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Exploring the Theranostic potential of binuclear amino acid Schiff base metal complexes derived from leucine

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Abstract : *The design and synthesis of the new biologically active binuclear amino acid Schiff base metal complexes. The Schiff base metal complexes were synthesized and characterized using different physicochemical studies as IR spectra, XRD analysis, elemental analyses, mass spectra, conductivity measurement, UV–vis Spectra, 1HNMR spectra and its metal complexes were screened for their antimicrobial activity. Furthermore, IR spectral studies of all the binuclear amino acids Schiff base metal complexes exhibit a similar aspect about the bonding mode of the ligand to the metal ions and reveal that the amino acid Schiff base ligand has coordinated through the deprotonated hydroxyl oxygen, carbonyl oxygen and imine nitrogen. The molar conductance data of the amino acid Schiff base binuclear complexes suggest them to be nonelectrolytes. The in vitro antibacterial activity results showed that most of the synthesized amino acid Schiff base binuclear complexes using leucine based Schiff bases possess good antibacterial activity against gram positive and gram negative bacteria. The cytotoxic effect on MCF-7 cell lines of the synthesized compounds shown potent cytotoxic activity.*

Keywords: *Amino acid Schiff base, antibacterial activity, MCF-7 cancer cell line.*

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I. Introduction

Schiff base metal complexes are some of the most widely used and easily synthesized organic compounds [1-2]. The moderate electron donor property, chelating nature, easily tunable electronic and steric effects have proved Schiff base metal complexes were highly versatile in nature. The development of Schiff base metal complexes based agents has had a tremendous role in the present progress in cancer chemotherapy. Recently, the amino acids Schiff base binuclear metal complexes have acquired special attention in pharmaceutical and medicinal field since they show outstanding biological activities [3]. Amino acids Schiff base ligands containing a variety of donor atoms such as Nitrogen, Oxygen, Sulphur, are important biological activities [4]. Schiff bases and their complexes have been studied for their interesting and important properties, like catalytic activity [5] and transfer of the amino group [6] biological activity [7], Industrial applications. Our interest in the synthesis, spectral characterization of novel amino acids Schiff bases and their binuclear metal complexes involve desired biological activity to ascertain bioactive replica complexes. The present paper deals with the Studies on the biologically active binucleating amino acid Schiff base metal complexes derived from Leucine and salicylaldehyde and to examine their bioefficacy of amino acid Schiff base ligand as well as binuclear metal complexes.

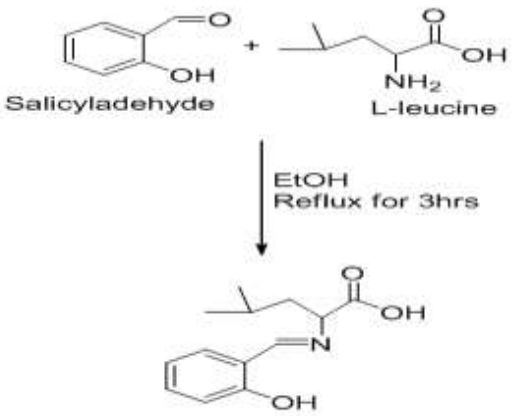
II. Experimental

2.1Materials and methods

The materials and reagents were obtained from commercial supplier (Sigma Aldrich) and were used without further purification. CHN analysis of the metal complexes was carried out on Elemental Analysersystemevario micro V1.6.2 GmbH. The percentage metal content in each complex was determined by standard EDTA complex metric titration. Melting points were determined on a Gallenkamp melting point apparatus. The molar conductances of the amino acid Schiff base metal complexes in DMSO at 10^{-3} M were measured on 4150 Jenway conductivity meter. The infrared spectra of the amino acid Schiff base ligand and its binuclear metal complexes were determined in the region 4000–400 cm^{-1} on Perkin Elmer spectrum 11 FT-IR Spectrophotometer. ^{1}HNMR spectrum was recorded with a model Bruker Advance DPZ-300 spectrometer operating at 300 MHz using DMSO-d6 as a solvent and TMS as an internal standard. The electronic spectra were obtained on Labomed double beam UV-visible Spectrophotometer in the ranges 200–400 nm and 400–800 nm for UV and visible regions respectively. The ligand and their metal chelates have been screened for their antibacterial activities using the disc diffusion method against the selected bacterias.

