

Preparation, Antibacterial and Antifungal Activity of Fe(II), Co(II) and Cu(II) Complexes of Hydroxamic Acid Derivatives

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ABSTRACT

At the present work Potassium 5-Chlorosalicylhydroxamate and its complexes Fe (II), Co (II) and Cu (II) were studied. Firstly 5-chlorosalicylhydroxamic acid had been prepared by the reaction of 5-chlorosalicylate and free hydroxylamine and was characterized by its melting point ($>200^{\circ}\text{C}$), FT IR showed characteristic spectral band at 3324 cm^{-1} due to (N-O) stretching frequency and at 1626 cm^{-1} due to (C=O) stretching frequency. The Proton NMR showed spectrum show singlets at around $11.60\text{ }\delta\text{ ppm}$ and $12.40\text{ }\delta\text{ ppm}$, which may be assigned to $-\text{NH}$ and phenolic $-\text{OH}$ of salicylhydroxamate group which show the

linkage of 5-chlorosalicylhydroxamate group through oxygen atoms of carbonyl and hydroxylamine group. The data from spectral studies suggested that the ligand act as a neutral bidentate ligand [O, O] ligand involving the hydroxamate ($-\text{NHO}$) and carbonyl oxygens, giving rise to penta-coordinated metal complexes in $[\text{M}(\text{HL})\text{Cl}_2]\text{K}$ and hexa-coordinated in $[\text{M}(\text{HL})_2\text{Cl}_2]\text{K}$. The antibacterial and anti-fungal of compounds was tested against bacterial strains- *Pseudomonas aeruginosa* and *Bacillus subtilis* using agar well diffusion method and fungal strains- *Sclerotinia sclerotiorum*, *Trichoderma harzianum*. Cycloheximide were used as the standard antifungal agents whereas Chloramphenicol was used in the technique as the standard antibacterial agent. Compound (1d); $[\text{Co}(\text{HL})_2\text{Cl}_2]\text{K}$ showed good antibacterial activity i.e. 33 mm and 24 mm against *P. aeruginosa* and *B. subtilis* and good antifungal activity i.e. 28 mm against *S. sclerotonia* and *T. harzianum*.

Keywords Potassium 5-Chlorosalicylhydroxamate, Metal complexes, Hydroxamic acid, Antibacterial and antifungal activity.

INTRODUCTION

Hydroxamic acids are a class of organic compounds characterized by the functional group $\text{R}-\text{CO}-\text{NHOH}$, where the hydroxylamine moiety provides strong coordination ability through both nitrogen and oxygen donor atoms (Kehl 1982). This unique bidentate chelating nature enables hydroxamic acids to form

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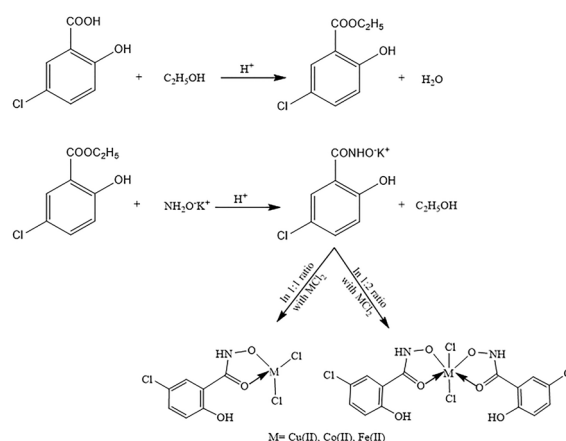
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stable complexes with a wide range of metal ions, particularly transition metals (Kurzak *et al.* 1992 ; Mehrotra 1982). The coordination chemistry of hydroxamic acids has attracted considerable attention due to their structural versatility, biological relevance, and potential pharmacological applications (Munson 1982). Principally known as strong polyfunctional iron chelators, they also display anti-inflammatory, antibacterial and anti- asthmatic behavior and hence have been used in the design of therapeutic targets for cancer (Thomas and Steward 2000 ; Steward 1999) alzheimer's disease (Domingo 1998), malaria (Cabantchik 1995) and haemochromatosis (Turcot *et al.* 2000, Miller 1989). Anion derived from hydroxamic acids i.e. hydroxamates are known to chelate to a number of metal ions (Muri *et al.* 2004 ; Codd 2008; Mizukami and Nagata 1968 ; Chatterjee 1978) to form stable complexes. The ability of hydroxamic acids to chelate metalions such as Fe (II), Co (II), Cu (II), and Zn (II) has also made them important in the design of metallodrugs and enzyme inhibitors, particularly in the inhibition of metalloproteins like matrix metalloproteinases and histone deacetylases. The biological activity of metal-hydroxamate complexes is influenced by several factors, including the nature of the metalions, the geometry of the complex, and the electronic and steric characteristics of the ligand. Recent research has focused on tailoring the structure of hydroxamic acids and selecting appropriate metal centers to enhance their activity against various microbial pathogens and cancer cells. This makes hydroxamic acid metal complexes a promising

