

The Antimicrobial Study of 3,3'-{1,3-phenylenebis[azanylylidene-(E)-methanylylidene]} di(quinolin-2-ol), with Ni(II), Cu(II), and Zn(II) transition metal ions

Tushar S. Umasare

Department of Chemistry, Vasantrya Naik College of Arts, commerce and Barrister A. R. Antulay Science College, Mhasala-Raigad 402105, Maharashtra, India

ABSTRACT:

This study reports on the synthesis of novel Quinoline-based Schiff base, 3,3'-{1,3-phenylenebis[azanylylidene-(E)-methanylylidene]} di(quinolin-2-ol), by condensing 2-hydroxy quinoline-3-carbaldehyde with m-phenylenediamine in 1:2 molar ratio. The progress of the reactions and the purity of the synthesized compounds were monitored by TLC. The prepared Schiff base was then used to form metal complexes with Cu(II), Ni(II), and Zn(II). The synthesized compounds were characterized by solubility tests, melting point determination, UV-visible spectra, FT-IR spectra, magnetic moments, Molar conductivity measurement, AAS and elemental analyses. The low conductivity values of the compounds show they are non-electrolytic. The FT-IR data show there are O, N, N and O coordination sites on the ligand. The magnetic moments of the complexes of Cu(II) and Ni(II) are paramagnetic. The antimicrobial potential of the synthesized Schiff base and its metal complexes was evaluated by the disc diffusion method on agar medium against selected Gram-positive and Gram-negative bacterial strains, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, along with the fungal strain *Candida albicans* and *Aspergillus niger*, at the different concentrations. All prepared compounds had some antimicrobial activity against the above organisms, with the Cu-complex having the greatest one with an inhibition zone ranging from 15 to 23 mm.

KEYWORDS: Quinoline, Schiff base, Metal complexes, Antimicrobial Activity

1. INTRODUCTION:

Schiff bases have become known as “privileged ligands” in terms of coordination chemistry because of their multi-faceted coordination ability. Over the last several years, there has been an increase in research that focuses on the synthesis and characterization of Schiff bases containing donor atoms such as nitrogen, oxygen, or sulfur, along with transition metal complexes with respect to their physicochemical and biological properties. Schiff bases have also attracted much interest in the field of medicinal chemistry because they exhibit a wide range of pharmacological activities, including

antibacterial, antifungal, antioxidant, antiviral, antimalarial, anti-HIV, antitumor, analgesic, anti-inflammatory, antitubercular, anticonvulsant, anticancer, antihypothermic, antihypertensive, antidiabetic, and antiproliferative activities. Therefore, there are numerous studies being conducted in order to synthesize biologically active derivatives of Schiff bases which have increased therapeutic activity and decreased toxicity for the treatment of multiple diseases [1-8].

Quinolines and their derivatives are naturally occurring alkaloids of importance and show various pharmacological activities like antimicrobial, antiproliferative, antineoplastic, antiinflammatory, antimalarial and anticonvulsant properties. They are important structural scaffolds in many compounds of medicinal interest. Among them, 2-oxoquinoline (2-hydroxyquinoline) is a naturally occurring alkaloid that has attracted significant attention for its remarkable antioxidant, antiproliferative, anti-inflammatory and anticancer activities [9-19]. For instance, quinoline derivatives have been reported by Afzal et al. [20] to exhibit anticancer effects through mechanisms such as cell cycle arrest, inhibition of angiogenesis, induction of apoptosis, and suppression of cell migration. El-Halim et al. [21] synthesized new transition metal complexes of a Schiff base ligand containing quinoline and studied the antibacterial properties of these complexes in vitro against fungi, Gram-positive bacteria, and Gram-negative bacteria. They also investigated the anticancer activity of the ligand and its metal complexes in vitro on both colon cancer and breast cancer cell lines. Among the metal complexes tested, the Cu(II) complex had the lowest IC₅₀ value against the breast cancer cell line, and all of the metal complexes had higher IC₅₀ values than the Schiff base ligand.