2.2Synthesis of amino acid Schiff base ligand

Aqueous solution of Leucine (0.001 mol) in 5 mL water containing NaOH (0.001 mol), salicyaldehyde in 5 mL ethanol was added drop wise with constant stirring and heated under reflux for 3 hrs on a hot plate at 50 °C. Then the reaction mixture was cooled to room temperature, fine shining yellow precipitate of the amino acid Schiff base ligand formed was filtered off, washed with ethanol-water mixture and stored in a vaccum desiccator over anhydrous calcium chloride [8].

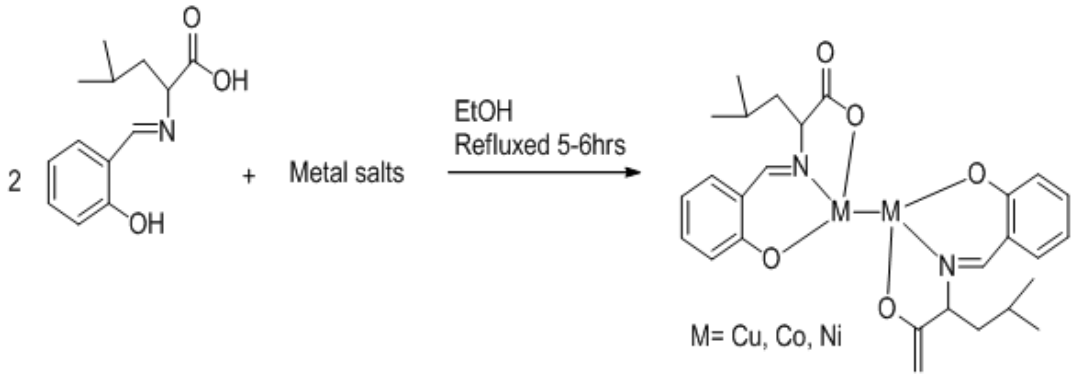


(*E*)-2-((2-hydroxybenzylidene)amino)-4-methylpentanoic acid

Scheme.1. Synthesis of amino acid Schiff base ligand

2.3Synthesis of Binuclear amino acid Schiff base complexes

To an ethanolic solution of the Schiff base ligand the metal acetate salts (M=Cu,Co,Ni) was dissolved in minimum water (5 mL), then added drop wise with constant stirring and finally heated under reflux for 5-6 hrs on a hot plate at 50 °C. A fine green precipitate of the solid complex formed was filtered off, washed with ethanol-water mixture and stored in a vacuum desiccator over anhydrous calcium chloride. All other transition metal complexes were synthesized using the same procedure.



Scheme.2. Synthesis of Binuclear amino acid Schiff base complexes of (Cu, Co, Ni)

III. Results And Discussion

The synthesized amino acid Schiff base ligand and its metal complexes were stable in air, partially soluble in water and completely soluble in common organic solvents. The presence of leucine and salicylaldehyde in the metal complexes has been confirmed by TLC after hydrolysis of the amino acid Schiff base metal complexes. The compounds were dissolved in EtOH and molar conductance 10^{-3} M of solution at 25 °C was measured. The molar conductance values of the amino acid Schiff base binuclear metal complexes fall in the range from 40.32 to 60.17Ω^{-1} cm^2 mol^{-1} indicating that these metal complexes are non-electrolytic in nature. The structure of synthesized amino acid Schiff base ligand along with binuclear metal complexes was investigated by different physico-chemical characterization as follows:

3.1. IR study

The most important IR spectral data of the amino acid Schiff base binuclear metal complexes have been determined by vigilant comparison with the spectra of amino acid Schiff base ligand derived from leucine and salicylaldehyde. The IR spectra predicted all the absorption bands of the amino acid Schiff base ligand and some new absorption bands at particular frequency confirmed the modes of absorption and the completion of the amino acid Schiff base ligand with the metal ions through nitrogen and oxygen.IR spectra of the amino acid Schiff base ligand shows band around 1630 cm^{-1} assigned to the azomethine functional group, this confirms the condensation between the amino group of leucine and the aldehyde group of salicylaldehyde in formation of the amino acid Schiff base [9]. In the complexes, the band shifts to higher frequency by 15 cm^{-1}, indicating involvement of nitrogen of the azomethine group. The medium intensity band of absorption in the amino acid Schiff base ligand around 3120 cm^{-1} due to the phenolic hydroxyl group of the amino acid Schiff base ligand and shifts to lower frequencies in the amino acid Schiff base binuclear metal complexes, indicating coordination of the metal ions to the phenolic oxygen atom [10]. The M–N bond and M–O bond appear in the complexes. In order to confirm the structure of the ligand and the coordination of the amino acid Schiff base complexes. We therefore conclude from the IR spectral data that the amino acid Schiff base ligand all has a similar bonding pattern, coordinating to the metal ion through the azomethine nitrogen atom and the phenolic oxygen atom.

