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SYNTHESIS, CHARACTERIZATION, DNA BINDING AND ANTIMICROBIAL ACTIVITY OF TRIDENTATE SCHIFF BASE LIGAND AND ITS COBALT(II) COMPLEXES

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ABSTRACT

New unsymmetrical tridentate Schiff base ligands and Cobalt(II) complexes were synthesized using 2-amino-3-hydroxypyridine, 2-aminophenol and 2-hydroxy-1-naphthaldehyde. The synthesized ligands and their Cobalt(II) complexes were characterized by using FT-IR, ^{1}H NMR,^{13}C NMR and UV-vis spectroscopic techniques. The infrared and electronic transition studies showed that the ligands are tridentate via the imine nitrogen and the phenolic oxygen atoms in a planar configuration. Binding interactions of the complexes with calf thymus DNA have been investigated by absorption spectrophotometer. The complexes were screened for their antibacterial and antifungal activity by disc diffusion method. The results of these studies showed that the metal complexes are more effective against selected antibacterial and antifungal pathogens as compared with Cobaltous chloride.

KEYWORDS: Schiff base, Cobalt(II), Antibacterial activity, DNA Binding.

INTRODUCTION

Schiff bases derived from the condensation of amines with aldehyde / ketone are multifunctional macrocyclic ligands.[1] A large number of Schiff bases and their complexes have been investigated for their interesting and important properties.[2] Pyridine ligands, which have been used in the coordination chemistry of a multiplicity of metals,[3-7] absorb a single position in the synthesis of biologically active compounds. Recent years a great arrangement of interest in the synthesis and characterization of Schiff bases involving a

pyridine ring has been witnessed mainly due to their structural relationship to compounds participating in pyridoxal phosphate chemistry.[8]

Cobalt is an essential trace element in humans, exhibiting many useful biological functions. Numerous compounds, naturally occurring and man-made, contain the cobalt at two common oxidation states Co(II) and Co(III). There is growing interest in investigating cobalt and other transition metal complexes for their interaction with DNA.[9-13] Cobalt is an element of biological interest and its role is mainly focused on its presence in the active center of vitamin B12, which regulates indirectly the synthesis of DNA.[14] Especially, lots of work has been done on the DNA binding of metal complexes with polypyridyl ligands.[15-17] Last few decades, transition metal complexes have largely been employed for these purposes, not only because of their versatile electronic and structural features, but also due to the fact that the DNA binding and cleavage ability of metal complexes can be tuned by changing the coordination environment.[18,19] Therefore, the design of new metal-based anticancer drugs that exhibit enhanced selectivity and various non-covalent DNA binding interaction modes, e.g. intercalation, groove binding and external electrostatic binding, are of considerable significance.

Complexes of Schiff bases showed promising applications in biological activity and biological modeling applications. Schiff bases are important class of compounds in medicinal and pharmaceutical fields. They show biological applications including antibacterial, antifungal, and antitumor activity.[20]

EXPERIMENTAL

MATERIALS AND METHODS

General chemicals such as methanol, ethanol, anhydrous diethyl ether, n-hexane and $CoCl_2.6H_2O$ were of the analytical reagent (AR) grade. They included 2-amino-3-hydroxypyridine, 2-aminophenol, and 2-hydroxy-1-naphthaldehyde were commercially obtained from Merck and Aldrich. Plasmid pBR322DNA was purchased from Bangalore Genie (India). Spectrograde solvents were used for spectral measurements.

