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RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL APPLICATION OF NOVEL METAL COMPLEXES

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ABSTRACT

The aim of this research work to built-up a novel transition metal complexes using various transition metals and Schiff base ligand for the antibacterial and anti fungal applications through well-diffusion method. Development of a new chemotherapeutic Schiff bases and their metal complexes are now attracting the attention of medicinal chemists. Complexes are characterized by Elemental analysis, UV- spectroscopy, FT-IR spectroscopy. Elemental analysis of the metal complexes were suggested that the stoichiometry ratio is (metal: ligand) 1:2. The Schiff base complexes have been screened for their invitro antibacterial activity against three bacteria as Staphylococcus aureus, Pseudomonas aeruginosa and Bacillus species and also studied antifungal activities against Aspergillus Niger and Aspergillus flavus. Nickel -Schiff base complexes exhibited a promising antibacterial activity compared to that of other metal complexes. Vanadium Schiff base complex show higher potential when compared to that of other complexes. Besides, Anti-oxidant properties of metal complexes have been studied.

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INTRODUCTION

Schiff bases are an important class of ligands in coordination chemistry and have studied extensively (Sabrina Belaid *et al*., 2015) as they are selective and sensitive toward various metal ions. Metal complexes of Schiff bases have found diverse applications in addition to interesting structural chemistry. Schiff bases easily form stable complexes with most transition metal ions. Schiff bases have played a special role as chelating ligands in main group and transition metal coordination chemistry because of their stability under a variety of redox conditions and because imine ligands are borderline Lewis bases. The important physical and biological properties of the Schiff bases are directly related to intermolecular hydrogen bonding and proton transfer equilibria. Coordination complexes play a major role in important biological activities. Transition metals are involved in many biological processes which are essential to life process. The metals can coordinate with O- or N-terminals from of proteins in a variety of models and play a crucial role in the conformation and function of biological macromolecules. Schiff base complexes are also used as anti-cancer agents and a recent review on this topic by Chinese workers has been chemical abstracted (Ejidike and Ajibade, 2015). The development of the field of bioorganic chemistry has increased the interest in Schiff base complexes, since it has been recognized that many of these complexes may serve as models for biologically important species (Ejidike and Ajibade, 2015; Raju *et al*., 2012; Viuda-Martos *et al*., 2010; Krishnamoorthy *et al*., 2011; Patole *et al*., 2003). Metal complexes containing Schiff- base ligands also have shown attractive properties, such as antibacterial behavior exhibit interesting magnetic properties and catalytic oxidation (Sreeja *et al*., 2003). During the recent years there have been intense investigations of different classes of indole derivative compounds. Many of these possess interesting biological properties such as antimicrobial and analgesic activities. The important criteria for the development of metallodrugs as chemotherapeutic agents are the ability of the metallo drug to bring about DNA cleavage. A large number of transition metal complexes because of their redox properties, have been found to promote DNA cleavage (Mathew *et al*., 2011). Schiff bases are known to be medicinally important and are used to design medicinal compounds (Budhani *et al*., 2010). The azomethine (C=N) linkage in Schiff bases imports in elucidating the mechanism of transamination reactions in biological system (Nair *et al*., 2012; Abou-Melha, 2008). It has been reported that the biological active compounds show greater activity when administered as metal complexes than as free organic compound (Patel *et al*., 2012). The bio medicinal properties of free organic molecule upon chelation with suitable metal ion led to the implementation of metal complexes for several biomedical applications as therapeutically active possessing analgesic (Shingnapurkar *et al*., 2012), antipyretic (Asiri and

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Khan, 2010), anti-inflammatory (Singh *et al*., 2011), cytotoxic (Syed Tajudeen and Kannappan, 2013), antiviral (Syed Tajudeen and Radha, 2009), anti-tumorous (Syed Tajudeen *et al*., 2009) and anti-tubercular activity (Coccoa *et al*., 1999) etc. besides their applications as antimicrobial (Sriram *et al*., 2005; Interleid, 1991). Anti oxidant can be defined as substances whose presence in relatively low concentrations significantly inhibits the rate of oxidation. These are the substances that may protect cells from the damage caused by unstable molecules known as free radicals. Scientific research now confirms that free radicals play a major role in the development of cancer, heart disease, aging, cataracts and impairment of the immune system. Antioxidants, vitamins and minerals should enhance the body's natural defense mechanisms and improve the quality and length of life. The DPPH radical had been used widely in the model system to investigate the scavenging activities of several natural compounds such as phenolic compounds, anthocyanins, or crude extracts of plants. DPPH radical was scavenged by antioxidants through the donation of hydrogen, forming the reduced DPPH-H•. The color changed from purple to yellow after reduction, which can be quantified by its decrease of absorbance at wavelength 517 nm.

