

Synthesis, Characterization, Anti-Microbial and Anti-Inflammatory activity, Studies of Novel Schiff base 3,3'-{1,2-PhenyleneBis [Nitrilo(E) Methylydine]} Diquinolin-2-ol and its Metal(II) Complexes

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Abstract: Novel complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) with a new schiff base 3,3'-{1,2-phenylenebis[nitrilo(E)methylylidine]}diquinolin-2-ol have been synthesized. Their structures were determined based on elemental analyses, magnetic susceptibility, IR NMR, FAB-mass, EPR and UV-Visible spectral data. Based on analytical and molar conductance data, the complexes may be formulated as $[M(L)(H_2O)_2]$ [where M = Co(II), Ni(II), Cu(II), Zn(II) and Cd(II)] and are non-electrolytic and 1:1 stoichiometric nature. Based on spectral studies, an octahedral geometry were assigned for all complexes. The ligand and its complexes were tested for their antibacterial activity against *Escherichia coli* & *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* & *Candida albicans* and anti-inflammatory activity for selected compounds.

Key words: Antimicrobial activity, Anti-inflammatory activity, Schiff base and EPR.

Introduction

Coordination chemistry encompasses a great diversity of substances and phenomena^{1,2}. Imines (Schiff bases) are an important class of ligands in coordination chemistry and have many applications³ in various fields. The chemistry of Schiff base complexes continues to attract many researchers⁴ because of its wide applications in food industry, dye

industry, analytical chemistry. These have been used as fungicides in agricultural field⁴. Schiff bases and their metal complexes have been found to possess important biological and catalytical activities⁵. In addition they have also been used as biological models and oxygen carriers⁶.

Quinoline derivatives represent the major class of heterocycles, and a number of preparations have

been known from the late 1980s. The quinoline ring occurs in various natural products, especially in alkaloids. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties. In 1820, quinine was isolated as the active ingredient from the bark of Cinchona trees and successively replaced the crude bark for the treatment of malaria. Despite its relatively low efficiency and tolerability, quinine still plays an important role in the treatment of multi-resistant malaria⁷. This molecule has also played a historical role in organic chemistry as a target for structural determination and total synthesis⁸, and recently both stereoselective and enantioselective total synthesis⁹.

A class of quinoline based compounds have been reported to inhibit platelet-activating factor (PAF) synthesis which contributes to anti-inflammatory properties.¹⁰ A large body of evidence underlines the role of copper in the pathology of inflammation¹¹. The therapeutic value of copper, of copper complexes with different ligands including anti-inflammatory drugs and of the copper containing enzyme super oxide dismutase (SOD) has been thoroughly investigated and the results obtained seem to support the very old idea of copper as an exogenous anti-inflammatory agent¹¹.

The study of transition metal quinoline complexes is an area of great current interest¹². Schiff bases are known to possess many pharmacological activities such as tuberculostatic, fungicidal, anti-inflammatory, antitumour, antiviral and antimicrobial activities¹³.

We report here the synthesis, characterization, antimicrobial activity and anti-inflammatory activity studies of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes of Schiff base derived from 3,3'-{1,2-phenylenebis[nitrilo(*E*)methylidene]}diquinolin-2-ol. This Schiff base behaves as ONNO-tetradentate ligand H₂L (Fig1).

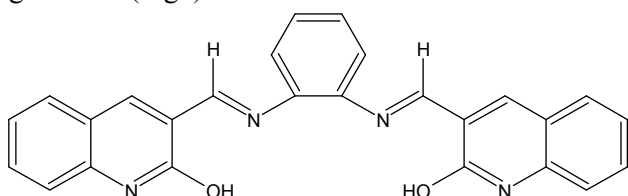


Fig1. Structural formula of the ligand (H₂L).

