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Research Article

METAL COMPLEXES OF NOVEL SCHIFF BASE CONTAINING ISATIN: CHARACTERIZATION, ANTIMICROBIAL, ANTIOXIDANT AND CATALYTIC ACTIVITY STUDY

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ABSTRACT

Objectives: The aim of our work was to synthesize novel mixed ligand-metal complexes and evaluation of antimicrobial, antioxidant assay, and analysis of catalytic oxidation of cyclohexane.

Methods: The complexes were characterized by means of various physicochemical techniques such as elemental analysis, molar conductance, magnetic susceptibility, infrared (IR), electronic absorption, ^{1}H NMR (proton magnetic resonance), and mass spectral studies. The antimicrobial screening study was done by disc diffusion method. The catalytic activity of the complexes was observed in the oxidation of cyclohexane using eco-friendly hydrogen peroxide as oxidant.

Results: On comparing the ^{1}H NMR and IR spectral data of free ligand and its complexes, it was found to be azomethine (CH=N) proton which is formed in the free ligand. During complexation, the azomethine proton is coordinated to the metal ion and the phenolic oxygen is coordinated to the metal ion by deprotonation. The analytical data and mass spectra of the ligand and the complexes confirm the stoichiometry of metal complexes as being of the (MLY)Cl type and the metal to ligand ratio is 1:1. The antimicrobial, antioxidant, and catalytic potential were evaluated and the result shows the better activity of the complexes than the ligand.

Conclusion: It was found to be copper(II) and zinc(II) complexes which are effective against all the bacteria when compared to standard drug streptomycin. Copper(II) complex was found to be effective antibacterial agent against *Aspergillus niger* and *Aspergillus flavus* in comparison to the standard drug Nystatin. The zinc complex exhibited good catalytic activity.

Keywords: Antimicrobial activity, Catalytic activity, Mixed ligand-metal complexes, Octahedral geometry, Radical scavenging activity.

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INTRODUCTION

The biologically active compound isatin (indole-2,3-dione) was first obtained in 1841 from the oxidation of indigo dye by nitric and chromic acids [1]. In nature, isatin is found in plants and widely distributed in mammalian tissues and body fluids [2]. The biologically active compound isatin's concentration in urine is to become a diagnostic marker for the clinical severity of Parkinson's disease in humans; however, electrophysiology, synthetic, and metabolic pathways of isatin in human system are yet to be fully established. In organic synthesis, isatin and its derivatives have widely used as key intermediate due to their biological and pharmacological properties [1,3]. The multicoordination centers form stable chelates with essential metal ions which, in turn, used in human's metabolism. Salicylaldehyde-based Schiff base metal complexes serve as high potential antibacterial agent [4]. The electrochemical determination of isatin and other nitrogen heterocycles using various electrode systems attains prominence in recent years. The derivatives of isatin were reported to show anti-HIV, anticonvulsant, antibacterial, antifungal, antiprotozoal, antiviral, and antioxidant activities [5-13].

A wide range of molecular disorder accumulated due to oxidative stress is originated as a result of an imbalance between the free radical production and antioxidant defenses [14,15]. Antioxidant acts as scavenger to prevent the damage of cell and tissue. The byproducts of normal metabolisms are O_2^- and OH^- (reactive oxygen species) and are detected in all types of organisms [16]. In addition to phenolic compounds, aromatic heterocyclic amines showed that antioxidant properties *in vitro* have been discussed from the view of chemical kinetics [17].

Oxidation of cyclohexane is an important industrial reaction. Most of the industries struggle with the manufacture of cyclohexanol and cyclohexanone from cyclohexane at high temperature and pressure. To overcome these difficulties, nowadays, Schiff base metal complexes act as a catalyst toward the oxidation of cyclohexane reaction at low temperature and pressure [18]. The Schiff base derived from isatin possesses significant enhancement antibacterial, antifungal, and antioxidant activities during complexation [19].

Bearing these facts in mind, to enhance the biological and catalytic properties of Schiff base metal complexes, we are planned to synthesis the metal complexes using mixed ligand. In this concerned, the hexacoordinated mixed ligand Cu(II), Zn(II), Ni(II), and Co(II) complexes were synthesized from the diimino-tetradentate Schiff base which was derived from the condensation of isatin with ethylenediamine and bipyridine. These metal complexes showed remarkable antimicrobial and antioxidant activities which may find their importance in medicinal chemistry. The metal complexes also exhibited catalytic activity toward the oxidation of cyclohexane using environmental-friendly hydrogen peroxide as oxidant.

