

Synthesis, Characterization, and In Vitro Antimicrobial Activity of Some Transition Metal Complexes of a Novel Quinoline-Based Schiff Base

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Abstract: This study describes the synthesis and characterization of a novel quinoline-based Schiff base ligand (DTQ), 3,3'-{1,3-phenylenebis[azanylylidene-(E)-methanylylidene]}di(quinoline-2-thiol), obtained through the condensation reaction of 2-mercapto-3-formyl-quinoline with 1,3-diaminobenzene in a 2:1 molar ratio. The progress of the reaction and purity of the synthesized compounds were monitored by thin-layer chromatography (TLC). The synthesized Schiff base ligand was subsequently employed for the preparation of its Cu(II), Ni(II), and Zn(II) metal complexes. The prepared ligand and its metal complexes were characterized by various physicochemical and spectroscopic techniques, including solubility studies, melting point determination, UV-Visible spectroscopy, FT-IR spectroscopy, magnetic susceptibility measurements, molar conductance analysis, atomic absorption spectroscopy (AAS), and elemental analysis. The low molar conductance values confirmed the non-electrolytic nature of the complexes. FT-IR spectral data revealed that the ligand coordinates to the metal ions through azomethine nitrogen and sulfhydryl sulfur donor atoms, forming tetradentate coordination sites. The Cu(II) and Ni(II) complexes exhibited paramagnetic behavior. The antimicrobial activity of the synthesized Schiff base and its metal complexes was evaluated using the disc diffusion method against selected Gram-positive bacteria, namely *Bacillus subtilis* and *Staphylococcus aureus*, Gram-negative bacteria including *Pseudomonas aeruginosa* and *Escherichia coli*, and fungal strains *Candida albicans* and *Aspergillus niger* at two different concentrations. All synthesized compounds exhibited noticeable antimicrobial activity against the tested microorganisms, with the Cu(II) complex showing the highest activity, displaying inhibition zones ranging from 19 to 23 mm.

Keywords: Quinoline, Schiff base, Tetradentate ligand, Metal complexes, Antimicrobial Activity

1. Introduction

Schiff bases derived from quinoline compounds and their metal co-ordinate compounds are of great interest within the fields of coordination and medicinal chemistry due to their wide range of biological activity and their multiple ways to coordinate to metal ions. Due to their ease of synthesis, diversity in chemical structure, and ability to co-ordinate to metal ions via donor atom types (N, O, S), Schiff bases are considered to be "privileged ligand" systems. The increased interest in ligand design and synthesis of Schiff bases and their metal co-ordinated compounds has resulted in an abundance of physicochemical, catalytic and pharmaceutical studies to characterise these compounds for their unique properties. Furthermore, many reports have shown that Schiff bases show a range of biological activity including antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, antimalarial, antitubercular, anticonvulsant, antidiabetic, antiproliferative and anticancer activities. Therefore, researching ways to develop biologically active Schiff base derivatives with augmented efficacy and reduced toxicity will continue to be a significant pursuit in the area of medicinal and bioinorganic chemistry. Quinoline derivatives are a group of naturally occurring heterocyclic compounds widely used in the field of medicine. Quinoline compounds are used as drugs and have various antifungal, nonsteroidal anti-inflammatory, and anti-cancer properties. Quinoline compounds, in particular, have been the subject of much research due to their antioxidant, anti-inflammatory, and anti-cancer activities [1]-[25]. Afzal et al. [26] reported that quinoline derivatives exert their anti-cancer effects via various pathways, such as inducing apoptosis, inhibiting

blood vessels from forming, preventing cell migration, and blocking the growth cycle. El-Halim et al. [27] studied the synthesis of metal complexes of quinoline-based Schiff bases. They tested these complexes for anti-infective and anti-cancer activities against gram-positive, gram-negative and fungal organisms, as well as breast and colon cancer cell lines. The researchers reported that the Cu(II) complexes demonstrated the greatest anti-cancer activity compared to other synthesized metal complexes.

