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Synthesis, Characterisation and Biological Activity of Schiff Base and its Cu(II), Pd(II), Pt(II) Complexes Derived from Tyrosine and Aromatic Aldehyde

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Abstract. Schiff base derived from the condensation of tyrosine and the salicylaldehyde has been synthesised and its Cu(II), Pd(II) and Pt(II) complexes have been prepared. The prepared Schiff base and its complexes were analysed and characterised by using different instrumental techniques, such as elemental analysis, FTIR, UV-Vis, ^{1}H NMR, thermal analysis and XRD. The analytical data revealed that the ligand L-1 can coordinate in tridentate manner via the phenolate-O, azomethine-N and tyrosine O-atoms, resulting in the formation of 1:1 [metal: ligand] complexes. Thermal analysis revealed the presence of water molecules in the complexes. In vitro antibacterial activity of the complexes was evaluated against different bacterial strains e.g., *Pseudomonas aeruginosa* and *Bacillus subtilis* by the well-diffusion method. The data showed that transition metal complexes have significant improved antibacterial activity than parent drug.

Keywords: Schiff base, amino acid, antibacterial activity, transition metal complexes

Introduction

Schiff bases and their bio-active complexes have been studied extensively over the past decade. Extensive investigations have been made on salicylidene-amino acid Schiff bases and their metal complexes (Sharma *et al.*, 1997). Metal chelates of the Schiff bases derived from salicylaldehyde and amino acids have been shown to an important class of compounds in elucidating the mechanism of transamination reaction in biological systems (Chohan *et al.*, 1997). The special structure and ligand diversity are important factors to determine the chemical and biological importance of the Schiff bases. Hodnett prepared a series of Schiff base metal complexes and carried out antitumor experiments, which indicated that aldehyde substituent was superior to amine substituent in anticancer effect and salicylaldehyde Schiff bases were superior to other aldehyde Schiff bases (Hodnett and Dunn, 1972).

Various studies have shown that amino acid metal complexes of Schiff bases have antibacterial (Venkatesh, 2011; Mounika *et al.*, 2010), anticancer (Miri *et al.*, 2013; Ali *et al.*, 2012) and antioxidant (Wei *et al.*, 2000) activities. The antibacterial (Chohan *et al.*,1997) and antifungal (Łukaszuk *et al.*, 2007) properties of a number of Cu(II) complexes have been evaluated against various pathogenic bacteria and fungi. Amino acid-palladium complexes have also revealed remarkable antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* bacteria (Cristina *et al.*, 2014). Schiff-bases of 1,1′ di-substituted ferrocene and their Pd(II) and Pt(IV) complexes were found to have valuable activity against the various bacterial strains Hegazy, 2012. In the present study, synthesis, characterisation and antibacterial evaluation of Schiff base and its complexes have been reported.

Materials and Methods

Tyrosine, salicylaldehyde, cupric acetate monohydrate, platinum chloride and palladium chloride were purchased from Sigma-Aldrich. KOH was obtained from Merk. All the solvents were of analytical grade and used as received without further purification.

The UV-spectra was recorded on UV-2800 spectrophotometer Hitachi, in the range of 200-800 nm. FTIR spectra were obtained by using Agilent-650 spectrophotometer in the region 4000-650 cm^{-1}. Elemental (CHN) analysis was performed by LECO (Truspec micro) apparatus at Forman Christian College, Lahore, Pakistan. The ^{1}H NMR spectra were obtained by the help of Bruker (Advance 400) spectrometer using ^{6}d-DMSO as a solvent at HEJ Research Institute of Chemistry, Karachi, Pakistan. Thermogravimetric analysis was performed using a simultaneous TGA-DSC analyzer (Instrument SDT Q600 V8.). The compounds were placed in

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aluminium pan and heated in nitrogen atmosphere (100 mL/ min) up to 1000°C at a rate of 10 °C/ min.

