceivable for the complexes and anti-cancer cells to interact and employ the medicine to treat cancer. (Diab *et al.,* 2019). Certain metal complexes have the ability to intercalate into DNA strands, resulting in breaks and structural abnormalities. Apoptosis results from this interaction's disruption of essential cellular functions like transcription and replication. For instance, by causing DNA breakage, copper (II) complexes have shown notable cytotoxic effects against cancer cell types. (Hassan *et al.,* 2022).

Table 7 Screening of the ligand and its complexes for anti-bacterial activity

Complexes	Concentration (ug/ml)/ Zone of inhibition (mm)					
	Staphylococcus Aureus			*Escherichia Coli*		
	250	125	62.5	250	125	62.5
Ligand	15	10	8	18	14	11
[CuL]	20	16	11	20	15	15
[NiL]	23	16	14	25	20	18
[ZnL]	22	19	16	22	19	15
Standard	34			32		

Standard = Tetracycline

Table 8 Schiff base and its metal (ii) complexes' anti-fungal sensitivity test

Complexes	Concentration (ug/ml)/ Zone of inhibition (mm)					
	Candida albican			*Mucur specie*		
	250	125	62.5	250	125	62.5
Ligand	17	16	10	16	13	08
[CuL]	-	15	10	19	15	12
[NiL]	20	-	-	21	18	15
[ZnL]	25	19	14	-	20	16
Standard	38			35		

Standard = Clotrimazole

Table 9: the ligand and complexes' molecular docking assay against (HER2-PY1196 4GFV) breast cancer cells

	Binding Energy (kcal/mol)	**Inhibition constant**	**Near residues**
LIGAND	-6.4	20.11μM	Lys-41,Tyr-68,Thr-48,Arg-268
[CuL]	-7.3	4.39 μM	Asp-64,Lys-63,Tyr-68,Thr-48
[NiL]	-7.6	2.64 μM	Asp-64,Gln-276,Ala-273,Lys-63
[ZnL]	-7.5	3.13 μM	Gln-276,Ala-273,Tyr-68,Asp-64
Control (Tamoxifen)	-5.9	2.72 μM	Leu-66,Cys-233,Asp-64,Val-65

Table 10: Docking Score for Standard Anti-cancer Drugs

S/N	NAME	TARGET	DOCKING SCORE	REFERENCE
1	Paclitaxel	Tubulin beta-1 chain	−5.86 kcal/mol	Ruma *et al.,* 2011
2	Etoposide	Tubulin	−4.916 kcal/mol	Manisha *et al.,* 2020
3	Topotecan	Tubulin	−4.916 kcal/mol	Manisha *et al.,* 2020
4	Satraplatin	DNA	−5.06 kcal/mol	Madhavi *et al.,* 2024
5	Picoplatin	DNA	−2.69 kcal/mol	Madhavi *e tal.,* 2024

CONCLUSION

The Schiff base and its metal complexes have been synthesized and studied by various analytical techniques. Job's method of Continuous variation shows that the metal-ligand ratio in all the complexes is 1:1. All the complexes are non-electrolytes in DMSO solvent. The decomposition temperature of the metal (II) complexes indicated that complexation has taken places. Based on magnetic susceptibility data, Cu and Ni Schiff base complexes are paramagnetic while Zn complex is diamagnetic. Based on the spectral studies, conductance data and magnetic susceptibility data, the synthesized ligand and its complexes are neutral tetradentate, coordinating through the Oxygen of the hydroxy group and Nitrogen of the azomethine group. The antimicrobial activity results indicate that all complexes have been found to be more effective than its ligand as the process of chelation dominantly affects the overall biological behavior of the compounds. The molecular docking study reveals that the interaction between the complexes and the anticancer cell use for drug in treating cancer is possible. Based on the analytical and spectral studies, we propose square planner geometry to all the complexes

FUNDING

TET-Fund IBR (2024) intervention.

