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Spectral Investigation of Schiff Base Monometallic Transition Metal Complexes as Bacteria and Fungus Inhibitors

¹Muhammad Pervaiz, ¹Muhammad Yousaf, ²Muhammad Sagir, ³Ansar Pervaiz and ⁴Muhammad Yasin Naz

¹Department of Chemistry, Government College University, Faisalabad, Pakistan

²Department of Chemical Engineering, University Technology PETRONAS, Malaysia

³Institute of Chemistry, University of the Punjab, Lahore, Pakistan

⁴Department of Physics, University of Agriculture, Faisalabad, Pakistan

Corresponding Author: Muhammad Pervaiz, Department of Chemistry, Government College University, Faisalabad, Pakistan

ABSTRACT

Different derivatives of phenylhydrazine were used in the synthesis of metal complexes and acted as antimicrobial agents. The titled series of monometallic complexes has been employed individually against a series of bacterial and fungal strains just to check the enhanceability of biological activities of the synthesized monometallic complexes as compared to the parental synthesized ligand which was derived by the condensation reaction of phenyl hydrazine with salicylaldehyde. Different bacterial and fungi strains were used to check the capability of the monometallic complexes and ligand as antibacterial and antifungicides. The results showed that the monometallic complexes exhibit strong effect against bacterial and fungal strains than the ligand. The ligand was further reacted individually with series of transition metals analysed by different spectroscopic tools as FT-IR, MS and NMR while the complexes were characterized by FT-IR and XRD. From the antimicrobial activity data, it was concluded that the ligand showed less values both for antifungal and antibacterial activity than metal complexes.

Key words: Schiff base, salicylaldehyde, tetra component solvent system, bacterial strains, fungal strains

INTRODUCTION

The Schiff bases and their metal complexes are considered to be very important due to their interest in a variety of biological mechanisms (Atkins *et al.*, 1985). Many transition metal complexes have been found to exhibit greater stability and are very active against different diseases. Depending upon the stability, the transition metals and their complexes have been used against tumor and cancer treatments (Chen and Crafts, 2006). The stability of complexes mainly depends on the chelating and donating powers of the ligand which ultimately facilitates oxidizing and electrophilic reactions. The less stability of metal complexes restricts their applications in some biological processes (Cozzi, 2004). Ligands made from salicylaldehyde exhibit higher values of antibacterial activities against different species including *S. aureus*, *P. mirabilis*, *H. influenza* and *Salmonella* spp. (Cuenca-Estrella *et al.*, 1999).

Apart from ligands and metal complexes salicylaldehyde is more frequently used as larvicide and fungicides. A number of biological components such as glucose, vitamins, drugs, nitrogenous bases and some heterocyclic compounds containing nitrogen atom acts as bioligands. These bioligands exhibit average antimicrobial activities which can be enhanced by coordination with transition metals. Complex formation promotes dissolving power of different drugs in lipid containing organisms and ultimately enhances the drugs effect against different diseases. The activities of anticancer, antitumor, antianalgesic and antibiotic drugs can be increased by complexing them with transition metals (Dogan *et al.*, 2009). Metallo-elements play significant role in the viral growth and restrict virus to enter into the host cell, for example sulfur and zinc occur in viruses and bacterium respectively. Zinc quickly coordinates with sulfur present at the outer layer of virus and can transfer virus into the host cell so, to break this coordination, transition metals are considered to be very important to arrest the sulfur. So viral growth depends on these metals and can be controlled by varying concentrations of metallo-elements (Elzahany *et al.*, 2008).

Therefore, in this research work, the titled series of monometallic complexes has been employed individually against a series of bacterial and fungal strains just to check the enhanciability of biological activities of the synthesized monometallic complexes as compared to the parental synthesized ligand which was derived by the condensation reaction of phenyl hydrazine with salicylaldehyde. Different bacterial and fungal strains were used to check the capability of the monometallic complexes and ligand as antibacterial and antifungicides. The ligand was further reacted individually with series of transition metals including Cd, Co, Mn and Cr, respectively. The ligand was analyzed by different spectroscopic tools as FT-IR, MS and NMR while the complexes were characterized by FT-IR and XRD.