class of compounds for the development of novel therapeutic agents. Literature contains reports that some chlorohydroxamic acid have been found to be most effective anti-tumor agent (Fazary *et al.* 2001; Sharma and Sharma 2012). Salicylhydroxamates including chlorosalicyl hydroxamates can chelate to the metal ions via a number of coordination modes (Fazary 2014 ; Khairy *et al.* 1996) not only the O, O' mode but also N, O– modes, most common being the chelation through O, O– mode (Sharma and Sharma 2012 ; Henderson *et al.* 2003 ; Hall *et al.* 2002).

MATERIALS AND METHODS

All the chemicals required were purchased from sigma aldrich and CDH used as received. FT-IR spectra were obtained were recorded in KBr pellets in the region 4000-400 cm^{-1} on a Nicolet iS50 FTIR Spectrometer. ^1H NMR spectra were recorded in DMSO- d_6 using TMS as an Internal reference on an NMR Cryo-magnet Spectrometer 400 MHz (Bruker) NMR spectrometer. The ligand and its metal complexes were also tested for their antimicrobial activity against bacterial and fungal strains. In the work presented here, Potassium 5-chlorosalicylhydroxamate ligand was synthesized by preparation of ethyl ester of 5-chlorosalicylic acid (Vogel 1975) ; after that potassium salt of 5-chlorosalicyl- hydroxamic acid prepared (Hauser and Renfrow 1953) and its co-ordination behavior with some transition metals was studied (Scheme 1). The potassium salt of 5-chlorosalicyl- hydroxamate has been obtained in two steps.



Scheme1. Synthesis reaction of Potassium 5-Chlorosalicylhydroxamate and metals complexes.

RESULTS AND DISCUSSION

Physical Measurements: Physical data such as molecular weight, color and yield was observed for the Potassium 5-chlorosalicylhydroxamate ligand and its Fe (II), Co (II) and Cu (II) complexes as given in Table 1.

Spectral Characterization: To characterize synthesized ligand and corresponding metal complexes, we carried out, FT-IR and ^1H NMR for the complexes. The data for each of the spectral analysis is presented in following subsections.

FT-IR Characterization: For the intervening functional groups, we carried out the FT-IR evaluation of Potassium 5-Chlorosalicylhydroxamate, its Fe (II), Co (II) and Cu (II) complexes. IR spectrum was run in the wave number range 400-4000 cm^{-1} . Interpreted results are summed up in Table 2. We interpreted the results by taking help from existing reports in literature.

The principal infrared absorption bands of ligand-HL are those due to $\nu(\text{C=O})$, $\nu(\text{C-N})$, $\nu(\text{N-O})$ and $\nu(\text{N-H})$ stretching vibrations of the hydroxamate group observed in the spectrum at 1626 cm^{-1} , 1354 cm^{-1} , 985 cm^{-1} and 3324 cm^{-1} respectively (Ibrahim

et al. 2021).

In metal complexes, the absorption band occurring at 1626 cm^{-1} attributes to $\nu(\text{C=O})$ mode, shifted to lower wave numbers and appeared at 1576-1554 cm^{-1} in complexes. The absorption band due to $\nu(\text{C-N})$ mode occurring at 1354 cm^{-1} in free ligand-HL has been found to shift towards higher region at 1470-1492 cm^{-1} in the complexes. The band at around 3324 cm^{-1} due to $\nu(\text{N-H})$ mode in ligand-HL would not be changed. These rules out the involvement of coordination through nitrogen atom. The sharp band occurring at 985 cm^{-1} in ligand-HL ascribed to $\nu(\text{N-O})$ mode has been observed to move towards higher wave number and appeared at 1049-1067 cm^{-1} in metal complexes (Fig. 1).

A shift in $\nu(\text{C=O})$ mode to lower wave number and $\nu(\text{N-O})$ mode to higher wave numbers are suggestive of bonding of 5-chlorosalicylhydroxamate ion via oxygen atoms of carbonyl and hydroxylamine group. The formation of M-O bond however, could be confirmed due to appearance of weak band in the region 588 – 619 cm^{-1} .