Preparation of Schiff base ligand L-1. To a solution of (1.81g, 10 mmol) tyrosine in 10 mL of ethanol, KOH (0.5611g, 10 mmol) pellets were dissolved by continuous stirring in a 100 mL RB flask. Salicylaldehyde (1.06 mL, 10 mmol) in 10 mL of ethanol was added slowly to the RB flask and refluxed the reaction mixture for 3h at 50 °C to 60 °C. The resulting yellow precipitates were collected by vacuum filtration, washed successively, dried in vacuum and recrystallized with absolute ethanol (Fig. 1).

Preparation of L-1 Cu(II), Pd(II), Pt(II) complexes. To a solution of (1.81g, 10 mmol) tyrosine in 10 mL of ethanol, KOH (0.5611g, 10 mmol) pellets were dissolved by continuous stirring in a 100mL RB flask. Salicylaldehyde (1.06 mL, 10 mmol) in 10 mL of ethanol was added slowly to the RB flask and refluxed the reaction mixture for 3h at 50 to 60 °C. A solution of metal salt, copper acetate monohydrate (10 mmol) and palladium chloride, platinum chloride (5 mmol) in 10mL aqueous methanol was added drop wise to the ligand solution under reflux for further 3h at 50 to 60 °C. The precipitated complex was filtered off, washed several times with ethanol and dried in vacuum.

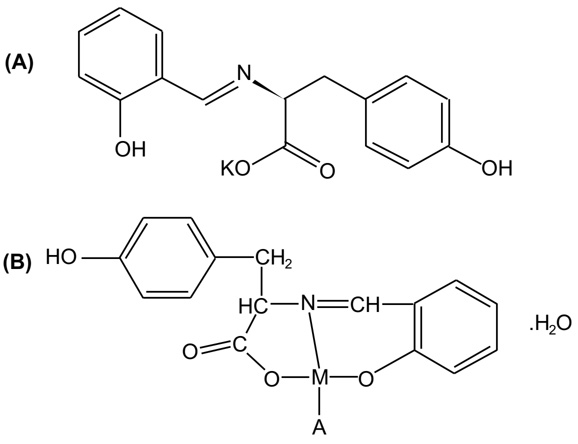
Antibacterial activity (*In vitro*). Antibacterial activities of the ligand and their complexes were checked *in vitro* against the bacterial species (*Pseudomonas aeruginosa, Bacillus subtilis*) by the well diffusion method. Nutrient broth E (LAB068) was dissolved in distilled water, autoclaved and inoculated with bacterial strains after cooling at 37 °C for 24h. In second day, nutrient agar (LAB008) was dissolved in distilled water and autoclaved. After cooling to 50 °C, 100 µL of the prepared bacterial culture added to the molten nutrient agar, and was poured into petri plates. Once the medium was solidified, wells were made with sterile borer (8 mm). A volume of 50 µL of the test sample (10,000 ppm) and positive control was poured into respective wells. The solvent in which sample was dissolved was used as negative control (Ihsan *et al.*, 2012). These plates were incubated at 37 °C for 24h of incubation. The diameter of the clear zones showing no growth of bacteria around each well was measured.

Results and Discussion

The paper describes the synthesis of Schiff base ligands L-1 like salicylaldehyde-tyrosine and its complexes with Cu (II), Pd(II), and Pt(II) metal ions. The structure of the ligand L-1 and its complexes was established from FTIR, UV-Vis, CHN and thermal analysis. Proposed structure for schiff base L-1 was represented in Fig.1.

Physical characteristics and elemental analysis of Schiff base L-1. Synthesized compounds possessed solid physical state and were polar in nature hence, insoluble in non polar solvents. Molecular formula, molecular weight and elemental analysis data was depicted in Table 1. CHN analysis was performed at 950°C degrees with O_2 gas used in combustion furnace along with the attached IR detector for giving the required percentages. Data of elemental analysis was in good agreement with theoretical values (Table 1). Colour, yield, melting points and solubility of the compounds were mentioned in Table 2.