MATERIALS AND METHODS

All solvents and reagents including Salicylaldehyde, Cadmium acetate, Cobalt acetate, Manganese acetate, Chromium acetate, Ethanol, Phenylhydrazine, Acetic acid, Toluene and Ethyl acetate of AR grade were imported from Sigma-Aldrich (Germany).

Synthesis of ligand: The ligand-hydroxyphenylidene-N-phenylamino-imine (L) was prepared by reacting equimolar quantities of salicylaldehyde and phenylhydrazine. Salicylaldehyde (12.2 g, 0.1 moles) and phenyl hydrazine (11.2 g, 0.1 moles) along with glacial acetic acid (1 mL) were refluxed along with stirring at room temperature in 100 mL flask by using toluene as a solvent (Geeta *et al.*, 2010). After the said time, the success of the reaction was checked by TLC test by using ethylacetate-pet. ether (1:1) solvent system. The solvent was removed by rotary evaporator and residue was washed with ethanol and toluene one by one in order to remove the reactants if any. The crude product was subjected to silica gel bearing column chromatography by using ethylacetate-pet. ether (1:1) solvent system. The eluent after removing the solvent by rotary evaporator was dried well under vacuum and productivity was calculated to be 78%. The pure product was identified by FT-IR, ^1H NMR, ^{13}C NMR and MS.

Synthesis of monometallic complexes: The four ligand (L) based monometallic complexes were prepared by reacting metal acetate and ligand (L) in 1:2 molar ratios, respectively in ethyl alcohol and toluene.

Synthesis of monometallic cadmium complex with ligand: Cadmium acetate dihydrate and ligand were reacted in 1:2 molar ratio by dissolving in ethanol and (3.2 g, 0.02 moles) of ligand in toluene. Ligand was mixed with Cd acetate in 250 mL flask and refluxed for about 6 h along with continuous stirring. The success of the reaction was checked by TLC test. When the entire reaction was completed, the solvent was removed by the rotary evaporator, washed with pet-ether. The crude product was recrystallized from toluene/pet-ether system. The purified complex after filtration was dried well under vacuum. The product was redissolved in the minimum quantity of the toluene and was put in the refrigerator at low temperature in order to get the crystals but microcrystalline material was obtained. Then the solvent was removed upto dryness and redissolved in combination of three solvents i.e., ethanol, toluene, and ethyl acetate (TCS by volume 50, 10 and 40%, respectively). The fine crystals were obtained at low temperature after 3-4 days. The crystals of monometallic complex were characterized by FT-IR and X-ray crystallography.

Synthesis of monometallic copper complex with ligand: Copper acetate monohydrate (1.99 g, 0.01 moles) was dissolved in ethanol and ligand (3.2 g, 0.02 moles) was dissolved in toluene. Both solvents containing copper acetate and ligand were heated, stirred separately and mixed together in 1:2 molar ratios. The reactants were allowed to react with continuous stirring in 250 mL flask for 6 h. The success of the reaction was checked by TLC test. After the reaction, the solvent was removed by the rotary evaporator, washed with pet-ether. The crude product was recrystallized from toluene/pet-ether system. The purified product after filtration was dried well under vacuum and the productivity was calculated upto 69%. The product was further characterized by IR technique.

Synthesis of monometallic manganese complex with ligand: This monometallic manganese complex was prepared by reacting manganese acetate (1.77 g, 0.01 moles) dissolved in ethanol and ligand (3.2 g, 0.02 moles) dissolved in toluene in 1:2 molar ratio. Both the mixtures were mixed and stirred in 250 mL flask adjusted with stirring system. Entire mixture was refluxed for 6-7 h then allowed to cool down. The success of the reaction was checked by TLC test. After the reaction, the solvent was removed by the rotary evaporator, washed with pet-ether. The crude product was recrystallized from toluene/pet-ether system. The resulting purified complex after filtration was dried well under vacuum and the productivity was calculated upto 72%. The product was characterized by FT-IR technique.

