Novel Cyclic Schiff Base and Its Transition Metal Complexes: Synthesis, Spectral and Biological Investigations

Aggarwal, Pallvi
Department of Chemistry, Maharishi Markandeshwar University, Sadopur-Ambala-134007, Haryana, INDIA

Singh Tuli, Hardeep
Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala-133207, Haryana, INDIA

Kumar, Manoj *+
Department of Chemistry, Maharishi Markandeshwar University, Sadopur-Ambala-134007, Haryana, INDIA

ABSTRACT: *2, 5-hexanedione,3,4-diacetyl, and ethylenediamine were condensed to obtain a novel Schiff base ligand. Ni(II) and Co(II) complexes have been synthesized by reacting ligands with metal salts in a 1:10 ratio. Elemental analysis, IR, ^{1}HNMR, and mass spectrometry revealed a unique structure, a cyclic decamer, of ligand and metal complexes. Synthesized compounds were screened for anti-microbial character against fungi viz. Aspergillus niger and Trichophyton rubrum and bacteria viz. Staphylococcus aureus and Klebsiella pneumonia, using well plate diffusion method. Investigation of antiangiogenic activity was done using CAM assay. The biological activities of ligands were found enhanced after coordination with metal ions.*

KEYWORDS: *2, 5-hexanedione,3,4-diacetyl; Schiff base; Antiangiogenic activity; Anti-microbial study.*

INTRODUCTION

Since the inception of metal complexes of Schiff bases intrigued the researchers to find the types of bonding of Schiff bases with metal ions but still, they are interrogating the theory of elementary bonding in their genesis [1]. Besides all these theories, Schiff bases and their metal complexes gained the huge attention of researchers because of their multifarious applications in a variety of fields like the food and dyes industry [2], analytical chemistry [3], catalysis [4-6], agriculture [7,8], polymer science [9,10] and biological systems [11,12]. However, a transfiguration in the applications of Schiff base metal complexes has been spotted by the discovery of cisplatin with anti-tumor activity [13]. Therefore, researchers further studied the innovative metal complexes for vast pharmacological properties like antitumor [14], antifungal [15], antibacterial [16,17], anticancer [18], anti-inflammatory [19], antiviral [20] and antioxidant [21]. Similarly, synthesizing the molecules that build ethical harmony with DNA is also

***** *To whom correspondence should be addressed.*
+ *E-mail*: *manojraju27@gmail.com*
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one of the interesting areas for research. Such molecules exhibit biological activity by interacting with DNA and are recognized as the best chemotherapeutic agent [22,23]. The factors that supervise the binding of molecules with DNA also play a key role in the synthesis of the molecules to possess potent chemotherapeutic properties [24]. Similarly, the Schiff base ligand and metal complexes both have a vast propensity to bind with DNA, but it is found that metal complexes have a better binding property in contrast to that of ligand and out of the metals, transition metals are known to show a high impulse to bind with DNA, the reason being that the transition metals can acquire a variety of oxidation states in contrast to other groups of metals [25,26]. P.Vasantha*et.al.* reported the DNA binding properties of Cu^{+2} complexes of metformin having ethylenediamine as one of the auxiliary ligands with calf thymus DNA in the buffer solution of tris HCl having pH=7 [27]. Similarly, the Schiff bases and metal complexes of ethylenediamine have a big array of applications in different areas as Schiff base Cu(II) complexes of ethylenediamine can be used as catalysts for the asymmetric epoxidation of olefins[28]. Along with this, *Sau-Fun Tan et.al* reported the synthesis and isolation of the asymmetric bis-Schiff bases from symmetric bis-Schiff bases ligands [29]. Similarly, *Sajjad Hussain Sumrra et.al.* synthesized a series of the ligand of ethylenediamine with a variety of aldehydes and their first transition series metal complexes and reveal their antimicrobial property[30]. Further, Zn(II) and Cd(II) complexes of Schiff base of ethylenediamine with acetophenone and 4-nitrobenzaldehyde have been prepared by *Anant Prakasha et.al*. and screened in vitro for their antibacterial property against *E. coli* and *S. aureus* [31] Similarly, literature also divulge that2,5-hexandione-3,4-diacetylpyrineand its metal complexes both possess myriad magnificent coordination and biological properties[32,33] such as a bridging ligand to synthesize the polynuclear complexes [34], as hydrogen gas absorption [35]as well as in food industry as a flavoring agent[36]. The review of this work also reveals that both 2,5-hexandione-3,4-diacetylpyrine and substituted ethylenediamine can coordinate with the metal ion without making a C=N bond (Schiff base) and possess the significant property[37]. So, in the present study, we synthesized Schiff base by condensation of 2,5-hexanedione-3,4-diacetyl with ethylenediamine, and its Ni(II) & Co(II) complexes. Further, their antiangiogenic and antimicrobial properties were scrutinized.

EXPERIMENTAL SECTION

Material and Measurements

The chemicals were purchased from Otto, Emerk, and Loba and are of analytical grade. Before use, all the solvents were distilled. IR spectra were observed as KBr pallets on the MB-3000 ABB FT-IR spectrophotometer. NMR spectrums were recorded on Bruker AvanceNEO 500 MHz NMR spectrometer marking TMS as the internal standard. IR and ^{1}HNMR were carried out at Kurukshetra University, Kurukshetra, and SAIF Punjab University, Chandigarh respectively. Mass was recorded on XEVO G2S QTOF from MRC, MNIT Jaipur.