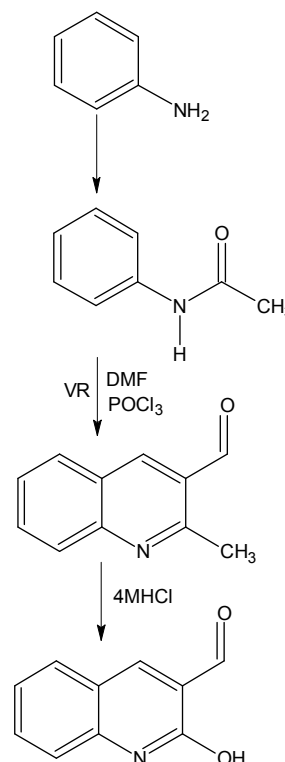
Experimental

Materials and methods

The chemicals used for preparing the ligands were of reagent grade. The solvents were distilled and dried before use by following standard procedure¹⁴. The acetanilides were prepared from the respective substituted anilines following the standard procedure¹⁵. These were used as the starting materials for the preparation of substituted 3-formyl-2-hydroxyquinoline. The metal(II) chlorides used were in their hydrated form.

Synthesis of Schiff base ligand 3-Formyl-2-hydroxyquinoline

A mixture of 2-chloro-3-formylquinoline (1.9g, 0.01mol) and aqueous hydrochloric acid (35ml:4M) was heated under reflux for 1h and then allowed to cool to room temperature. Then the reaction mixture was poured onto crushed ice. 3-Formyl-2-hydroxyquinoline was separated out as a yellow solid was collected by filtration and recrystallized from aqueous acetic acid into yellow silky needles¹⁶. (Yield 69%, m.p.295-297°C, lit.297°C).

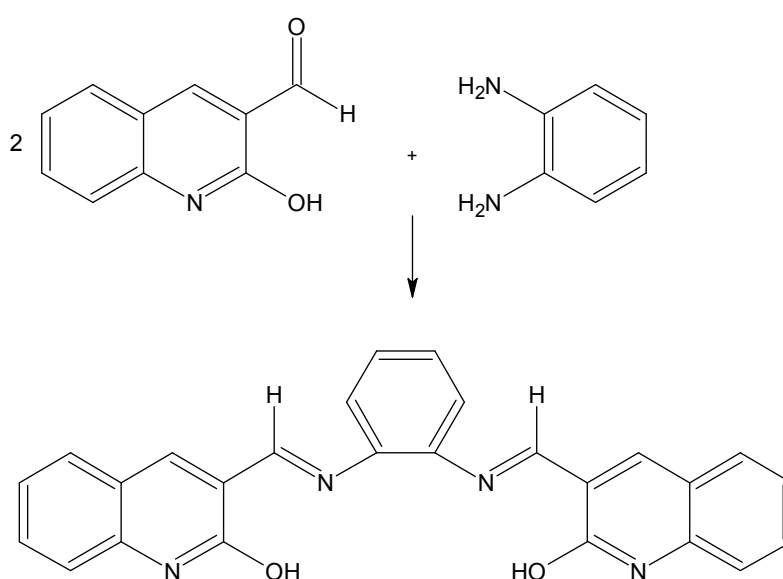


Scheme.1- Preparation of precursor 3-Formyl-2-hydroxyquinoline

Synthesis of 3,3'-{1,2-phenylenebis[nitrilo(*E*)methylidene]}diquinolin-2-ol

A mixture of 2-hydroxy-3-formylquinoline (0.002mol) and *o*-phenylenediamine (0.108g, 0.001mol) in ethanol (30ml) was refluxed in presence of catalytic amount of glacial acetic acid (1-2 drops) for about 5 h on water bath. The reaction mixture was cooled to room temperature, the separated Schiff base

was collected by filtration, dried and recrystallized from 1, 4-dioxane. (Table. 1) m.p (256-258 °C) Yield (70 %).



Scheme 2. Preparation and structural formula of the ligand

Synthesis of Co(II), Zn(II) and Cd(II) complexes

To the hot ethanolic solution of ligand (0.01mol) (30 ml), a hot ethanolic solution (10ml) of metal(II) chloride (0.01mol) was added and the reaction mixture was refluxed on a water bath for 4h to get clear solution. Sodium acetate (0.5g) was added to the reaction mixture just to adjust the pH of the solution. The contents of the flask further refluxed for

2-3h more. The resulting mixture was decomposed by pouring into a 100ml of distilled water with stirring. The suspended solid complexes were allowed to settle and collected by filtration, washed with sufficient quantity of distilled water and then with little hot ethanol to apparent dryness and dried in vacuum over anhydrous calcium chloride in desiccator. (Yield, 60-70%) (Table – 1).