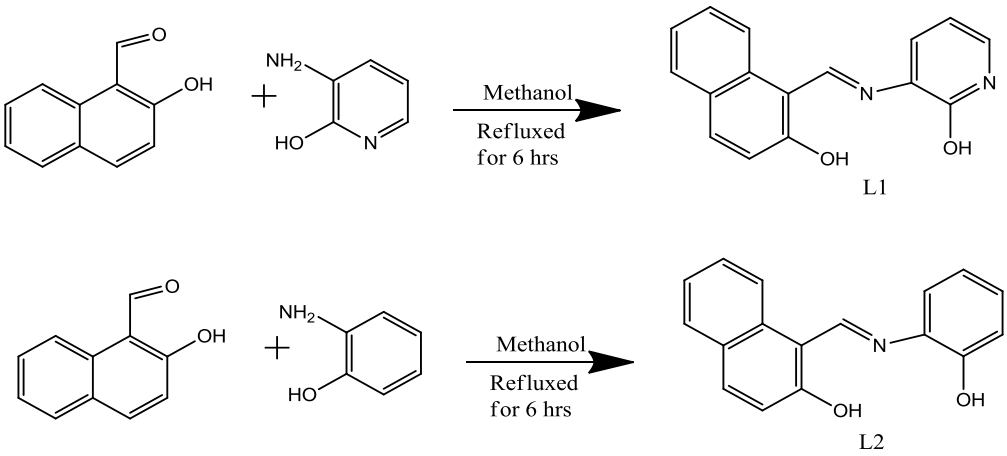
Physical Measurements

The UV-vis spectra of the complexes were recorded on a Shimadzu UV-2450 spectrophotometer. FT-IR spectra were recorded on a Perkin Elmer spectrometer using KBr

pellets (4000-400cm-^{1}), ^{1}H NMR and ^{13}C NMR spectra were obtained at room temperature in DMSO-d_6 using a Bruker 400 MHz spectrometer and TMS as an internal standard.

Synthesis of the tridentate Schiff base ligands (L1 and L2)

The Schiff base ligands (L1 & L2) were synthesized by the reaction between 2-hydroxy-1-naphthaldehyde (0.0344g, 0.2mmol) in methanol (10ml) and 2-amino-3-hydroxypyridine / 2-aminophenol (0.0218g, 0.2mmol) in methanol (10ml) (Scheme - 1). The reaction mixture was refluxed on a water bath for 6h. After reducing the volume of the solution one third, the flask was kept back at ambient temperature for 5h. On cooling, the yellowish-brown(L1) and yellow(L2) Schiff-base ligands were collected by filtration, washed twice with the distilled water, The solid ligands were then dried in a desiccator over anhydrous calcium chloride. Finally, the ligands were recrystallized from ethanol.



Scheme 1: Synthesis of Schiff base ligands L1 & L2.

Ligand L1: $C_{16}H_{12}N_2O_2$. FT-IR (KBr, cm^{-1}): 3375(υO-H), 3063(υC-H),1609(υC=N), 1573, 1491 (υC =C), 1343(υC-O).^{1}H NMR(400MHz, DMSO-d_6 δ, ppm):10.92 (OH), 9.72 (HC=N), 7.15-7.99(ArH), 6.73(H_{Pyr}). ^{13}C NMR (400MHZ, DMSO-d_6 δ, ppm): 145.34 (Ar-OH), 181.09 (Ar-N=C), 129.33, 128.83, 126.08, 123.17, 121.91, 119.O6 (Ar-C), 139.69 (C-N).UV-vis (υ_{max}, nm, methanol): 225nm, 269nm.

Ligand L2: $C_{17}H_{13}NO_2$. FT-IR (KBr, cm-^{1}): 3307(υO-H), 3023(υC-H), 1607(υC=N), 1583, 1417 (υC=C), 1339(υC-O). ^{1}H NMR (400MHZ, DMSO-d_6 δ, ppm): 10.34 (OH), 9.51(HC=N), 7.01-7.99(ArH).^{13}CNMR(400MHZ,DMSO-d_6δ,ppm)149.41(Ar-OH), 177.61(Ar-N=C), 128.98, 128.58,126.74,125.09,123.02,119.82,117.57(Ar-C),137.92(C-N).UV-vis(υ_{max}, nm, methanol): 271nm, 296nm.