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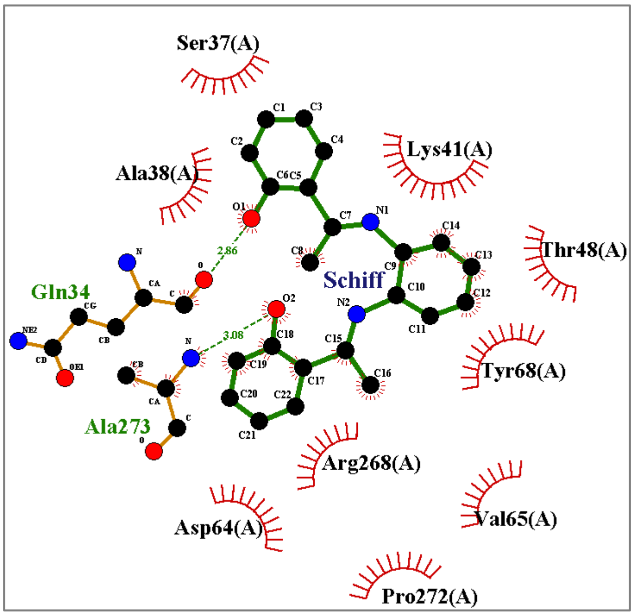
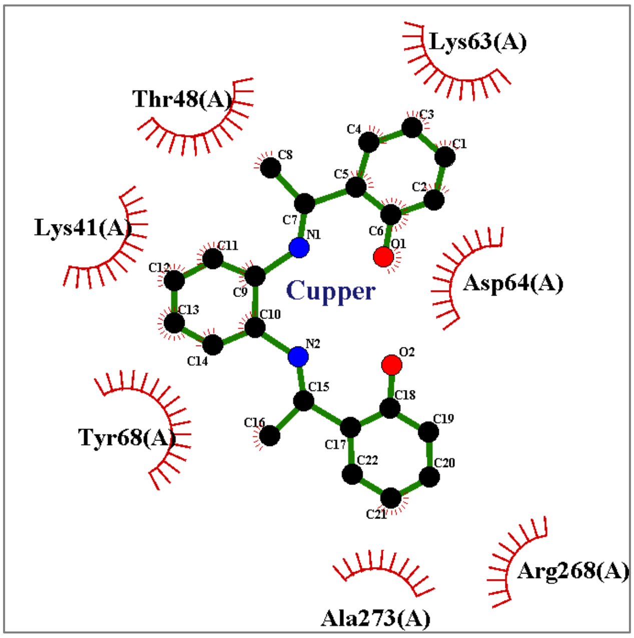
APPENDIX

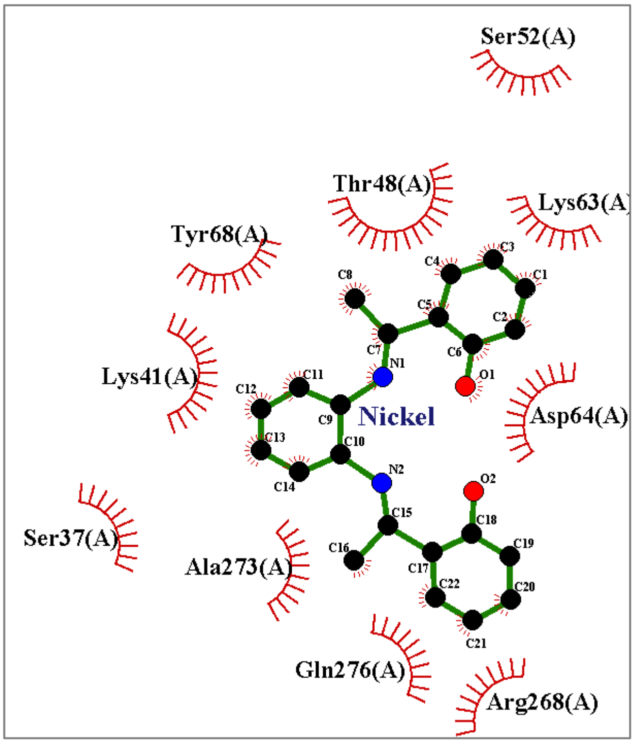
MOLECULAR DOCKING ENZYMES INTERACTIONS



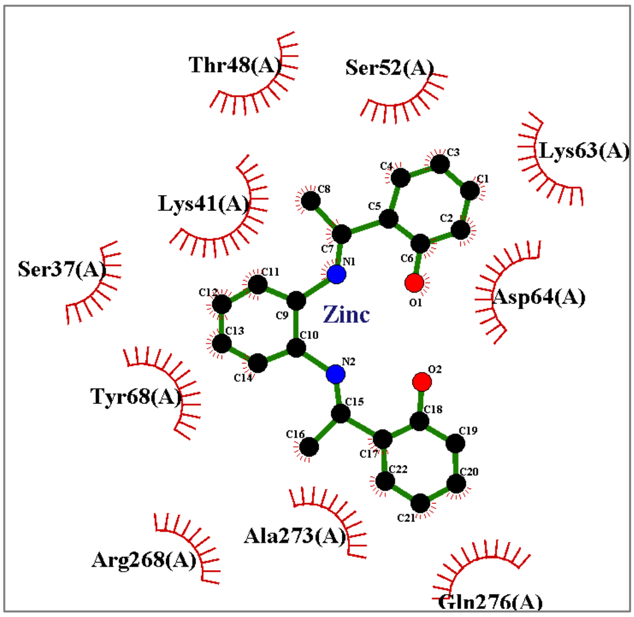
Appendix Ia : Schiff base molecular docking interaction