Synthesis of monometallic Chromium complex with ligand: Stichiometric quantities of Chromium acetate tetrahydrated (2.49 g, 0.01 moles) and ligand (3.2 g, 0.02 moles) were allowed to react in (1: 2) molar ratios. Ligand and Chromium acetate were dissolved in toluene and ethanol seperately and then were mixed along with stirring in 250 mL flask. The whole contents of the flask were refluxed along with stirring for 6 h. The success of the reaction was checked by TLC test. After the reaction, the solvent was removed by the rotary evaporator, washed with pet-ether. The washed product was crystallized by toluene/pet-ether system. The purified complex after filtration was dried well under vacuum and characterized by FT-IR technique.

Antimicrobial activity: Disc diffusion method was used to test the antibacterial and anti fungal activity. Different strains were engaged to check the antibacterial and antifungal activities.

Antibacterial activity: Different strains were used to test the antibacterial activity. The selected strains were *Pseudomonas aeruginosa*, *Vibrio cholera* and *Salmonella typhi* (Gold, 1987). The ligand and bimetallic complexes were employed for antibacterial activity by using Disc diffusion method CLSI, 2007. Nutrient agar was mixed in distilled water and dispersed homogenously. Sterilization of the medium was carried out by means of autoclave at 121°C for 20 min. Medium was treated with Inoculums before it is transferred to Petri plates. Hereafter, filter paper discs were placed parallel on growth medium which contains 100 µL (micro liters) of bimetallic complexes and ligand. The incubation of Petri plates was taken for 24 h at 37°C for bacterial growth. The complexes and ligand full of antibacterial activities inhibited the growth of bacteria and formed clear zones. Zone reader was employed to measure the inhibition zones in mili meters. The standard drug used was Rifamipic (Kovacic, 1967).

Antifungal activity: Fungal strains were used to test the antifungal activity. The selected strains were *Candida albicans*, *Fusarium solani* and *Rhizopus solani* (De Logua *et al.*, 2002). The growth medium was synthesized, sterilized and then transferred to the Petri plates. Petri dishes were incubated for 48 h at 28°C for fungus growth. Filter paper discs were cited on growth medium for the growth of fungus. The bimetallic complexes and ligand were applied up to 100 µL on each disc. Petri plates were then incubated and the complexes and ligand which showed antifungal activities were inhibited the growth of fungus and clear zones were produced. The standard drug used for antifungal activity of complexes and ligand was Fluconazol (Raman *et al.*, 2007).

RESULTS AND DISCUSSION

Synthetic route for 2-hydroxyphenylidene-N-phenylamino-imine (L) and its monometallic complexes (Fig. 1).

Physical properties of ligand and monometallic complexes with ligand: The ligand and monometallic complexes with ligand showed sharp melting points and were soluble in most of the organic solvents as expressed in Table 1.

Crystallization of monometallic complexes with ligand in tetra component solvent system: Three independent solvents were checked for crystallization of the obtained complex. Even so, the dissolution of the titled complex in single solvent was not successfully done and hinders the

Table 1: Solubility of ligand and its complexes

Compound	Solubility			Mixed solvent system (Ethanol. Toluene. Ethyl acetate, DMSO)
	DMSO	Chloroform	Ethyl alcohol	
L	+	+	+	+
Cd (L)	Slightly soluble	Slightly soluble	Slightly soluble	+
Co (L)	Slightly soluble	Slightly soluble	Slightly soluble	+
Mn (L)	Slightly soluble	Slightly soluble	Slightly soluble	+
Cr (L)	Slightly soluble	Slightly soluble	Slightly soluble	+