In view of the biological and coordination potential of quinoline-based Schiff bases, the present study describes the synthesis and characterization of a new tetradentate Schiff base ligand (DTQ), 3,3'-{1,3-phenylenebis[azanylylidene-(E)-methanylylidene]}di(quinoline-2-thiol) obtained through the condensation of 1,3-diaminobenzene with 2-mercaptoquinoline-3-carbaldehyde. The synthesized ligand provides an SNNS donor coordination environment through two azomethine nitrogen atoms and two sulfhydryl sulfur atoms. In addition, the corresponding Ni(II), Cu(II), and Zn(II) complexes were synthesized and characterized using various physicochemical and spectroscopic techniques. The ligand and its metal complexes were further evaluated for their in vitro antibacterial and antifungal activities.

2. Materials and Methods

Sigma-Aldrich, E. Merck (India), SD Fine, and Hi-Media Chemicals provided all the necessary chemicals, which were used exactly as specified. Melting points were determined in open capillary tubes. Using KBr pellets, the Shimadzu FTIR model 4800S spectrophotometer captured the infrared

spectra in the 4000-400 cm^{-1} region. Thin layer chromatography (TLC) on aluminum plates coated with a layer of silica gel, provided by Merck, was used to assess the purity of prepared compounds and the progress of all reactions. An iodine chamber was used to visualize the spots. Microanalyses for the elements C, H, and N were recorded using a CHNS microanalyzer. The electronic spectra in DMSO were recorded using a Shimadzu UV-160 spectrophotometer. Molar conductance in DMSO solution at concentrations of 10^{-3} M was measured using an Elico CM 180 conductivity meter. The Digital Gouy Balance GMX-02 model was used to measure the magnetic moment using the Gouy method. The quantity of metal in the complexes was determined using the Shimadzu Atomic Absorption 160 Spectrophotometer.

2.1 Synthesis of Schiff base ligand (DTQ)

According to the method described in the literature [28]-[30], 2-chloroquinoline-3-carbaldehyde was prepared by conducting the Vilsmeier-Haack reaction with acetanilide (Fig.1, step 1). Subsequently, 2-mercapto quinoline-3-carbaldehyde was achieved from 2-chloroquinoline-3-carbaldehyde as an intermediate product (Fig.1, step 2). The obtained intermediate was further used for the formation of the final Schiff base ligand (DTQ). A warm ethanolic solution of 1,3-diaminobenzene (20 mmol) with a few drops of acetic acid was progressively mixed with an ethanolic solution of 2-mercapto quinoline-3-carbaldehyde (40 mmol), stirring constantly. For about 5 hours, the reaction mixture was refluxed. Using a solvent system consisting of a mixture of ethyl acetate and n-hexane, the TLC method was used to monitor the reaction's progress. Following refluxation, the concentrated solution was allowed to cool at room temperature after the excess solvent was eliminated by distillation at low pressure. After cooling, the yellow solid was filtered, washed with excess of cold ethanol, dried, and recrystallized from ethanol. The product's purity was assessed on a TLC method using the same solvent solution, $m.p. > 280$ °C (Fig.1, step 3).

2.3 Synthesis of transition metal (II) complexes

The following method was used to prepare solid Ni(II), Cu(II), and Zn(II) complexes of Schiff base ligand (DTQ). A hot ethanolic solution of Schiff base (4 mmol) was gradually mixed with a 4 mmol corresponding metal(II) chloride salt (nickel chloride hexahydrate, copper chloride dihydrate, or zinc chloride) dissolved in a suitable quantity of ethanol while being continuously stirred. The reaction mixture was then enriched with a few drops of 4% NaOH solution to maintain basic conditions (pH = 7.2-7.6). For an additional two hours, the reaction mixture was refluxed. The resultant solution is distilled at lower pressure after reflux, which reduces its volume by half. The colorful solid metal (II) complexes were separated, filtered, and repeatedly washed with cold ethanol and ether after being allowed to cool overnight at room temperature. The final products dried over anhydrous CaCl_2 in a vacuum desiccators (Fig.1, step 4).