^{1}H NMR spectral analysis. ^{1}H NMR spectral analysis in ^{6}d-DMSO of the synthesized ligand L-1 was summarized in Table 1. In ^{1}H NMR spectra, the peak obtained at 14·34 ppm (s, 1H) was attributed to the phenolic –OH group and a broad singlet peak at 9.16 ppm may be for -OH_{tyr} group. The characteristic imino proton (H-C=N) was appeared at its expected value 8.021 ppm as singlet. The spectra exhibit the signals at 7.17 ppm (2m, 1H), 6.45 ppm (d, ^{1}H) and 6.56ppm (t, 1H) due to $(–CH)_{sali}$. Doublet signals at 6.90 ppm and at 6.67 ppm were attributed to $(–CH)_{tyr}$. Furthermore,



where M= Cu, Pt ions and A= CH_3 COO- for Cu-complex and A= Cl, for Pd and Pt complexes

Fig.1a. **(A)** Proposed structure for Schiff base L-1; **(B)** Proposed structure for Schiff base L-1 complexes

Table 1. Analytical data for Schiff base L-1

Schiff base	Mol. formula	Mol. weight	Elemental analysis found (calc.)%				^{1}H NMR spectral data (ppm)					
			C	N	H	S	-OH$_{salicy.}$	-OH$_{tyr.}$	-CH=N	Ar(-CH)	-CH	-CH$_2$
L-1	$C_{16}H_{14}KNO_4$	323.1	58.49 (59.42)	4.61 (4.32)	5.41 (4.36)	0 (0)	14.34 (s,1H,br)	9.16 (s,1H,br)	8.021 (s, 1H)	6.56-7.17 (m,1H)	3.13 (dd, 1H)	2.77 (dd,2H)

Table 2. Physical characterisation data of Schiff bases and their metal complexes

Compounds	Colour	Yield (%)	Melting point	Solubility
L-1	Pale yellow	54.32	222°C	Water, Methanol
L-1 Cu(II) complex	Green	41.46	140°C	Methanol
L-1 Pd(II) complex	Greyish brown	45.64	272°C	Ethanol
L-1 Pt(II) complex	Light brown	40.01	235°C	DMSO

the –CH and –CH$_2$ signals were found at 3.13 ppm and 2.77 ppm as doublet-doublet. The disappearance of aldehyde (δ = 9 10ppm) and amino (δ = 4-6 ppm) protons in the ligands spectra was the indication of its purity.

FTIR spectroscopy. The spectra were measured at room temperature (Table 3). The azomethine (C=N stretching) band at 1639 cm^{-1} in the FTIR spectrum of the ligand L-1 representing the formation of Schiff base. This bond in the Cu(II), Pd(II) and Pt(II) complexes shifted to 1641, 1609 and 1641 cm^{-1}, respectively suggesting the coordination of metal ion with azomethine nitrogen atom (Khander *et al.*, 2005; Yusuff and Sreekala, 1991).

The bands in ligand L-1 at 1587 and 1372 cm^{-1} might be of $(COO^-)_{as}$ and $(COO^-)_s$, respectively. In the spectra of the complexes, the shift of carboxyl group bands $[(\nu)_{as}$ and $(\nu)_s]$ means that the carboxyl group was in coordination with metal ion. In addition, the further evidence of this coordination was observed by the positive shift of the ν(phenolic C-O)band about ($\approx$10 cm^{-1}) in the IR spectra of the Cu(II), Pd(II) and Pt(II) complexes, when compared to the IR spectrum of the free ligand with phenolic C-O band at 1248 cm^{-1} (Socrates, 2001; Hadi 2009). Accordingly, the ligand acts as a tridentate chelating agent, bonded to the metal ion via the phenolate-O, tyrosine-O and azomethine-N atoms.

