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Synthesis, characterization and biological evaluation of naphthalene-1,8-diylbis(azaneylylidene)bis(methaneylylidene))diphenol Schiff base and its Cu(II), Ni (II) and Co(II) complexes

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ABSTRACT

The synthesis and characterization of novel transition Metal (Cu(II), Co(II) and Ni(II)) complexes of 4,4'-(naphthalene-1,8-diylbis(azaneylylidene))bis(methaneylylidene))diphenol (L) have been reported. The ligand and its metal complexes were characterized by nuclear magnetic resonance (NMR), Fourier Transform infrared (FTIR) spectroscopy, Electronic spectroscopy, and Mass Spectrometry. The FTIR spectra data suggested that the ligand behaves as a bidentate ligand coordinates to the metal ions through the oxygen atoms of the hydroxyl group. Electronic spectra data suggested that the complexes of Cu(II), Co(II) and Ni(II) had square planar geometry around metal ions. *In vitro*, antibacterial activities of the ligand and metal complexes were carried out using agar diffusion and broth dilution methods against two Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus substilis*) and two gram-negative bacteria (*Escherichia coli*, *Serratia marcescens*). The results showed that all the metal complexes had higher antibacterial activities against the four micro-organisms when compared to the free ligand. Among these compounds, Cu(II) complex showed the highest antibacterial activity with minimum inhibitory concentration (MIC) in the range 62.5-125 (mg/ml) with inhibition zone ranging from 15-25 mm diameter.

Keywords: *naphthalene, bidentate ligand, hydroxyl group, square planar, anti-bacterial activity.*

1. INTRODUCTION

Schiff bases derived from the condensation reaction of aromatic or aliphatic aldehydes with primary amines represented in various organic compounds [1]. Schiff bases are important in both biochemistry and industrial chemistry due to their wide range of applications [2]. This kind of ligands contain various donor atoms (N, O,S) in which they can bond to metal ions and prepare stable metal complexes [3]. Schiff bases and their metal complexes have been prepared because of their interesting and important properties, for instance, ability to bond to heavy metal atoms, catalytic activity and photochromism [4, 5]. In biological processes, inorganic compounds play significant roles and it is known that the existence of metal ions bonded to biologically active ligands may enhance their activities [6]. Schiff base metal complexes show great diversity in their biological activities, for example, anti-convulsant, antifungal, anti-HIV, antiviral, anticancer and antibacterial agents [7-9]. Several studies have also shown that naphthalene-derived Schiff bases and their metal complexes have additional applications, especially in antimicrobial properties [10].

Nosocomial infections (NI) during the past decade have developed in patients during hospitalization or after discharge worldwide by multi-drug resistant to Gram-positive and Gram-negative pathogens [11]. Searching for a novel antimicrobial agent is in demand to intervene the danger caused by these life-threatening infections [12]. The treatment of hospital infections such as resistant to *Staphylococcus aureus* has become an important problem to deal with owing to their multidrug resistance [13]. Since the resistance towards the available antibiotics among pathogenic bacteria has grown rapidly, there is a clear need for the development of new and effective antimicrobial agent [14]. Therefore, the success in designing antimicrobial agents which are different from those of the classical antibiotics is essential for treating infectious diseases [15].

In view of the wide interest in the biological activity of Schiff bases derived from benzaldehydes, herein we described the synthesis and characterization of Schiff base ligand derived from 4-hydroxybenzaldehydes and 1 8-diaminonaphthalene and its metal complexes. The antibacterial activities of the synthesized compounds were evaluated against G(+) and G(-) bacterial strains using micro-broth and disc diffusion tests.

2. EXPERIMENTAL SECTION

1 8-diaminonaphthalene, 4-hydroxybenzaldehyde, metal salts and all the solvents were purchased from Merck and used without further purification. Thin layer chromatography (TLC) was used on silica gel poly gram SILG/UV 254 nm plates for monitoring of all the reactions. Melting points of compounds were measured by an Electrothermal type 9100 melting point apparatus.

^{1}H-NMR (Nuclear magnetic resonance) spectra of the ligand were performed on a Brucker AMX 500 MHz spectrometer in DMSO-d_6 with tetramethylsilane (TMS) as an internal standard. Mass spectra of complexes were determined with Agilent technologies apparatus at 70 eV at 230 °C. Fourier-transform infrared spectroscopy (FT-IR) of compounds were taken in KBr pellets using Shimidzo 300 spectrometer. Ultraviolet-visible (UV-Visible) spectra of ligand and complexes were recorded on a Varian Cary 100 UV-Vis spectrophotometer.