Table 1: Analytical and molar conductance data of ligand and its complexes.

Empirical Formula/ Molecular formula	Mol. Wt.	M.P. (^o C) Yield, (%)	Elemental Analysis (%)				Molar. Cond. (λ_M) ohm ⁻¹ cm ² mol ⁻¹
			M	C	H	N	
C ₂₆ H ₁₈ N ₄ O ₂	418.44	256 (70)	--	74.56 (74.46)	4.30 (4.28)	13.44 (13.40)	
[Cu(L)(H ₂ O) ₂]	516.00	289 (72)	12.31 (12.25)	60.46 (60.42)	3.87 (3.84)	10.85 (10.80)	24
Cu(C ₂₆ H ₂₀ N ₄ O ₄)							
[Ni(L)(H ₂ O) ₂]	511.17	248(d) (62)	11.48 (11.43)	61.03 (60.99)	3.91 (3.87)	10.95 (10.91)	27
Ni(C ₂₆ H ₂₀ N ₄ O ₄)							
Co[(L)(H ₂ O) ₂]	511.39	253 (67)	11.52 (11.47)	61.01 (60.95)	3.91 (3.88)	10.95 (10.93)	22
Co(C ₂₆ H ₂₀ N ₄ O ₄)							
[Zn(L)(H ₂ O) ₂]	517.83	252(d) (53)	12.62 (12.50)	60.25 (60.20)	3.86 (3.85)	10.81 (10.79)	20
Zn(C ₂₆ H ₂₀ N ₄ O ₄)							
[Cd(L)(H ₂ O) ₂]	564.86	>300 (67)	19.90 (19.84)	55.23 (55.20)	3.54 (3.52)	9.91 (9.88)	18
Cd(C ₂₆ H ₂₀ N ₄ O ₄)							

Synthesis of Cu(II) and Ni(II) complexes

To the hot ethanolic solution of ligand (0.01mol) (30 ml), a hot ethanolic solution (10ml) of metal chloride (0.01mol) was added and the reaction mixture refluxed on a water bath for 6-8h. The reaction mixture was then cooled to room temperature. The separated solid complexes were collected by filtration, washed with hot ethanol to apparent dryness and dried in vacuum over anhydrous calcium chloride in a desiccator. (Yield, 60-70%) (Table-1).

Physical measurements

IR spectra of the synthesized compounds were recorded as KBr pellets on PERKIN-ELMER Spectrum One FT-IR spectrometer. ¹H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. UV-Vis spectra of the complexes were recorded on Elico-SL 164 double beam spectrometer in the range 200-1200 nm in DMF solution (1 × 10⁻³ M). FAB-mass spectrum of the ligand and Cu(II) complex were obtained on JEOL SX 102/DA-6000 mass spectrometer using Argon/Xenon as the gas. The accelerating voltage was 10KV and the spectrum was recorded at room temperature using meta-dinitrobenzyl alcohol as a matrix. Elemental analyses were obtained from HERAEUS C, H, N-O rapid analyzer and metal analyses were carried out by following the standard methods. ESR measurements were carried out on a BRUKER BioSpin GmbH spectrometer working at a microwave frequency of 9.903 GHz. The experiment

was carried out by using, diphenylpicrylhydrazyl (DPPH) as reference with the field set at 3200 Gauss. Magnetic susceptibility were determined by the Faraday method using a model 300 Lewis coil Force Magnetometer of tesla field strength at room temperature. The instrument was calibrated with Hg[Co(SCN)₄]¹⁷.

Results and Discussion

All the synthesized complexes are coloured and amorphous in nature and stable in air. All these complexes found to be insoluble in common organic solvents but are soluble in solvents such as DMF and DMSO. The analytical data of all the complexes are given in the Table 1. From the analytical data, it was found that all the complexes have exhibited 1:1 stoichiometry. Molar conductivity data obtained in DMF suggest that all the complexes are of non-electrolyte type.