Based on the importance of quinoline based Schiff bases and their associated metal complexes, we report herein the results of our efforts to synthesize and characterize a new Schiff base (DHQ) named 3,3'-{1,3-phenylenebis[azanylylidene-(*E*)-methanylylidene]}di(quinolin-2-ol), by condensing the *m*-phenylenediamine with the aldehydic group of 2-hydroxyquinoline-3-carbaldehyde. The resulting ligand will provide an ONNO coordination environment comprised of the two phenolic-OH groups and the two azomethine nitrogen atoms of the ligand. In addition, we synthesized coordination complexes of the ligand (DHQ) with Ni(II), Cu(II) and Zn(II) metal ions. All of the isolated compounds were also evaluated for their in vitro antibacterial and antifungal activities.

2. EXPERIMENTAL

Material 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.

3. METHODOLOGY

Synthesis of Schiff base ligand (DHQ):

3,3'-[1,3-phenylenebis[azanylylidene-(E)-methanylylidene]]di(quinolin-2-ol)

According to the method described in the literature [22-24], 2-chloroquinoline-3-carbaldehyde was prepared by conducting the Vilsmeier-Haack reaction with acetanilide (Scheme, step 1). Subsequently, 2-hydroxyquinoline-3-carbaldehyde from was achieved 2-chloroquinoline-3-carbaldehyde as an intermediate product (Scheme, step 2). The obtained intermediate was further used for the formation of the final Schiff base ligand (DHQ). A warm ethanolic solution of m-phenylenediamine (20 mmol) with a few drops of acetic acid was progressively mixed with an ethanolic solution of 2-hydroxyquinoline-3-carbaldehyde (40 mmol), stirring constantly. For four 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 (Scheme, step 3).

Synthesis of transition metal (II) complexes of Schiff base (DHQ):

The following method was used to prepare solid Ni(II), Cu(II), and Zn(II) complexes of Schiff base ligand (DHQ).

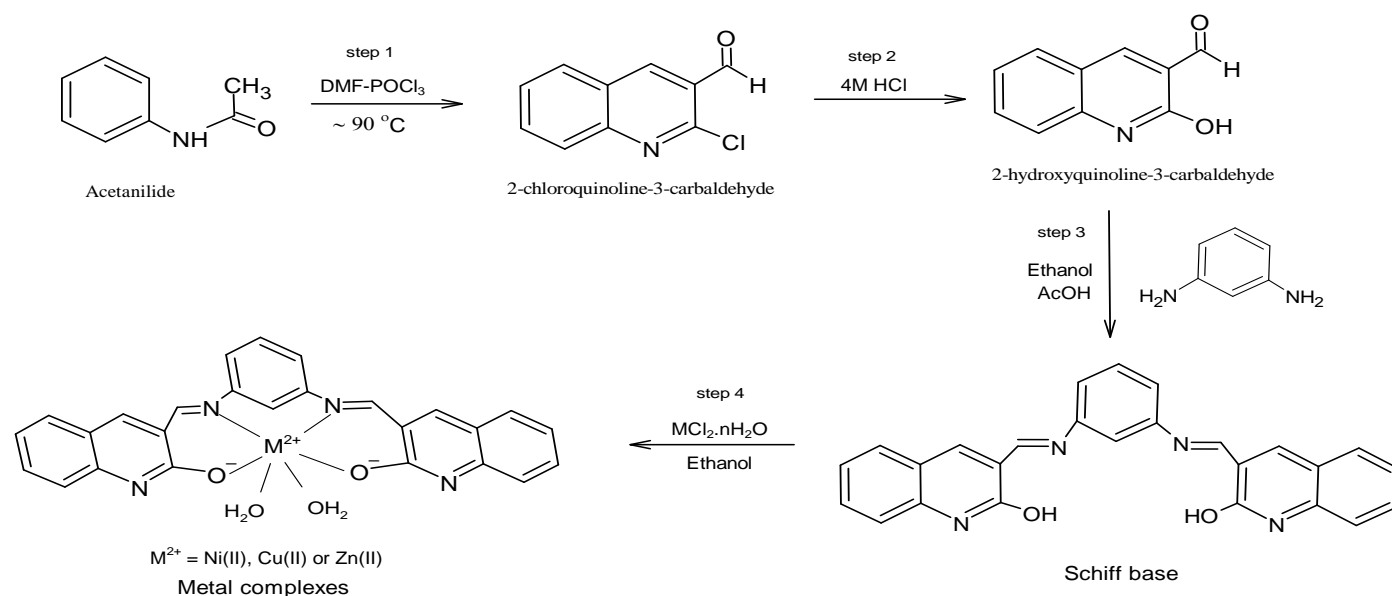
A hot ethanolic solution of Schiff base (4 mmol) was gradually mixed with a 4 mmol corresponding metal (II) chloride salt (NiCl₂.6H₂O, CuCl₂.2H₂O, or ZnCl₂) dissolved in a suitable quantity of ethanol while being continuously stirred. The reaction mixture was then enriched with a few drops of 4% NaOH solution to maintain basic conditions (pH = 7.4-7.8). 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 CaCl₂ in a vacuum desiccators (Scheme, step 4).

