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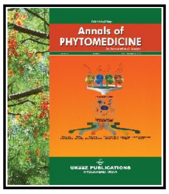

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Synthesis, characterization and *in vitro* antimicrobial activities of p-chlorobenzylidene-o-aminophenol metal complexes

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Abstract

The Schiff bases ligand, p-chlorobenzylidene-o-aminophenol (CBAP) were synthesized by the condensation reaction of 2-aminophenol with p-chlorobenzaldehyde and its transition metal complexes with Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) were also formed. The characterization of the compounds was carried out by elemental analyses, Molar conductance, FT-IR, UV-Visible, 1H-NMR, 13C-NMR spectral studies. The data from spectral studies revealed that the Schiff base (CBAP) act as a neutral bidentate ligand. The complexes were screened out for antibacterial activities against *Xanthomonas* sp. and *Staphylococcus aureus* VTCC BAA20. Antifungal activity against *Fusarium oxysporum* f. sp. *lycopersici* and *Candida albicans* was also carried out by using agar well diffusion method. It is concluded that all the metal complexes were more potent than the parent ligand.

1. Introduction

First of all, Schiff Bases were discovered by Hugo Schiff in 1864 by the reaction of primary amines (RNH$_2$) with aldehydes (Schiff, 1869). Schiff base was synthesized by the condensation reaction of a primary amines with carbonyl compound which are replaced by the azomethine (–HCN–) functional group (Hemmert *et al*., 2001). The class of chelating ligands which consists N, O, and S donor atoms showed wide variety of biological activities. Due to the coordination of metal ions with various Schiff bases, different studies were demonstrated, leads to improvement in antimicrobial potential (Emami *et al*., 2007). In the last decades, transition metal complexes were widely used in the cure of different disease conditions, but the lack of accurate knowledge between the toxic and therapeutic doses minimal their uses. Over the years, the demand for transition metal complexes for the treatment of cancer diseases has been increased. A broad range of transition metal complexes were synthesized due to changes in the chemical structures and exchange of the ligand molecule, some of them confirmed with improved cancer profile (Kashyap *et al*., 2018). Due to the nitrogen and oxygen donor atoms, Schiff base ligands act as a good chelating agent for the non-transition and transition metal ions (Boraseet *al*., 2021). The main benefits of Schiff base metal complexes are due to transition metal ions, as they have diverse applications in industrial and pharmaceutical areas(Nair *et al*., 2016). The included metals in the matrix of donor atoms of Schiff base changes the pharmacological, morphological and physiological activities of the compounds (Chaudhary and Mishra, 2017).

Some of the Schiff base complexes consisting N and O donor atoms act as catalysts for reduction (Aoyama *et al*., 1986), oxidation (Beyazit *et al*., 2017), biocidal activity (Sengupta *et al*., 2001) and hydrolysis (Kilinc and Sahin, 2019). Schiff base is important and widespread ligand because of their synthetic flexibility, moderate electron-donor, chelated structure and structural resemblances with natural biomolecules (Vamsikrishna *et al*., 2020). Transition metal complexes contain a significant class of compounds and play a crucial role in the area of biological activity due to characteristic electrochemical or photochemical properties and well-defined coordination geometries that enhance their functionalities as DNA binding agents with their natural affinity to interact with DNA (Maiti *et al*., 2020).

There has been considerable increase in the aspire towards the discovery of safe and effective therapeutic agents for the new drug designing due to the studies of Schiff bases and its complexes having a broad spectrum of biological (Chandrasekar *et al*., 2021) and pharmaceutical activities as antifungal (Devi *et al*., 2007; Abdallah *et al*., 2009), antioxidant (Ding *et al*., 2014), antibacterial (Abou-Melha, 2008; El-Sherif *et al*., 2012) and antitumor agents (Costes *et al*., 2008). These activities are described to involve pharmacological applications like antimicrobial (Abdel-Rahman *et al*., 2013), antibacterial (Prashanthi *et al*., 2007), antifungal (Mezey *et al*., 2016), antimalarial (Mishra and Gautam, 2004), anticorrosion (Nwankwo *et al*., 2016), antidiabetic (Miyazaki *et al*., 2016), antiulcer (Ibrahim *et al*., 2012), antifeedant (Huang *et al*., 1988), anti-inflammatory (Rakesh *et al*., 2015), anticancer (Shokohi-Pour *et al*., 2016),