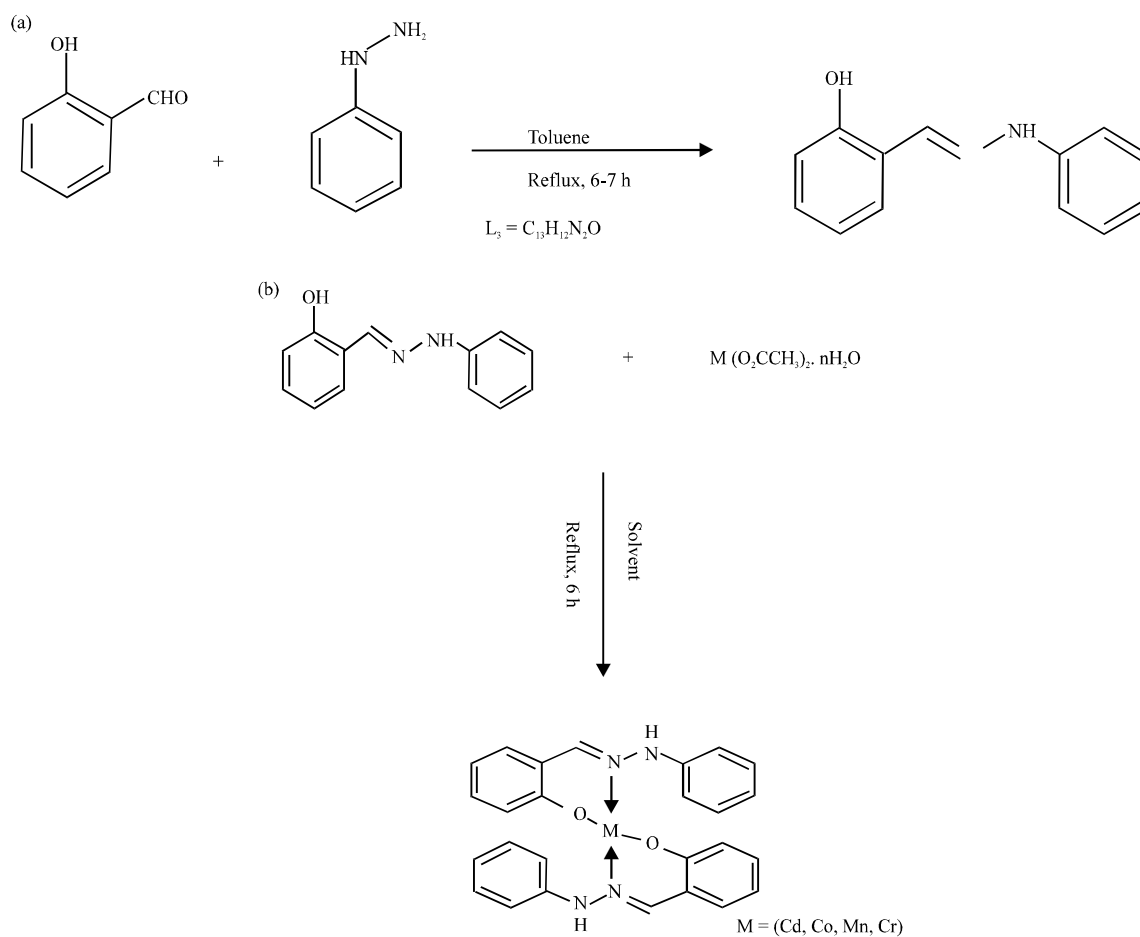


Fig.1(a-b): Synthetic route of (a) 2-hydroxyphenylidene-N-phenylamin-imine and (b) its monometallic complexes

proper crystal formation. Solubility of the titled complex by using 0.5 g in three separate solvents i.e., in Ethyl acetate, Toluene, DMSO and Ethanol was 1.2, 0.5, 1.1 and 0.1%, correspondingly. On the basis of previously reported results (Salavati-Niasari *et al.*, 2009; Singh *et al.*, 2010; Sun *et al.*, 2009), the solubility of the metal complex was increased successfully by employing a combination of four solvents and the results showed that solubility of the metal complex was up to 11% for 0.5 g of the complex. This was due to the intermolecular bonding and bridging of the used solvents as expressed in Table 1.