MATERIALS AND METHODS

The chemicals and solvents were used as AR grade. All the reagents used for the preparation of the ligand and metal complexes were obtained from Sigma Aldrich. The electronic spectra of the ligand and their complexes have been recorded Schimadzu UV-1800 in DMSO solvent in the range of 200—800nm. FT-IR spectra recorded using KBr pellets in Schimadzu FT-IR 8201 spectrometer (4000-400cm^{-1}).

Synthesis of Ligand (L1)

A solution of 2'-hydroxyacetophenone (20 m.mol) in alcohol was added to 2-amino phenol (20 m.mol) in alcohol. The mixture was stirred and refluxed about 6 hours. The progress of the reaction was monitored by TLC. After the completion of the reaction, the resulting precipitate was filtered and washed with ethanol and dried in an air oven.

Synthesis of Schiff Base metal Complexes

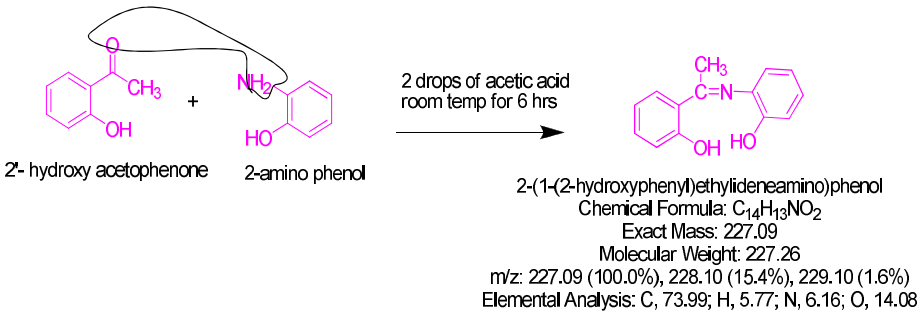
An ethanolic solution of Schiff base ligand L_1 was added to a solution of the metal salts in a molar ratio (1:2). The mixture was refluxed for about 6hrs, a solid precipitate was formed. It was filtered and dried in an air oven.

Spectral Characterization

UV-Visible Spectra

The UV visible electronic spectra (200-800nm) were recorded by UV-Vis-1800 series (Shimadzu) double beam spectrophotometer using DMSO solvent.The electronic spectral measurements were used for assigning the stereo chemistry of metal ions in the complexes based on the positions and number of d-d transition peaks. It is very useful to measure the number of conjugated double bonds and also aromatic conjugation within the various molecules. The electronic absorption spectra of the Schiff base and its metal complexes were recorded at room temperature.

Scheme:1 Synthesis of Ligand



Scheme:2. Synthesis of Metal Complex

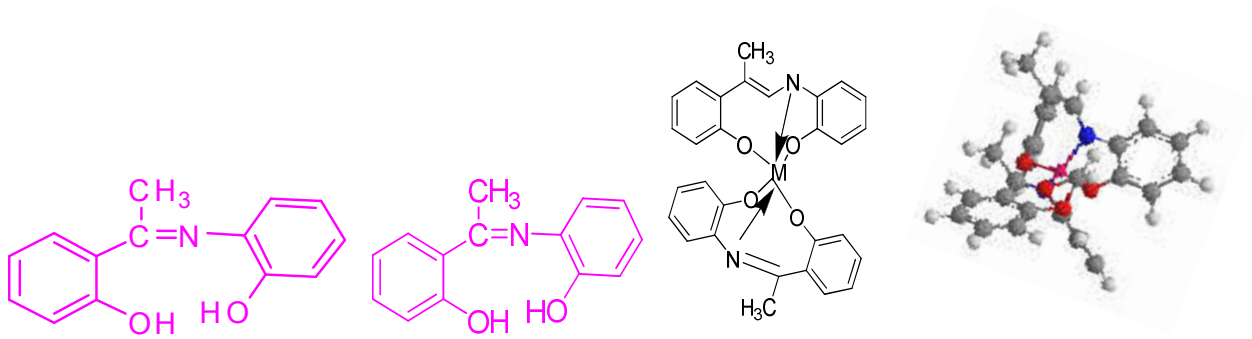


Fig. 1. 3-Dimensional figure of metal complex

FT-IR spectra

FT-IR spectra were recorded using KBr pellets in Schimadzu FT-IR 8201 spectrometer (4000-400cm^{-1}).