IR spectra

The IR spectrum of the free ligand exhibit characteristic strong intensity sharpened band in the region 1671cm⁻¹, attributed to the both azomethine $\nu_{C=N}$ vibrations¹⁸. The band due to $\nu_{C=N}$ is observed in the ligand at 1671 cm⁻¹ shows a negative shift of 18-56 cm⁻¹ in all the complexes confirms the coordination through both the azomethine nitrogen atoms¹⁸. The band due to hydrogen bonded -OH group was observed at 2861 cm⁻¹ in the case of ligand¹⁹. In all

complexes a weak band (OH group) which was there in the ligand in the region 2861cm^{-1} has been disappeared, the absence of this band in all complexes indicate the deprotonation of intra-molecular hydrogen bonded phenolic –OH group upon complexation²⁰. Thus –OH group has coordinated to the metal ion via deprotonation. A broad band appeared in the region $3380\text{-}3551\text{ cm}^{-1}$ in all complexes indicates the presence of coordinated water²⁰. In addition to these bands in the ligand, the band appeared at 1488 cm^{-1} , is assigned to $\nu_{\text{C}=\text{C}}$ stretching of the aromatic ring system. The high intensity band observed in the region 1256 cm^{-1} is due to the phenolic $\nu_{\text{C}-\text{O}}$ vibration^{21,22}.

The assignment of the band to various $\nu_{\text{M}-\text{O}}$ and $\nu_{\text{M}-\text{N}}$ vibrations in the lower frequency region appears to be complicated as the ligand vibrations interfere in this region. The assignments made here are therefore tentative and are based on the previous works. The low frequency skeletal vibrations due to M-O and M-N stretching provide direct evidence for the complexation. In the present study bands $414\text{-}447\text{ cm}^{-1}$ and $455\text{-}561\text{ cm}^{-1}$ respectively have been assigned for $\nu_{\text{M}-\text{O}}$ and $\nu_{\text{M}-\text{N}}$ vibrations respectively^{20,23,24}.

Electronic spectra

The electronic spectra of Cu(II), Ni(II) and Co(II) complexes of the ligand were recorded in DMF solution at 10^{-3} molar concentration. The Cu(II) complex showed three bands at $13503, 18782, 33871\text{ cm}^{-1}$ respectively²⁵. The observed broad band in the case of present Cu(II) complex can be assigned to the envelope of ${}^2\text{B}_{1g} \rightarrow {}^2\text{E}_g$, ${}^2\text{B}_{2g}$ and ${}^2\text{A}_{1g}$ transitions in distorted octahedral geometry of Cu(II)²⁶. In the electronic spectrum of Co(II) complex, the three absorption bands observed at 10482 , 16410 and 19524 cm^{-1} due to the ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{2g}(\text{F})$ (ν_1), ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{A}_{2g}(\text{F})$ (ν_2) and ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{P})$ (ν_3) transitions respectively. These transitions suggest octahedral geometry for the Co(II) complex^{27,28}. The electronic spectra of Ni(II) complex exhibited three bands in the region 10615 , 16628 and 24261 cm^{-1} respectively. These bands are assigned ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{2g}(\text{F})(\nu_1)$, ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ (ν_2) and ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$ (ν_3) transitions respectively. Moreover, the ratio ν_2/ν_1 is in the range $1.566\text{-}1.611$ is indicative of octahedral stereochemistry for the Ni(II) complex^{29,30}.

¹H NMR Spectra

¹H NMR Spectrum of the ligand HL

Ligand showed a signal at δ 12.65 (s, 2H) due to –OH protons at the 2, 2' positions of the quinoline rings. The singlet at δ 9.1 (s, 2H) due to the proton on

the both azomethine groups. The aromatic protons due to quinoline and phenyl rings have resonated in the region δ 6.8 - 8.6 (m, 14H) as a multiplet.

NMR Spectrum of Zn (II) complex

In ¹H NMR spectrum of Zn (II) complex of ligand a singlet at δ 12.65 (s, 2H) due to phenolic –OH protons in the ligand has been disappeared indicating the involvement of phenolic oxygen in the coordination via deprotonation³¹. The azomethine protons appeared at δ 9.1 in the ligand has shown a down field shift of δ 0.15 and appeared at δ 9.25. This indicates coordination of both azomethine nitrogens in the complexation. The aromatic protons have been observed in the region δ 6.8-8.6 (m, 14H) as a multiplet.