Antimicrobial Screening

The synthesized Schiff base and its metal complexes were evaluated for their in vitro antifungal activity against *Candida albicans* and *Aspergillus niger*, as well as for their antibacterial activities against the gram-positive bacteria *Bacillus subtilis* and *Staphylococcus aureus*, and the gram-negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*, using a disc diffusion method. Bacterial and fungal cultures were grown on Mueller-Hinton agar and Sabouraud dextrose agar, respectively. A total of 100 µL of freshly made microbial culture was added per agar plate, evenly distributed over the agar surface and allowed to dry aseptically. A stock solution of 10 mg test compound was prepared by dissolving the

test compound in 10 mL DMSO. The DMSO solutions containing the test compound at concentrations of 500 and 1000 $\mu\text{g/mL}$ were then used to impregnate sterile paper discs. The impregnated discs were aseptically placed at equal intervals onto pre-inoculated agar plates and gently pressed down. The plates were incubated at 37 °C for 24 hours for the bacterial strains and 48 hours for the fungal strain. DMSO impregnated discs served as negative controls, while commercial antibacterial and antifungal agents served as positive controls. After incubation, the diameter of the zone of inhibition (mm) for each disc was measured [25,26].

Reaction Scheme



4. RESULTS AND DISCUSSION

The structure of the Schiff base (*DHQ*) 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 9 to 14 $\text{cm}^2 \text{Ohm}^{-1} \text{mol}^{-1}$. 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) [27,28] 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 (*DHQ*) and its metal complexes

Compounds (Mol.)	M.W. g mol^{-1}	Color	Yield	Elemental Composition in % Found (Calculated)	Λ_m ($\text{cm}^2 \Omega^{-1} \text{mol}^{-1}$)	μ_{eff}

Formula)			%	C	H	N	M	in DMSO	B.M.
DHQ,(LH ₂) (C ₂₆ H ₁₈ N ₄ O ₂)	418.45	Yellow	78	74.56 (74.63)	4.29 (4.34)	13.32 (13.39)	---	---	---
[Ni(L)(H ₂ O) ₂] (NiC ₂₆ H ₂₀ N ₄ O ₄)	511.15	Green	71	61.18 (61.09)	4.01 (3.94)	10.94 (10.96)	11.12 (11.48)	14	3.26
[Cu(L)(H ₂ O) ₂] (CuC ₂₆ H ₂₀ N ₄ O ₄)	516.01	Green	72	60.62 (60.52)	3.99 (3.91)	10.92 (10.86)	12.08 (12.31)	09	1.86
[Zn(L)(H ₂ O) ₂] (ZnC ₂₆ H ₂₀ N ₄ O ₄)	517.84	Dark yellow	68	60.42 (60.30)	3.96 (3.89)	10.89 (10.82)	12.33 (12.63)	11	Dia*

Infrared spectral studies

The ligand binding sites with the metal ions were found by comparing the IR spectra of the Schiff base ligand (DHQ) 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 1 and 2, respectively, while Table 2 summarizes the infrared spectral bands and their assignments.