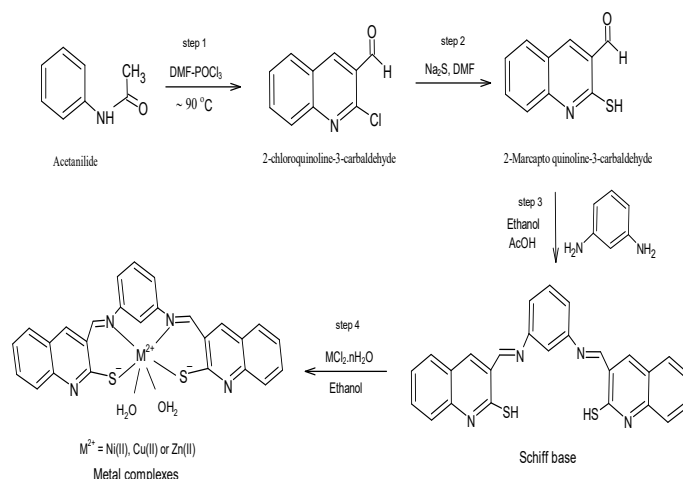


Figure 1: Synthesis route of Schiff base (DTQ) and its metal complexes

2.3 Antimicrobial screening

The synthesized Schiff base ligand and its metal complexes were screened for their in vitro antimicrobial activity against the fungal strains *Candida albicans* and *Aspergillus niger*, as well as against the Gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*, and the Gram-negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli* using the disc diffusion method. The bacterial and fungal cultures were cultivated on Mueller–Hinton agar and Sabouraud dextrose agar media, respectively. Approximately 100 μL of freshly prepared microbial suspension was uniformly spread over the surface of the respective agar plates under aseptic conditions and allowed to dry. Stock solutions of the test compounds were prepared in dimethyl sulfoxide (DMSO), and sterile paper discs were impregnated with solutions containing concentrations of 500 and 1000 $\mu\text{g/mL}$. The impregnated discs were then aseptically placed on the inoculated agar plates at equal distances and gently pressed onto the medium surface. The plates were incubated at 37 °C for 24 h for bacterial strains and 48 h for fungal strains. Discs containing only DMSO served as negative controls, while standard antibacterial and antifungal drugs were used as positive controls. Following incubation, the antimicrobial activity was assessed by measuring the diameter of the zone of inhibition around each disc in millimeters [31]-[32].

3. Results and Discussion

The structure of the Schiff base (DTQ) was confirmed by several analytical and physical techniques. All of the metal (II) complexes that have been produced are solid, stable in the presence of air, and non-hygroscopic. The complexes show considerable solubility in dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO) solvents, but insolubility in water and poor solubility in common organic solvents. The molar conductance of the metal complexes in DMSO solvent at a concentration of 0.001 M ranged from 7 to 10 $\text{cm}^2 \text{Ohm}^{-1} \text{mol}^{-1}$. The complexes could therefore be considered non-electrolytes. The acquired elemental data agree well with the theoretically calculated values. The addition of AgNO_3 (Precipitation method) [33]-[34] further verified whether or not chloride ions were present outside the coordination sphere. The analytical findings showed that the compounds were fully formed. The results also showed that the metal to

ligand ratio in all metal complexes is 1:1. The molar conductance values and other physical and analytical data related to the Schiff base ligand and its metal complexes are compiled in Table 1.

Table 1: Physical and analytical data of Schiff base (DTQ) and its metal complexes

Compounds (Mol. Formula)	M.W. gmol ⁻¹	Yield%	Elemental Composition in % Found (Calculated)					$\Lambda_m(\text{cm}^2\Omega^{-1}\text{mol}^{-1})$ in DMSO	μ_{eff} B.M.
			C	H	N	S	M		
DTQ,(LH ₂) (C ₂₆ H ₁₈ N ₄ S ₂)	450.57	68	69.23 (69.31)	4.08 (4.03)	12.31 (12.43)	12.31 (12.43)	---	---	---
[Ni(L)(H ₂ O) ₂] (NiC ₂₆ H ₂₀ N ₄ S ₂ O ₂)	543.29	62	51.32 (51.48)	3.76 (3.71)	10.22 (10.31)	11.69 (11.80)	10.06 (10.80)	9.2	3.32
[Cu(L)(H ₂ O) ₂] (CuC ₂₆ H ₂₀ N ₄ S ₂ O ₂)	548.14	64	56.75 (56.97)	3.74 (3.68)	10.11 (10.22)	11.59 (11.70)	11.19 (11.59)	7.4	1.89
[Zn(L)(H ₂ O) ₂] (ZnC ₂₆ H ₂₀ N ₄ S ₂ O ₂)	550.0	65	56.62 (56.78)	3.75 (3.67)	10.09 (10.19)	10.51 (11.66)	11.24 (11.89)	9.7	Dia*