Synthesis of Schiff base Ligand. The Schiff base ligand was prepared by reaction of 1,8-diaminonaphtalene and 4-hydroxy benzaldehydealdehyde in the molar ratio 1:2 in the presence of Fe_3O_4@L-proline-SO_3H. The magnetic nanoparticles (MNP-L-proline-SO_3H) was used as a catalyst. MNP-L-proline-SO_3H was prepared by chemical co-precipitation according to the previous literature [16]. Each reactant was dissolved in a minimum amount of methanol, then mixed together and followed by addition of 0.1 g (MNP-L-proline-SO_3H). The solution was refluxed for 2 h and then allowed to cool to room temperature and catalyst used was separated by an external magnet. Finally, the solvent was evaporated; the crude solid product was recrystallized in ethanol and dried at 60°C under vacuum.

Synthesis of metal complexes. The metal complexes were prepared by treating 1 mmol warm dry methanol solution of chloride of Cu(II), Co(II) and Ni(II) with 2 mmol corresponding ligands in the same solvent. The resulting mixture was refluxed for 2-3 h at 45 °C; after this period of time precipitate was formed. The resulting products were filtered, washed with warm methanol, and finally dried in a vacuum desiccator.

Antibacterial activities. The antibacterial activities of Schiff base ligand and its metal complexes were carried out with the following microorganisms under the disc diffusion and broth dilution methods:

- *Staphylococcus aureus* (ATCC: 6838)
- *Bacillus subtilis* (ATCC: 6633)
- *Escherichia coli* (ATCC: 25922)
- *Serratia marcescens* (ATCC: 13880)

Both disc diffusion and broth dilution tests are known as the standard *in vitro* susceptibility tests and recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [17]. The microorganisms were cultured onto Muller-Hinton agar plate and incubated for 18-24 h at 35 °C. The density of the bacteria culture required for the tests was adjusted to 0.5 McFarland (1.5×10^8 CFU/ml) (CFU=Colony Forming Unit).

Disc diffusion method. The solution of synthesized compounds was prepared by dissolving 2 mg of each compound in 1ml DMSO. A bacteria culture was swabbed across Hinton agar medium. Paper discs were impregnated individually with 100 µl of the stock solution of the compounds. Next, the discs were placed on the inoculated agar medium. Finally, the plates incubated for 18-24 h at 35 °C. After the incubation time, the antibacterial activity of compounds was recorded by measuring the clear inhibition zone around each disc. Standard antibiotic drug (Tetracycline) was also used as positive control.

Broth dilution method. Minimal Inhibitory Concentration (MIC) value of all the synthesized compounds was also measured to give a quantitative estimate of the susceptibility for the microorganism. MIC is the lowest concentration of the antimicrobial agent which is required to inhibit the growth of the bacteria strain. In this method, 1 ml of sterile Muller Hinton Broth medium was poured in the tube 1-13 with two-fold dilutions of the synthesized compound (1000 to 1.95 $\mu g ml^{-1}$) and inoculated with a standardized inoculum of the bacteria (1.5×10^8); then it was incubated under standardized conditions. After 18-24 h of incubation at 35°C, the MIC was recorded as the lowest concentration of antimicrobial agent with no visible turbidity.

3. RESULTS SECTION

Characterization of synthesized compounds. Schiff base Ligand (L) was prepared by condensation reaction of 1,8-diaminonaphtalene and 4-hydroxybenzaldehyde in the presence of Fe_3O_4@L-proline-SO_3H nanoparticles under optimized condition. The magnetic nanoparticles were synthesized according to the previous literature [16]. The method for the synthesis of the corresponding ligand is given in Figure 1.

In order to optimize the reaction condition, the reaction of 1,8-diaminonaphtalene (1 mmol) and 4-hydroxybenzaldehyde (2 mmol) was carried out in different conditions using different solvents, different catalyst, and catalyst content to obtain the maximum yield. The ligand was characterized by nuclear magnetic resonance (1H-NMR), Fourier-transform infrared spectroscopy (FT-IR) and ultraviolet-visible (UV-Visible).

According to data which is presented in Table 1, the solvent was observed to have an extreme effect on the yield of the reaction. The highest yield achieved using methanol as the solvent. In the next step, the amount of catalyst was also examined. As it is observed in Table1, it is apparent that increasing the amount of catalyst didn’t have a positive effect on the yield of the product. In this experiment p-Toluenesulfonic acid (PTSA) was also used as the catalyst which led to a longer reaction time with a lower yield. The best reaction condition for this Schiff base ligand was achieved to be: methanol as the solvent and 0.1 g Fe_3O_4@L-proline-SO_3H as a catalyst.