Synthesis of metal complexes

The Schiff base complex 1 was prepared by mixing hot saturated ethanolic solution of the Schiff base ligand(L1) (0.0528g, 0.2mmol) and aqueous solution of $CoCl_2.6H_2O$ (0.0237g,0.1mmol) with the molar ratio of 2:1 (2L1:1M). The mixture was stirred for 4 h at 60°C. The resulting complex was filtered and washed several times with hot water until the filtrates become clear. The solid complex was then dried in a desiccator over anhydrous calcium chloride. The Schiff base complex 2 was prepared by similar manner.

Complex1: 66%, $C_{32}H_{20}CON_4O_4$. FT-IR (KBr, cm^{-1}): 3047(υC-H), 1616(υC=N), 1525, 1471(υC=C), 1323(υC-O), 561(υCo-O) 476 (Co-N). ^{1}H NMR (400MHZ, DMSO d_6 δ, ppm): 9.71(HC=N) 6.56-7.62 (ArH), 6.41(H_{Pyr}). ^{13}C NMR (400MHZ, DMSO-d_6 δ, ppm): 134.68 (ArN=C), 128.79, 127.94, 125.98, 122.48, 119.59 (Ar-C), 181.09 (C-N). UV-vis ($υ_{max}$, nm, methanol): 225nm, 269nm, 606nm.

Complex2: 61%, $C_{34}H_{22}CON_2O_4$. FT-IR (KBr,cm^{-1}): 3018 (υC-H), 1606 (υC=N), 1573, 1401 (υC=C), 1288 (υC-O), 503 (υCo-O), 437 (υCo-N). ^{1}H NMR (400MHZ, DMSO-d_6 δ, ppm): 8.48 (HC=N) 6.52-7.62 (ArH). ^{13}C NMR (400MHZ, DMSO-d_6, δ, ppm): 134.92 (Ar-N=C), 128.46, 127.13, 125.61, 121.14, 117.70 (Ar-C), 168.86 (C-N). UV-vis ($υ_{max}$, nm, methanol): 271nm, 296nm, 618nm.

RESULTS AND DISCUSSION

Characterization of Ligands and complexes

Infrared spectra

In FT-IR spectra the O-H stretching frequency of the ligands were observed in 3375and 3307cm^{-1}. For the complexes disappearance of this band is estimated due to phenolic OH group are coordinated to central metal of cobalt. The sharp band of an imines at1609 and 1607 υ(C=N) cm^{-1} which was shifted to1616 and 1606 cm^{-1} in the complexes.[21,22] The ring skeletal vibrations υ(C=C) are in region of 1400-1600 cm^{-1}.[23] The medium intensity bands at 476, 437 cm^{-1} and 561, 503 cm^{-1} were attributed to υ(Co-N) and υ(Co-O) respectively (Figure 1 & 2).