3.1 Infrared spectral studies

The ligand binding sites with the metal ions were found by comparing the IR spectra of the Schiff base ligand (DTQ) and its metal complexes. The ligand was the source of the majority of the spectral bands seen in the complexes. The spectra of the ligand and its Ni(II) complex are displayed in Figures 2 and 3, respectively, while Table 2 summarizes the infrared spectral bands and their assignments. The FTIR spectrum of the Schiff base ligand (DTQ) displayed broad absorption bands at about 3411, 2558, and 1142 cm⁻¹ corresponding to the stretching vibrations of $\nu(\text{N-H})$, $\nu(\text{S-H})$, and $\nu(>\text{C}=\text{S})$ groups of the quinoline ring moiety, which indicates that the ligand exists in the thiol-thione tautomeric form. This confirms the subsequent substitution of the SH group by removing the chlorine present at the second position of the quinoline. Also, the symmetric and asymmetric stretching vibrations of the $\nu(\text{C-H})$ aromatic groups are responsible for the medium intensity peaks that are seen in the 3100–2850 cm⁻¹ region. The strong intense band at 1641 cm⁻¹ was assigned to the azomethine $\nu(\text{C}=\text{N})$ stretching vibration, which confirms the formation of the Schiff base. The band at 680 cm⁻¹ was assigned to phenolic $\nu(\text{C-S})$ stretching of the quinoline moiety. Absorption bands between 1618 and 1424 cm⁻¹ were assigned to the aromatic $\nu(\text{C}=\text{C})$ vibrations and conjugation between the aromatic ring and azomethine ($>\text{C}=\text{N}-$) group. A set of bands in the range of 1300–1000 cm⁻¹ and 960–750 cm⁻¹ could be assigned to the in-plane and out-of-plane deformation vibrations of the $\delta(\text{C-C-C})$ and $\delta(\text{C-H})$ bonds of the aromatic rings. In the infrared spectra of the Ni(II), Cu(II), and Zn(II) complexes, the ligand band assigned to $\nu(\text{C}=\text{N})$ of the azomethine group and $\nu(\text{C-S})$ was shifted from 1641 and 680 cm⁻¹ to lower frequencies (1618, 1622, and 1615 cm⁻¹) and (668, 670, and 665 cm⁻¹), respectively. This negative shift in their stretching vibrations supports the coordination of imine and thiol groups with metal ions through imine-N and sulfhydryl-S.

The appearance of a broad band in the 3680–3000 cm⁻¹ region with maxima at 3416, 3422, and 3419 cm⁻¹ is indicative of coordinated water molecules in Ni(II), Cu(II), and Zn(II) complexes, respectively. Evidence for this is also the non-ligand bands in the region 850-930 cm⁻¹, which are attributed to the bending vibration of water molecules. The new non-ligand bands in the low-frequency region at 571–419 cm⁻¹ for metal complexes are assigned to $\nu(\text{M-N})$ and $\nu(\text{M-S})$ bonds. This supports the proposed sites of coordination of the ligand. Therefore, it can be concluded that the ligand (DTQ) coordinated to metal ions through its

two sulfhydryl-S and two azomethine-N atoms and acts as a dianionic tetradentate ligand [35]-[39].

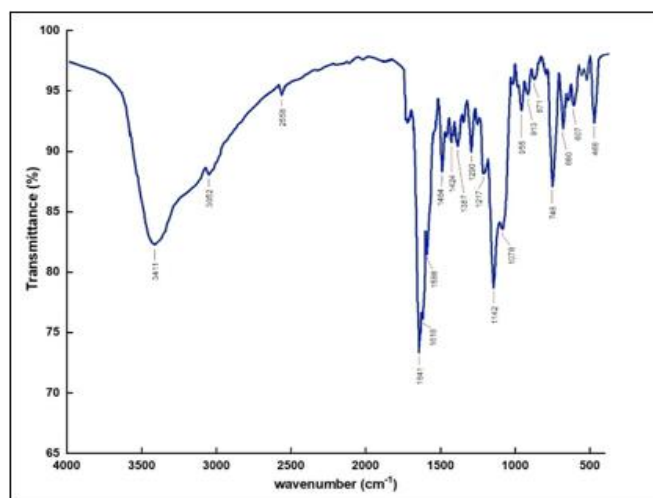


Figure 2: FTIR spectrum of the Schiff base (DTQ)