^1H NMR Characterization: ^1H NMR spectral analysis was carried out for the 5-chloro-salicylhydroxamate and its metal complexes with Fe (II), Co (II) and

Table 1. Physical data for potassium 5-chlorosalicylhydroxamate and its metal complexes.

Compound Id	Compounds	Empirical Formula	Molecular Weight	Color (Yield %)
1	Ligand-HL	$\text{C}_7\text{H}_5\text{ClKNO}_3$	225.67	White (70%)
1a	$[\text{Cu}(\text{HL})\text{Cl}_2]\text{K}$	$\text{C}_7\text{H}_5\text{Cl}_3\text{CuNO}_3$	321.02	Olive green (80)
1b	$[\text{Cu}(\text{HL})_2\text{Cl}_2]\text{K}$	$\text{C}_{14}\text{H}_{10}\text{Cl}_4\text{CuN}_2\text{O}_6$	507.60	Dark green (84)
1c	$[\text{Co}(\text{HL})\text{Cl}_2]\text{K}$	$\text{C}_7\text{H}_5\text{Cl}_3\text{CoNO}_3$	316.41	Light pink (81)
1d	$[\text{Co}(\text{HL})_2\text{Cl}_2]\text{K}$	$\text{C}_{14}\text{H}_{10}\text{Cl}_4\text{CoN}_2\text{O}_6$	502.98	Light purple (85)
1e	$[\text{Fe}(\text{HL})\text{Cl}_2]\text{K}$	$\text{C}_7\text{H}_5\text{Cl}_3\text{FeNO}_3$	313.32	Brown (79)
1f	$[\text{Fe}(\text{HL})_2\text{Cl}_2]\text{K}$	$\text{C}_{14}\text{H}_{10}\text{Cl}_4\text{FeN}_2\text{O}_6$	499.90	Dark brown (84)

Table 2. IR data (cm^{-1}) for Potassium 5-Chlorosalicylhydroxamate and its metal complexes.

Compounds	Phenolic -O-H	$\nu(\text{N-H})$	$\nu(\text{C=O})$	$\nu(\text{C-N})$	$\nu(\text{N-O})$	$\nu(\text{M-O})$
1	—	3324	1626	1354	985	—
1a	1344	3245	1575	1470	1051	609
1b	1346	3283	1576	1492	1049	567
1c	1346	3284	1576	1491	1049	550
1d	1346	3284	1575	1491	1049	619
1e	1366	3299	1554	1471	1067	589
1f	1362	3246	1556	1471	1066	588