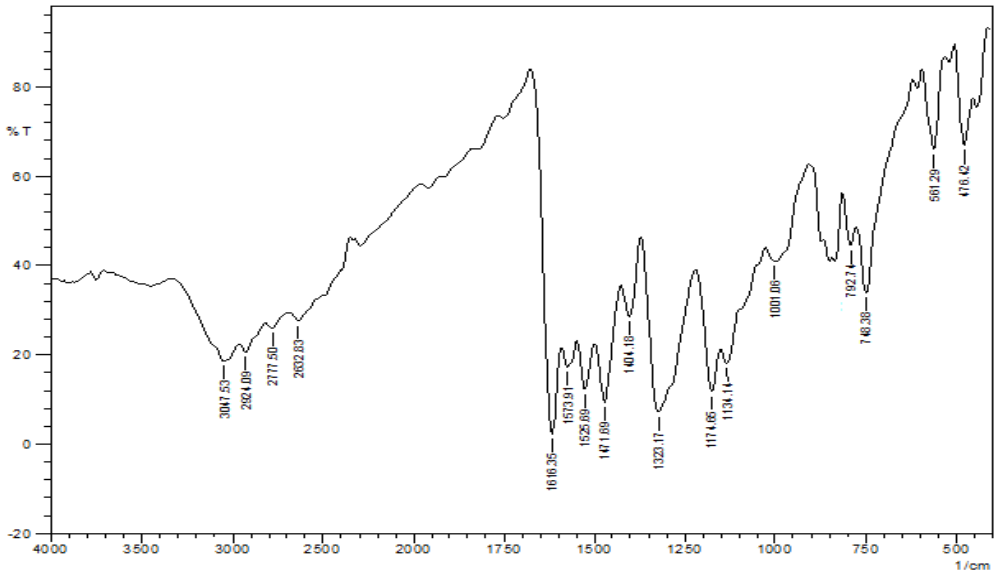


Figure 1: FT-IR spectrum of complex 1.

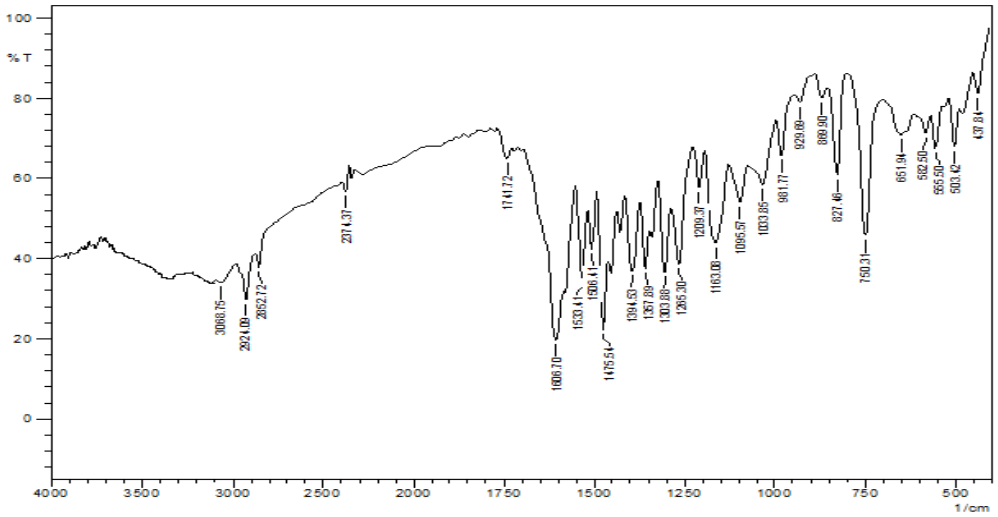


Figure 2: FT-IR spectrum of complex 2.

^{1}H and ^{13}C NMR spectral studies

The ^{1}H NMR spectra of the Schiff base ligands L1, L2 and complexes C1,C2 were recorded in DMSO-d_6 solvent. ^{1}H NMR spectrum of ligand exhibited azomethine proton (HC=N) signal at 9.72 ppm and 9.51 ppm was shifted to 9.71 ppm and 8.42 ppm in complexes C1 and C2 respectively, this shifted was indicating of coordination through azomethine nitrogen. The signal of OH proton in the ligand exhibited at 10.92 ppm and 10.34 ppm was disappearance in complexes supporting the coordination of phenolic group to metal center *via* deprotonation. The multiplets at 6.56-7.62ppm have been assigned to the aromatic ring protons in the complexes (Figure 3, 4 & 5).