UV spectroscopy. The wavelengths of maximum absorbance (λ_{max}), of the ligand and its complexes were scanned and summarized in Table 3. The electronic absorption spectra of the Schiff base L-1 and its complexes showed π - π * (aromatic ring) and n -π * (HC=N) transitions.

The UV spectra of the ligand L -1 showed three bands. The absorption band appeared at 254 nm (L-1), may be attributed to the benzenoid π - π * transition. The absorption band at 226 nm (L-1) may be assigned to the azomethine n -π * transitions, while the band at 320 nm (L-1) may be due to the carbonyl group of the compounds.

The band corresponding to the azomethine group showed broadening and shifting to a longer wavelength on going from ligand to complex, indicating the coordination of ligand to metal through the azomethine moiety (Amundsen *et al.*, 1977). Further, colour of the complexes was different from the ligands and salts which was also an important indication of coordination

Table 3. FTIR and UV data of Schiff base and its complex

Compounds	IR Frequencies (cm^{-1})				
	νC=N	$\upsilon(COO^-)_{asy.}$	$\upsilon(COO^-)_{sym.}$	υ(phenolic C-O).	λ max(nm).
L-1	1639	1587	1372	1248	226,254,320
L-1 Cu(II)complex	1641	1574	1404	1246	242,366,652
L-1 Pd(II)complex	1609	1587	1419	1246	224,276
L-1 Pt(II) complex	1641	1579	1410	1244	278,368

resulting in different absorption bands in their intensity and position (Al-Jeboori *et al.*, 2014).

Complexes of L-1 showed a number of bands. The absorption bands appeared in two main wavelength zones, e.g., 224-278 nm (lower wavelength bands) and 276-368 nm (higher wavelength bans). The peaks appeared in the lower wavelength zones might be due to aromatic nature of Schiff base ligand and the peaks in the higher wavelength could be due to the presence of C=N or C=O or a combination of them.

The bands in the visible region at 652 nm (L-1 Cu(II) complex), also indicated that the imino nitrogen was involved in coordination to the metal ion which suggested the square planar geometry of the complexes (Byers *et al.*, 1968).

Thermal analysis TGA and DSC were carried out to evaluate the thermal stability of the prepared Schiff base ligand L-1 and its Cu(II), Pd(II) and Pt(II) complexes (Table 4).

TGA & DSC analysis of L-1. The TGA scan of Schiff base L-1 showed the loss in weight in three stages. The initial loss was 10% in the temperature range of 60-260°C which may be due to water loss. Second loss 51.28% occurred at the temperature range of 260-769°C corresponding to the loss of 50.13% organic moiety ($C_9H_8NO_2$). Third loss about 23.12% was observed from 769-948°C corresponding to the calculated loss (24.14%) of benzene. The DSC curve of Schiff base L-1 showed two exothermic peaks at 455 °C, 592 °C and two endothermic peaks at 260 °C and at 819 °C. The endothermic peaks were probably attributed to phase transition and the exothermic peaks attributed to decomposition of compound.

TGA & DSC analysis of L-1 Cu(II) complex. The thermal decomposition of L-1 Cu(II) complex occurred in different stages . The initial loss of about 4.0% was noticed from 50-185°C temperature range. It may be due to the elimination of water molecule (calc. 4.25%). This range of temperature had two peaks at 98.27 °C (endo) and 165 °C (exo). The second stage of decomposition was occurred in 185-253°C temperature range, due to melting and partial decomposition of the ligand bringing the weight loss of about 27.0% (calc. 27.86%, for C_8H_8N moiety of the ligand) having a peak in DSC curve at 210 °C (endo). The decomposition of about 13.0% in the third temperature range 253-528 °C was in agreement with the calculated value 13.93%, CH_3COO^- loss. This temperature range had exothermic peak at 476°C. 35.0% loss in weight (calc. 35.93%) was noticed in the range of temperature 528-998 °C involving the formation of intermediates that may be C_7H_6O, COO^-. Fourth temperature range nearly 998-1000°C showed 18% weight loss which was in agreement with calculated weight 18% of CuO residue.