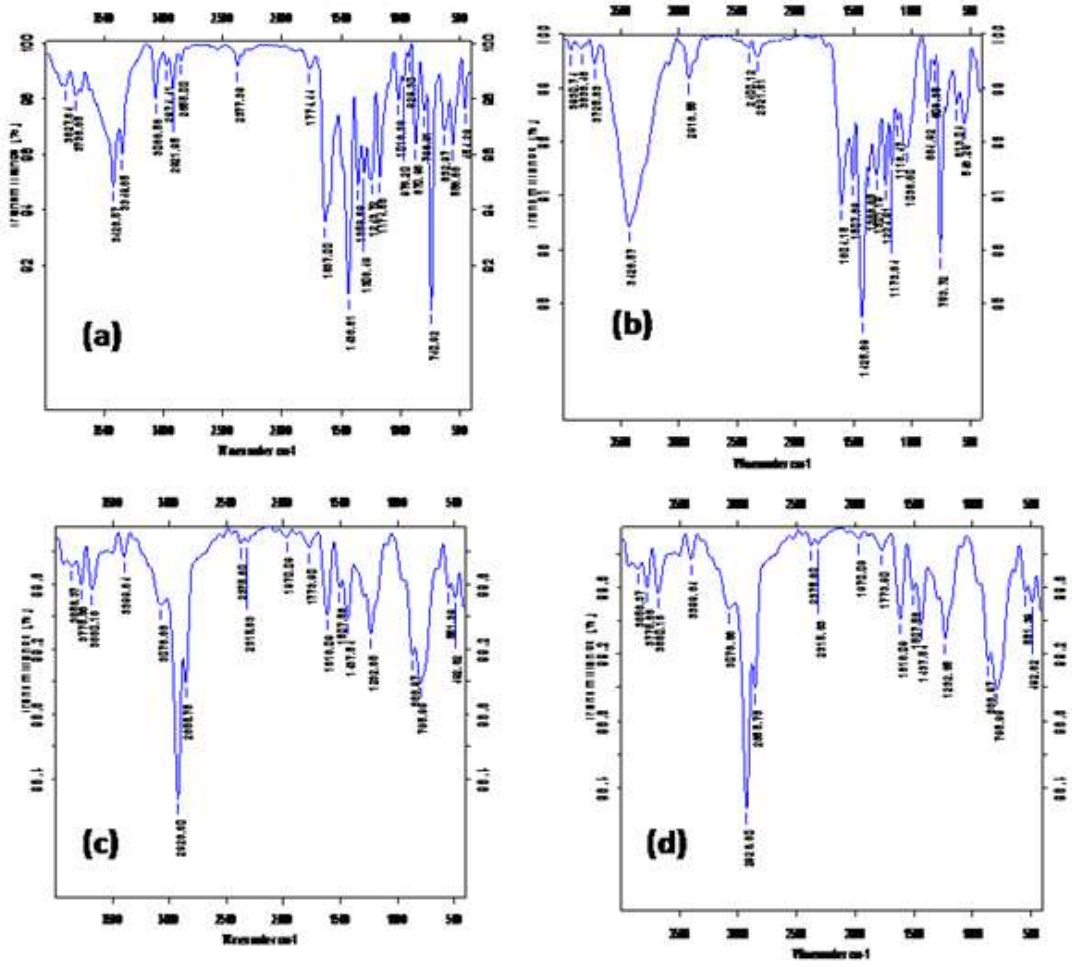


Fig.1. IR spectrum of the (a).amino acid Schiff base ligand (b).Cu (c).Co, (d).Ni

3.2. ^{1}HNMR Spectrum

^{1}HNMR spectrum was recorded in DMSO-d6. All assignments of the proton and carbon atoms were found in their expected region. The NMR spectra of amino acid Schiff base ligand confirmed the absence of aldehyde peak at δ 9-10 ppm and presence of azomethine at δ 8.43.

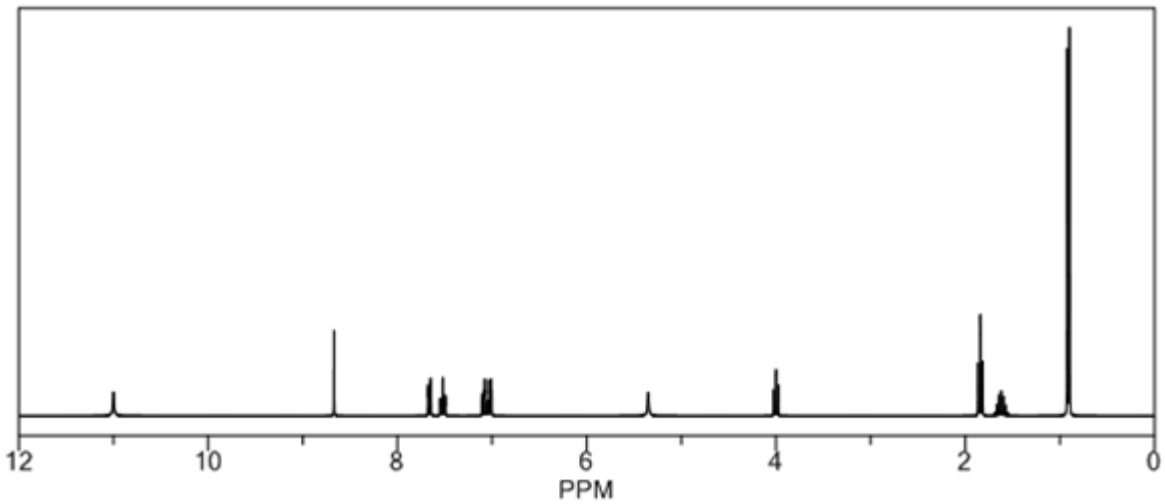


Fig.2. [1]HNMR Spectrum of amino acid Schiff base ligand

Fig.2. [1]HNMR Spectrum of amino acid Schiff base ligand

3.3. Electronic Spectra

The electronic spectra of the amino acid Schiff base ligand and their binuclear metal complexes were recorded in EtOH. The variety of bands observed were assigned to inter ligand, charge transfer of n-π* transition and d-d transition according to their energies and intensities.