Characterization of ligand and monometallic complexes: FT-IR was used to confirm the monometallic complexes and ligand's functional groups. The range used for the FT-IR spectra was $4000-400\text{ cm}^{-1}$ as KBr pallets. NMR spectra (^1H NMR and ^{13}C NMR) of the ligand were recorded by using-ECX60 FT NMR (60 MHz) and solvent used was CDCl_3 . Reference standard used was TMS. The ligand was analyzed for molecular mass on the basis of previous reported results, the data was elucidated and confirmed (Chiarella *et al.*, 2007; Pervaiz *et al.*, 2013). Apex-II Bruker X-Ray diffractometer was used to establish the structure, bond angles and lengths of monometallic complexes.

Table 2: Characteristic IR absorption frequencies of ligand and its monometallic complexes in cm^{-1} due to bending vibrations for imine group

Compound	Observed value (cm^{-1})	Standard value (cm^{-1})
Ligand	1600.7, 1566.30	~1575, 1630
Cd (L)	1602.65, 1578.7	~1575, 1630
Cu (L)	1601.7, 1570.20	~1575, 1630
Mn (L)	1600.9, 1568.10	~1575, 1630
Cr (L)	1601.2, 1572.40	~1575, 1630

Table 3: Characteristic IR absorption frequencies of ligand and its monometallic complexes

Compound	Observed value (cm^{-1})	Standard value (cm^{-1})
Ligand	1358, 1159.6	Sharp at 1410-1310, ~1200
Cd (L)	Not found	Sharp at 1410-1310, ~1200
Cu (L)	Not found	Sharp at 1410-1310, ~1200
Mn (L)	Not found	Sharp at 1410-1310, ~1200
Cr (L)	Not found	Sharp at 1410-1310, ~1200

Table 4: Characteristic IR absorption frequencies of ligand and its monometallic complexes

Compound	Observed value (cm^{-1})	Standard value (cm^{-1})
Ligand	3284.8	~3300
Cd (L)	3452.7	~3300
Cu (L)	3448.9	~3300
Mn (L)	3446.2	~3300
Cr (L)	3450.0	~3300

In IR spectra of compounds of Ligand, the stretching vibration of N–H in secondary amine group was observed at 3285 cm^{-1} . Vibrations for CH = N group was observed at 1600.7 and 1566.3 cm^{-1} . Bending vibrations for phenolic OH group was observed at 1358 and 1159.6 cm^{-1} as given in Table 2, 3 and 4.

Mass spectrometry (MS) analysis of Ligand (L): The ligand was analyzed for molecular mass. On the basis of previous reported results, the data was elucidated and confirmed (Yousaf *et al.*, 2013). Molecular ion peak of L was observed at 212 which is also a base peak. The molecular ion fragment was disintegrated by the cleavage of OH group resulting in the fragment peak at 194. The fragment pattern of the molecules was observed by the cleavage of nitrogen-nitrogen bond and two fragments were observed one with Molecular mass 120 and other 92. Isotopic peak for the molecule was observed at 213 with intensity of about 1% of the molecular ion peak as shown in Fig. 2.

Nuclear Magnetic Resonance Spectroscopy (NMR) analysis of Ligand (L)

^1H NMR: NMR spectra were recorded by using -ECX60 FT NMR (60 MHz) and solvent used was CDCl_3 . Reference standard used was TMS. In the ^1H NMR spectra of L hydroxyl proton was observed at 11.26 ppm as a singlet peak due to strong deshielding effect of oxygen atom while amine proton was observed at 11.21 ppm as singlet. The protons of CH = N group were observed at 8.84 ppm as singlet. These are deshielded due to π electrons of CH = N and were observed at high ppm value. There were four protons on phenolic ring in the molecule. All these four protons have different environments and these labeled as C_1 --- C_4 . C_1 was at ortho position of hydroxyl