When the ¹H NMR spectra of the ligand and complex are compared, it was observed that the signals of the protons of different functionalities of the ligand have been shifted towards the downfield region indicating the coordination of the ligand to the metal ion.

FAB-mass spectral analysis

Mass spectrum of ligand showed a molecular ion peak M^+ appeared at m/z 418, (24.32%) which is equivalent to its molecular weight. The molecular ion by the loss of $\text{C}_{10}\text{H}_6\text{NO}$ species gave a fragment ion peak A_1 at m/z 262 ($\text{M}^+ - \text{C}_{10}\text{H}_6\text{NO} = \text{A}_1$, 46%). The fragment ion A_1 by the loss of $\text{C}_{10}\text{H}_6\text{NO}$ gave another fragment ion A_2 at m/z 106 ($\text{A}_1 - \text{C}_{10}\text{H}_6\text{NO} = \text{A}_2$, 5%) (Scheme 3).

FAB mass spectra of Cu(II) complex

FAB Mass spectrum of Cu(II) complex shows a molecular ion peak M^+ , at m/z 515 that can be attributed to $\{[\text{Cu}(\text{L})].2\text{H}_2\text{O}\}^+$ which is equivalent to the molecular weight of the Cu(II) complex. Molecular ion by the expulsion of two water molecule gave another fragment ion peak A_1 at m/z 479. Fragment ion A_1 by the loss of $[\text{C}_{10}\text{H}_6\text{NO}]^+$ molecule gave another fragment ion peak A_2 , m/z 323. Fragment ion A_2 by the loss of $[\text{C}_{10}\text{H}_6\text{NO}]^+$ species yielded another fragment ion A_3 at m/z 167, which corresponds to the $[\text{Cu}(\text{C}_6\text{H}_4\text{N}_2)]$. This clearly indicates that the Copper complex has the stoichiometry 1:1 (M:L)

Magnetic Susceptibility data

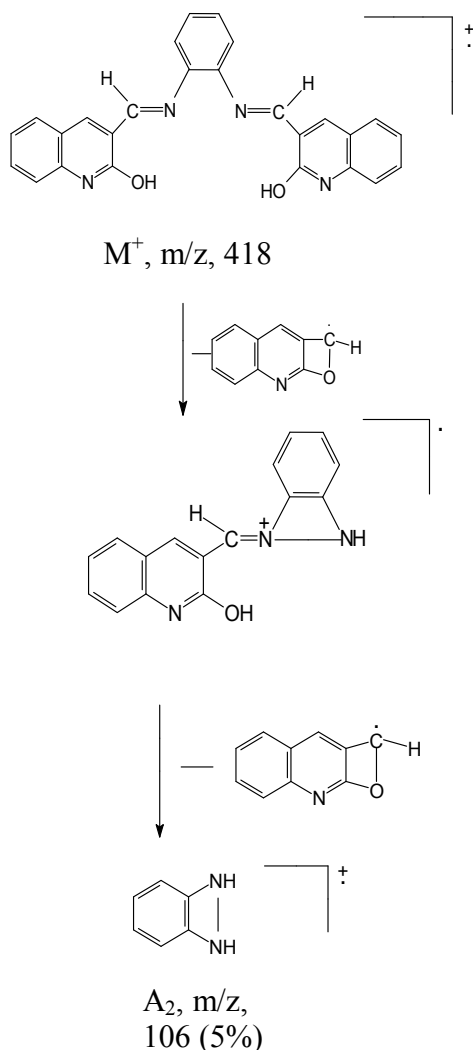
The magnetic susceptibility measurements of the complexes were performed at room temperature (Table 1). In octahedral Co(II) complexes the ground state is ${}^4\text{T}_{1g}$ and a large orbital contribution to the magnetic moment is expected. The mixing of the

singlet states lowers the magnetic moments. The reported magnetic moment values for various Co(II) complexes in the range 4.7-5.2 **B.M.** for octahedral complexes³². In the present investigation the observed magnetic moment value for Co(II) complex is 5.06 **B.M.** which indicates octahedral geometry for these Co(II) complex³². For Ni(II) complex the observed magnetic moment is 2.90 **B.M.** which is well within the

expected range for Ni(II) complexes with octahedral stereochemistry^{32,33}. The present Cu(II) complex has a magnetic moment value is 1.92 **B.M.** Thus the present Cu(II) complex is devoid of any spin interactions with distorted octahedral geometry^{34,35}. The Zn(II) and Cd(II) complexes shows a diamagnetic behaviour having a d^{10} system which is as per expectation.