Anti Microbial Studies

Antibacterial activity of compounds against bacterial pathogens using Well diffusion method

Antibacterial activity of the extract of compounds was determined using well diffusion method. It was performed by sterilizing Muller Hinton agar media. After solidification, wells were cut on the Muller Hinton agar using cork borer. The test bacterial pathogens were swabbed onto the surface of Muller Hinton agar plates. Wells were impregnated with 25µl of the test samples. The plates were incubated for 30 min to allow the extract to diffuse into the medium. The plates were incubated at 30°C for 24 hrs, and then the diameters of the zone of inhibition were measured in millimeters. Each antibacterial assay was performed in triplicate and mean values were reported.

Antifungal activity of Ligand and its complexes against fungal pathogens using well diffusion method

Antifungal activity of the extract of compounds was determined using well diffusion method. It was performed by sterilizing Mueller Hinton agar media. After solidification, wells were cut on the Mueller Hinton agar using cork borer. The test fungal pathogens were swabbed onto the surface of Mueller Hinton agar plates. Wells were impregnated with 25 µl of the test samples. The plates were incubated for 30 min to allow the extract to diffuse into the medium. The plates were incubated at 30°C for 24 hrs, and then the diameters of the zone of inhibition were measured in millimeters. Each antifungal assay was performed in triplicate and mean values were reported.

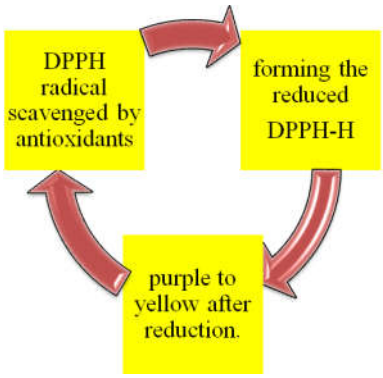


Fig. 2. Scavenging activity of DPPH radical

Anti Oxidant Studies

Anti Oxidant investigations are usually regarded as the potential method to cure various life-style related diseases (Earnshawa, 1968). And in this paper, the antioxidant activity of the ligand and its transition metal complexes was studied by comparing their scavenging effects on superoxide anion and hydroxyl radical. The inhibitory effects of the tested compounds on $O_2^{(-)}$ and HO. are concentration related and the suppression ratio increases with the increasing sample concentration in the range of the tested concentrations. The antioxidant activity of the compounds is expressed as 50% inhibitory concentration (IC50 in µM). Dissolve inhibitor in buffer to make various concentrations. Buffer is ethanol (or) DMSO (depends on solubility). The different concentrations of standardwas centrifuged at 3000 rpm using a centrifuge machine for 10 minutes and supernatant was collected. Dissolve DPPH in buffer to make 300 micro molar concentration. The supernatant of the extract was added to DMSO solution of DPPH in a test tube. Shake at 37 ℃ for 30minutes. The absorbance of the residual DPPH solution was determined at 517 nm in a UV-Visible Spectrophotometer. The experiment was performed in triplicate. Vitamin C (Ascorbic acid) was used as positive control. The percentage of inhibition (I) was calculated in following formula,

$$I (\%) = 100 \times (A_0-A_1)/A \quad \text{---------- (1)}$$

Where,

A_0 is the absorbance of the control, A_1 is the absorbance of the standard, respectively.

A percent inhibition versus concentration curve was plotted and the concentration of sample required for 50% inhibition was determined and expressed as IC_{50} value. The lower the IC_{50} value indicates high antioxidant capacity.

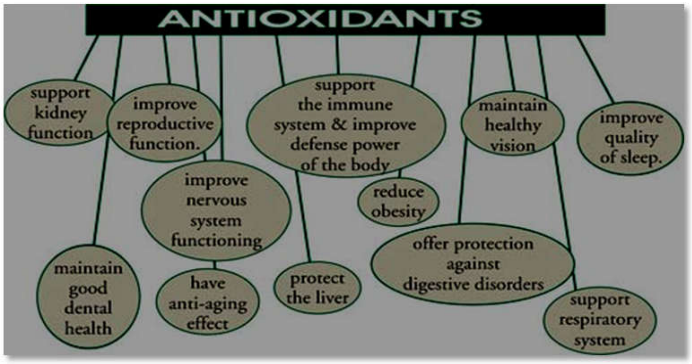


Fig.3. Role of Anti Oxidants

SEM Analysis

A SEM analysis of the final deposit shows that the morphology of the films was excellent, with no grains, islands or other imperfections. The surface morphology of the complexes was studied using JSM-5610 Scanning Electron Microscope.