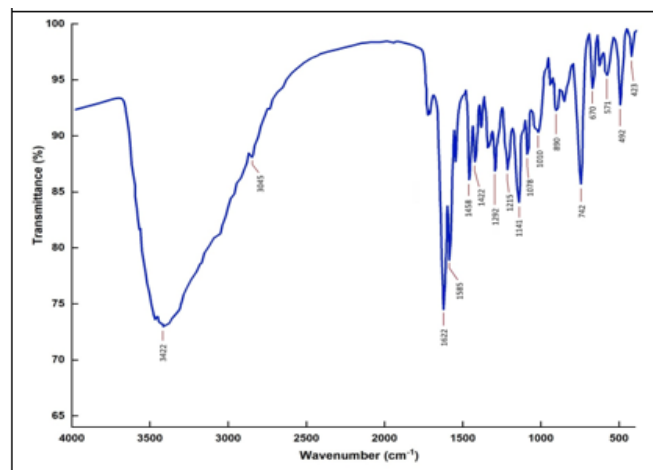


Figure 3: FTIR spectrum of the Cu-complex

Table 2: Selected FTIR frequencies of Schiff base (DTQ) and its metal complexes in cm⁻¹

Compds	Ligand (DTQ)	Ni- complex	Cu- complex	Zn- complex
$\nu(\text{S-H})/(\text{N-H})$	3411	---	---	---
$\nu(\text{H}_2\text{O})$	---	3416	3422	3419
$\nu(\text{C}=\text{N})$	1641	1618	1622	1615
$\nu(\text{C-S})$	680	668	670	665
$\nu(\text{M-N})$	---	545	571	542
$\nu(\text{M-S})$	---	422	419	427

3.2 UV-Visible spectral and magnetic moment studies

The electronic spectrum of Schiff base was recorded in DMSO at a concentration of 10^{-3} M. Schiff base has transition bands at 294 and 364 nm because of the part and the azomethine group of Schiff base. These bands are due to the $\pi-\pi^*$ and $n-\pi^*$ transitions. For the metal complexes of Ni(II) Cu(II) and Zn(II) the transition bands for $\pi-\pi^*$ and $n-\pi^*$ are seen at wavelengths. The bands are at 319.5 and 377 nm for Ni(II) complexes, 322 and 379.5 nm for Cu(II) complexes and 324.5 and 378 nm for Zn(II) complexes. When Schiff base coordinates with a central metal ion the transition band shifts to longer wavelengths in the metal complexes. The intensities of these bands increase when they shift to a wavelength in the metal complexes. This shift happens because the nitrogen of the azomethine groups of Schiff base donates a pair of electrons to the metal ion. The magnetic moment susceptibility of the metal complexes of Cu(II) and Ni(II) was measured at room temperature. These metal complexes are paramagnetic. The magnetic moment of the Cu(II) complex is 1.89 B.M. This is slightly higher than the spin value for one unpaired electron, which is 1.73 B.M., for a distorted octahedral geometry. The magnetic moment value of the Ni(II) complex is 3.32 B.M. This value's in the range of the expected value, for an octahedral geometry of the metal complex, which is 2.83–3.50 B.M. [35]-[39].

3.3 In vitro Antimicrobial studies

The antibacterial and antifungal activities of the synthesized Schiff base and its metal complexes were evaluated against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Aspergillus niger* and *Candida albicans* by disc diffusion method on agar medium. Table 3 and Figure 4 show the results of antimicrobial screening of the tests performed on the compounds in different doses. The antibacterial activity of the investigated compounds was studied and it was found that among all the prepared compounds, Cu (II) complex showed excellent antibacterial activity against the gram positive and gram negative bacteria. Activity order against bacterial strains with inhibition zone 14–17 mm at lowest concentration and 19–23 mm at highest concentration are *S. aureus* > *B. subtilis* > *E. coli* > *P.*