Synthesis

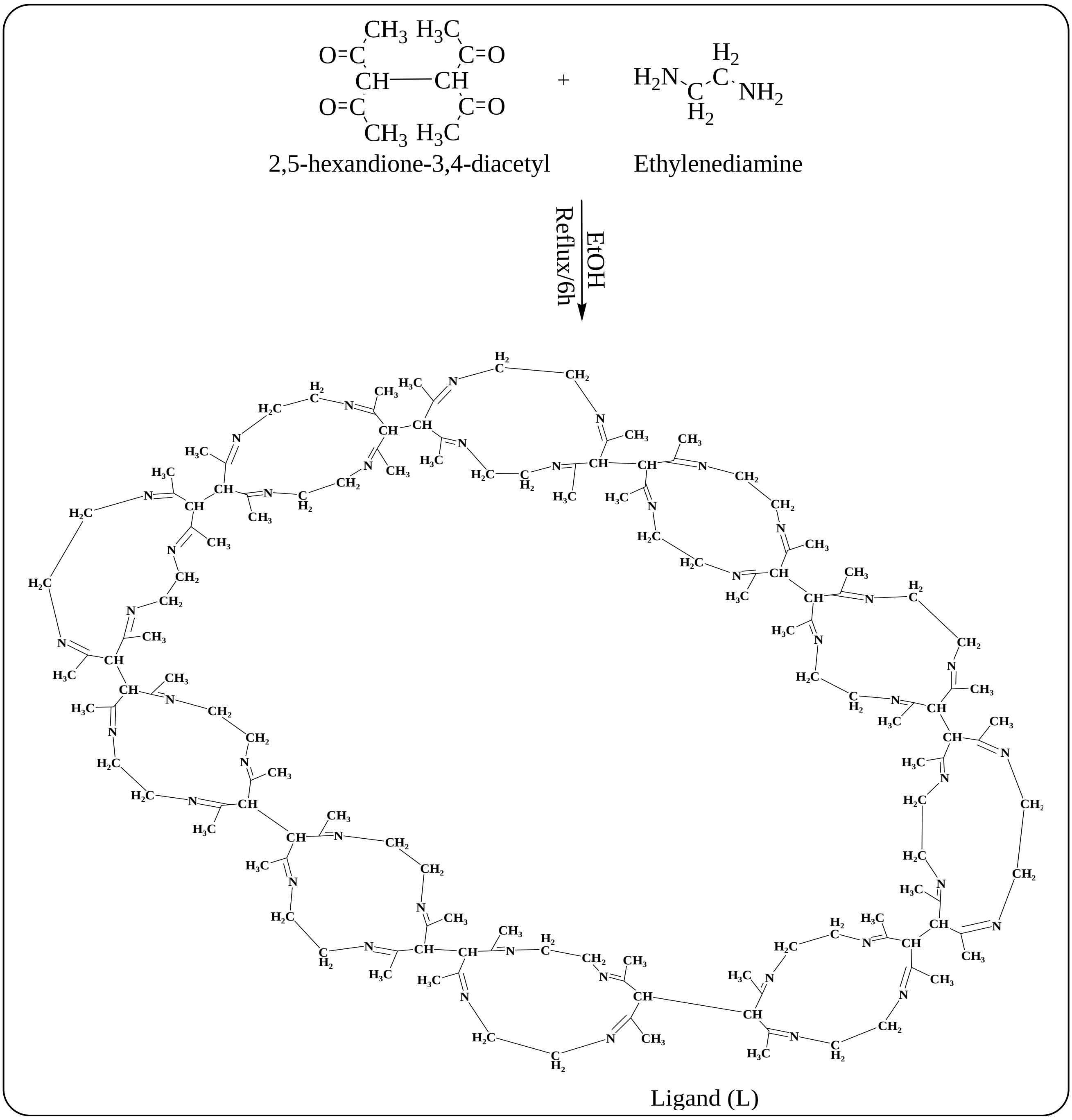
Synthesis of ligand

2, 5-hexanedione-3, 4-diacetyl was prepared using the well-known reported method [38]. 1.98g (1 mol) of 2, 5-hexanedione-3, 4-diacetyl was dissolved in ethanol(99%) and intimately mixed to the ethanolic solution of 2.40g(4mol)of ethylenediamine in the round bottom flask subsequently refluxed for 06 hours in a water bath followed by keeping the whole content undisturbed overnight. The homogeneous solid was collected on the Buckner funnel by filtration on the suction pump. Further, the purity of the compound was obtained by recrystallization in ethanol and confirmed by Thin-Layer Chromatography (TLC). The product was dried by keeping them overnight in a vacuum desiccator with anhydrous calcium chloride and weighed to yield 2.0g of light orange color, defined as a ligand (L). The route used to synthesize the cyclic Schiff base ligand is shown in Scheme-1.

Ligand (L): Yield: 71-76%. m.p.$\geq$ 360°C. IR (KBr, ν_{max}, cm^{-1}): 1643(C=N), 1504(CH_2 bending), 2800(CH_2 stretching), 2901(CH stretching), 2970(CH_3 stretching).^{1}HNMR (500 MHz, DMSO, ppm) δ: 2.5(s, CH_3), 3.0-3.3(d, -CH), 8.1(t, CH_2).Anal. calcd. for $C_{140}H_{220}N_{40}$: C,68.29; H,8.94; N,22.76%. Observed: C,68.49; H,8.00; N,22.20%. GCMS (m/z):2460.

Preparation of nickel complex [NiL]

2.4g (1 mol) ligand was dissolved in 20 ml ethanol and added to the ethanolic solution of 2.3g (10 mol) of metal salts ($NiCl_2{\cdot}6H_2O$) in the round bottom flask and refluxed



Scheme1: Route used to synthesize the cyclic Schiff base ligand (L).

for about 5 hours using a water bath and the solution was kept undisturbed overnight. The crude product was collected on Buckner funnel by filtration on the suction pump and purified by recrystallization using ethanol. Further, thin layer chromatography was used to confirm the purity of the product. The product was kept in vacuum desiccators overnight to dry. The scheme used to synthesize the metal complex as given inscheme-2.