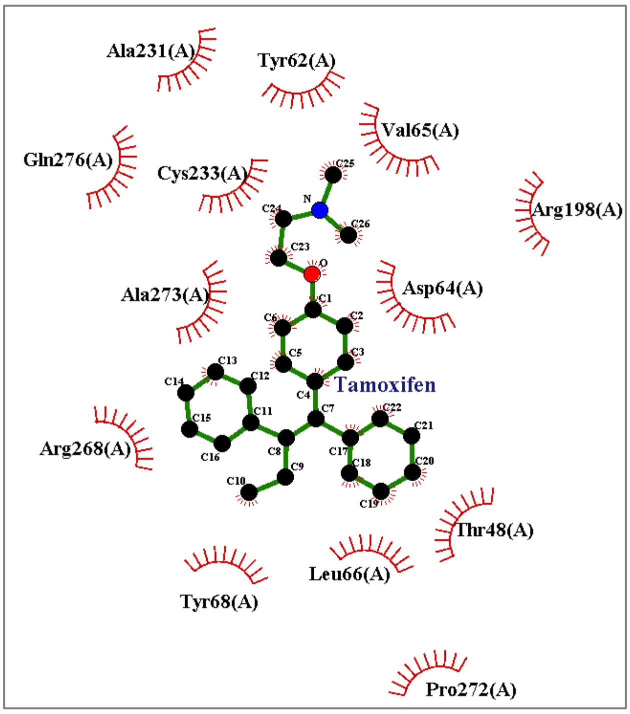
Appendix Ib: Cupper molecular docking interaction



Appendix Ic: Nickel molecular docking interaction

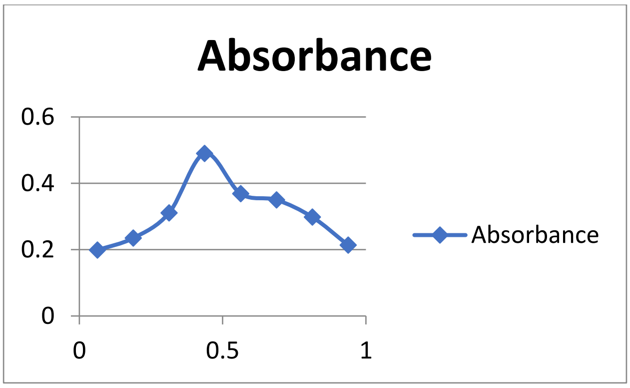


Appendix Ic: Zinc molecular docking interaction

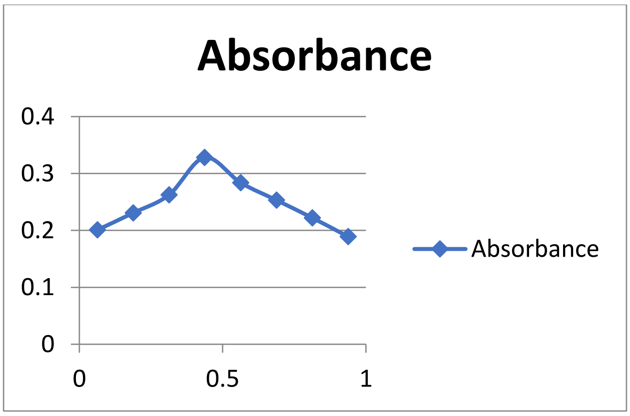


Appendix Id: Tamoxifen molecular docking interaction

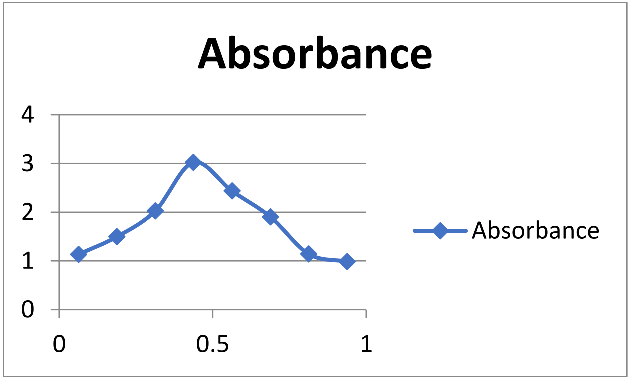
GRAPHS OF CONTINUOUS VARIATION METHOD



Appendix IIa: CuL absorption in relation to the mole fraction.



Appendix IIb: NiL absorption in relation to the mole fraction.



Appendix IIc: ZnL absorption in relation to the mole fraction.