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antitubercular (Budhani *et al*., 2010), antiviral (Reddy *et al*., 2011), anti-proliferative (Buldurun *et al*., 2019), anticonvulsant (Pandeya and Rajput, 2012), anti-HIV (Munawar *et al*., 2018), antiparasitic (Saadeh *et al*., 2012), antiprotozoal (Hossain and Zakaria, 2017) and analgesic properties (Piscitelli *et al*., 2010). Due to the significant attention bring out by *p*-chlorobenzaldehyde and their complexes as a tool for studies of pharmacological constituents with respect to biological activity (Iorungwa *et al*., 2019). The aim of this paper is to discuss the synthesis, characterization and biological activities of selected Schiff base and its transition metal complexes.

2. Materials and Methods

2.1 Synthesis of Schiff base and its complexes

The chemicals and reagents were purchased from Merck, HiMedia and CDH of analytical grade (AR) which was used in the experiments with high purity, without any additional processing.

Schiff base ligand was synthesized by the condensation of *p*-chlorobenzaldehyde (10 mmol, 1.40 gm) with 2-aminophenol (10 mmol, 1.09 gm) and its co-ordination behaviour with different metal complexes were studied. The mixture of reaction which consists the saturated methanolic solution (10 ml) of Schiff base *p*-chlorobenzylidene-*o*-aminophenol (2 mmol, 0.462 gm) and methanolic solution of metal salt of halides (2 mmol) were refluxed for 2 h at room temperature (25°C) (Pahontu, 2017) (Figure 1).The yield of the compound was 70-85%.

2.2 Characterization of Schiff base and its compounds

The structures of these complexes were determined by elemental analyses, Molar conductance, FT-IR, UV-Visible, ^{1}H NMR ^{13}C NMR. Infrared spectra were recorded in KBr pellets in the region of 4000-400 cm^{-1} on Nicolet iS50 FTIR spectrometer. The solution was prepared in ethanol to obtain the UV-Visible spectra of complexes in the range of 200-800 nm which was recorded by using Model SHIMADZU (UV 3600 PLUS) UV-Visible spectrophotometer. Proton and carbon magnetic resonance spectra of Schiff base and its metal complexes were recorded in DMSO using TMS as an internal reference on a FT-NMR cryo-magnet spectrometer 400 MHz (Bruker) NMR spectrometer. The Schiff base and its metal complexes were also tested for their antimicrobial activities.

3. Results

The synthesized compounds were crystalline solids having different colors. The ligand and their metal complexes are insoluble in water and generally soluble in common polar organic solvents such as chloroform, DMSO, DMF, methanol and ethanol (Ali and Bose, 1977). They are usually non-hygroscopic and also stable at room temperature.

3.1 Elemental analyses

Element analysis like nitrogen, hydrogen and carbon of synthesized Schiff base ligands and its metal complexes were carried outon FLASH 2000 CHN elemental analyser by the Volhard's method (Vogel, 1975) (Table 1).