The FTIR spectrum of the Schiff base ligand (DHQ) exhibited a broad absorption at $\sim 3413\text{ cm}^{-1}$ and a band at 3048 cm^{-1} corresponding to the stretching vibrations of the phenolic $\nu(\text{O-H})$ group of the quinoline moiety and $\nu(\text{C-H})$ group, respectively. The strong intense band at 1638 cm^{-1} was assigned to the azomethine $\nu(\text{C=N})$ stretching vibration, which confirms the formation of the Schiff base. The band at 1288 cm^{-1} was assigned to phenolic $\nu(\text{C-O})$ stretching of the quinoline moiety. Absorption bands at 1578 , 1482 and 1451 cm^{-1} were assigned to the aromatic $\nu(\text{C=C})$ vibrations and conjugation between the aromatic ring and azomethine ($>\text{C=N-}$) group. A set of bands in the range of $1300\text{--}1000\text{ cm}^{-1}$, and $960\text{--}750\text{ cm}^{-1}$ 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 $\nu(\text{C=N})$ of the imine group was shifted from 1638 cm^{-1} to lower frequencies, 1615 , 1620 and 1618 cm^{-1} , respectively. This negative shift in their stretching vibrations supports the coordination of imine groups with metal ions through imine-N. The appearance of a broad band in the $3680\text{--}3000\text{ cm}^{-1}$ region with maxima at 3410 , 3398 and 3404 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 $860\text{--}930\text{ cm}^{-1}$ which are attributed to the bending vibration of water molecules. The new non-ligand bands in the low frequency region at ($522\text{--}532\text{ cm}^{-1}$) and ($422\text{--}430\text{ cm}^{-1}$) for metal complexes are assigned to $\nu(\text{M-N})$ and $\nu(\text{M-O})$ bonds, respectively. This supports the proposed sites of coordination of ligand. Therefore, it can be concluded that the ligand (DHQ) coordinated to metal ions through its two phenolic-O and two azomethine-N atoms and acts as a dianionic tetradentate ligand [29-33].

Table 2 selected FTIR frequencies of Schiff base (*DHQ*) and its metal complexes in cm^{-1}

Compounds	$\nu(\text{O-H})_{\text{phenolic}}$	$\nu(\text{H}_2\text{O})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C-O})$	$\nu(\text{M-N})$	$\nu(\text{M-O})$
$\text{C}_{26}\text{H}_{18}\text{N}_4\text{O}_2$ (<i>DHQ</i>)	3413	---	1638	1288	---	---
$(\text{C}_{26}\text{H}_{20}\text{N}_4\text{O}_4)\text{Ni}$	---	3410	1615	1280	522	422
$(\text{C}_{26}\text{H}_{20}\text{N}_4\text{O}_4)\text{Cu}$	---	3398	1620	1282	525	436
$(\text{C}_{26}\text{H}_{20}\text{N}_4\text{O}_4)\text{Zn}$	---	3404	1618	1280	532	430