EXPERIMENTAL

Materials

All chemicals used in the present work, namely, isatin, salicylaldehyde, ethylenediamine, bipyridine, copper, zinc, cobalt, and nickel chlorides were of analytical reagent grade (Merk, Germany). Solvents were purified according to the standard procedures described in Weissenburg series [20] and in quantitative analysis by Vogel [21].

Physical measurements

The elemental analysis (C, H, and N) was performed using a Carlo Erba 1108 analyzer. The molar conductivity of the complex was measured using a Systronics model-304 digital direct reading conductivity meter. Magnetic susceptibility measurements were carried out by employing the Gouy method at room temperature on powder sample of the complex. Infrared (IR) spectra of the Schiff base and its metal complexes were recorded as KBr discs in the range 400–4000 cm^{-1} on a Shimadzu spectrophotometer. The electronic absorption spectra of the Schiff base and its metal complexes were recorded on a Shimadzu ultraviolet (UV)-1601 spectrophotometer. The proton NMR spectra of the Schiff base and its zinc complex in dimethylsulfoxide (DMSO)-d_6 were recorded using tetramethylsilane as internal standard. Electrospray ionization mass spectrometry (ESI-MS) analysis was performed in the positive ion mode on a liquid chromatography-ion trap MS.

Estimation of metal

The metals were estimated gravimetrically as their oxides [22] by fusion with AnalaR ammonium oxalate. In a typical experiment, about 0.3 g of the dried complex was accurately weighed in a previously weighed silica crucible. AnalaR ammonium oxalate, roughly three parts by weight of the complex, was added and the mixture was incinerated slowly at first and then strongly using a Bunsen burner for 3 h. It was then cooled in a desiccator and weighed. The procedure was repeated until the final oxide weight was constant. From the weight, the percentage of metal in the complex was calculated.

Determination of chloride content

The chloride present in the complexes was determined gravimetrically as silver nitrate test [21].

Synthesis of ligand (HL)

A methanolic solution of ethylenediamine (0.03 mol, 2.01 ml) was added dropwise to equimolar solution of isatin (0.03 mol, 4.414 g) and salicylaldehyde (0.03 mol, 3.664 g) in methanol. The reaction mixture was refluxed for ca. 4 h. The resulting precipitate was filtered and recrystallized from methanol and dried *in vacuo* over silica gel, yield=87%. The schematic representation of the Schiff base is given in Fig. 1.

Synthesis of metal complexes

A hot methanolic solution of the Schiff base ligand (0.003 mol) was added to the methanolic solution of metal(II) chlorides (0.003 mol) and refluxed for ca. 3 h. To the above mixture, a methanolic solution of bipyridine (0.003 mol) was added in a 1:1:1 molar ratio and refluxed for about ca. 2 h. The solid product formed was filtered and washed with methanol.

Biological studies

Antibacterial studies

Antibacterial activity of Schiff base and its complexes was evaluated using disc diffusion concept of the Kirby–Bauer sensitivity test. Human pathogens such as *Bacillus subtilis, Staphylococcus aureus, Escherichia coli,* and *Proteus mirabilis* are used in the current study. Nutrient agar was used as a basal medium for the culture of the test bacteria. The agar plates were then inoculated with broth cultures diluted to 0.5 McFarland turbidity (~1.5×10^8 cells/mL). The stock solutions were prepared by dissolving the compounds in appropriate solvents (DMSO). Discs (5 mm diameter and 1 mm thickness) containing known amounts of an antimicrobial agent were placed on the surface of an agar plate that has been inoculated with a standardized suspension of microorganisms to be tested. Paper discs with only DMSO were used as negative controls. Then, the plates were incubated at 37°C for 24 h. During this period, the test solution diffused and affected the growth of the inoculated bacteria. The susceptibility of bacterial species was determined by the diameter of zone of inhibition (in millimeter) [23]. Streptomycin was used as standard.