RESULTS AND DISCUSSION

The micro-elemental analysis for C, H, N and S as well as the molecular weight of the complexes obtained were in agreement with the predicted formula for complexes.

UV-Visible Spectra

The Schiff base ligand shows two type of transition n→π* and π→π* respectively these transition were existed also in the spectra of the complexes, but they shifted to lower intensity, confirming the co –ordination of the ligand to the metal ion. In the spectra the weak band should be at 400-500nm due to intra ligand charge transfer bands in the complexes which is absence in the ligand. The Schiff base has lower wave length range between 215nm to 230nm. Ligand (L_1) the UV-visible spectrum exhibited two bands occur at 275.50(36297.64cm^{-1}) & 222.50 (44923.82cm^{-1}) these peaks are due to n→π* of imine group and π→π* of benzene ring.

Compounds	Physical appearance	Melting point (°C)	Elemental (%) Calc (found)					m/z
			C	H	N	O	M (metal)	
Ligand (L_1)	Red	135	73.99 (73.83)	5.77 (5.75)	6.16 (6.11)	14.08 (14.04)	–	227.09
Cu - L	Black	158	66.95 (67.35)	5.07 (4.72)	5.04 (5.48)	11.51 (11.21)	11.43 (11.22)	555.13
Co - L	Brown	163	67.51 (67.87)	5.12 (5.49)	5.08 (4.63)	11.60 (11.40)	10.69 (10.80)	551.14
Mn - L	Black	96	68.01 (67.79)	5.15 (4.80)	5.12 (4.75)	11.69 (11.46)	10.03 (10.24)	547.14
V - L	Brown	132	68.51 (68.91)	5.19 (4.84)	5.15 (4.80)	11.77 (11.57)	9.37 (9.48)	543.15
Ni - L	Dark Green	136	67.54 (67.84)	5.12 (4.87)	5.08 (5.52)	11.61 (11.82)	10.65 (10.21)	550.14

Table 1. UV spectra for ligand and its metal complexes

Compounds	Frequency		ε_{max}	Transition	Geometry	BM
	Nm	cm^{-1}				
Ligand (L_1)	275.50	36297.64	-	n→π*	-	-
	222.50	44943.82		π→π*		
Cu(II)-complex	595.50	16792.61	10	$^2E_g \rightarrow {}^2T_{2g}$		
	276.00	36231.88	10^2	n→π*	Octahedral	2.02
Ni(II)-complex	599.50	16680.57		$^3A_{2g} \rightarrow {}^3T_{2g}(F)$		
	431.00	23201.86	10^2	$^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$	Octahedral	2.97
	277.00	36101.08		n→π*		
V(V)- complex	350.0	28571.43				
	257.50	38834.95	10^{3-4}	LMCT	Octahedral	-
	215.00	46511.63				

Table 2. Antibacterial activity of the Ligand and its complexes against bacterial pathogens

Test organisms	Zone of inhibition in millimeter (in diameter)							
	L1	Cu	Co	Ni	Mn	V	Solvent control	Standard Amk 30µg
Staphylococcus aureus	15	13	1	19	16	15	NZ	16
Pseudomonas aeruginosa	17	17	23	27	17	14	NZ	14
Bacillus species	13	15	18	19	12	17	NZ	21