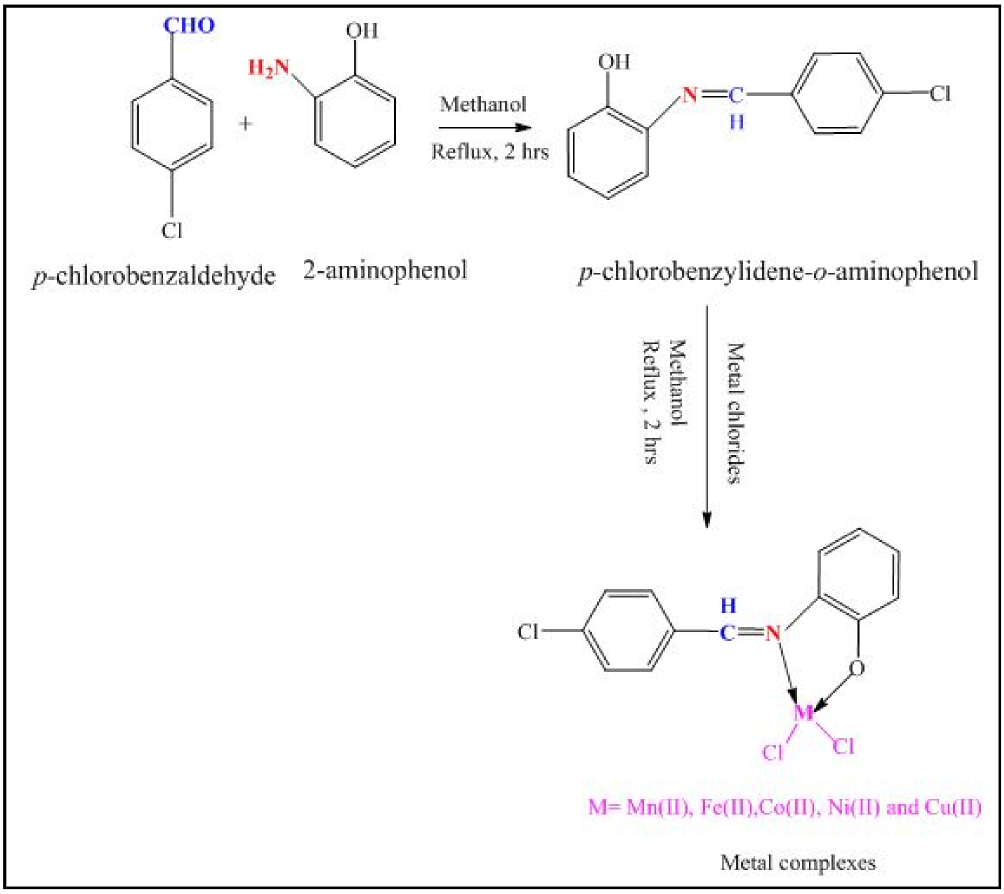

Figure 1: Synthesis of Schiff base and its metal complexes.

Table 1: Physical, analytical data and molar conductance for CBAP and its metal complexes

S. No.	Compound	Empirical formula (Formula Weight)	M. pt. (°C)	Color	Yield (%)	Calculated (Found) (%)			*Molar conductance (Λ_m) S cm² mol⁻¹
						C	H	N	
2	CBAP	$C_{15}H_{16}ClNO$ (261.09)	102-103	Pale yellow	81	68.83 (68.69)	6.16 (6.02)	5.35 (5.21)	-
2a	$[Mn(CBAP)Cl_2]$	$C_{15}H_{15}Cl_3MnNO$ (384.96)	175-178	Dark brown	85	46.60 (46.51)	3.91 (3.76)	3.62 (3.50)	21.32
2b	$[Fe(CBAP)Cl_2]$	$C_{15}H_{15}Cl_3FeNO$ (385.96)	182-184	Light brown	80	46.50 (46.39)	3.90 (3.74)	3.61 (3.53)	32.73
2c	$[Co(CBAP)Cl_2]$	$C_{15}H_{15}Cl_3CoNO$ (388.96)	163-165	Brown	85	46.13 (45.89)	3.87 (3.71)	3.59 (3.44)	34.33
2d	$[Ni(CBAP)Cl_2]$	$C_{15}H_{15}Cl_3NiNO$ (387.96)	194-196	Black	70	46.16 (46.02)	3.87 (3.69)	3.59 (3.43)	17.63
2e	$[Cu(CBAP)Cl_2]$	$C_{15}H_{15}Cl_3CuNO$ (392.95)	186-188	Brown	80	45.59 (45.48)	3.83 (3.75)	3.54 (3.39)	19.02

*The results of molar conductance are in the range of (17-35) S cm² mol⁻¹, telling that the compounds are non-electrolyte, it also shows that chlorides ions are present inside the coordination sphere (Geary, 1971; Greenwood, 1968) in Table 1.