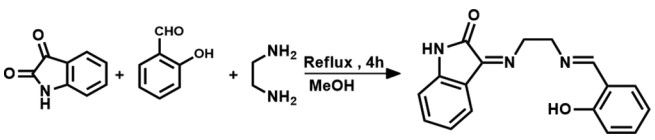


Fig. 1: Synthesis of the Schiff base

Antifungal studies

The *in vitro* antifungal screening of the Schiff base and its complexes was evaluated by the disc diffusion method [24] against the fungi such as *Aspergillus niger, Aspergillus flavus, Rhizoctonia bataticola,* and *Candida albicans*. Potato dextrose agar was used as medium for the evaluation of antifungal activity. For preparing the agar media, 200 g of potato extract, 20 g of agar, and 20 g of dextrose were dissolved in 1000 mL of distilled water in a clean conical flask. The solution was boiled to dissolve the medium completely and sterilized by autoclaving at 15 psi pressure (120°C) for 30 min. After sterilization, 20 mL of media was poured into the sterilized Petri plates. These Petri plates were kept at room temperature for sometimes. After few minutes, the medium got solidified in the plates. Then, it was inoculated with microorganisms using sterile swabs. The 5 mm diameter and 1 mm thickness of the disc were filled with the test solution (100 µg/ml) using a micropipette and the plates were incubated at 37°C for 72 h. During this period, the test solution diffused and affected the growth of the inoculated fungi. After 72 h of incubation at 37°C, the diameter of the zone of inhibition was measured [23]. Nystatin was used as standard.

Antioxidant studies (1,1-diphenyl-2-picrylhydrazyl [DPPH] assay)

The evaluation of antioxidant activity of newly synthesized compounds was done by DPPH radical scavenging activity assay [25]. Different concentrations (100, 50, 25, and 12.5 µg/ml) of Schiff base metal complexes were weighed respectively and dissolved in DMSO. Then, 5 ml of 0.1 mM methanolic solution of DPPH was added to each of the test tube containing the sample and the tubes were shaken vigorously. They were then allowed to stand at room temperature for 30 min. The control was prepared without any compound and methanol was used for baseline corrections in absorbance odds ratios of samples measured at 517 nm. For each concentration, the decrease in the absorbance was recorded and percentage quenching of DPPH was calculated. The radical scavenging activities were expressed as percentage scavenging activity and were calculated by the following formula.

$$\%\ \text{Radical scavenging activity} = \frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}} \times 100$$

Catalytic activities

The oxidation of cyclohexane has always been an area of intensive research because it is one of the essential steps in the production of nylon. The catalytic oxidation of cyclohexane was carried out in acetonitrile solvent using hydrogen peroxide as an oxidant in the presence of mixed ligand-metal complex [MLY]Cl as catalyst. In a typical reaction, about 0.1 mol H_2O_2 was added to the mixture of 0.1 mol cyclohexane and 0.001mol [MLY]Cl in acetonitrile and the reaction mixture was stirred for 5 h at 343 K. The reaction progress and its completion were checked by analyzing the reaction mixture using thin-layer chromatography by withdrawing small aliquots of the reaction mixture at specific interval of time. The percentage yield of the products was noted.

RESULTS AND DISCUSSION

Analytical studies

The complexes of the type [MLY]Cl where, M=Cu(II), Zn(II), Ni(II), and Co(II), L=tetradentate Schiff base, and Y=bipyridine were synthesized by the reaction of tetradentate ligand, metal(II) chlorides, and bipyridine in a 1:1:1 molar ratio in methanol. In DMSO, the complexes showed higher molar conductance value indicates the electrolytic nature.

IR spectra

The IR spectrum of the free ligand showed a band at 1618 cm^{-1} which can be attributed to azomethine moiety. This band is shifted to lower frequency around 1606–1598 cm^{-1} in the spectra of complexes which indicate the coordination of metal to the azomethine nitrogen. The absorption band appeared at 1757 cm^{-1} is due to νC=0. This band shifted to lower wavenumber in the complexes indicates involvement of νC=0 with metal center during complexation. The ligand showed that a band at 3400 cm^{-1} is due to phenolic OH group. The absence of νOH band in all the complexes suggests subsequent deprotonation of phenolic group and coordination of phenolic oxygen to the metal ion. The band at 3160 cm^{-1} in the spectrum of free ligand assigned to νN-H stretching vibration. The position of this band remains nearly the same frequency in the spectra of metal complexes suggesting the uncoordination of this group [26]. The band at 1280 cm^{-1} is due to phenolic C-O. This band shifted to lower wavenumber in the complexes indicates coordination of metal to the phenolic C-O. The appearance of two new bands in the regions 545–525 cm^{-1} and 459–422 cm^{-1} in the spectra of complexes was due to νM-N and νM-O stretching vibrations, respectively [27].