Solvent used : DMSO (Dimethyl Sulphoxide) **Standard used**: Amikacin 30 µg

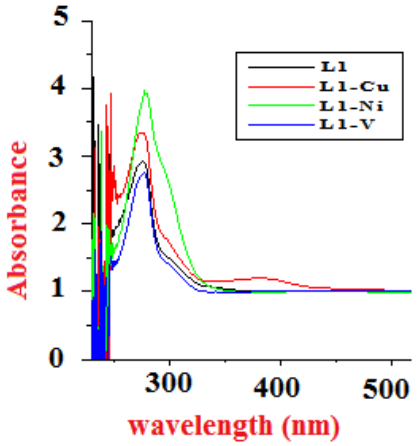


Fig. 4. UV spectra for ligand and its metal complexes

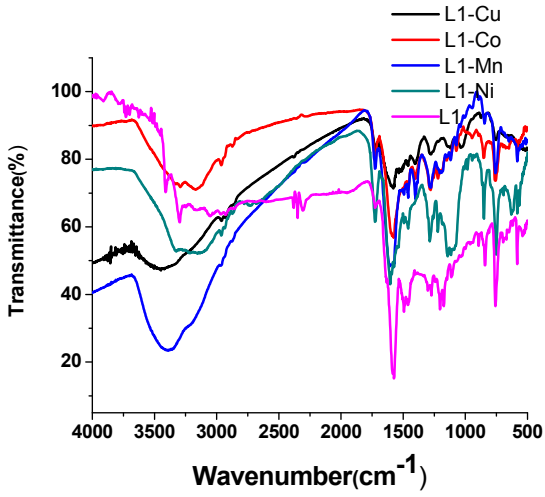


Fig.5. FT-IR spectra for ligand and its metal complexes

FT-IR spectra

The peak at 1573.91 cm^{-1} shows that there is a presence of C=N stretching. The C=N stretching frequency is decreased for all the complexes namely Cu, CO, Ni, Mn, V. Another peak at 1462cm^{-1} for ligand shows that C-O stretching. The M-N bonding peaks shows in the range of 450 to 565 cm^{-1} for complexes. Similarly M-O bonding is present in all the complexes in the range of 580- 640cm^{-1}.

Antibacterial activity

From the results it is inferred that metal complexes were more active than their ligands. The Nickel (II) Schiff base complex show higher efficiency when compared with the standard. This would suggest that the chelation could facilitate the ability of a complex to cross a cell membrane (Mabbs and Machin, 1973) and can be explained by Tweedy's chelation theory (Kettle, 1969). Chelation considerably reduces the polarity of the metal ion because of partial sharing of its positive charge with donor groups and possible π- electron delocalization over the whole

chelate ring and enhances the penetration of the complexes. A possible explanation for this increase in the activity upon chelation is that, in chelated complex, positive charge of the metal is partially shared with donor atoms present on the ligands and there is an electron delocalization over the whole chelating ring. This in turn, increases the lipid layers of the bacterial membranes. Generally it is suggested that the chelated complexes deactivate various cellular enzymes which play a vital role in various metabolic pathways of these microorganisms (Cottton and Wilkinson, 1998; Day and Selbim, 1969; Banerjea, 1998).

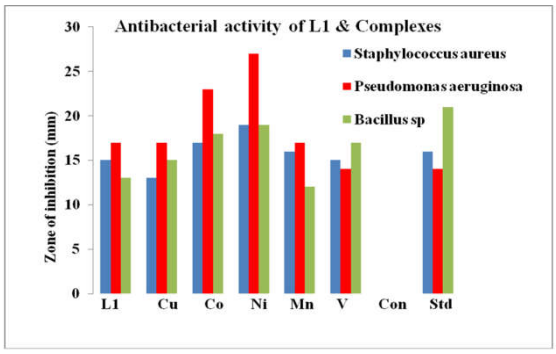


Fig. 6. Antibacterial activity of Ligand and Complexes

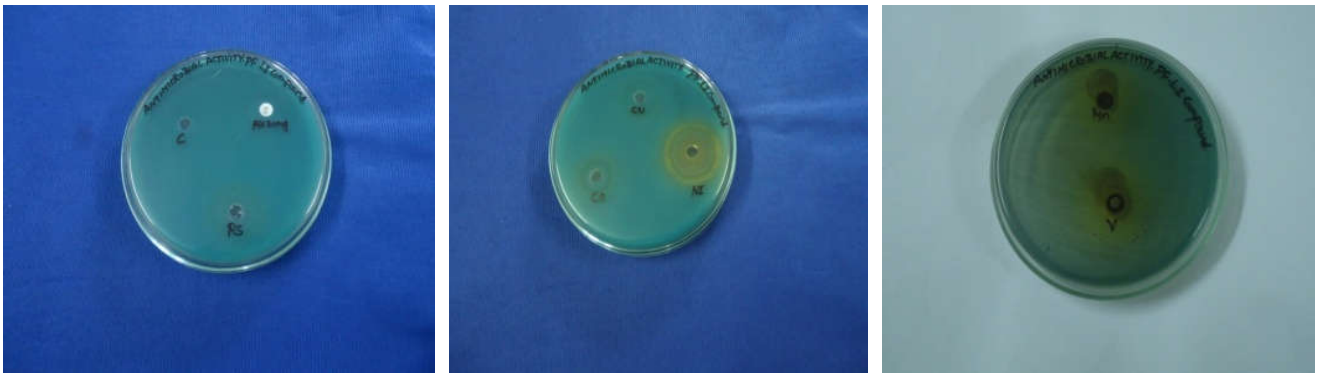


Fig: 7. Plate: 1,2,3: Antibacterial activity of Ligand and Cu, Co, Ni, Mn, V complexes treated against *Pseudomonas aeruginosa*