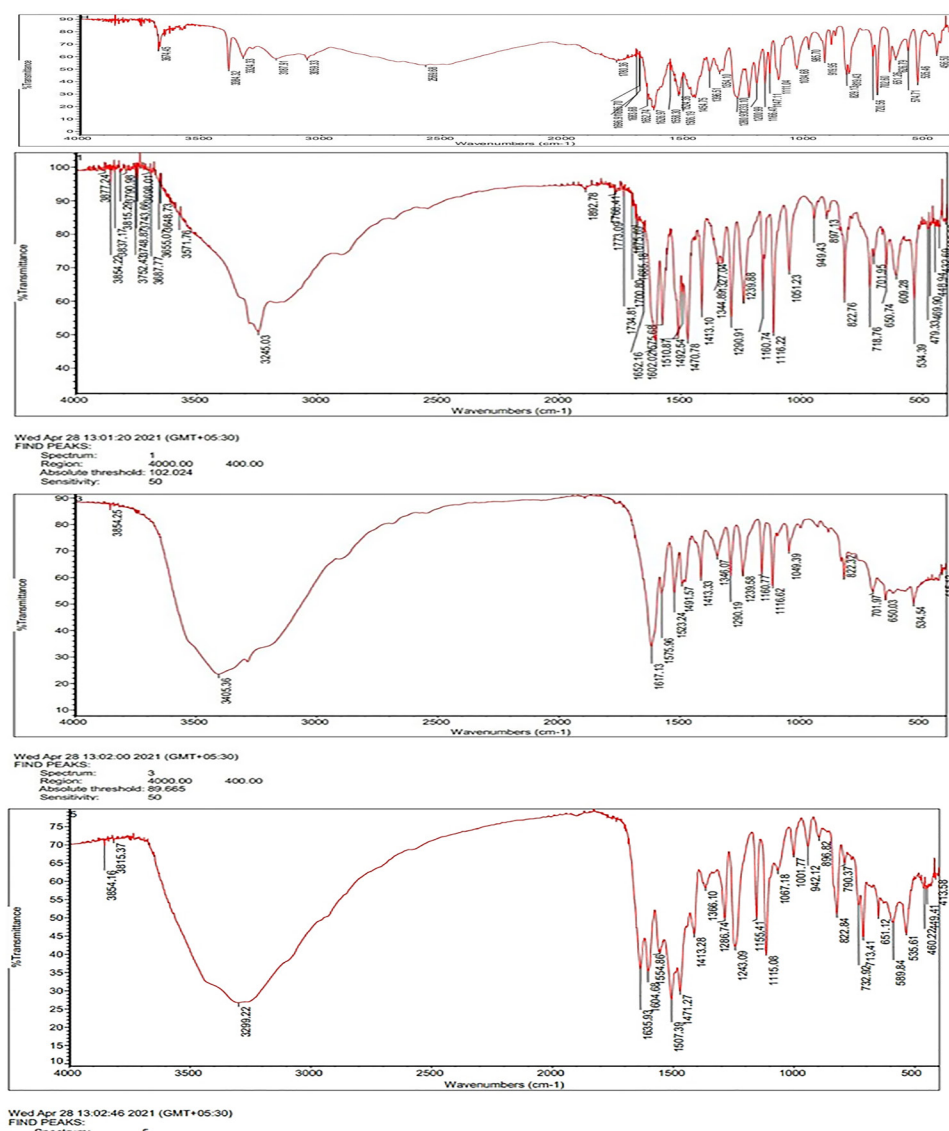


Fig. 1. IR Spectra of Potassium 5-chlorosalicylhydroxamate and its complexes(1a, 1c, 1e).

Table 3. ^1H NMR (δ ppm) data for potassium 5-chlorosalicylhydroxamate and complexes.

Compounds	$\nu(\text{N-H})$	Phenolic -OH
1	11.60	12.40
1a	10.67	10.76
1b	10.79	11.90
1c	10.69	10.79
1d	9.45	12.11
1e	10.76	12.07
1f	12.04	12.83

Cu (II). The results for the spectrum are summarized in Table 3. The interpretation of NMR data has been done with help of existing literature reports.

All the complexes show singlets at around 11.60 δ ppm and 12.40 δ ppm, which may be assigned to $-\text{NH}$ and phenolic $-\text{OH}$ of salicylhydroxamate group (Fig. 2). This rule out the linkage of 5- chlorosalicyl hydroxamate group through oxygen atoms of carbonyl and hydroxylamine group (Ibrahim *et al.* 2021).