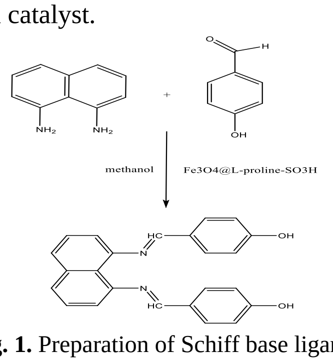


Fig. 1. Preparation of Schiff base ligand.

In the ^{1}H-NMR spectra of ligand, the aromatic protons observed in the range of 8.06-6.82 ppm as multiples, while C=NH (azomethine) protons appeared as a singlet in 2.77 ppm. The OH signals are observed at 9.68 ppm. The absence of amine and aldehyde protons has also confirmed the preparation of Schiff base ligand.

Table 1. Optimized condition for preparation of Schiff base ligand.

Entry	Catalyst (g)	Solvent	Time (min)	Yield (%)
1	Fe_3O_4@L-proline-SO_3H (0.1)	Ethanol	180	81
2	Fe_3O_4@L-proline-SO_3H (0.1)	Methanol	120	84
3	Fe_3O_4@L-proline-SO_3H (0.1)	Water	300	45
4	Fe_3O_4@L-proline-SO_3H (0.125)	Methanol	150	63
5	Fe_3O_4@L-proline-SO_3H (0.075)	Methanol	180	75
6	Fe_3O_4@L-proline-SO_3H (0.05)	Methanol	200	52
7	Fe_3O_4@L-proline-SO_3H (0.025)	Metanol	260	35
8	PTSA (0.1)	Methanol	400	35

Physical properties of all the ligand and metal complexes are listed in Table 2. The metal complexes were prepared in good yield (65-87%), which were insoluble in ethanol, methanol, chloroform or organic solvents but soluble in DMSO and DMF. The melting points of the synthesized compounds showed a significant decrease in the melting point when compared to the free ligand. This is because hydrogen band (OH group) in the ligand is eliminated by attaching to the metals and this resulted in a reduction of the melting point in these metal complexes.

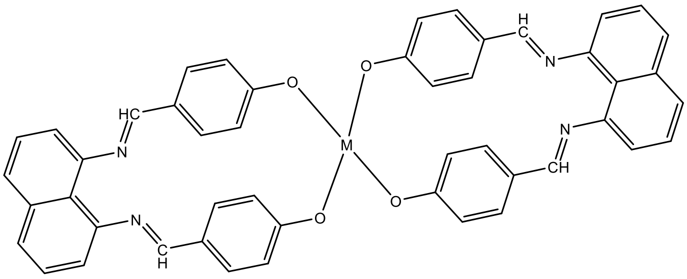
Table 2. Physical properties of synthesized compounds.

compounds	M.W. (g/mol)	Color	Yield (%)	M.P (°C)
L	366	Brown	84	250-252
CuL	692	Dark blue	87	187-189
CoL	786	Dark green	75	152-154
NiL	787	Yellow	65	153-155

The FTIR spectra of the Schiff base ligand showed a band in 1628 cm^{-1} which can be attributed to the C=N stretching. The C-H (aromatic) and OH bands are observed at 2947 and 3338 cm^{-1}, respectively. The FTIR spectra of the metal complexes were compared to the free ligand to determine the coordination site. A comparative study in FTIR spectra of the complexes with that of ligand showed the coordination of Schiff base ligand to metal ions has an effect on $\upsilon_{(OH)}$ frequency. The disappearance of OH band in all the complexes confirmed the ligand bonded to the metals through OH group. The Cu-O, Co-O, and Ni-O frequencies are also observed in 668, 641, and 669 cm^{-1}, respectively.

The electronic spectra of all the synthesized compounds were recorded in DMSO as a solvent. In the UV-Visible spectra of Schiff base ligand two peaks appeared at 260 and 340 nm which are assigned to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions, respectively. In all the metal complexes these peaks shifted to the lower wavelength through the coordination of ligand to the metal ions. The UV-Visible spectra of Cu(II) complex showed the square planar geometry for this complex. Based on electron confirmation of cu^{2+} complexes, one spin-allowed band are expected in the square planar geometry, i.e. $^2B_1g\rightarrow{}^2B_2g$. The Co(II) complex showed one peak at 665 nm. This band is assigned to $^4A_2g\rightarrow{}^4Eg$ d-d transition and confirmed the square planar for this complex. In Ni(II) complex one peak observed at 610 nm, which is related to $^3A_2g\rightarrow{}^3Eg$ transition and confirmed the square planar geometry of this complex.