3.2 Conductance studies

Molar conductance of all the metal complexes (2a-2e) were carried out in DMSO at ca. 1× 10^{-3}M at 25°C by using digital conductivity meter (Model Eutech CON 700). All the data of molar conductance (Λ_m) values for the complexes are compiled in Table 1. Molar conductance of all the complexes shows low values (17-35 S cm² mol⁻¹) telling that they are non-electrolytic in nature (Chohan *et al.*, 2001).

3.3 IR spectra

The IR spectrum (Figure 2) of the free ligand (CBAP) showed characteristic bands at 1628 cm⁻¹ due to ν(C=N), respectively. Another stretching frequency in free ligand due to phenolic group ν(C-OH) is observed at 2983 cm⁻¹ and the absence of these spectral bands in all metal complexes indicated the bond formation between phenolic-oxygen to metal ions. In the spectra of the complexes, the presence of bands in the region of 768-779 cm⁻¹ were due to ν(M–O) stretching vibration which was absent in the spectra of free ligand. In the spectra of the complexes, the azomethine band at 1628 cm⁻¹ shifts to lower frequencies ranging to 1605-1617 cm⁻¹ due to coordination of azomethine nitrogen atom to the metal ion. In the IR spectra of these complexes, the new bands is observed in the region of 627-632 cm⁻¹ because of the ν (M-N) vibration, but these bands are not observed in the spectra of free ligand which indicates that there is no complexations (Table 2) (Safia, 2017).

Table 2: IR data (cm⁻¹) for CBAP and its metal complexes

S. No.	Compound	ν(C-OH)	ν(C=N)	ν(M-N)	ν(M-O)
2	CBAP	2983	1628	-	-
2a	$[Mn(CBAP)Cl_2]$	-	1605	632	776
2b	$[Fe(CBAP)Cl_2]$	-	1617	630	773
2c	$[Co(CBAP)Cl_2]$	-	1606	629	768
2d	$[Ni(CBAP)Cl_2]$	-	1610	628	778
2e	$[Cu(CBAP)Cl_2]$	-	1606	627	779

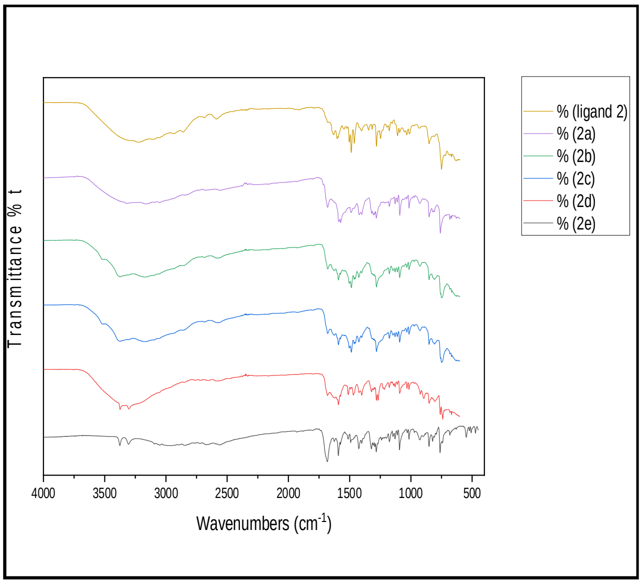

Figure 2: IR spectra of CBAP and its complexes.

3.4 UV-Visible spectra

In the spectra (Figure 3) of the free ligand, CBAP shows band at of 225 nm which is attributed to π-π* transition of the benzene ring of the ligand, where this band is slightly changed in the spectra of complexes. The absorption spectra of the free ligand show a band at 235 nm that attributed to the π-π* transitions of the azomethine group. During the formation of the complexes, this band is shifted to higher wavelength (red shift). Furthermore, another electronic spectral band seen at 320 nm, indicating the n-π* transitions of the azomethine chromophore on complexation, this weak band is shifted to lower wavelength called as blue shift (Safia, 2017). This blue shift suggests that the nitrogen atom of the azomethine group is coordinated to the metal ion (Table 3).