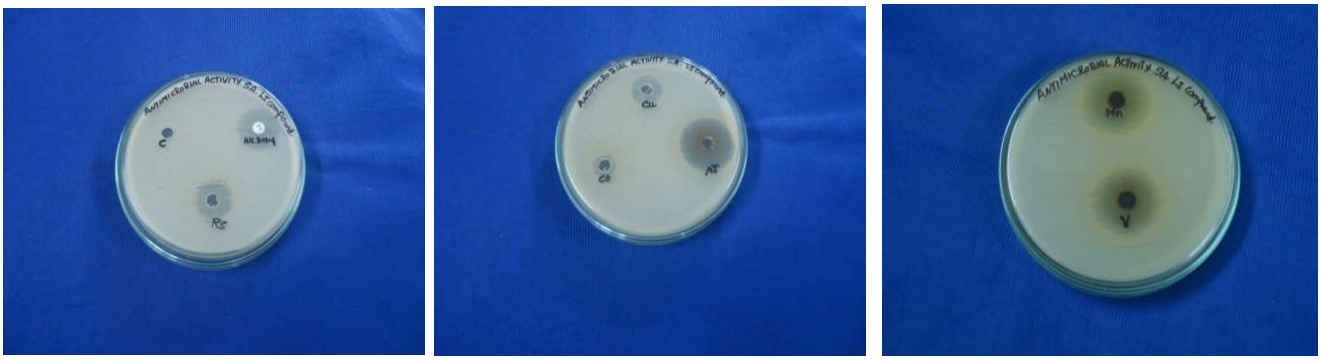


Plate: 4,5,6: Antibacterial activity of Ligand and Cu, Co, Ni, Mn, V complexes treated against *Staphylococcusaureus*

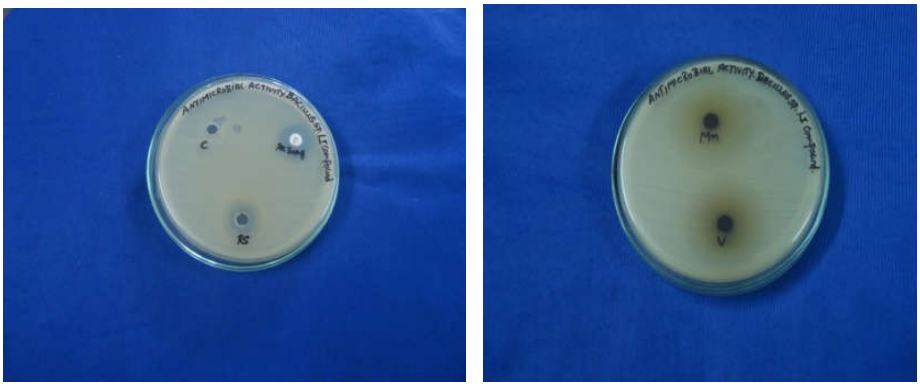


Plate: 7,8- Antibacterial activity of Ligand and Cu, Co, Ni, Mn, V complexes treated against *Bacillus species*

Table 3. Antifungal activity of the Ligand compounds treated against fungal pathogens

Test organisms	Zone of inhibition in millimeter (in diameter)							
	L1	Cu	Co	Ni	Mn	V	Solvent control	Standard Streptomycin
Aspergillusniger	11	16	12	15	13	17	NZ	19
Aspergillusflavus	13	15	17	19	16	16	NZ	16

Solvent used: DMSO (Dimethyl Sulphoxide) **Standard used**: Streptomycin

Table 4. Antioxidant Property of the Ligand and complexes

S.No	DPPH (ml)	Inhibition concentration [I]	Buffer	Absorbance			
				Cu	Co	Ni	Mn
1	2.5	-	7.5	0.062	0.059	0.063	0.054
2	2.5	0.002	7.1	0.054	0.052	0.055	0.049
3	2.5	0.004	6.7	0.043	0.045	0.048	0.047
4	2.5	0.006	6.3	0.037	0.040	0.042	0.036
5	2.5	0.008	5.9	0.027	0.032	0.035	0.029
6	2.5	0.010	5.5	0.018	0.022	0.025	0.020