aeruginosa. The free ligand, Ni(II) and Zn(II) complexes showed comparatively lower level of anti-bacterial activity. The free ligand was found to be very less effective against all the tested strains of bacteria even at the highest concentration. The order of antibacterial activity of synthesized compounds against bacterial strains is as follows: Cu(II)-complex > Ni(II) = Zn(II) complexes > Ligand. The ligand and the Ni(II) and Zn(II) complexes were less active than the Cu(II) complex against the fungi in an antifungal study, with the latter showing an inhibition zone of 20–22 mm. It was found that in the same experiment the chelated Schiff base showed more antimicrobial activities than the non-chelated Schiff base. Chelation theory is used to explain the improved effectiveness of metal chelates. Chelation reduces the polarity of the metal ion by partially sharing the positive charge of the metal ion with ligand donor sites by delocalization of electrons through the chelated ring. The resulting metal chelate becomes more lipophilic thereby enabling it to penetrate and rupture the lipid bilayer of microbial cell membranes. In addition, interactions between ligands and metal ions may influence the antibacterial capability by influencing the solubility, dipole moment and conductivity of the system [40]-[42].

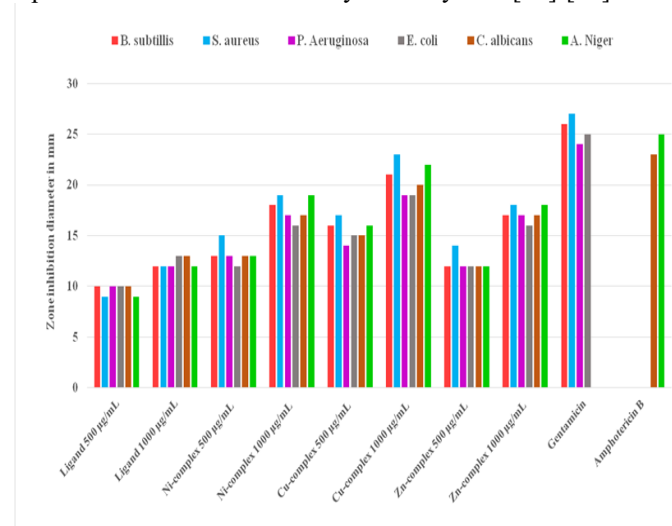


Figure 4: Graphical representation of antimicrobial activity of the Schiff base and its metal complexes

Table 3: Antibacterial and antifungal activities of the Schiff base (DTQ) and its metal complexes

Compds	Conc. µg/mL	Zone Inhibition Diameter (mm)					
		Gram +ve Bacteria		Gram -ve Bacteria		Fungi	
		B. subtilis	S. aureus	P. aeruginosa	E. coli	C. albicans	A. Niger
Ligand (DTQ)	500	10	09	10	10	10	09
	1000	12	12	12	13	13	12
Ni-complex	500	13	15	13	12	13	13
	1000	18	19	17	16	17	19
Cu-complex	500	16	17	14	15	15	16
	1000	21	23	19	19	20	22
Zn-complex	500	12	14	12	12	12	12
	1000	17	18	17	16	17	18
Gentamicin		26	27	24	25	---	---
Amphotericin B		---	---	---	---	23	25

3. Conclusion

In the present study, a quinoline-derived Schiff base ligand (DTQ) and its transition metal (II) complexes were

successfully synthesized and characterized using various physicochemical, spectroscopic, and analytical techniques. The analytical data confirmed a 1:1 metal-to-ligand stoichiometry for all synthesized complexes. The low molar conductance values indicated the non-electrolytic nature of

the metal complexes. Spectral studies revealed that the Schiff base behaves as a dianionic tetradentate ligand, coordinating through azomethine nitrogen and sulfhydryl sulfur donor atoms to form octahedral geometries around the respective metal ions. The synthesized ligand and its metal complexes were further evaluated for their in vitro antimicrobial activity against Gram-positive bacteria, namely *Bacillus subtilis* and *Staphylococcus aureus*, Gram-negative bacteria including *Pseudomonas aeruginosa* and *Escherichia coli*, and fungal strains *Aspergillus niger* and *Candida albicans* using the disc diffusion method. The results demonstrated that all metal complexes exhibited enhanced antimicrobial activity compared to the free Schiff base ligand. Among the synthesized compounds, the Cu(II) complex showed the highest inhibitory activity against all tested microorganisms, with zones of inhibition ranging from 19–23 mm, indicating its promising antimicrobial potential.

4. Future Scope

The synthesized compounds showed promising antimicrobial activity and can be potential therapeutic agents. Further studies on anticancer activity, molecular docking and toxicity evaluation may provide better insights towards their pharmaceutical potential.

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