Table 3: UV-Visible spectra data for Schiff base, CBAP and its metals complexes

S. No.	Compounds	Benzenoid $\pi - \pi^*$	Azomethine chromophore	
			$\pi - \pi^*$	$n - \pi^*$
2	CBAP	225	235	320
2a	$[Mn(CBAP)Cl_2]$	232	246	308
2b	$[Fe(CBAP)Cl_2]$	227	241	310
2c	$[Co(CBAP)Cl_2]$	236	252	305
2d	$[Ni(CBAP)Cl_2]$	238	250	312
2e	$[Cu(CBAP)Cl_2]$	235	248	309

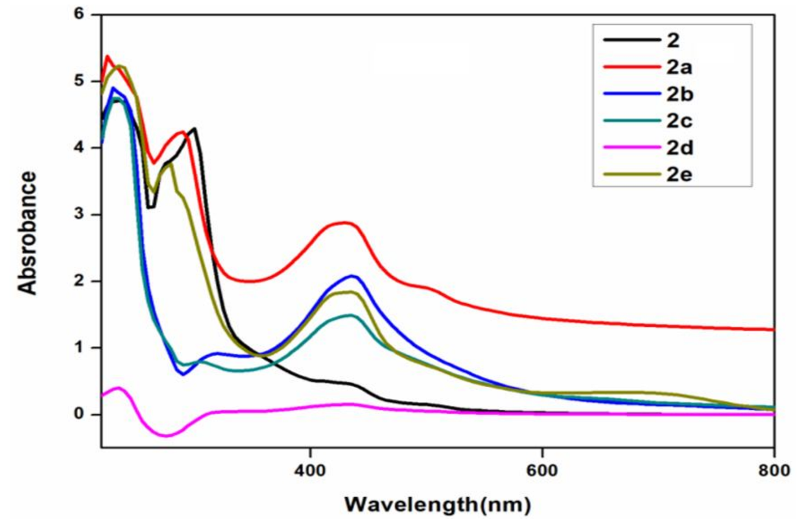

Figure 3: UV-Visible spectra of CBAP and its complexes.

3.5 ^{1}H NMR and ^{13}C NMR spectra

In the ^{1}H NMR spectra (Figure 4 and 5) of Schiff base ligand, a singlet peak appeared at 8.07 δ ppm was assigned due to protons of azomethine group. In the metal complexes, there was a downfield shift of this peak in the range of 9.18-9.54 δ ppm, indicating the coordination of azomethine nitrogen to metal ion. The aromatic protons also displayed multiplet peaks in the range of 6.18-7.96 δppm. The phenolic OH group assigned a broad singlet at 8.73 δ ppm in spectra of the Schiff base ligand. In the metal complexes, this broad singlet was disappeared confirming the absence of OH phenolic proton and involvement of the oxygen atom on complexation (Korzec *et al*., 2019) (Table 4).

^{13}C NMR of ligand shows signal corresponding to carbon atom attached to the azomethine nitrogen, phenolic oxygen is observed at 163.7 δ ppm and 154.4 δ ppm, respectively, which show down-field shift in all the metal complexes, indicating the coordination from ligand to metal ion *via* azomethine nitrogen and phenolic oxygen. Other signals in the range of 121.2-132.0 δ ppm in the spectra of ligand and complexes was assigned due to aromatic carbon signals.

Table 4: ^{1}H NMR data (δ ppm) for CBAP and its metal complexes

S. No.	Compounds	Protons of phenolics ring	Aromatic protons	Azomethine protons(-CH=N-)
2	CBAP	8.73	6.39-7.96	8.07
2a	$[Mn(CBAP)Cl_2]$	-	6.24-7.78	9.18
2b	$[Fe(CBAP)Cl_2]$	-	6.32-7.89	9.32
2c	$[Co(CBAP)Cl_2]$	-	6.28-7.87	9.22
2d	$[Ni(CBAP)Cl_2]$	-	6.35-7.92	9.28
2e	$[Cu(CBAP)Cl_2]$	-	6.18-7.96	9.54