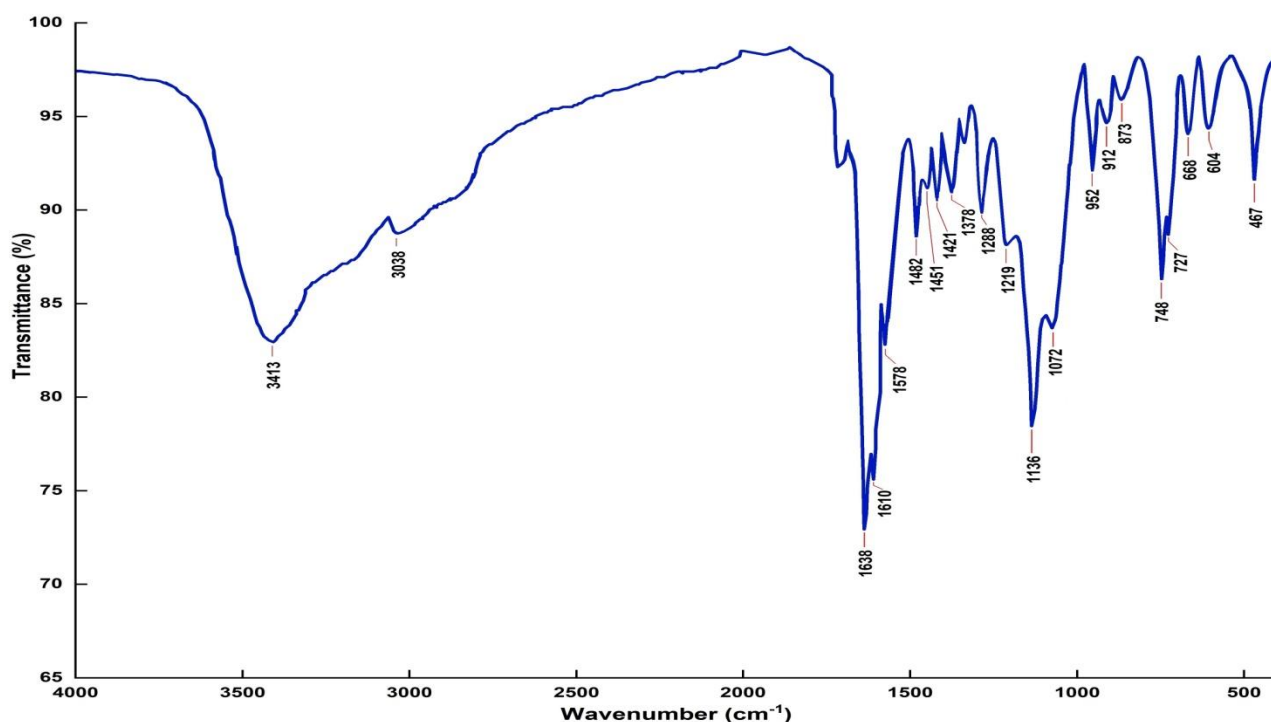


Figure 1 FTIR spectrum of the Schiff base ligand (*DHQ*)