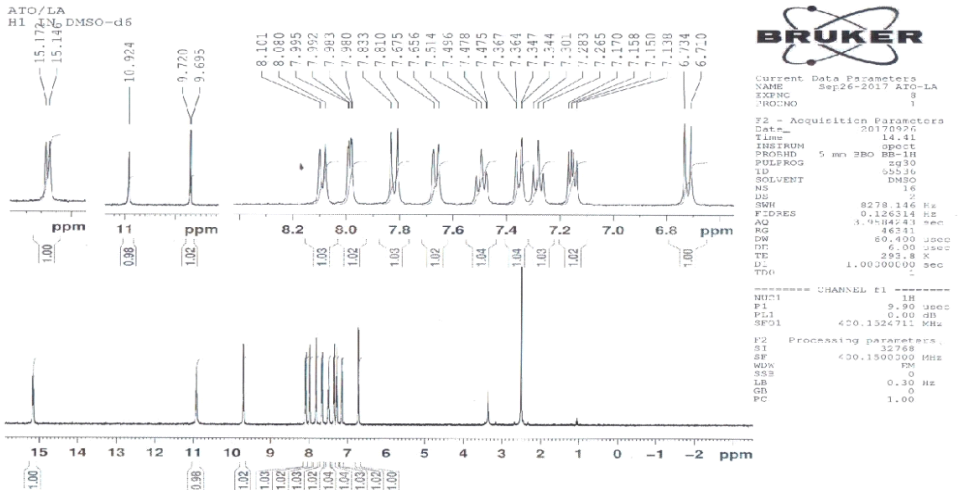


Figure 3: ^{1}H NMR spectrum of the ligand 1.

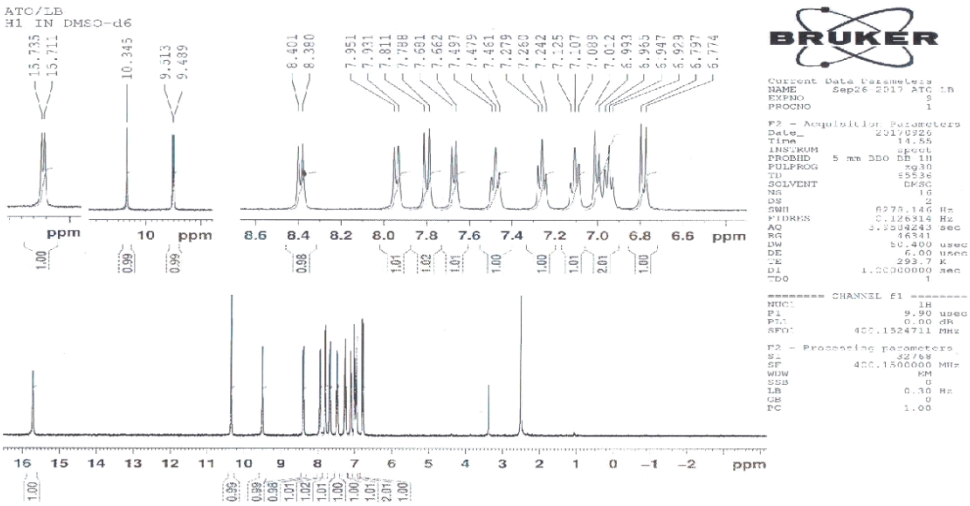


Figure 4: ^{1}H NMR spectrum of the ligand 2.