Electronic absorption spectra and magnetic measurement

The electronic spectra of ligand and its complexes were recorded in methanol. The ligand shows two bands at 40323 and 32787 cm^{-1} assigned for π π* and n π* electronic transitions, respectively [28]. Nickel(II) complex exhibits three bands at 12,919, 15,924, and 20,833 cm^{-1} attributed to $^3A_{2g}$ (F) $\rightarrow {}^3T_{2g}$(F), $^3A_{2g}$ (F) $\rightarrow {}^3T_{1g}$(F), and A_{2g} (F) $\rightarrow {}^3T_{1g}$(P) transitions indicating octahedral geometry. The nickel(II) complex showed magnetic moment value of 3.14 B.M corresponding to two unpaired electrons in an octahedral environment [29]. Copper complex shows a band at 16,556 cm^{-1} assigned for $^2E_g \rightarrow {}^2T_g$ transition suggesting a distorted octahedral geometry [30] which was further supported by its magnetic moment value of 1.88 B.M. The cobalt(II) complex exhibits two bands at 33,003 and 21,368 cm^{-1} assigned to $^4T_{1g}$(F) $\rightarrow {}^4T_{1g}$(P) and $^4T_{1g}$(F) $\rightarrow {}^4A_{2g}$ transitions. The magnetic moment value of Co(II) complex was 4.86 B.M., which favors octahedral geometry [31]. Zn(II) complex does not show d-d transition due to its diamagnetic nature [32].

Proton magnetic resonance spectra

The proton magnetic resonance spectra of ligand and its Zn(II) complex were recorded in DMSO-d_6. The ^{1}H NMR spectrum of ligand and its zinc(II) complex exhibited signals at 10.3 ppm and 2.6 ppm due to NH proton of isatin moiety [33] and N-CH_2 protons [34]. The phenyl multiplet appeared at 6.8–7.2 ppm. The spectrum of the free ligand exhibited a signal at 13.3 ppm due to phenolic protons [35]. The azomethine (CH=N) proton appeared as a singlet at 8.43 ppm. However, in the spectrum of zinc(II) complex, the azomethine (CH=N) proton showed a downfield shift at 8.9 ppm, thereby suggesting the coordination of imino nitrogen to zinc ion. In the Zn(II) complex, the phenolic proton was disappeared indicating the coordination of these to Zn(II) ion by deprotonation. The signals at 7.60–7.76 and 8.20–8.39 ppm were assigned to bipyridine protons. The proton magnetic resonance spectra of the ligand and its zinc complex are given in Figs. 2 and 3.

Mass spectra

The ESI mass spectra of the ligand and its Zn(II) complex were recorded and the obtained molecular ion peak confirmed the proposed formulae. The mass spectrum of the ligand exhibited peak m/z at 293(M^+) with 100% abundance which was also confirmed by "nitrogen rule." The mass spectrum of Zinc(II) complex showed a molecular ion peak m/z at 549 which is equivalent to its molecular weight and also exhibited two additional peaks m/z at 550 and 551, which are corresponding to (M+1) and (M+2) peaks, respectively.

Based on the elemental analysis, molar conductance, magnetic moments, IR, UV-Vis., proton NMR, and mass spectral data, the proposed structure of the complexes is given in Fig. 4.