The electronic spectrum of the amino acid Schiff base ligand and its binuclear metal complexes were given in Fig. 3 respectively and the spectral data has been given in the absorption of the amino acid Schiff base ligand was characterized by four main absorption bands in the regions 200-400 nm. The band at λmax = 240 nm and λmax = 260 nm is attributed to $\pi \rightarrow \pi^*$ transition [11].The band at λmax = 334 nm corresponds to the $n \rightarrow \pi^*$ transition of the azomethine group andλmax = 425 nm is attributed to the $n \rightarrow \pi^*$ transition associated with the azomethine groupwith intra molecular charge transfer [12]. The electronic spectrum of the Cu complex shows the shoulder of charge transfer transition at 255 nm and broad d–d absorption bands at about 552 and 407 nm, which can assigned to $^2B_1g \rightarrow {}^2A_1g$ and $^2B_1g \rightarrow {}^2Eg$ transitions, respectively. This transition suggests the square-planar geometry around the Cu(II) ions.

The electronic spectrum of Cobalt showed bands at 258, 273 nm and the band appears in the range from 388-452 nm which may be assigned to intra ligand charge transfer, ligand metal charge transfer and to $^2B_1g \rightarrow {}^1A_1g$ and $^1B_1g \rightarrow {}^2Eg$ transitions which also supports square-planar geometry. The electronic spectrum of Ni(II) complex also displayed two bands at 431 and 562 nm which assigned to $^1A_1g \rightarrow {}^1A_2g$ and $^1A_1g \rightarrow {}^1B_1g$ –d transitions, respectively. It confirms the square planar geometry around each Ni(II) ions. Based on the physical, chemical and spectral data, a four coordinate and Trans square planar geometry has been suggested for the amino acid Schiff base binuclear metal complexes.

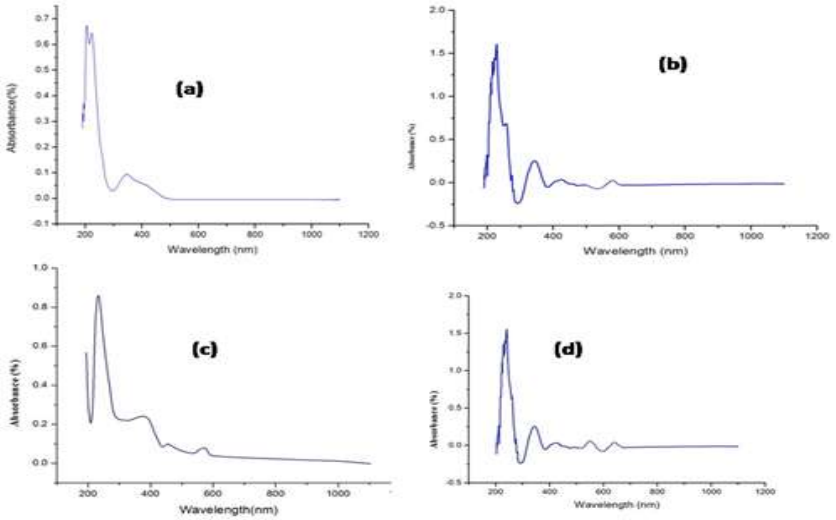


Fig.3. Electronic spectrum of the (a).amino acid Schiff base ligand (b).Cu (c).Co, (d).Ni

3.4. X-ray powder diffraction

The crystal lattice parameters of the complexes of Cu, Ni and Co were measured by recording X-ray diffractogram (Figs. 4.) in the range 5º to 120º 2θ value was performed to obtain further evidence about the structure of the metal complexes. The XRD patterns indicate crystalline nature for the complexes and this behavior is due to the incorporation of water molecules into the coordination sphere Complexes [13-14]. X-ray diffraction studies suggest orthorhombic crystal system for all the metal complexes. It is expected that these complexes may have better value towards biological activity.