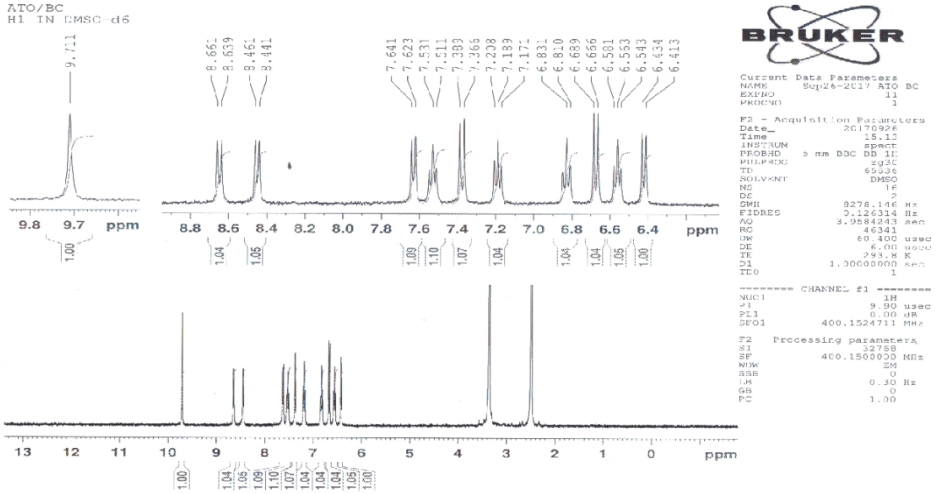


Figure 5: ^{1}H NMR of the Complex 1.

The ^{13}C NMR spectrum of the Schiff base ligands L1 and L2 exhibited signals at181.09 and 177.6 (HC=N), 139.69 and 137.92 (C-N), 129.33-119.06 and 128.98-117.57 (Ar-C). However, the ^{13}C NMR spectra of complexes C1 and C2 exhibited resonance at 168.86 and 165.31 and 164.01 (HC=N), 134.92 and 131.76 (C-N), 128.46-112.57 and 127.31-115.53 (Ar-C) respectively (Figure 6).

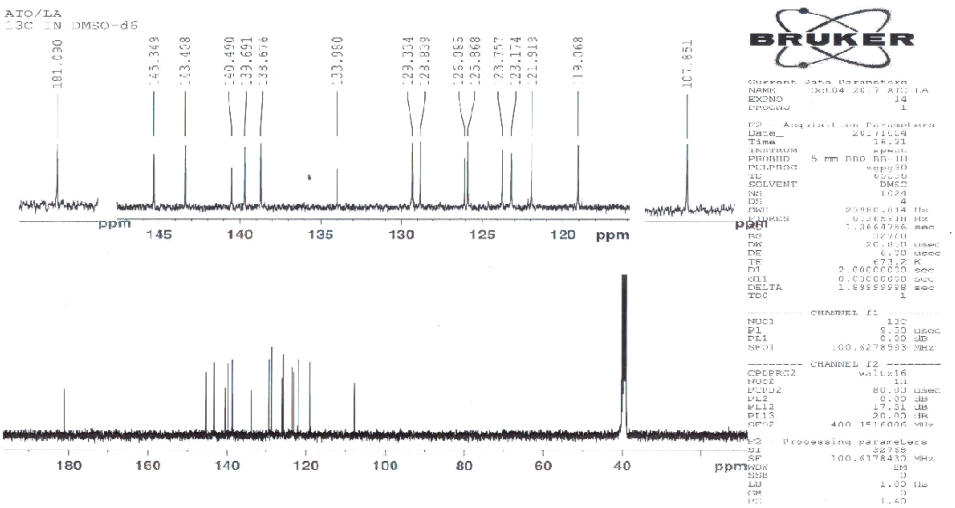


Figure 6: ^{13}NMR spectra of ligand 1.

Electronic Spectra

The Electronic Spectrum of the ligands L1, L2 and complexes C1, C2 were recorded in methanol solvent. The spectrum of the free Schiff base ligand1 gave two bands at 272 (L1), 285 (L2) and 342 (L1), 349 (L2) nm, which can be attributed to π→π* (benzene ring), π–π* (C=N group) respectively.[24] The complex1display a d-d band at 606(C2), 618(C2)nm in addition to the ligand centered bands in the UV region (Figure 7 & 8). Based on the spectral evidences the structure of the complexes may be given in Figure 9.