Table 5: ^1H NMR data of ligand

Position of protons	Type of peak	Value in ppm
C_1	Doublet	7.02
C_2	Triplet	7.52
C_3	Triplet	7.08
C_4	Doublet	7.66
$\text{C}1'$	Doublet	7.35
$\text{C}2'$	Triplet	7.20
$\text{C}3'$	Triplet	6.81

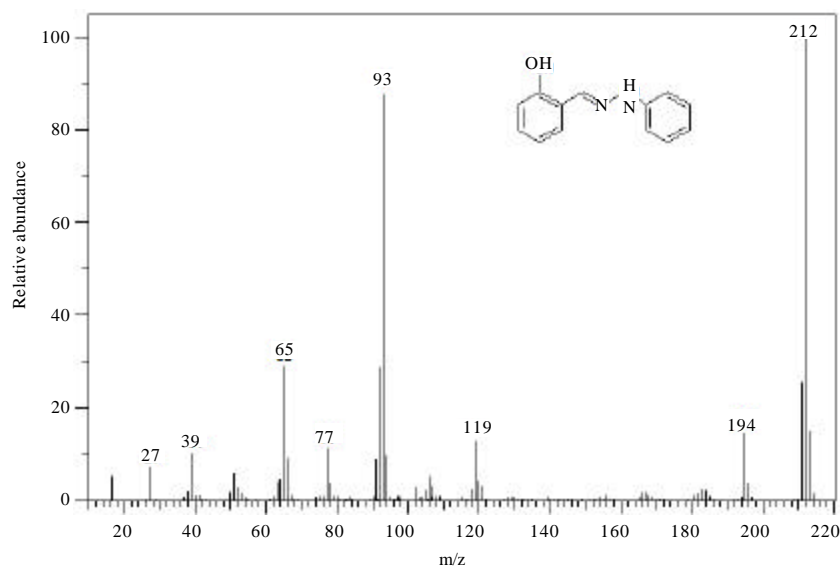


Fig. 2: Mass spectrum of ligand

group. Protons of C_1 , C_2 , C_3 and C_4 were observed as doublet, triplet, triplet and doublet at 7.02, 7.52, 7.08 and 7.66 ppm, respectively. The other aromatic ring in the molecule have five protons and these are labeled as $\text{C}1'$ --- $\text{C}5'$. $\text{C}1'$ and $\text{C}5'$, $\text{C}2'$ and $\text{C}4'$ have same environment. The protons of $\text{C}1'$, $\text{C}2'$ and $\text{C}3'$ are observed as doublet, triplet and triplet at 7.35, 7.2 and 6.81 ppm, respectively as expressed in Table 5.

C^{13}NMR : The numbering of the carbon atoms in the ligand molecule is started from phenolic carbon as C_1 - C_{19} . The CH carbon (C_7) of $\text{CH}=\text{N}$ group exhibited sp^2 hybridization which was not terminal and is commonly found at 140 ppm but here was found 143.3 ppm. The presence of electronegative Nitrogen (N) was correlated with the observed value of carbon which showed some deviation. Also the aryl group contains carbon atoms (C_1 - C_6) which were observed from 120-130 ppm whereas the phenolic carbon (C_1) of the molecule showed peak at 157.2 ppm. This explained the presence of more electronegative oxygen atom (O) which was bonded to carbon and described the downfield shift. On the contrary oxygen atoms also contain lone pair which was correlated with the ortho (C_2) and para (C_4) carbon of the phenol which exhibited the up field shift by mesomeric effect with observed value 117.8 and 121.4 ppm, respectively. The meta carbon (C_3) of phenol was remained unchanged with observed value 132.4 ppm. On the other hand C_5 , C_6 and C_7 were