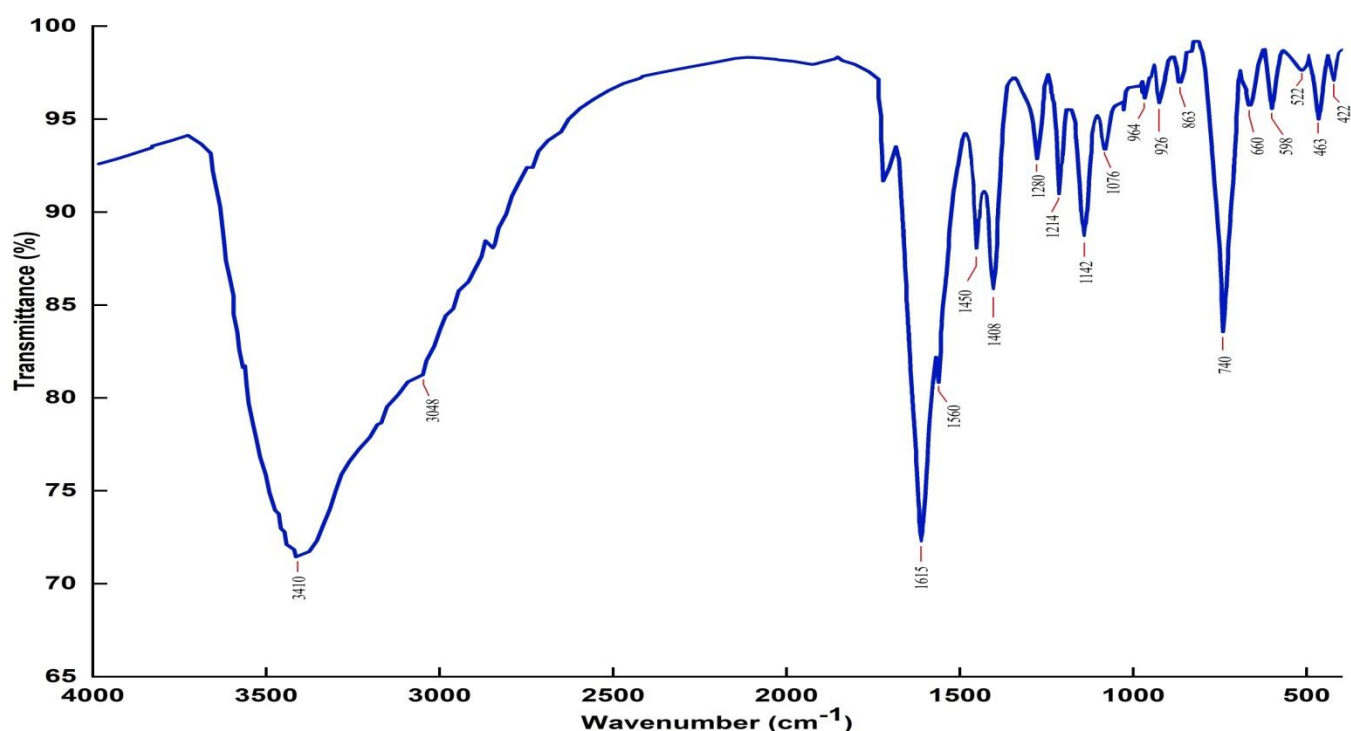


Figure 2 FTIR spectrum of the Ni-complex

UV-Visible spectral and magnetic moment studies

The electronic spectrum of Schiff base was recorded in DMSO at the concentration 10^{-3} M. The $\pi-\pi^*$ and $n-\pi^*$ transitions are responsible for the appearance of the transition bands at 290 and 355 nm respectively due to the heterocyclic moiety and azomethine group of Schiff base. For the Ni(II), Cu(II) and Zn(II) metal complexes the transition bands for $\pi-\pi^*$ and $n-\pi^*$ were seen at 312.5 and 364 nm, 318 and 369.5 nm and 315 and 368.5 nm respectively. The coordination of the Schiff base with a central metal ion caused the transition band to shift to longer wavelengths in the metal complexes. The intensities of these bands were increased by shifting to a longer wave length in the metal complexes. The reason for this shift may be the donation of lone pair of electrons from the nitrogen of azomethine group of Schiff base ligand to a metal ion. The magnetic moment susceptibility of the metal complexes was measured at room temperature for Cu(II), Ni(II) complexes and they were found to be paramagnetic. The magnetic moment for Cu(II) complex was found to be 1.86 B.M. which is slightly higher than spin only value for one unpaired electron 1.73 B.M. for distorted octahedral geometry. The magnetic moment value of Ni (II) complex was 3.26 B.M. which was in the range of expected value for octahedral geometry of metal complex 2.83–3.50 B.M [29-33].

In vitro Antimicrobial studies

The synthesized Schiff base and its metal complexes were evaluated for antibacterial and antifungal activities against *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Aspergillus niger* and *Candida albicans* by the disc diffusion method on agar medium. Results of

antimicrobial screening of tests performed on the compounds at different doses are shown in Table 3 and Figure 3. 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 both gram-positive and gram-negative bacteria. The order of activity against bacterial strain with inhibition zone in the range 15–23 mm at highest concentration is *B. subtilis* > *S. aureus* > *P. aeruginosa* > *E. coli*. The free ligand, Ni(II) and Zn(II) complexes showed relatively lower level of anti-bacterial activity. The free ligand was very less effective against *E. coli*, *P. aeruginosa* and comparatively more active against *B. subtilis* and *S. aureus* even at highest concentration. The general order of antibacterial activity of the synthesized compounds against bacterial strains is as follows: Cu(II)-complex > Ni(II) = Zn(II) complexes > Ligand. An antifungal study found that while the ligand, Ni(II) and Zn(II) complexes have lower activity against fungi as compared to Cu(II) complex that produced an inhibition zone of 18–22mm. In the same experiment, it was noted that chelated Schiff base demonstrated greater antibacterial abilities than the non-chelated Schiff base. This increased effectiveness of metal chelates can be explained via chelation theory. By delocalized electrons throughout the chelated ring, chelation decreases the polarity of the metal ion by partially sharing the positive charge of the metal ion with ligand donor sites; the resulting metal chelate becomes more lipophilic enabling it to penetrate and rupture the lipid bilayer of microbial cell membranes. Furthermore, the interaction between ligands and metal ions can influence the antibacterial capability by affecting solubility, dipole moment, and conductivity of the system [34-36].

Table 3 Antibacterial and antifungal activities of the Schiff base (*DHQ*) and its metal complexes

Compounds	Conc. µg/mL	Zone Inhibition Diameter (mm)					
		Gram +ve Bacteria		Gram –ve Bacteria		Fungi	
		<i>B. subtilis</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. Niger</i>
Ligand (<i>DHQ</i>)	500	11	12	10	10	10	12
	1000	14	15	13	12	13	16
Ni-complex	500	14	14	11	11	12	15
	1000	19	19	15	13	16	19
Cu-complex	500	17	16	14	12	14	17
	1000	23	22	18	15	18	22
Zn-complex	500	14	14	12	12	13	15
	1000	19	18	16	14	17	19
Gentamicin		28	27	25	24	---	---
Amphotericin B		---	---	---	---	21	26