[NiL]: Yield: 72-79%. m.p.$\geq$ 360°C. IR (KBr, νmax, cm^{-1}): 1600(C=N), 440(Ni-N). ^{1}HNMR (500 MHz, DMSO, ppm) δ: 2.5(s, CH_3), 3.0-3.3(d, -CH), 8.5(m,CH_2). Anal. calcd. for $C_{140}H_{220}N_{40}Ni_{10}Cl_{20}$: C,44.71; H,5.8; N,14.90; Ni,15.62; Cl,18.89%. Found: C,44.80; H,5.7; N,15.67; Ni, 15.60; Cl, 18.90%. GCMS (m/z): 3756.

$$\text{Ligand} + \text{Metal Salt} \xrightarrow[\text{Reflux/5h}]{\text{EtOH}} \text{Ligand Metal Complex}$$

$$\text{Metal Salt} = NiCl_2.6H_2O\ ,\ CoCl_2.6H_2O$$

Scheme 2: Preparation of transition metal complexes of ligand (L).

Preparation of cobalt complex [CoL]

Both 2.4g (1mol) of ligand and 2.3g (10 mol) of metal salts ($CoCl_2 \cdot 6H_2O$) were dissolved in 20 ml of hot ethanol separately and finally mixed in a round bottom flask. This reaction mixture was refluxed for about 5 hours on the water bath and conserved undisturbed overnight. The product was recrystallized using ethanol to purify and further the purity was confirmed by TLC. The uniform product was collected on the Buchner funnel by filtration on the suction pump and put up to dry in vacuum desiccators overnight. The adopted route to synthesize the metal complex is shown in Scheme-2.

[CoL]: Yield: 74 %. m.p.$\geq$ 360°C. IR (KBr, νmax, cm^{-1}): 1620(C=N), 450(Co-N). ^{1}HNMR (500 MHz, DMSO, ppm) δ: 2.5(s,CH_3), 3.0-3.3(d, -CH), 8.5(m, CH_2). Anal. calcd. for $C_{140}H_{220}N_{40}Co_{10}Cl_{20}$: C,44.68; H,5.8; N,14.89; Co,15.67; Cl,18.88%. Found: C,44.90; H,5.9; N,14.77; Co,15.61; Cl,18.90%.GCMS(m/z): 3760.

Biological study

Antimicrobial activity

In-vitro antimicrobial activity of the synthesized ligand and their metal complexes against the selected bacterial strain (*Staphylococcus aureus* and *Klebsiella pneumoniae*) and fungal strain (*Aspergillus niger* and *Trichophyton rubrum*) were investigated by well plate diffusion method [39]. The sterilized Petri plates (150 mm in diameter) were used throughout the investigation. To make pour plates sterilized melted nutrient agar for bacteria and potato dextrose agar for fungi were used. After the solidification of pour plates, bacteria and fungi under investigation were separately spread uniformly over the plates with the help of a sterilized glass spreader. In each case, the control plate was also maintained with DMSO. Firstly, the plates were kept at room temperature for about 4 hours and during this time the test chemicals were diffused from the well to the surrounding medium. Then the plates were incubated at (27 ± 2) °C for the growth of bacteria and fungi under investigation and were observed at 24 and 48 hours intervals. The activity was expressed in terms of the zone of inhibition in mm. The various concentrations of ligand and its metal complexes *viz.* 100, 250, 400, and 500 μg/mL were loaded in wells followed by incubation at 30°C for 24 and 72 hours to evaluate the effect of the compound on bacterial and fungal growth respectively. Commercial antifungal Fluconazole and antibacterial Neomycin were used as standard drugs for anti-microbial activity [40,41].

Antiangiogenic Activity

The antiangiogenic activity was assessed by *ex-vivo* Chorioallantoicmembrane assay (CAM). To avoid infection, the fertilized eggs were cleaned with alcohol (70%) and kept at 37ºC in a humidified (70%) chamber for 72 hours. After the incubation period, the eggshell from the blunt side was removed to make a window and the sterilized filter disc of 5mm was loaded with the different concentrations of the prepared ligand and its metal complexes and placed on CAM layer. The window was sealed with sterilized laboratory tape and eggs were kept for incubation for 48hours. The blood vessel inhibitory effect of synthesized compounds was calculated in terms of blood vessel branch points over CAM in comparison to the control group.

$$\text{Inhibition percentage} = \frac{\text{Data of control - Data of treated}}{\text{Data of control}} \text{ X 100}$$

RESULTS AND DISCUSSION

The new possible N-donor Schiff base ligand(L) and its metal complexes (CoL and NiL) were prepared. Complexes are colored, stable in air, non–hygroscopic solid and even they don't decompose after storing for many weeks. All the compounds are soluble in DMSO but are not soluble in other organic solvents as well as water. Experimental values of elemental analysis (C, H, and N) to determine the purity of the compounds are comparable with theoretical values. FT-IR confirms the donor sites present in ligand for complexation similarly ^{1}HNMR endorses the types of proton present and GCMS upholds the fragmentation. To shape out the structure of compounds completely, success was not in hand even after driving the changes in conditions of single-crystal development. However, the elemental and spectroscopic data are congruous with the proposed structure.

Spectral Investigations

IR

IR spectra were recorded for the ligand and metal complexes to evaluate the donor site in the ligand and compared with spectra of complexes. The measured range to depict the stretching frequency for IR data is 4000-500cm^{-1}. A high-intensity band is observed at 1643cm^{-1}in the free ligand[42] which indicates that the condensation had occurred and this band undergoes a bathochromic shift by 20-40 cm^{-1}in metal complexes, observed at 1600-1620cm^{-1}[43] and this shift can be explained based on that the nitrogen atom of azomethine donates its lone pair of electrons to the empty d-orbital of metal ion which favors the complexation also[44]. The new band appeared at 440-450cm^{-1} in the IR spectra of metal complexes which affirms the M-N stretching[45]. Moreover, similar stretching and bending bands are also observed in both ligand and metal complexes spectral data for CH_2(bending, stretching), CH, and CH_3 stretching at 1504, 2800, 2901, and 2970cm^{-1} respectively[46] (Fig.7).