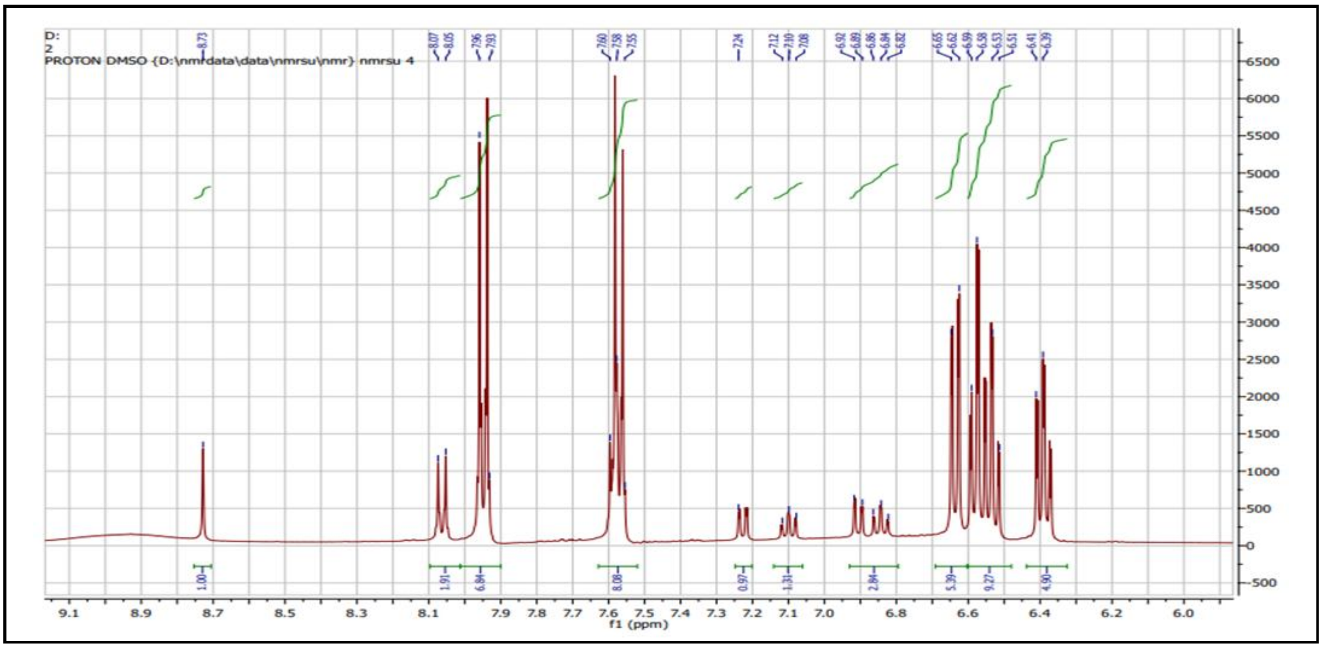

Figure 4: ^{1}H **NMR spectrum of Schiff base, CBAP.**

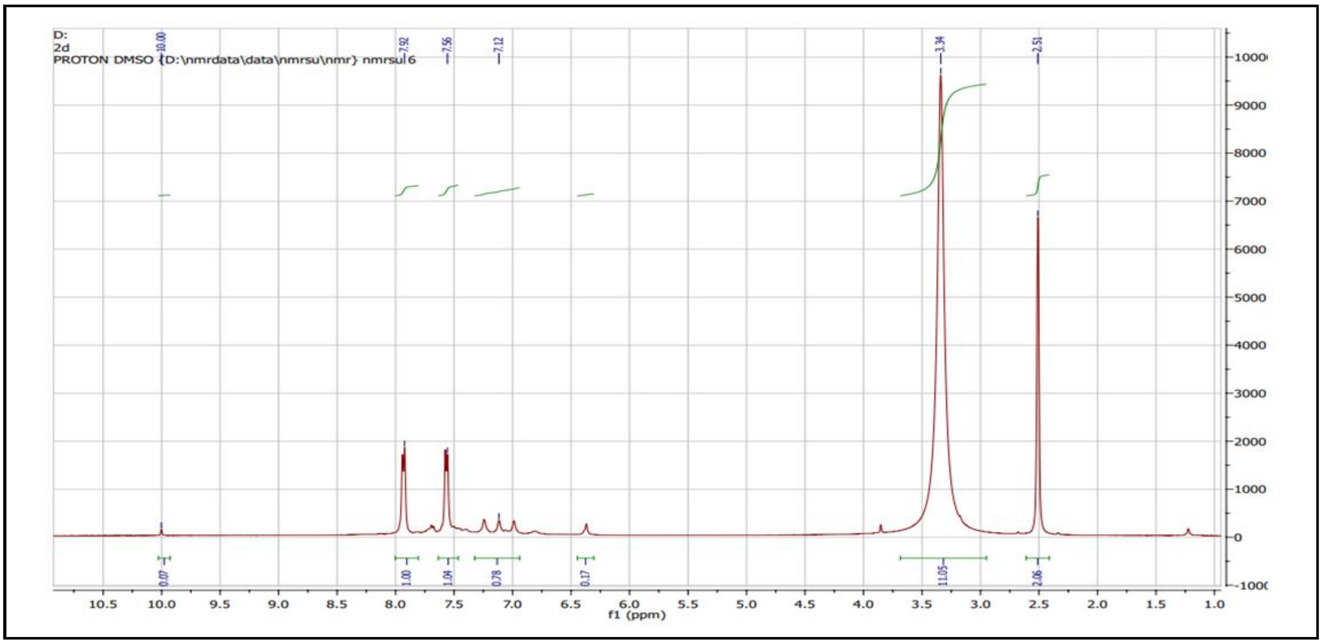

Figure 5: ^{1}H **NMR spectrum of** $[Ni(CBAP)Cl_2]$ **complexes.**

3.6 Antimicrobial activities

The antimicrobial activity of the Schiff bases and its metal complexes was carried out against two bacteria (*Xanthomonas* sp. and *Staphylococcus aureus* VTCC BAA *20*) in Mueller Hinton-Agar medium (MHA) and two fungal strains (*Fusarium oxysporum* f. sp. *lycopersici* and *Candida albicans*) in potato dextrose agar (PDA) media by using agar well diffusion method (Al Momani *et al.*, 2013). Nutrient agar was used for the inoculation of bacterial/fungal cultures and incubated at 30 ± 0.1°C for 24 h and sterile petri dishes were immersed with MHA/PDA and let it to solidify. The inoculums of each bacterial/fungal culture were dispensed on MHA/PDA plates with the help of sterile brush. Later on, wells with a diameter of 7 mm were made on the agar medium and poured with 20 µl (2mg/ml) of synthesized compounds, which were then allowed to disperse for 2 h at room temperature (25°C). At 37°C, the bacterial plates were incubated for 24 h and fungal plates were incubated for 48 h in an upright position. After incubation, the growth of inhibition zones was measured in the form of diameter in millimeters. Chloramphenicol and cycloheximide were used for the antibacterial and antifungal agent.

Zone of inhibition in mm for the Schiff base and its complexes are listed in Table 5 and shown in Figure 6. From the results of the antibacterial activities, it was found that maximum *Xanthomonas* sp. growth was inhibited by compounds [Mn(CBAP)Cl_2] (2a) and [Ni(CBAP)Cl_2] (2d) which showed inhibition zone of 23 and 20 mm. Moderate *Staphylococcus aureus* VTCC BAA20 growth was also inhibited by the compound [Ni(CBAP)Cl_2] (2d) showing inhibition zone of 15 mm. The free Schiff base, CBAP exhibit moderate antibacterial activities.

From the results of the antifungal activities, it was found that maximum *Candida albicans* growth was inhibited by compound [Fe(CBAP)Cl_2] (2b) which showed inhibition zone of 39 mm, better activity as compared to the control cycloheximide. All the complexes showed their best results against both the fungal strains. The free Schiff base also showed their best results against *Fusarium oxysporum* f. sp. *lycopersici* and *Candida albicans*.