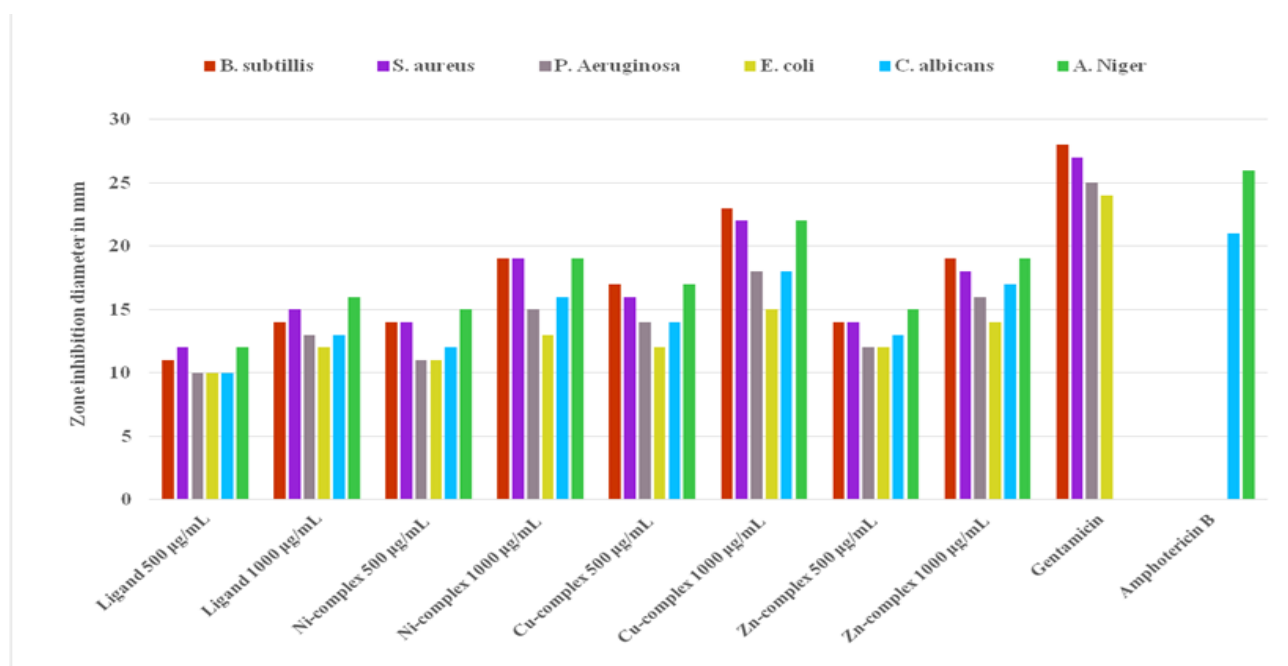


Figure 4 Graphical representation of antimicrobial activity of the Schiff base and its metal complexes

5. CONCLUSION

The quinoline derived Schiff base (DHQ) and metal(II) complexes were characterized by various physical, spectroscopic and analytical methods. The ratio of metal to ligand was 1:1 for all the complexes. The non-electrolytic nature of all the metal complexes is confirmed from the observed low molar conductivity values. The Schiff base acts as a dianionic tetradentate ligand for metal ions through azomethine nitrogen and phenolic oxygen atoms, leading to octahedral shaped coordination sites for their respective metal ions. In vitro antimicrobial activity of the prepared compounds was screened against two species of Gram positive bacteria (*Bacillus subtilis* & *Staphylococcus aureus*), two Gram negative bacteria (*Pseudomonas aeruginosa* & *Escherichia coli*) and two species of fungi (*Aspergillus niger* & *Candida albicans*) by disc diffusion method. All metal complexes showed higher antimicrobial activity against all the tested organisms than the free ligand. The Cu(II) complex exhibited the maximum inhibitory activity against *Bacillus subtilis*, *Staphylococcus aureus* and *Aspergillus niger* with a zone of inhibition of 22-23 mm among the all complexes.

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7. CONFLICT OF INTEREST

The author declares that there is no conflict of interests regarding the publication of this article.

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