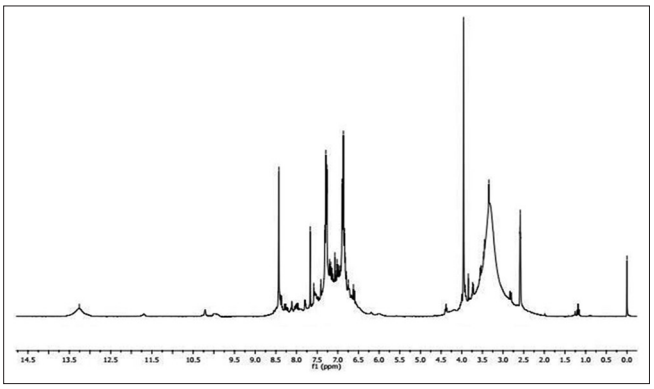


Fig. 2: ^{1}H NMR spectra of ligand

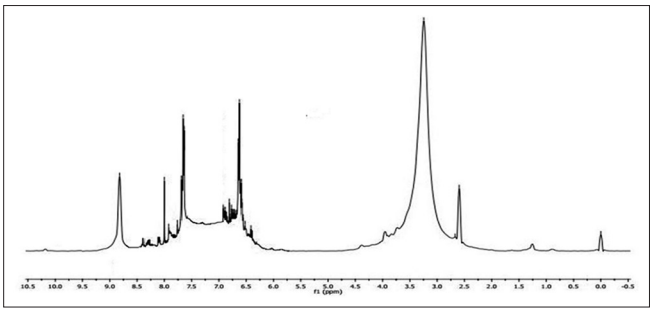
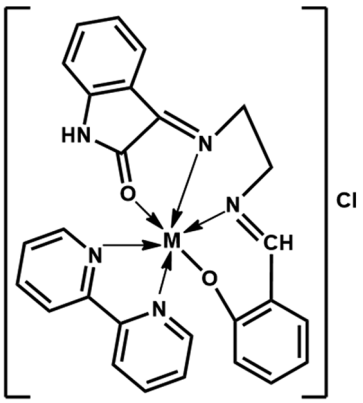


Fig. 3: ^{1}H NMR spectra of [ZnLY] Cl



where, M = Cu(II),Co(II),Ni(II),Zn(II)

Fig. 4: Structure of synthesized complexes

Antibacterial studies

The antibacterial efficacy of the ligand and its metal complexes was tested against the human pathogens such as *B. subtilis, S. aureus, E. coli,* and *P. mirabilis*. Three different concentrations (25 µg/ml, 50 µg/ml, and 75 µg/ml) of the compounds have been tested for antibacterial assay. The results are presented in Table 1. The results of the antibacterial activity showed that all the complexes possess good activity against *B. subtilis, S. aureus, E. coli,* and *P. mirabilis*. The Cu(II) and Zn(II) complexes exhibited enhanced activity against all the bacteria examined than the standard drug streptomycin. The enhanced activity of the complexes may be attributed to chelation of Schiff base with metal ion [36]. The partial sharing of positive charge with the donor groups and possible π-electron delocalization within the chelate ring system makes the metal ion as less polar. Due to this reduced polarity of the metal ion, the lipophilicity of the complex increases, and hence, diffusion of metal ion through cell membrane becomes easier. Thus, chelating effect makes the metal complex as powerful antibacterial

Table 1: Antibacterial activity of ligand and its metal(II) complexes (zone of inhibition in mm)

Compound	Gram-positive bacteria					
	B. subtilis			*S. aureus*		
	25 (μg)	50 (μg)	75 (μg)	25 (μg)	50 (μg)	75 (μg)
HL	8±0.4	11±0.55	13±0.65	13±0.65	15±0.75	17±0.85
[CuLY]Cl	21±1.05	24±1.2	28±1.4	25±1.25	27±1.35	28±1.4
[ZnLY]Cl	17±0.85	20±1	23±1.15	20±1	23±1.15	26±1.3
[NiLY]Cl	13±0.65	14±0.7	17±0.85	16±0.8	17±0.85	18±0.9
[CoLY]Cl	12±0.6	13±0.65	15±0.75	16±0.8	18±0.9	20±1
Streptomycin	13±0.65	15±0.75	20±1	18±0.9	22±1.1	24±1.2
Compound	**Gram-negative bacteria**					
	E. coli			*P. mirabilis*		
	25 (μg)	50 (μg)	75 (μg)	25 (μg)	50 (μg)	75 (μg)
HL	17±0.85	19±0.95	21±1.05	9±0.45	12±0.6	13±0.65
[CuLY]Cl	24±1.2	26±1.3	30±1.5	10±1.35	28±1.4	31±1.55
[ZnLY]Cl	22±1.1	24±1.2	27±1.35	11±1.05	23±1.15	25±1.25
[NiLY]Cl	21±1.05	22±1.1	28±1.25	12±0.65	15±0.75	17±0.85
[CoLY]Cl	20±1	22±1.1	29±1.2	13±0.6	13±0.65	15±0.75
Streptomycin	22±1.1	23±1.15	30±1.3	14±0.75	18±0.9	20±1

*All the experiments were repeated independently 3 times and the values were represented as an average mean±standard deviation. *E. coli*: *Escherichia coli*, *P. mirabilis*: *Proteus mirabilis, B. subtilis*: *Bacillus subtilis*, *S. aureus*: *Staphylococcus aureus*

Table 2: Antifungal activity of ligand and its metal(II) complexes

Compound	Zone of inhibition in mm			
	A. niger	*A. flavus*	*R. bataticola*	*C. albicans*
HL	7±0.35	5±0.25	6±0.3	9±0.45
[CuLY]Cl	15±0.75	13±0.65	10±0.5	14±0.7
[ZnLY]Cl	12±0.6	7±0.35	9±0.45	13±0.65
[NiLY]Cl	10±0.5	7±0.35	6±0.3	12±0.6
[CoLY]Cl	9±0.45	10±0.5	7±0.35	10±0.5
Nystatin	14±0.7	12±0.6	13±0.65	16±0.8