Table 5: Zone of inhibition of CBAP and its metal complexes

S. No.	Compounds	Zone of inhibition (diameter in mm)			
		Xanthomonas sp.	*Staphylococcus aureus* VTCC BAA20	*Fusarium oxysporum* sp. *lycopersici*	*Candida albicans*
2	CBAP	10	13	33	24
2a	[Mn(CBAP)Cl_2]	23	-	36	26
2b	[Fe(CBAP)Cl_2]	-	-	34	39
2c	[Co(CBAP)Cl_2]	-	-	28	31
2d	[Ni(CBAP)Cl_2]	20	15	34	36
2e	[Cu(CBAP)Cl_2]	-	-	36	24
	Chloramphenicol	30	31	-	-
	Cycloheximide	-	-	26	35

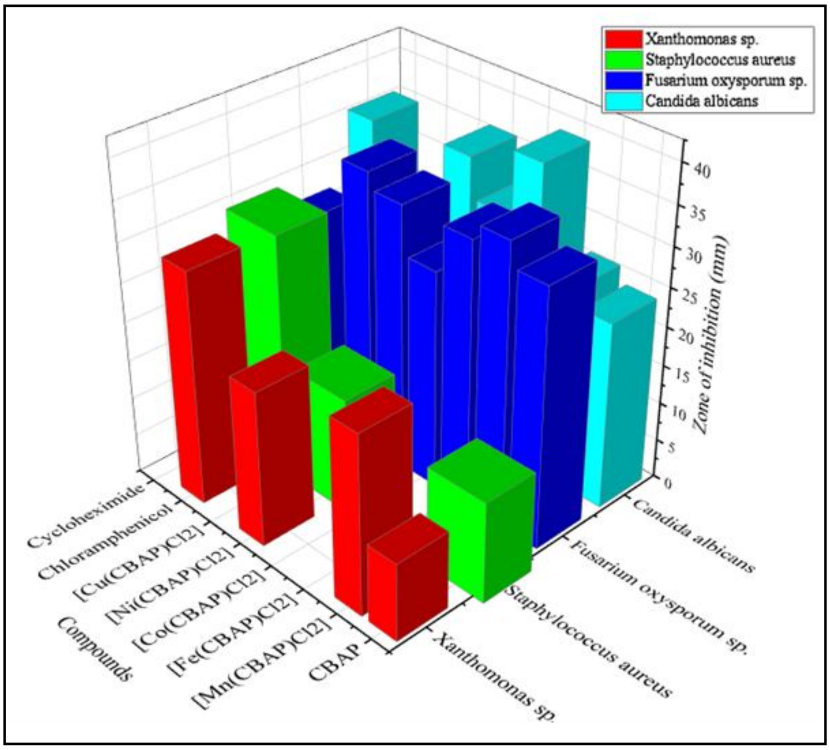

Figure 6: Zone of inhibition of CBAP and its metal complexes.

4. Discussion

Transition metal complexes of Mn^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} were prepared from Schiff base ligand (CBAP) *via* condensation reaction. All the synthesized compounds were characterized by elemental analyses, Molar conductance, FT-IR, UV-Visible and ^{1}H NMR ^{13}C NMR studies. All complexes were non-hygroscopic in nature. All the compounds were insoluble in water but soluble in organic solvents like chloroform, DMSO and DMF, methanol and ethanol. On the basis of all spectral data, it was found that CBAP was neutral bidentate ligand and all the complexes showed tetrahedral geometry. The antimicrobial activity of the ligand and their metal complexes were screened out against bacterial and fungal strains. The study shows that metal complexes showed more inhibition activity against fungal strains (*Fusarium oxysporum* f. sp. *lycopersici* and *Candida albicans*) and bacteria strains (*Xanthomonas* sp. and *Staphylococcus aureus* VTCC BAA 20) as compared to parent ligand (CBAP).

5. Conclusion

Antibacterial and antifungal activity was confirmed in all the synthesized metal complexes, although the results showed that different complexes exhibit distinct inhibitory action against fungal strains (*Fusarium oxysporum* f. sp. *lycopersici* and *Candida albicans*) and bacteria strains (*Xanthomonas* sp. and *Staphylococcus aureus* VTCC BAA 20). The results of the present study revealed that compounds reported more potent antifungal than antibacterial activities. Based on the study, we could conclude that Schiff base and its complexes serve as a good antifungal agents in the field of pharmaceutical as well as agriculture.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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