Table 2. Electronic spectral, magnetic susceptibility and EPR data of the complexes

Complex	Electronic spectral data(cm^{-1})				μ_{eff} (B.M.)	ESR Data			
	ν_1	ν_2	ν_3	ν_4		g_{\parallel}	g_{\perp}	g_{av}	G
[Cu(L)(H ₂ O) ₂]	13503	18782	--	33871	1.92	2.14	2.03	2.07	4.42
[Ni(L)(H ₂ O) ₂]	10615	16628	24261	---	2.90				
Co[(L)(H ₂ O) ₂]	10482	16410	19524	---	5.06				



Scheme-3

Table 3: I.R spectral data (cm⁻¹) of ligand and its complexes.

Ligand/ Complex	H-bonded OH/ H ₂ O	$\nu_{C=N}$	Phenolic ν_{C-O}	$\nu_{C=C}$	ν_{M-O}	ν_{M-N}
Ligand (H ₂ L)	2861w	1671s	1256s	1488	--	--
[Cu(L)(H ₂ O) ₂]	3404b	1649s	1284s	1520	437	471
[Ni(L)(H ₂ O) ₂]	3410b	1615s	1328s	1511	428	469
Co[(L)(H ₂ O) ₂]	3551b	1653s	1310s	1512	425	465
[Zn(L)(H ₂ O) ₂]	3380b	1651s	1283s	1509	414	470
[Cd(L)(H ₂ O) ₂]	3443b	1652s	1282s	1511	415	513

EPR spectrum

The X-band EPR spectrum of the powder Cu(II) complex was recorded at room temperature using DPPH as a reference standard. One unpaired electron in Cu(II) complex with ²B_{1g} as ground state lies in d_{x²-y²} orbital and follows the trend g_{||} > g_⊥ > g_e (g_e=2.0036-free ion value). The observed g_{||}= 2.14 and g_⊥ = 2.03 values of the Cu(II) complex under the present study followed the same trend g_{||} > g_⊥ > g_e which suggest that the presence of unpaired electron in d_{x²-y²} orbital giving octahedral geometry³⁶. The observed , G = 4.67 for the complex under present study evidenced the monomeric nature of the

complex³⁷. This fact is in agreement with its electronic spectral data for octahedral geometry.

In vitro Antimicrobial Study

A cup plate method was employed for the *in vitro* study of antibacterial and antifungal effect against, *Staphylococcus aureus*, *E. coli*, *C. albicans* and *A. niger*. The inhibitory effect of ligand and its complexes against these organisms are given in table 4. The antimicrobial screening data show that the metal chelates exhibit a higher inhibitory effect than the free ligand. The increased activity of the metal chelates can be explained based on the chelation theory^{38,39}.

Table 4: Antibacterial activity and Antifungal activity of Ligand and its complexes

Ligand/ Complex	Zone of inhibition in (mm)			
	<i>S. aureas</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. niger</i>
Ligand (H ₂ L)	14	15	12	13
[Cu(L)(H ₂ O) ₂]	16	17	17	21
[Ni(L)(H ₂ O) ₂]	15	17	15	15
Co[(L)(H ₂ O) ₂]	18	19	16	18
[Zn(L)(H ₂ O) ₂]	16	21	15	16
[Cd(L)(H ₂ O) ₂]	21	23	16	19

Table: 5. Anti-inflammatory activity of Ligand and its complexes.