*All the experiments were repeated independently 3 times and the values were represented as an average mean±standard deviation. *A. niger*: *Aspergillus niger*, *A. flavus*: *Aspergillus flavus*, *R. bataticola*: *Rhizoctonia bataticola*, *C. albicans*: *Candida albicans*

agents and thereby inhibits the growth of microorganisms or destroys the microbes due to blocking their active sites.

Antifungal studies

The antifungal activity was carried out by disc diffusion method. The ligand and its Cu(II), Zn(II), Ni(II), and Co(II) complexes have been tested for their antifungal activity at 100 μg/ml concentration. The results are shown in Table 2. The results showed that copper complex exhibits enhanced activity against *A. niger* and *A. flavus* than the standard drug nystatin and it showed moderate effect on *R. bataticola* and *C. albicans.* In this regard, copper and zinc complexes exhibited good activity against *A. niger, A. flavus, R. bataticola,* and *C. albicans.* Nickel and cobalt complexes exhibited moderate activity against niger, *A. flavus, R. bataticola,* and *C. albicans.*

Antioxidant studies

The capability of DPPH to receive an electron or hydrogen from antioxidant molecule makes it become a stable diamagnetic molecule [37,38]. The antioxidant assay is a dynamic method to anticipate the scavenging ability of metal complexes, tested with respect to different concentrations (100, 50, 25, and 12.5 μg/ml) of Cu(II), Zn(II), Ni(II), and Co(II) metal complexes with DPPH radical. The data revealed that Cu(II) and Zn(II) complexes exhibited potent antioxidant activity even in minimum concentration (12.5 μg/ml) level than the Ni(II) and Co(II) complexes. The free radical scavenging ability of the metal complexes is presented in Table 3.

Table 3: Antioxidant activity metal(II) complexes

Concentration	% of radical scavenging activity			
	[CuLX]	[ZnLX]	[NiLX]	[CoLX]
100 μg/ml	71.3	57.1	50.4	69.5
50 μg/ml	60.1	48.0	41.3	58.3
25 μg/ml	49.5	39.2	32.0	47.1
12.5 μg/ml	39.0	27.5	24.6	36.3
IC_{50} (μM)	48.4	123.8	183.9	59.6

Table 4: Catalytic oxidation of cyclohexane by [MLY]Cl

Compound	Products (% yield)	
	Cyclohexanol	Cyclohexanone
[CuLY]Cl	31.4	10.1
[ZnLY]Cl	35.3	11
[NiLY]Cl	27.5	9.5
[CoLY]Cl	29.6	9.3

Catalytic activities

The catalytic activities of the synthesized metal complexes were examined for their activity toward the oxidation of cyclohexane using H_2O_2 as the oxidant in CH_3CN. The major and minor products were found to be cyclohexanol and cyclohexanone, respectively. No significant amount of adipic acid was obtained. In the absence of catalyst, no oxidation products were produced. This indicates that hydrogen peroxide alone is unable to oxidize cyclohexane. The results are given in Table 4.

CONCLUSION

In this work, a new series of novel Schiff base ligand and its metal complexes of Cu(II), Zn(II), Ni(II), and Co(II) were reported and their potential of antimicrobial, antioxidant, and catalytic activity was also explored. The structure of these complexes was investigated by UV-Vis., IR, proton NMR, and mass spectral studies and they exposed the octahedral nature of the complexes. The high molar conductance value revealed the electrolytic nature of the complexes. The antibacterial and antifungal activities of the free ligand and its complexes showed efficient biocidal and fungicidal activity. Copper and zinc complexes

exhibited efficient biocidal activity compared to the free ligand and other complexes even than the standard drug streptomycin. Copper complex exhibited enhanced activity against *A. niger* and *A. flavus* than the standard drug nystatin. It was found that all the complexes are good potential antioxidants. Especially, Cu(II) and Zn(II) complexes possessed enhanced antioxidant activity. The catalytic activity of the synthesized mixed ligand-metal complexes was tested in the cyclohexane oxidation reaction using H_2O_2 as oxidant. It was found to be zinc complex exhibits good catalytic activities than the other complexes.

AUTHORS' CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest concerning the publication of this paper.

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