TGA & DSC analysis of L-1 Pd(II) complex. The thermal decomposition of L-1 Pd(II) complex was observed in number of stages. The first stage of 2.0%

Table 4. Thermogravimetric results of Schiff base metal complexes

Compounds	Temperature range (°C)	Loss in weight		DSC peak (°C)	Loss type
		Found	Calc.(%)		
L-1	60-260°C	10.00	10.52	260°C (endo)	2OH
	260-769°C	51.28	50.13	455°C(exo), 592°C(exo)	$C_9H_8NO_2$
	269-948°C	23.12	24.14	819°C (exo)	Residue of CH+K
L-1 Cu(II)complex	50-185°C	4.0	4.25	98.27°C(endo),165°C(exo)	H_2O
	185-253°C	27.0	27.86	210°C (endo)	C_8H_8N
	253-528°C	13.0	13.93	476°C(exo)	CH_3COO^-
	528-998°C	35.0	35.93	-	C_7H_6O,COO^-
	~998–1000°C	18.0	18.0	-	CuO
L-1 Pd(II)complex	50-259°C	2.0	2.59	-	H_2O
	~259–302°C	51.0	51.0	258°C	$H_{32}O_{22}NO_3$
	302-840°C	27.0	27.0	305°C	$C_9H_6NO_4$
	~840-1000°C	17.0	17.67	764°C(endo),779°C(exo)	PdO
L-1 Pt(II) complex	~50-250°C	3.0	3.38	-	H_2O
	250-300°C	20.0	20.13	290°C(exo),291°C(endo)	C_7H_7O
	300-700°C	36.0	36.78	-	$C_9H_6NO_2Cl$
	~700-1000°C	39.0	39.6	-	PtO

mass loss was in agreement with calculated 2.59% loss of H_2O molecule in 50-259 °C temperature range with an exothermic peak at 258 °C. The second stage of decomposition occured in the temperature range of nearly 259-302 °C, due to melting and partial decomposition of the ligand showing one endothermic peak at 305°C, involing the weight loss of about 51.0% which was same to the calculated value 51.0%, corresponding to the loss of $C_{32}H_{22}NO_3$ molecule. The decomposition temperature range from 302-833 °C was involved 27.0% weight loss in third stage which was close to the calculated value 27.7%. This may be due to the removal of $C_9H_6NO_4$ moiety involving two peaks at 764 °C (endo) and 779 °C(exo). In temperature range ~833-964 °C, 17 % lose was observed that was near to the calculated 17.67 % mass loss. This may be attributed to Pd oxide residue.

TGA & DSC analysis of L-1 Pt(II) complex. The thermal decomposition of L-1 Pt(II) complex was observed in three stages. The first stage of degradation was 3.0% (Calc.3.38%) in the temperature range nearly 50-250 °C. It may be due attributed to the elimination of water molecule. In the second stage of decomposition about 20.0 % was occurred in 250-300 °C temperature range, with one exothermic peak at 255 °C and one endothermic peak at 291°C, due to further decomposition and removal of C_7H_7O moiety of the ligand (cal.20.13%). The decomposition range (300-700 °C) is third stage showing 36.0% weight loss which was in agreement (calculated 36.78%) of $C_9H_6NO_2Cl$ loss from the complex. The final remnant mass 39.0% loss may be of metallic oxide in the temperature range nearly 700-1000 °C.