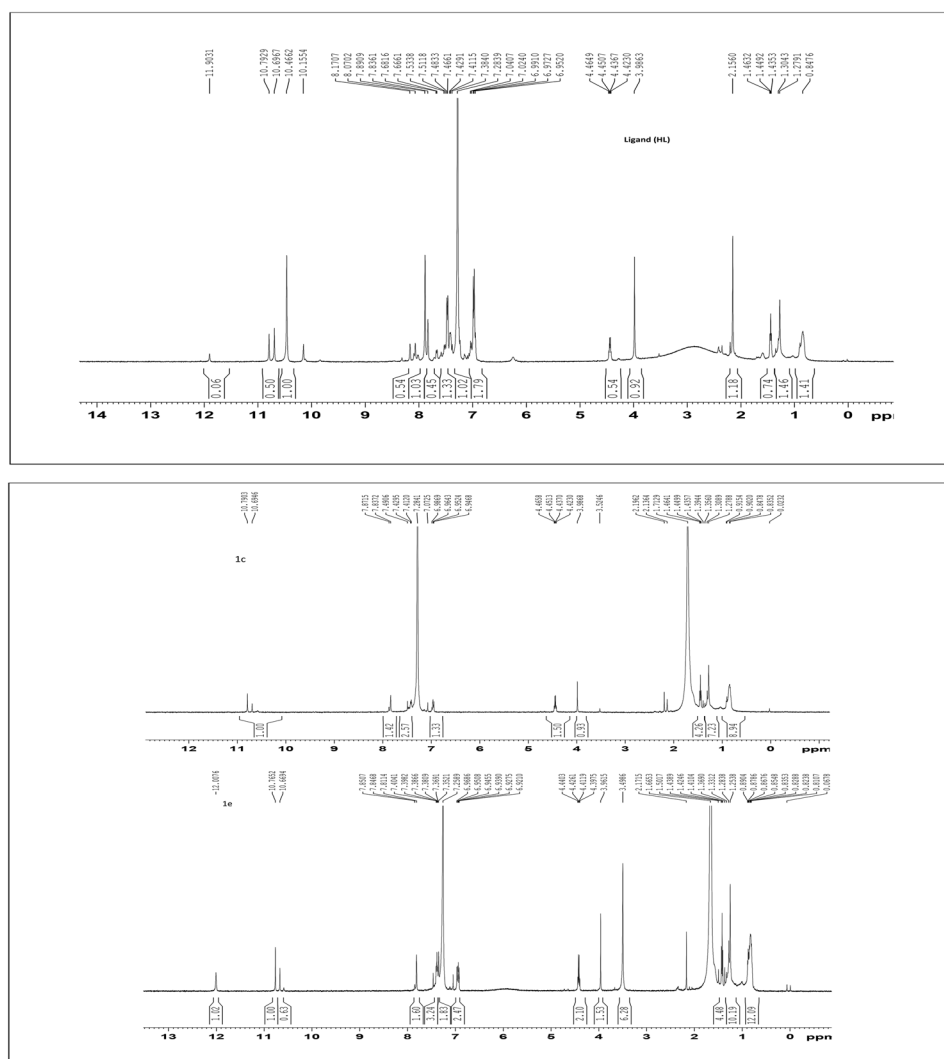


Fig. 2. ^1H NMR of Potassium 5-chlorosalicylhydroxamate and its complexes(1c and 1e).

Thus, on the basis of infrared and proton magnetic resonance spectral studies it may be concluded that 5-chlorosalicylhydroxamate acts as a neutral bidentate [*O, O*] ligand involving the hydroxamate (–NHO) and carbonyl oxygens, giving rise to penta-coordinated metal complexes in [M(HL)Cl₂]K and hexa-coordinated in [M(HL),Cl]₂K.

In vitro antimicrobial activity

Antibacterial activity of the ligands and their complexes were tested against the bacterial species such as

Pseudomonas aeruginosa and *Bacillus subtilis* using agar well diffusion method (Valgas *et al.* 2007). The ligands and complexes were also tested against the fungal species *Sclerotinia sclerotiorum*, *Trichoderma harzianum* (Magaldi *et al.* 2004). Fungal cultures were grown on potato dextrose agar and bacterial cultures were grown on Mueller Hilton agar. Cycloheximide were used as the standard antifungal agents whereas Chloramphenicol was used in the technique as the standard antibacterial agent. The compounds were prepared in DMSO. Eighteen to 24 hrs single colonies on agar plates were used to prepare the bac-

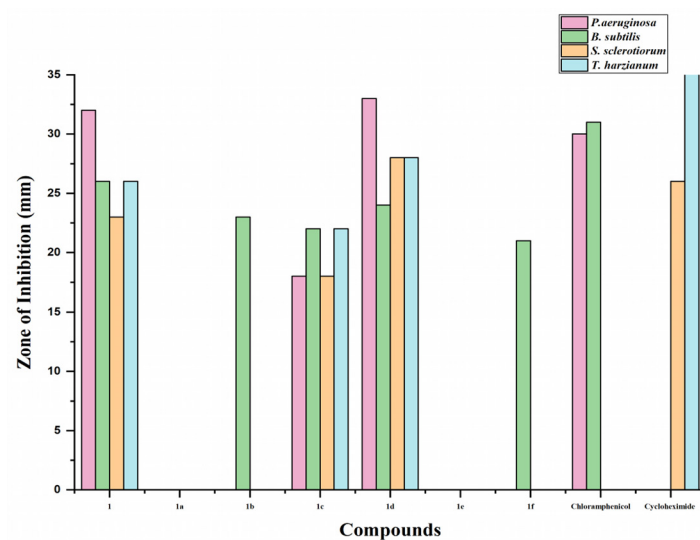


Fig. 3. Comparative results of Zone of inhibition of ligand and its complexes.