Ligand/ Complexes	Difference in paw volume After 3 hrs \pm S.E.M	% Inhibition
Ligand	0.67 \pm 0.04	40.17
[Cu(L)(H ₂ O) ₂]	0.33 \pm 0.02	70.53
[Ni(L)(H ₂ O) ₂]	0.46 \pm 0.03	58.92
Co[(L)(H ₂ O) ₂]	0.56 \pm 0.03	50.00
[Zn(L)(H ₂ O) ₂]	0.43 \pm 0.03	61.60
Control:2% Aqueous gum acacia (0.2ml)	32.00 \pm 2.76	-
Standard: Diclofenac Sodium 100mg/kg	6.38 \pm 0.98	80.06

In vivo Anti-inflammatory Study

Acute inflammatory model carrageenan induced rat hind paw edema. (Method of Winter *et al.*⁴⁰)

Inflammation is a normal, essential, protective response to any noxious stimulus that may threaten the whole organism. Rheumatic diseases are inflammatory conditions causing major disability.

The rats were divided into groups of six animals. One group consisting of six animals served as control, while the other groups of animals received the test compounds or standard drug. The rats were dosed (100mg/kg) orally with the test compound one-hour before injection of 0.05ml of 1% suspension of carrageenan into the sub plantar region of the rat hind paw. Additional groups were similarly treated with 100mg/kg 2% aqueous gum acacia (vehicle controls). The volume of the injected paw was measured by water displacement in a plethysmograph in (Fig 1 and 2) immediately after carrageenan injection and again after 3 hours. A mark was made at the lateral molecules and the foot was dipped to the same distance in to the arm of the plethysmograph.

Average edema volumes for test compound-treated and positive control rats were compared statistically with those of the vehicle treated control animals and expressed as the percent edema inhibition, (Table-5) which was calculated using the formula.

Percent edema inhibition = $100(1-V_t/V_c)$

Where, V_c = Volume of the edema in the control group

V_t = Volume of the edema in the treated group.

All the synthesized Ligand and its complexes showed good anti-inflammatory activity. The anti-inflammatory activity data shows that the metal chelates showed significant anti-inflammatory activity than the free ligand when compared with that of standard diclofenac. The increased activity of the metal chelates can be explained based on the chelation theory^{38,39}. The literature shows that the compounds having methoxy, nitro, hydroxyl groups possess significant anti inflammatory activity, when compared to other groups. The synthesized ligand possess OH group in its structure. So the anti inflammatory activity may be due to the presence of the respective functional groups as evidence in literature.

Conclusions

The present study revealed octahedral geometry for the Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes, respectively. The ligand acts in a tetradentate manner coordinating through two nitrogens of the azomethine groups and two of hydroxyl group in an O N N O fashion. Moreover, the antimicrobial activity and anti-inflammatory activity data revealed that the complexes were superior to the free ligand. It is proposed that concentration plays a vital role in increasing the degree of inhibition the activity increased with increasing concentration of the complexes. All the complexes isolated possess 1:1 (M:L) in stoichiometry. On the basis of elemental analysis, electronic spectra, magnetic susceptibility, IR, NMR, ESR and FAB Mass spectral data the following tentative structure can be assigned for the present complexes. (Fig 2).

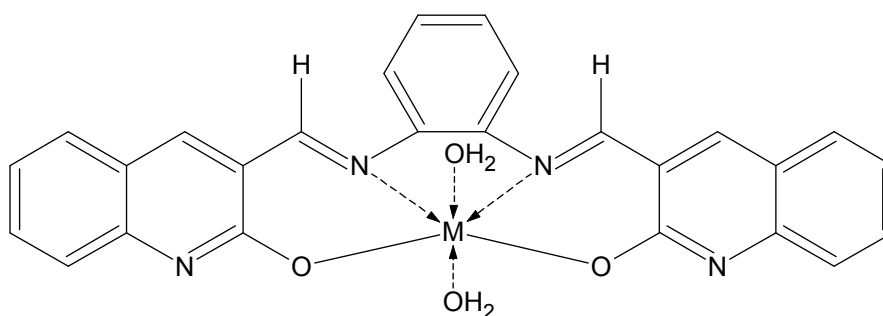


Fig 2. Suggested geometries of the complexes, where M=Cu(II), Ni(II), Co(II), Zn(II) and Cd(II)

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