^{1}HNMR

In ^{1}H NMR spectra of ligand and metal complex, a singlet and a doublet appeared at δ=2.5 and 3.0-3.3ppm corresponding to -$CH_3$and-CHprotons respectively [47]. The appearance of the triplet at δ=8.1-8.3ppm confirms the azomethine protons in ligand while in the case of complexes it appeared further downfield at δ=8.6-8.9 ppm which establishes the coordination of the azomethine nitrogen with the metal ion [48] (Fig. 8).

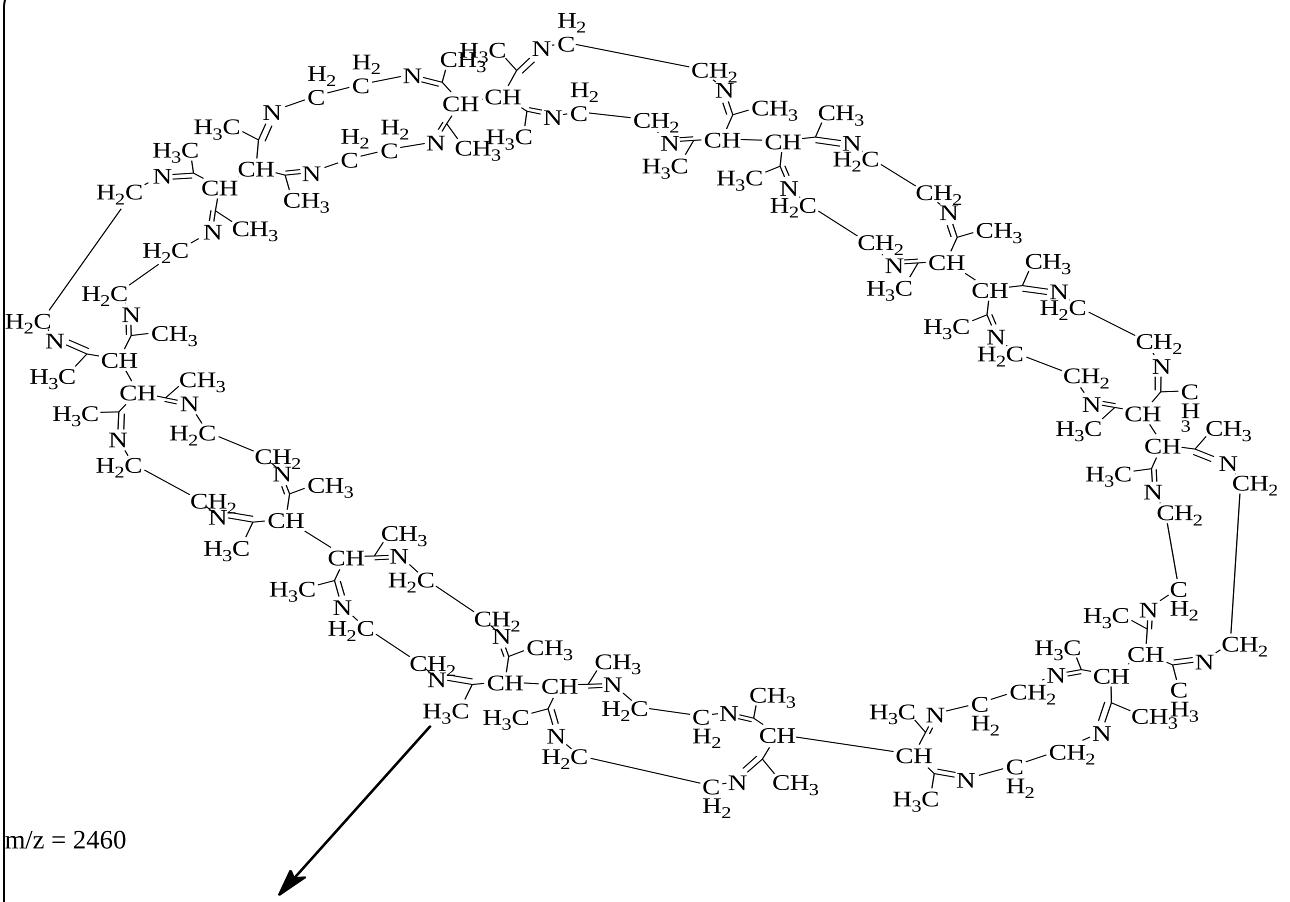
Mass Spectrometry

The cyclic nature of the ligand and metal complex was further corroborated by the mass data. The m/z value of molecular ion and base peak appeared at 2460 and 1624 respectively. Along these peaks, several fragments of medium and strong intensity were observed at 2164, 1917,1680, 1348. The fragmentation pattern is given under Scheme 3.

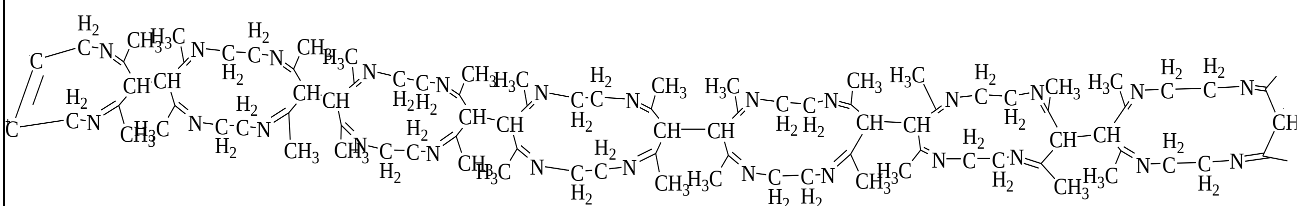
Based on the spectroscopic and elemental analysis study the proposed structure of the ligand, Monomer unit, and its transition metal complexes are given under Figs.1-4.