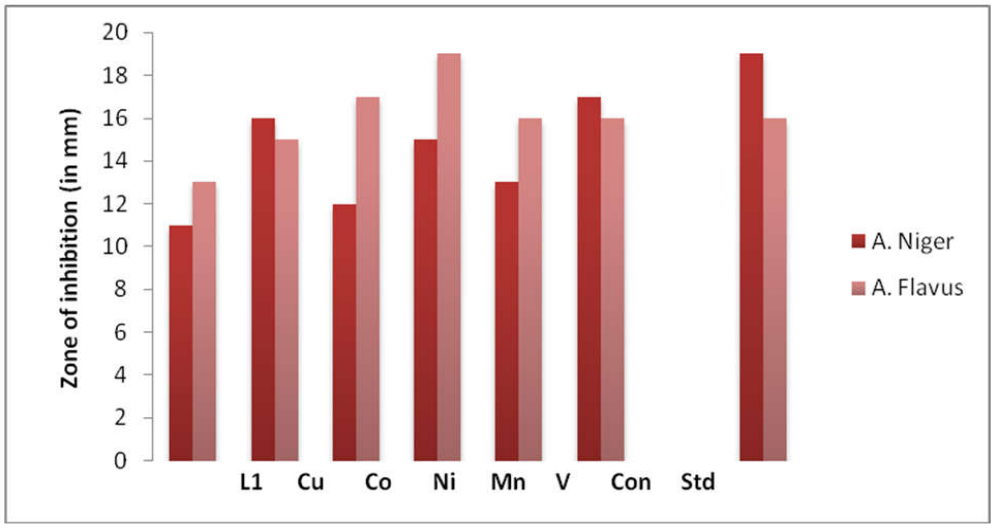


Fig. 8. Antifungal activity of the Ligand compounds treated against fungal pathogens

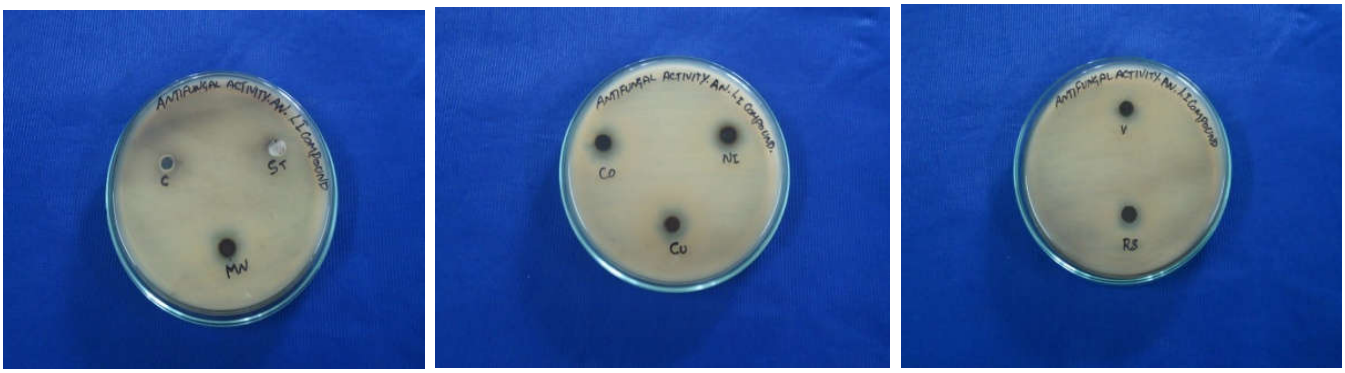


Fig.9. Plate: 1,2,3: Antifungal activity of Ligand and Cu, Co, Ni, Mn, V complexes treated against *Aspergillusniger*

Plate: 4,5,6: Antifungal activity of Ligand and Cu, Co, Ni, Mn, V complexes treated against *Aspergillusflavus*