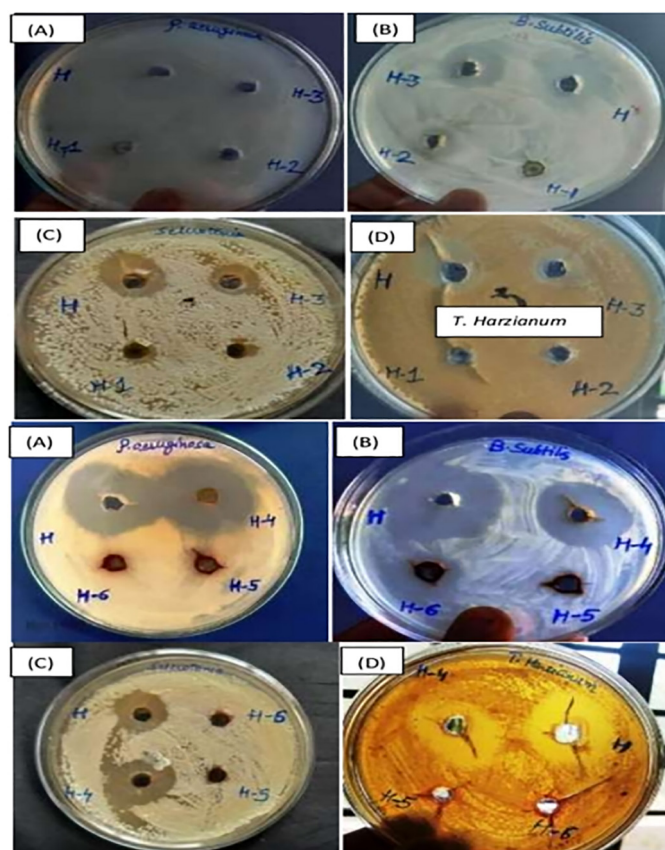


Fig. 4. Antimicrobial activity of compounds against A) *P. aeruginosa*, B) *B. subtilis*, C) *S. Sclerotonia*, D) *Trichoderma harzianum*.

Table 4. Antimicrobial activity of 5-chlorosalicylhydroxamate and its complexes.

Compounds	Zone of inhibition			
	Antibacterial activity (mm)		Antifungal activity (mm)	
	<i>P.aeruginosa</i>	<i>B. subtilis</i>	<i>S. sclerot-T. harzia-</i> <i>iorum</i>	<i>num</i>
1	32	26	23	26
1a	-	-	-	-
1b	-	23	-	-
1c	18	22	18	22
1d	33	24	28	28
1e	-	-	-	-
1f	-	21	-	-
Chloramphenicol	30	31	-	-
Cycloheximide	-	-	26	35

terial suspension with the turbidity of 0.5 McFarland (equal to 1.5×10^8 colony-forming units (CFU)/ml). Turbidity of the bacterial suspension were measured at 600 nm. MHA agar plates and Potato dextrose agar were inoculated with bacterial strain and fungal strain respectively under aseptic conditions and wells (diameter = 6 mm) were filled with 50 μ l of the test samples and incubated at 37°C for 24 hours for bacteria and 72 hours for fungi. After the incubation period, the diameter of the growth inhibition zones was measured. Zone around each well was measured after 24 h for bacteria and 72 h for fungi. All the experiments were performed in triplicate to reduce error. Table 4 shows the results obtained by biological activity evaluation for synthesized complexes (Figs. 3 & 4).

The results show that ligands have moderate antifungal activity against fungal species while showed better antibacterial activity against bacterial species i.e *P. aeruginosa* and *B. subtilis*. Compound $[\text{Co}(\text{HL})_2\text{Cl}_2]\text{K}$ (1d) showed good antibacterial activity against *P. aeruginosa* and *B. Subtilis*. Also $[\text{Co}(\text{HL})_2\text{Cl}_2]\text{K}$ (1d) showed good antifungal activity against *S. Sclerotonia* and *T. harzianum*.

CONCLUSION

Metal complexes of Fe (II), Co (II) and Cu (II) were synthesized from 5-chlorosalicylhydroxamate ligand

via condensation reaction. All the synthesized compounds were characterized by FT-IR, and ^1H NMR. 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 the ligand act as a neutral bidentate $[O, O]$ ligand involving the hydroxamate ($-\text{NHO}$) and carbonyl oxygens, giving rise to penta-coordinated metal complexes in $[\text{M}(\text{HL})\text{Cl}_2]\text{K}$ and hexa-coordinated in $[\text{M}(\text{HL})_2\text{Cl}_2]\text{K}$. Compound (1d) ; $[\text{Co}(\text{HL})_2\text{Cl}_2]\text{K}$ showed good antibacterial activity against *P. aeruginosa* and *B. subtilis* and good antifungal activity against *S. sclerotonia* and *T. harzianum*.

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