Antimicrobial study

Bacteria and Fungi mutated themselves against the used antibiotics under the aegis of morphological and biochemical variations[49] and this gave a bright way to researchers to synthesize the novel Schiff bases and their metal complexes that have to heighten antimicrobial properties. Therefore, to achieve this need, several Schiff bases and their metal complexes have been synthesized and screened for their antimicrobial properties against both gram-positive and gram-negative bacteria and fungi [50-52]. Similarly, in the present study, the synthesized Schiff base ligand and its transition metal complexes were investigated against the selected fungi viz. *Aspergillus niger* and *Trichophyton rubrum* and bacteria viz. *Staphylococcus aureus* and *Klebsiella pneumoniae*. It was observed that all the compounds quenched the multiplication of the selected fungal and bacterial strains with some deviations[53]and this deviation can be subjected to the diversity in the ribosome and impenetrability of the cell membrane of microorganisms[54]. Further, the Minimum Inhibitory Concentration (MIC) of all synthesized compounds was evaluated (Table- 1-3) which reveals that the metal complexes have a more potent antimicrobial property than ligand. This transformation can be elucidated employing Tweedy's chelation theory which considers that, the overlapping of orbitals of ligand reduced the polarity of metal ions which increases the lipophilicity character of complexes. Further, this increment in the lipophilicity character results in the enhanced anti-microbial property of metal complexes as compared to ligand[55,56]. Moreover, concentration is also one of the important factors to calculate the zone of inhibition [57], and observed that the synthesized compounds showed maximum activity up to 500 ppm[58]. The average mean value with ±0.6 to ±0.9 the standard deviation of three values is represented by the data given in tables- 1-3 and the antimicrobial assay under Fig.5.



m/z = 2460



m/z=1624
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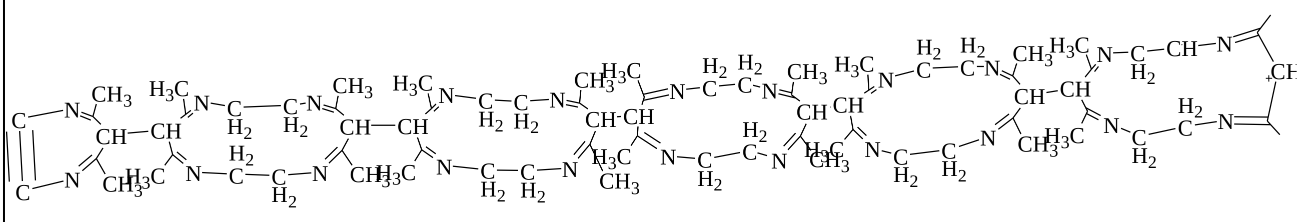
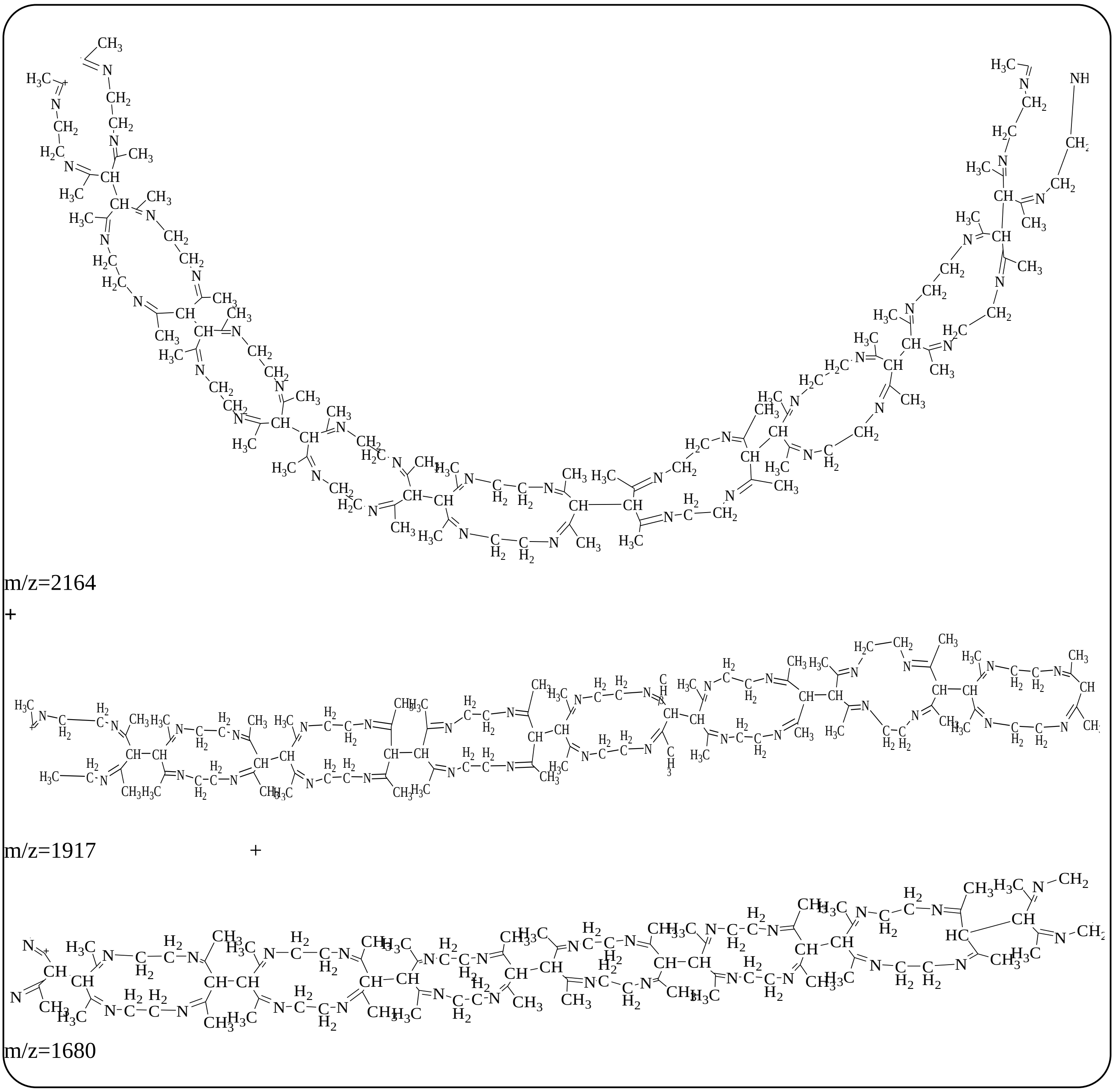


m/z=1348
+

Scheme 3: Mass fragmentationpattern followed by ligand.