X-ray powder diffraction studies. The X-ray diffraction study was performed on Panalytical automated X-ray powdered diffractometer. The following experimental conditions in reading the pattern were employed. The operating target voltage was 40-45 kV. Copper was employed as anode and 1.54060Å wavelength for K-Alpha1 [Å] and K-Alpha2 [Å] was used. The powdered XRD analysis was carried out to determine the crystalline or amorphous nature of the compounds. The complex formation was confirmed by the appearance of strong and broad peak. In the diffractograms of ligand L-1 and its complexes namely L-1 Cu(II), L-1 Pd(II) and L-1 Pt(II), sharp peaks were obtained that confirmed there crystalline nature.

The average particles size for ligand L-1 and its L-1 Cu(II), L-1 Pd(II) and L-1 Pt(II) complexes, were

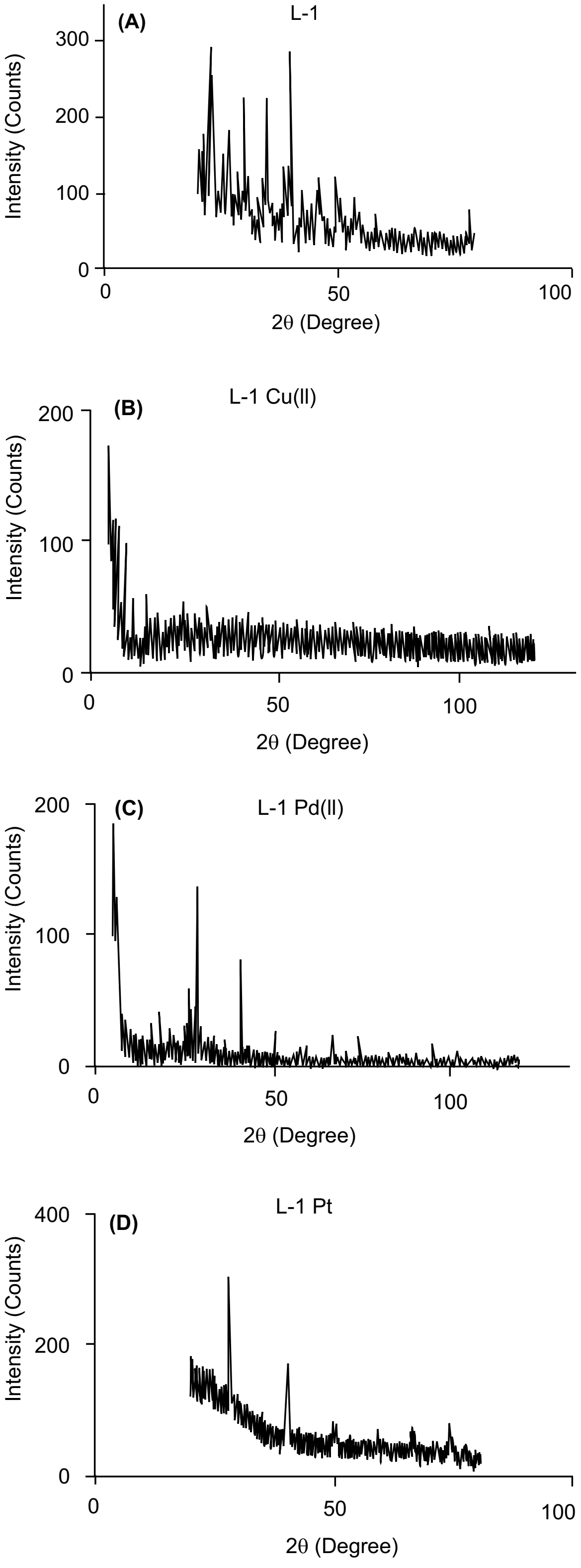


Fig. 2. XRD Diffractogram of **(A)** ligand L-1, **(B)** L-1 Cu(II) Complex, **(C)** L-1 Pd(II) Complex and **(D)** L1-Pt Complex

calculated to be about 67.51, 84.56, 108.85 and 36.23 nm, respectively by applying full width at half maximum (FWHM) and the value of 2θ of characteristic peak using the Debye-Scherer equation.