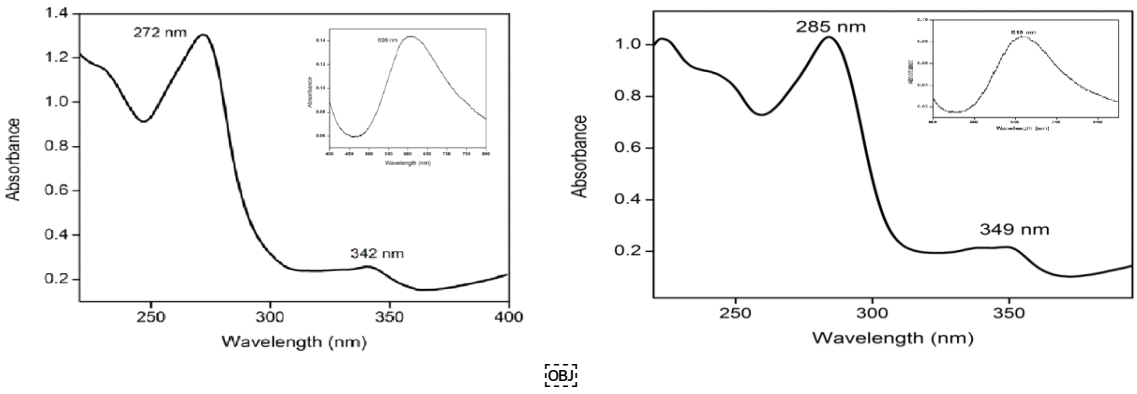
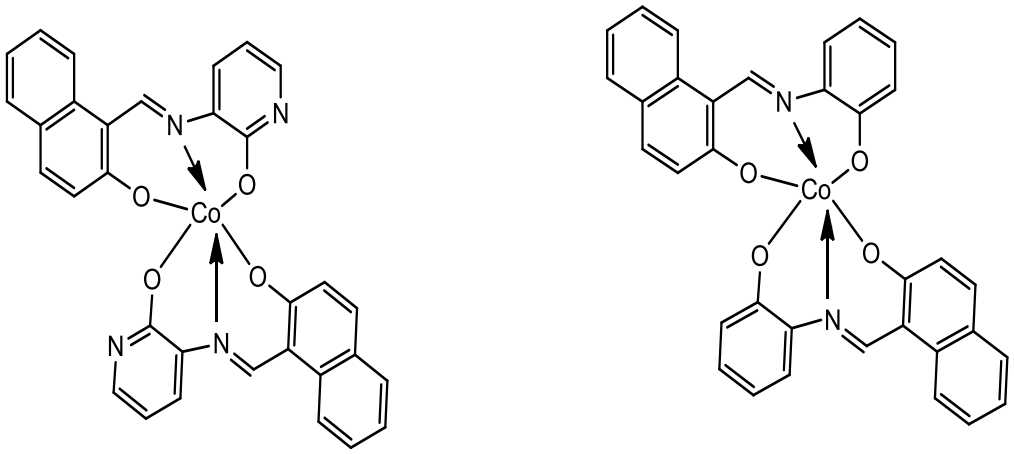


Figure 7 & 8 Electronic Spectra of the ligands and complexes 1 and 2.



Complex1 (C1) **Complex2 (C2)**

Figure 9 Structure of the complexes.

DNA binding studies

Electronic Absorption Spectral Study

The absorption titration experiment was carried out to investigate the binding affinity of the cobalt complexes with CT DNA helix. The complexes bound to DNA during intercalation is characterized by the modification in absorbance due to a strong stacking interaction between the aromatic chromophore and the DNA base pairs.[25-27] The absorption spectra of the complexes in the absence and presence of calf thymus DNA are shown in (Figure 10 & 11). In the UV region, the cobalt complexes exhibit two intense absorption bands of the complex1 272,342 nm and complex 2 285,349 nm, which is assigned to the intraligand (π-π*) transitions of the aromatic chromophore. With decreasing CT DNA, the absorption bands of the complexes were affected. The absorption spectra indicate that, upon addition of DNA to complex. The binding constant K_b of complex 1and 2 8.010 $X10^3$ M^{-1} and 7.110 $X10^3$ M^{-1}, was determined from the plot of DNA]/(εa − εf) vs. [DNA] Using the absorption at 273 nm.