Scheme 3: Mass fragmentationpattern followed by ligand.

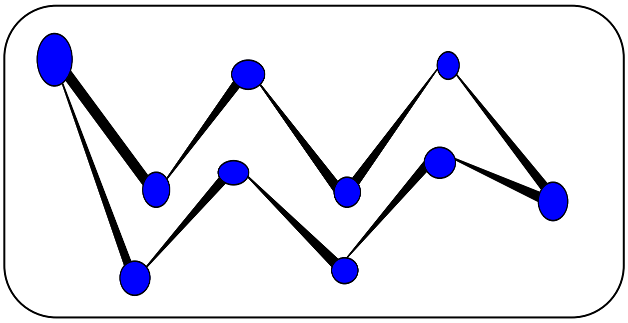


Fig. 1: Structure of ligand (L).

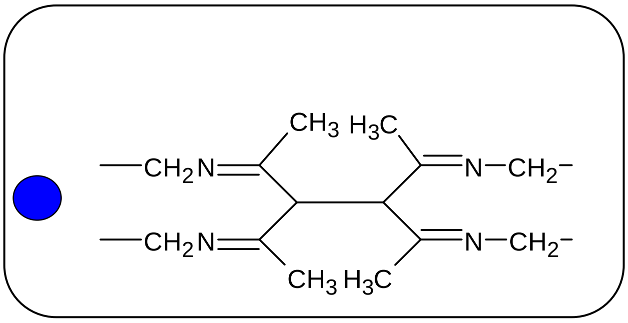


Fig. 2: Monomer unit.

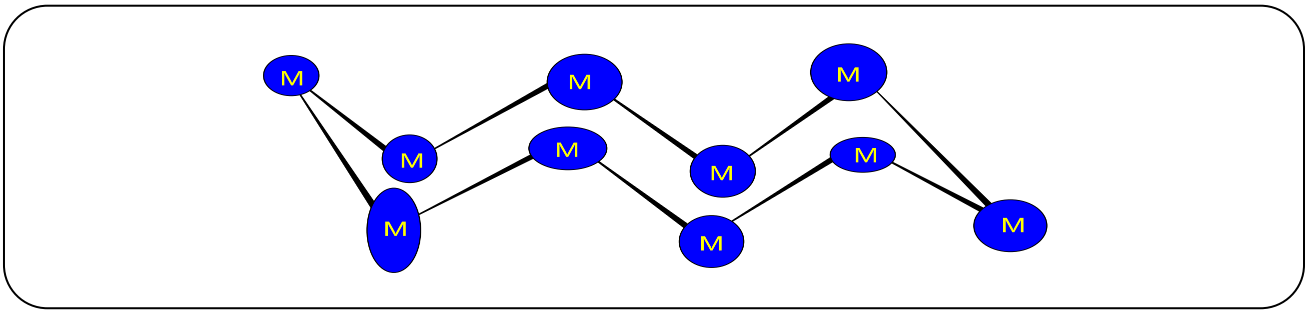


Fig.3: Structure of metal complex(M= Co(II) and Ni(II)).