Table 6: C^{13} NMR data of ligand

Position of carbon	Observed value in ppm	Peak area equivalent to no. of carbon
C ₁	157.2	One
C ₂	117.8	One
C ₃	132.4	One
C ₄	121.4	One
C ₅	127.5	One
C ₆	131.8	One
C ₇	143.3	One
C ₈	143.0	One
C ₉ , C ₁₃	113.9	Two
C ₁₀ , C ₁₂	129.5	Two
C ₁₁	122.4	One

observed at 127.5, 131.8 and 143.3 ppm, respectively. Their deviation could be correlated with the adjacent double bond of CH = N. The six carbon atoms of the other ring present in the molecule showed normal behavior and values except (C₈) which was bonded to the more electronegative nitrogen atom as given in Table 6.

Characterization of monometallic complexes

Fourier Transform Infrared spectroscopy (FTIR) analysis: The monometallic complexes were analyzed by FTIR. The range used for FTIR spectra of the titled complexes was from 4000-400 cm^{-1} as KBr pellets. On the bases of previously reported work this assignment was made. Stretching vibrations of N-H group for Cadmium (L₃), Copper (L₃), Manganese (L₃) and Chromium (L₃) were observed at 3452, 3448.9, 3446.2 and 3450.7 cm^{-1} , correspondingly due to the coordinate covalent bond formed by metal with imine nitrogen lone pair. Bending vibrations for CH = N group for Cadmium (L₃), Copper (L₃), Manganese (L₃) and Chromium (L₃) were observed at 1602.65 and 1578.7 cm^{-1} , 1601.7 and 1570.2 cm^{-1} , 1600.9 and 1568.1 cm^{-1} and 1601.2 and 1572.4 cm^{-1} , respectively. Metal complexes do not contain phenolic OH groups so these vibrations were absent in metal complexes.

XRD analysis of monometallic Cadmium complex with L: The structure of the complex (Cd (C₁₃H₁₁N₂O)₂) was confirmed by X-ray crystallography. The crystallographic data and atomic numbering scheme is shown in Table 7.

Antimicrobial activity analyses: The antimicrobial activity was determined by using disc diffusion method against different species of fungus and bacteria. The results confirmed that the activity of bimetallic complexes is considerable high against bacteria and fungus as compared to ligand.

Antibacterial activity: The ligand (L) and monometallic complexes with (L) were tested for their activity against different strains using Rifampicin as positive control (Kovancic, 1967). The ligand (L) showed less activity as compared to monometallic complexes. The highest activity was shown against *Pseudomonas aeruginosa* with cadmium 8.75±1.258 mm. The activity against *Vibrio cholera* and *Salmonella typhi* were average with zones 7.25±1.258 and 7.5±0.577 mm, respectively. All results are given in comparison with standard drug (Rifampicin) which gave the zone 24.5±0.577 mm as given in Table 8 and Fig. 3.

Table 7: Crystallographic data

Parameters	Description
Formula	C ₂₆ H ₂₂ ZnN ₄ O ₂
F. wt.	487
Crystal class	Monoclinic
Space group C	2/c
a	21.932(3)
b	6.0755(5)
c	14.208(2)
Alpha	90
Beta	97.471(5)
Gamma	90
Colour	White
Shape	Prism
Volume	1883.18(7)
Z	4
Radiation type	Mo K α
Wavelength	0.710730
Dx	1.62
Theta max	28.32
H min, H max	-35, 35
K min, K max	-9, 8
L min, L max	-19, 19
R-factor	0.05
Max shift/su	0.0003
Weighted R-factor	0.08
Delta Rho min	-1.69
Delta Rho max	2.92
Reflections used	3328
Sigma (I) limit	-10.00
No. of parameters	191
Goodness of fit	1.096