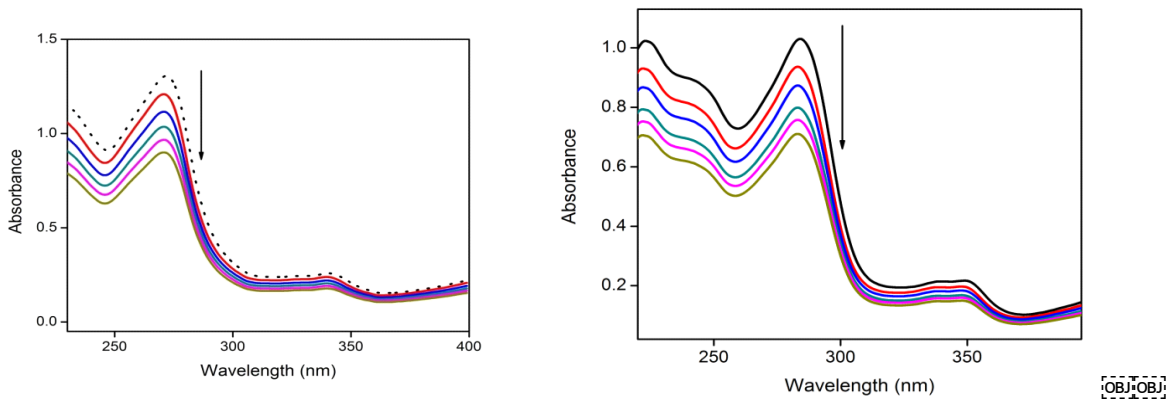


Figure 10 & 11 DNA binding study.

Antimicrobial activity

The in vitro antibacterial and antifungal activity tests were performed through the well diffusion method[28] using Ciproflaxacin as control for bacteria, Amphotericin for the fungi, respectively. The bacterial organisms used are Gram(+) bacteria *Enterococcus faecalis* and *Staphylococcus aureus*, Gram(-) bacteria, *Escherichia coli* and fungi *Aspergillus fumicatus*, *Mucor sps*. Stocksolution (0.001 mol) was prepared by dissolving the compounds in DMSO. The diameter of the inhibition zones was measured in millimeters.[29] The results of these studies showed that the metal complexes are more effective antibacterial and antifungal agents as compared with Cobaltous chloride (Table 1).

Table 1: Antimicrobial activity of cobalt(II) complexes.

S.No	Micro Organisms	Complex 1	Complex 2	Cobaltous chloride	Ciproflaxacin
		Zone of Inhibition (mm)			
Bacteria					
1	*Escherichia coli*	19	20	15	26
2	*Enterococcus faecalis*	27	22	19	29
3	*Staphylococcus aureus*	22	24	20	28
Fungi					
S.No	**Micro Organisms**	**Complex 1**	**Complex 2**	**Cobaltous chloride**	**Amphotericin-B**
		Zone of Inhibition (mm)			
5	*Aspergillus fumicatus*	20	18	16	20
6	*Mucor sps*	22	20	14	22

CONCLUSION

In this present work, two new unsymmetrical tridentate Schiff base ligands and their cobalt(II) complexes were synthesized and characterized by using FT-IR, ^{1}H NMR,^{13}C NMR and UV-vis spectroscopic techniques. The infrared and electronic transition studies showed that the tridentate ligands are coordinated to cobalt complexes, coordinating via the imine nitrogen and the phenolic oxygen atoms in a planar configuration. Binding interactions of the complexes with calf thymus DNA have been investigated by absorption spectrophotometer, the binding constant shows that the DNA-binding affinity of complex1 is more than the complexs2. The results of the antimicrobial studies showed that the metal complexes are good results as compared with Cobaltous chloride.

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