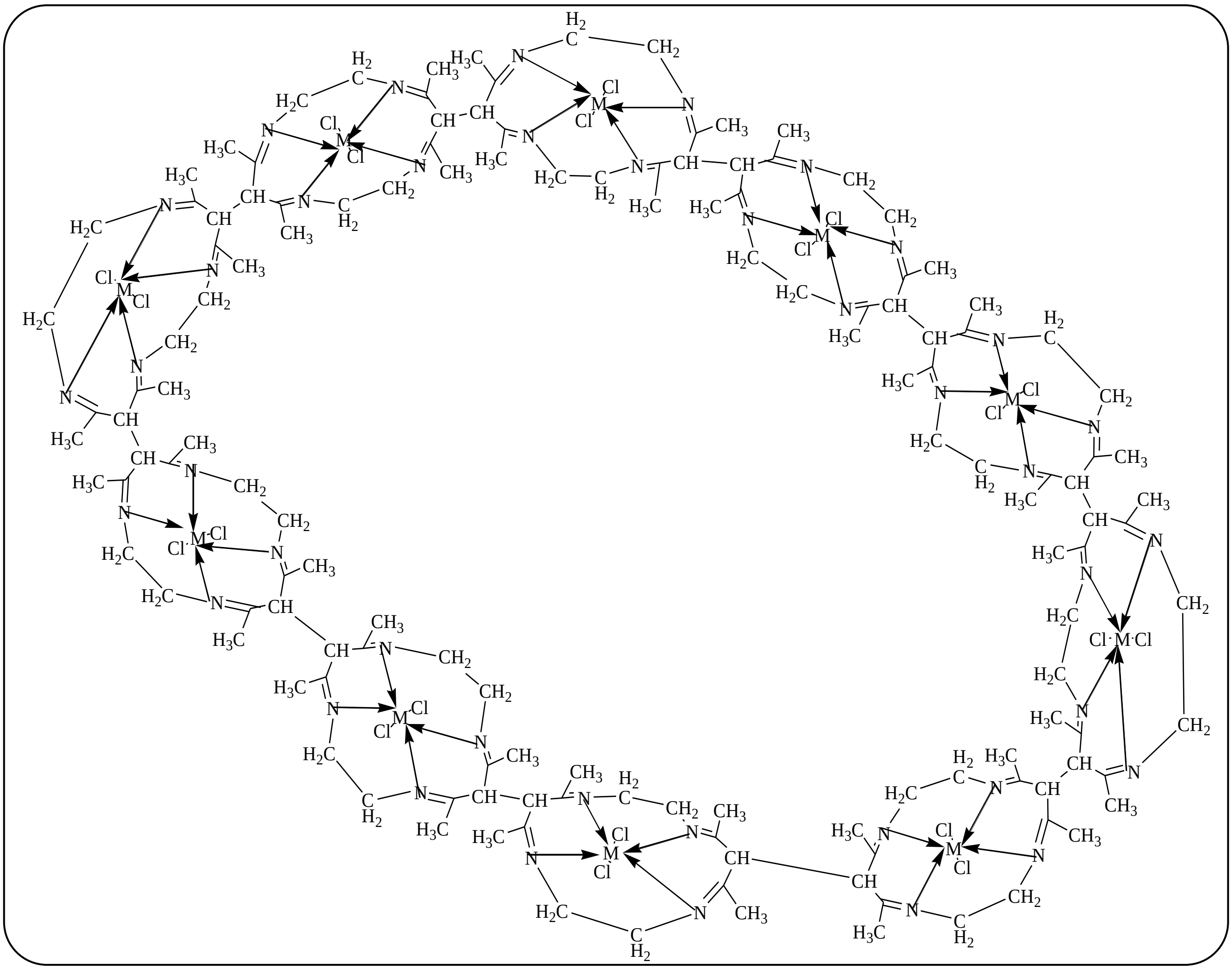


Fig.4: Suggested complete structure of metal complex (M = Co(II) and Ni(II)).

Antiangiogenic Activity

Blood vessel branch points were significantly reduced by synthesized ligands and their metal complexes. It has been found that Ni and Co complexes were more effective in inhibit91 and 96 % blood vessel formation on developing the CAM layer respectively (Fig.6). Recently, *Ambika et.al.* have reported the promising role of Schiff base compounds inhibit blood vessels [59]. It has been reported that proliferative tumors gain nourishment and oxygen through developing blood vessels [60,61]. Furthermore, studies have revealed that antiangiogenic agents may consider a potent anti-tumoragent [62,63].

Table 1: Anti-microbial activity of Ligand(L).

Ligand (L)	Bacterial Strains (Zone of inhibition in mm)								Fungal Strains (Zone of inhibition in mm)							
	S. aureus				K. pneumoniaae				A. niger				Trichophytonrubrum			
Dosages	100 ppm	250 ppm	400 ppm	500ppm	100 ppm	250 ppm	400 ppm	500 ppm	100 ppm	250 ppm	400 ppm	500 ppm	100 ppm	250 ppm	400 ppm	500 ppm
Zone of Inhibition	10 mm ±0.6	15 mm ±0.8	17 mm ±0.7	20 mm ±0.7	11 mm ±0.6	14 mm ±0.6	17 mm ±0.6	21 mm ±0.8	12 mm ±0.6	17 mm ±0.6	19 mm ±0.6	22 mm ±0.7	11 mm ±0.7	15 mm ±0.5	16 mm ±0.6	18 mm ±0.8
Standards	250 ppm				250 ppm				250 ppm				250 ppm			
	21 mm (Neomycin)				23 mm (Neomycin)				(24 mm) Fluconazole				(19 mm) Fluconazole			
Solvent	3mm				3mm				Not observable				3mm			

Table 2: Anti-microbial activity of nickel complex (NiL).

Nickel Complex (NiL)	Bacterial Strains (Zone of inhibition in mm)								Fungal Strains (Zone of inhibition in mm)							
	S. aureus				*K. pneumoniaae*				*A. niger*				*Trichophytonrubrum*			
Dosages	100 ppm	250 ppm	400 ppm	500 ppm	100 ppm	250 ppm	400 ppm	500 ppm	100 ppm	250 ppm	400 ppm	500 ppm	100 ppm	250 ppm	400 ppm	500 ppm
Zone of Inhibition	12 mm ±0.7	19 mm ±0.9	21 mm ±0.8	23 mm ±0.8	15 mm ±0.7	16 mm ±0.7	19 mm ±0.7	22 mm ±0.9	16 mm ±0.7	19 mm ±0.7	21 mm ±0.6	22 mm ±0.8	15 mm ±0.9	17 mm ±0.6	18 mm ±0.7	20 mm ±0.8
Standards	250 ppm				250 ppm				250 ppm				250 ppm			
	21 mm (Neomycin)				23 mm (Neomycin)				(24 mm) Fluconazole				(19 mm) Fluconazole			
Solvent	3mm				2mm				Not observable				3mm			

Table 3: Antimicrobial activity of cobalt complex (CoL).

Cobalt Complex (CoL)	Bacterial Strains (Zone of inhibition in mm)								Fungal Strains (Zone of inhibition in mm)							
	S. aureus				K. pneumoniaae				A. niger				Trichophytonrubrum			
Dosages	100 ppm	250 ppm	400 ppm	500 ppm	100 ppm	250 ppm	400 ppm	500 ppm	100 ppm	250 ppm	400 ppm	500 ppm	100 ppm	250 ppm	400 ppm	500 ppm
Zone of Inhibition	13 mm ±0.6	18 mm ±0.8	20 mm ±0.7	22 mm ±0.7	14 mm ±0.6	15 mm ±0.6	18 mm ±0.6	21 mm ±0.8	15 mm ±0.6	18 mm ±0.6	20 mm ±0.6	23 mm ±0.7	14 mm ±0.8	16 mm ±0.5	17 mm ±0.6	19 mm ±0.7
Standards	250 ppm				250 ppm				250 ppm				250 ppm			
	21 mm (Neomycin)				23 mm (Neomycin)				(24 mm) Fluconazole				(19 mm) Fluconazole			
Solvent	3mm				2mm				Not observable				3mm			