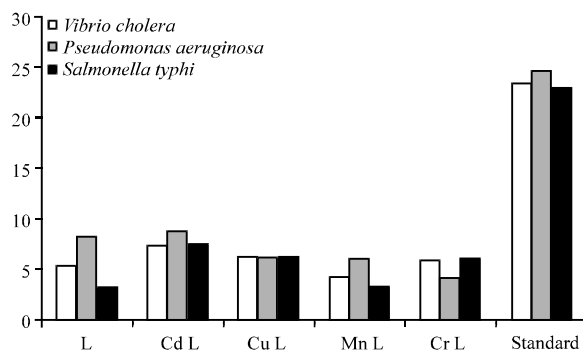


Fig. 3: Antibacterial activity data of Ligand (L) and complexes with ligand

Antifungal activity: The ligand (L) and monometallic complexes with (L) were tested for their activity against various fungus starins (*A. alternata*, *A. niger*, *A. flavis*) by using disc diffusion method. Fluconazol is used as standard drug. The highest activity was shown by monometallic

Table 8: Antibacterial activity data of ligand and complexes

Compounds	Tested microorganism diameter of inhibition zone	
	<i>E. coli</i>	Structure
Ligand	5.25±0.957	C ₁₃ H ₁₂ ON ₂
Cd (L)	5.75±0.500	Cd (C ₁₃ H ₁₂ ON ₂) ₂
Cu (L)	6.25±0.957	Cu (C ₁₃ H ₁₂ ON ₂) ₂
Mn (L)	4.25±0.957	Mn(C ₁₃ H ₁₂ ON ₂) ₂
Cr (L)	7.25±1.258	Cr (C ₁₃ H ₁₂ ON ₂) ₂
Standard	23.25±2.061	Standard

Table 9: Antifungal activity data of ligand and complexes

Compounds	Tested microorganism diameter of inhibition zone	
	<i>A. niger</i>	Structure
Ligand	5.25±0.957	C ₁₃ H ₁₂ ON ₂
Cd (L)	5.75±0.500	Cd (C ₁₃ H ₁₂ ON ₂) ₂
Cu (L)	6.25±0.957	Cu (C ₁₃ H ₁₂ ON ₂) ₂
Mn (L)	4.25±0.957	Mn(C ₁₃ H ₁₂ ON ₂) ₂
Cr (L)	7.25±1.258	Cr (C ₁₃ H ₁₂ ON ₂) ₂
Standard	24.5±0.5770	Standard

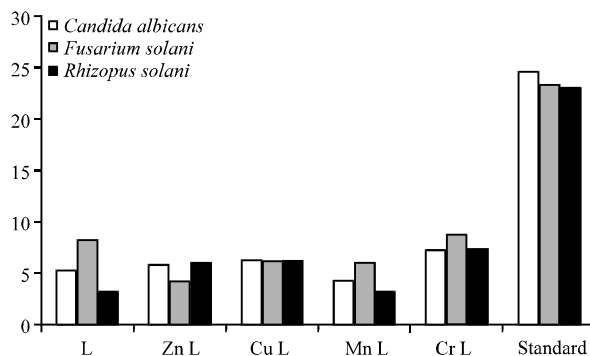


Fig. 4: Antifungal activity data of ligand (L) and complexes with L

complexes. The highest activity was against *Fusarium solani* with zone 8.75±1.258 mm and activity against *Candida albicans* and *Rhizopus solani* was average with zone 7.25±1.258 and 7.5±0.577 mm, respectively. All above results are in comparison with standard drug (Fluconazol) which gave the zone 24.0±0.577 mm as given in Table 9 and Fig. 4.

It is recommended that the antimicrobial activity of the complexes is due to either by killing the microbes or inhibiting their development by jamming their active sites. The values designated that most complexes have higher antimicrobial activity than the free ligands. The enhanced activity of metal complexes can be explained on the basis of chelation. On chelation, the polarity of the metal ion will be decreased to a greater extent due to the overlap of the ligand (Betteridge *et al.*, 2003).

CONCLUSION

From the results it was concluded that by using multi component solvent system the crystallization of the product can be enhanced. The studies also indicate that the chelating power

of the metal ion was enhanced by coordination with ligand which ultimately help the metal complexes to restrict the growth of bacteria and fungus as compared to ligand.

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