The Mass spectra of the ligand and metal complexes are in good agreement with the proposed structures. The molecular ion peak for Schiff base ligand observed at m/z= 366 while for Cu (Ⅱ), Ni (Ⅱ) and Co (Ⅱ) complexes were observed at m/z= 692, 786 and 787, respectively which are equal to their molecular weight. The other peaks in the mass spectrum were attributed to the fragmentation of complex inside the molecule.



M= Cu, Co, Ni

Fig. 2. Proposed structure for metal complexes.

Antibacterial evaluation. Antibacterial activities of the ligand and its metal complexes were carried out against *Escherichia coli* and *Serratia maracescens* as Gram negative bacteria and *Bacillus subtilis* and *Staphylococcus aureus*, as Gram positive bacteria strains using disk diffusion and broth dilution methods. The biological activity is also assayed for the pure solvent DMSO and the standard drug tetracycline for each microorganism. In the antibacterial sensibility test by disk diffusion (Figure 3), all the synthesized compounds showed moderate to good antibacterial activities compared to the standard antibiotic drug against the bacteria strains. The Schiff base ligand had better inhibitory effect against *Escherichia coli* and *Serratia marcescens* with diameter inhibition zone of 12 mm. The data from inhabitation zone and minimal inhibitory concentration of each compound are represented in Figure 3 and Table 3, respectively.

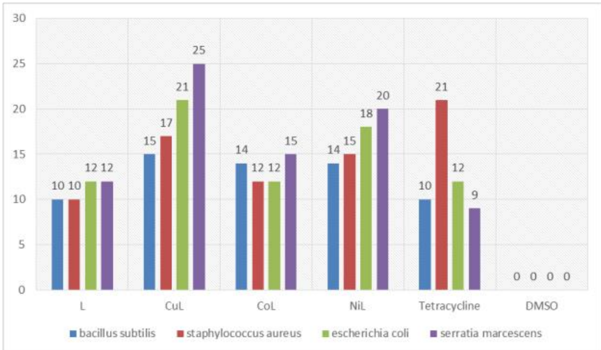


Fig. 3. Graphical presentation of anti-bacterial activity as inhibition zone diameters (mm) of synthesized compound.

It is obvious from this study that metal complexes had higher antibacterial activities when compared to the free ligand. This higher biological activities of these metal complexes can be explained on the basis of the chelation theory [18-20]. According to this theory, the polarity of the metal ion is reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of p-electrons over the whole chelate ring and enhances the lipophilicity of the complex. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of metal binding sites on the enzymes of the microorganism.

The results given in Figure 3 demonstrated that inhibition zone values of synthesized compounds increased in the order CuL>CoL=NiL>L against *Bacillus subtilis*. The inhibition zone against *Escherichia coli*, *Serratia maracescens* and *Staphylococcus aureus* showed similar trend increasing in the order CuL>NiL>CoL>L. The DMSO was used as the solvent and showed no antibacterial activity against these microorganisms.

The broth dilution test was also performed in order to achieve a lowest concentration of each compound that can inhibit the growth of the microorganisms and results are given in Table 4. The data given in Table 4 are in good agreement with the results obtained from the disk diffusion test.

Table 3. Minimal inhibitory concentration (mg/ml) ligand and metal complexes based on broth dilution method.

	G(+)		G(-)	
Compounds	*B. subtilis*	*S. aureus*	*E. coli*	*S. marcescen*
L	1000	1000	500	500
CuL	125	125	62.5	62.5
CoL	250	500	500	250
NiL	250	250	125	125
DMSO	-	-	-	-

4. CONCLUSIONS

In this study, we successfully reported the synthesis of the Schiff base ligand and its Cu(II), Co (II) and Ni(II) complexes from the condensation of 1,8- diaminonaphthalene with 4-hydroxybenzaldehyde with high yields. The preparation of Schiff base ligand was performed under optimized condition. Magnetic nanoparticles (MNP-L-proline-SO_3H) mg) was used as a suitable catalyst and methanol as the solvent for the synthesis of ligand. The structure of synthesized compounds was characterized by FTIR, ^{1}H-NMR, UV-Vis and mass spectroscopy. Antibacterial activities of ligand and metal complexes were evaluated and the results demonstrated that the Schiff base ligand with OH group was more effective against *Staphylococcus aureus* and *Bacillus subtilis*. In general, metal complexes showed much better antibacterial activities against all the bacteria strains.

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