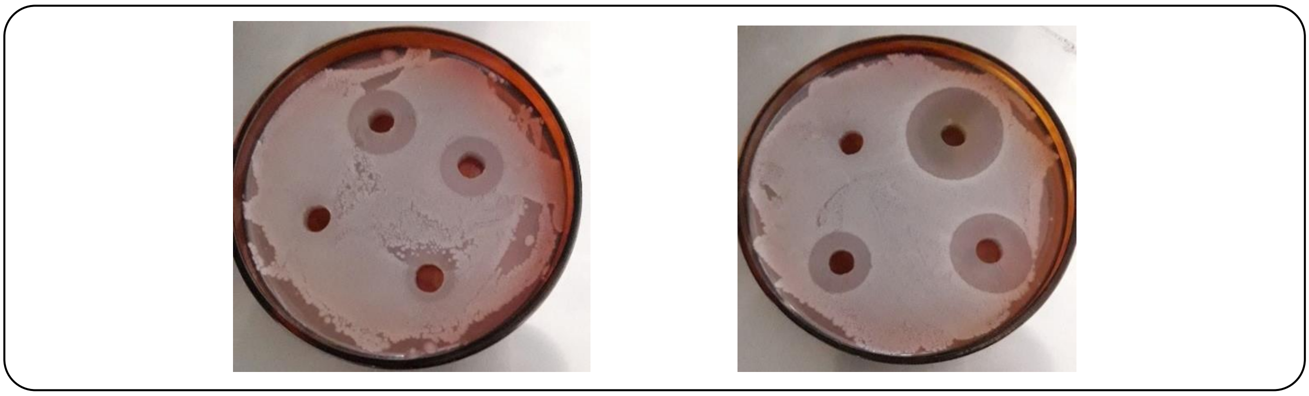


Fig. 5: Antimicrobial assay.

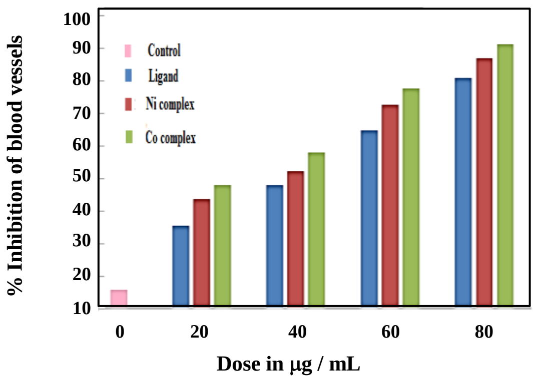


Fig. 6: Antiangiogenic activity of the ligand and its Ni and Co complexes.

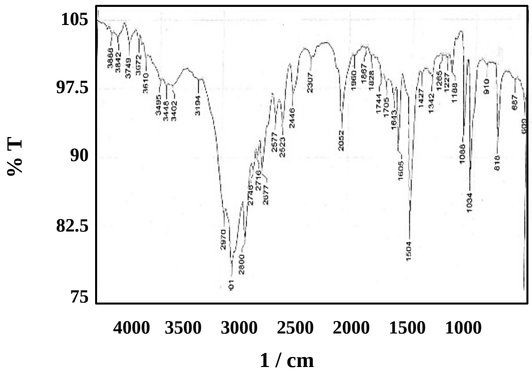


Fig. 7: IR spectra of ligand (L).

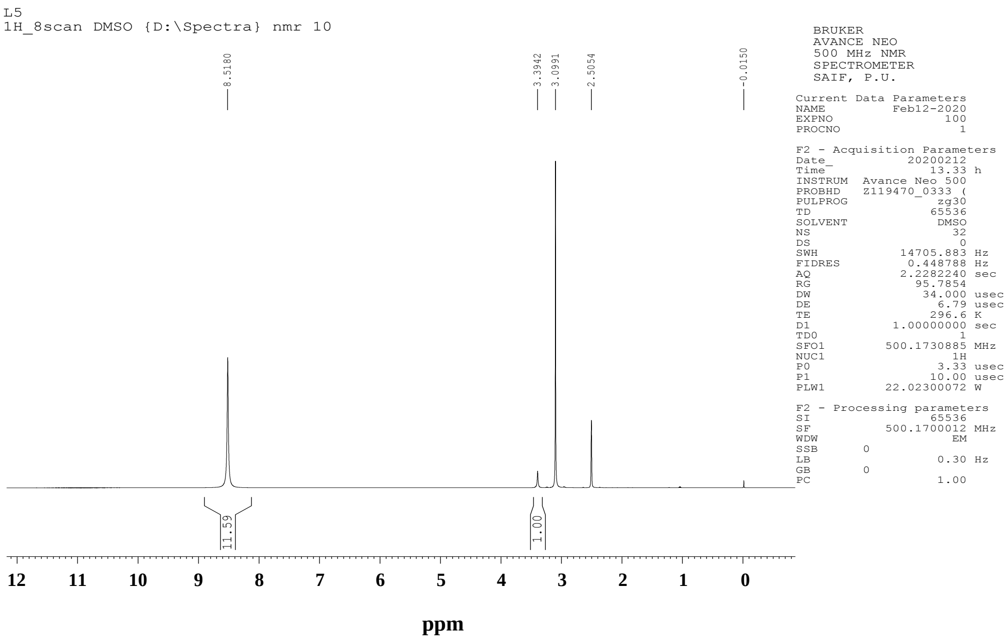


Fig.8: NMR spectra of ligand (L).

CONCLUSIONS

In summary, a novel Schiff base ligand has been synthesized using a condensation reaction between ethylenediamine and 2,5-hexandione-3,4-diacetyl. Further, the ligand was coordinated with Nickel and Cobalt metal ions to get the respective metal complexes. The structure of all the synthesized compounds was confirmed by the analytical and spectral data which are in good agreement with the proposed structure. Moreover, the anti-microbial and anti-angiogenic activity of the compounds was also evaluated by adopting the well plate diffusion method and CAM assay respectively. The biological study of the synthesized compounds reveals that the metal complexes are more potent than the ligand against the selected bacterial and fungal strains. In the future ligand may be engaged with various other metals to prepare a variety of complexes that are supposed to have important pharmacological properties.

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