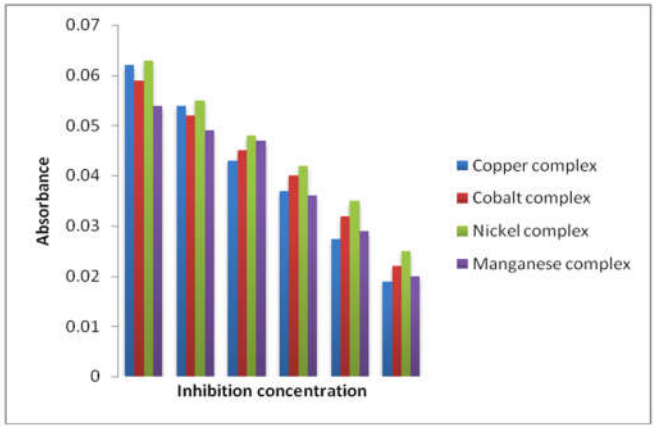


Fig. 10. Antioxidant activity

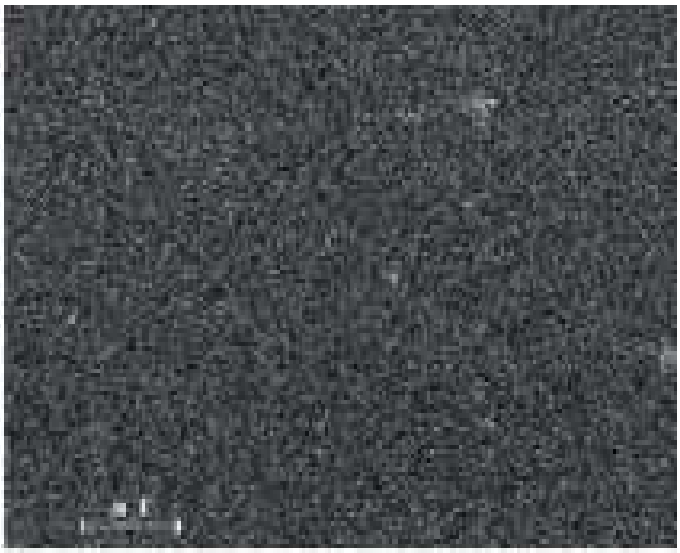


Fig. 11. SEM image of copper complex

Antifungal activity

From the results it is inferred that metal complexes were more active than their ligands. The Vanadium Schiff base complex show superior efficiency against Aspergillusniger when compared with the standard. Similarly Nickel complex has greater efficiency against Aspergillusflavus fungi. The most significant results observed in this study were that the metal complexes were more active against bacteria than in case of fungi. In case of solvent control disc no zone of inhibition was observed as for as our study is concerned DMSO as a solvent is having no effect on the tested organisms. The antimicrobial behavior of the complexes when compared with standard antibacterial and antifungal drugs showed momentous and identical biological properties.

Antioxidant Studies

From the results it is inferred that the absorbance of ligand and its metal complexes decreases with increase in concentration. Therefore the Schiff base complexes show higher anti oxidant property. The metal complexes clearly show higher scavenging hydroxyl radicals activity compared with that of standard antioxidants like mannitol. In comparison with all the compounds, complex shows higher scavenging effect than the other compounds. The metal complexes are better antioxidants than the ligand and the scavenging superoxide anon ability of Cu(II) complex is stronger than other complexes. It is reported that the value of Ascorbic acid (Vc a standard agent for non-enzymatic reaction) for $^{\cdot}OH$ is 8.727 m.mol and the scavenging of V_c for $O_2^{\cdot}$ is only 25% at 9.94 m.mol. Notably the ligand and its metal complexes posses much stronger antioxidant activities than the standard antioxidants. In addition, we can find that the prepared compounds exert differential and selective effects on scavenging radicals in the biological system due to the chelations of organic molecules to the metal ions. It was believed that the information obtained from present work would be useful to develop new potential antioxidants and therapeutic agents for some diseases.

SEM Analysis

From the pictograph, the complex has uniform morphology and the particle size of the Cu(II) complex is 1µm and microcrystalline in nature. This leads to believe that we are dealing with homogeneous phase material.

Conclusion

In this paper, we describe the spectroscopic and biological studies of a new mixed 2-(1-(2-hydroxyphenyl) ethylideneamino)phenol Schiff base ligand and its Cu(II), Co(II), Ni(II), Mn(II) and V complexes. On the basis of spectral studies an octahedral geometry for complexes have been assigned. The antimicrobial screening data confirm that the metal chelates exhibit a higher inhibitory effect than the free ligand. Chelation tends to make the ligand act as more powerful and potent bactericidal agent. As far as our results are concerned these complexes that could be a promising future in the field of infectious diseases. These metal complexes can thus be explored in future as an alternative for decreasing pathogenic potential of infecting bacterial and fungal species.

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