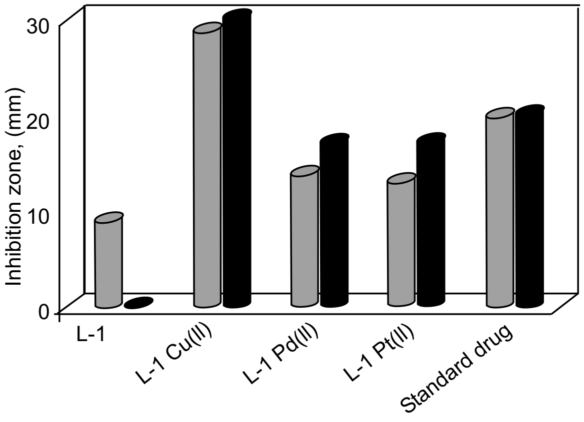
$$D = k\lambda / \beta \cos\theta$$

Where:

D was the average size,K was a constant(ca. 0.9), λ was the wavelength of Cu Kα, β was the full width at half maximum (FWHM) of the diffraction peak and θ was the Bragg's angle.The diffractogram of compounds were shown in Fig. 2 (A-D).

Antibacterial activity (*In vitro*). All the synthesized Schiff base ligand L-1 and its metal complexes were screened (*in vitro)* for their antibacterial activity against bacteria such as *Pseudomonas aeruginosa* and *Bacillus subtilis* by well diffusion method. The zone of inhibition values were measured in mm. The antibacterial activity results were depicted in Fig 3.

The compound L-1 showed antibacterial activity against *P. aeruginosa* and no activity against *B. subtilis,* while the complexes of L-1 Schiff base exhibited highest activity against *B. subtilis* bacteria and least in *P. aeruginosa* bacteria. When compared to the Schiff base ligand L-1, all the complexes exhibited higher zone of inhibition against both the bacterial strains due to the differences in their structures.



Bacterial strains	L-1	L1-Cu(II)	L1-PD(II)	L1-Pt(II)	Std.Drug (100ppm)
▨ *P.aeruginosa*	9	29	14	13	20
■ *B. subitilis*	0	30	17	17	20

Fig. 3. Effect of ligand L-1 and its Cu(II), Pd(II) and Pt(II) complexes toward *Pseudomonas aeruginosa* and *Bacillus subtilis* at 10,000 ppm concentration.

The higher antibacterial of metal complexes than those of the free ligand can be explained on the basis of Chelation theory. On chelation, the metal ion polarity will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of pi-electrons over the whole chelating ring and increases the complexes penetration into lipid membranes and blocking of the metal binding sites in the enzymes of micoorganisms. (Singh *et al*., 2008; Iqbal *et al*., 2006).

Conclusion

In the present research study, mononuclear transition metal complexes of Cu(II), Pd(II) and Pt(II) with a newly synthesised ligand derived from salicylaldehyde and tyrosine were prepared. The synthesised compounds were characterised by various physicochemical and spectral analyses. The results exhibited that the ligand L-1 was bonded to the metal (Cu(II), Pd(II) and Pt(II)) ion in a tridentate manner *via* the phenolate-O, tyrosine O-and azomethine-N atoms. The antibacterial data showed that the metal complexes have more biological activity compared to that of free ligand. The copper complexes have remarked antibacterial activities towards bacterial strains, *Pseudomonas aeruginosa* and *Bacillus subtilis*. The L-1 Cu(II) complex showed excellent antibacterial activity against *Bacillus subtilis* strain relative to the Pd (II) and Pt(II) complexes. L-1 Cu(II) complex also showed more antibacterial potency then the control drug. The promising antimicrobial results of ligand and complexes are encouraging further research for application against infections caused by microbial pathogens. Further investigations may prove some of these complexes as suitable agents for future antibiotic drugs especially for the treatment of infections caused by any of these particular bacterial strains.

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