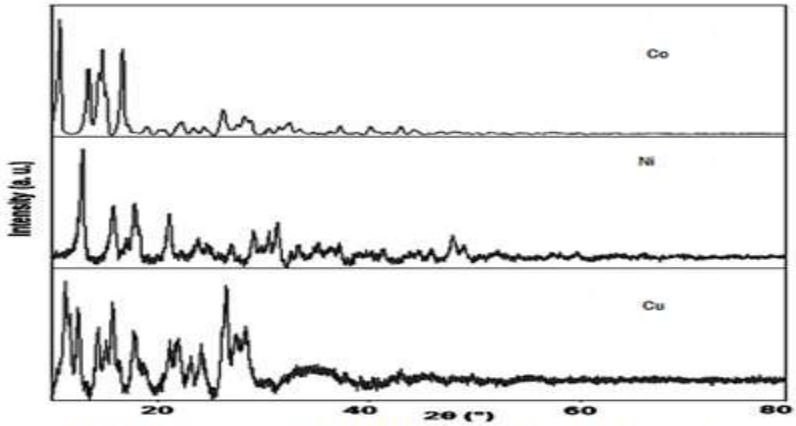


Fig.4. X-ray powder diffraction of the Cu, Co, Ni

3.5. Scanning electron microscopy- EDAX analysis.

The surface morphology of amino acid Schiff base ligand and Cu, Ni, Co complex has been examined using scanning electron microscope at a magnification of 2000 X. The distinct morphology of amino acid Schiff base ligand and Cu, Ni, Co can be observed. Purity and morphology of the complexes obtained were studied by SEM. The obtained SEM micrographs, shown in Fig. 5. allow verifying that the Cu, Ni, and Co, complexes are the ones with the well-formed amorphous shape. EDAX analysis is used to calculate the percentage level of various elements present in the metal complex. The results by energy dispersive X-ray analysis (EDAX) indicated that there is no contamination. The percentages of elements present in the complex are in agreement with the proposed structure. The results of the study are shown in Fig.6.

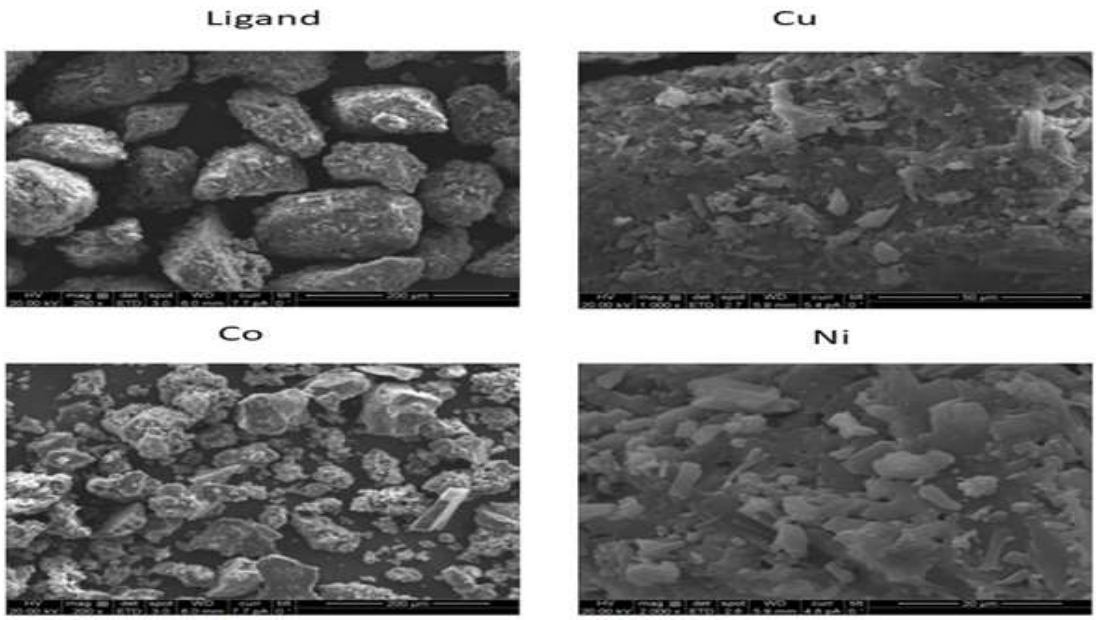


Fig. 5. SEM images of amino acid Schiff base ligand and Cu, Ni, Co complex

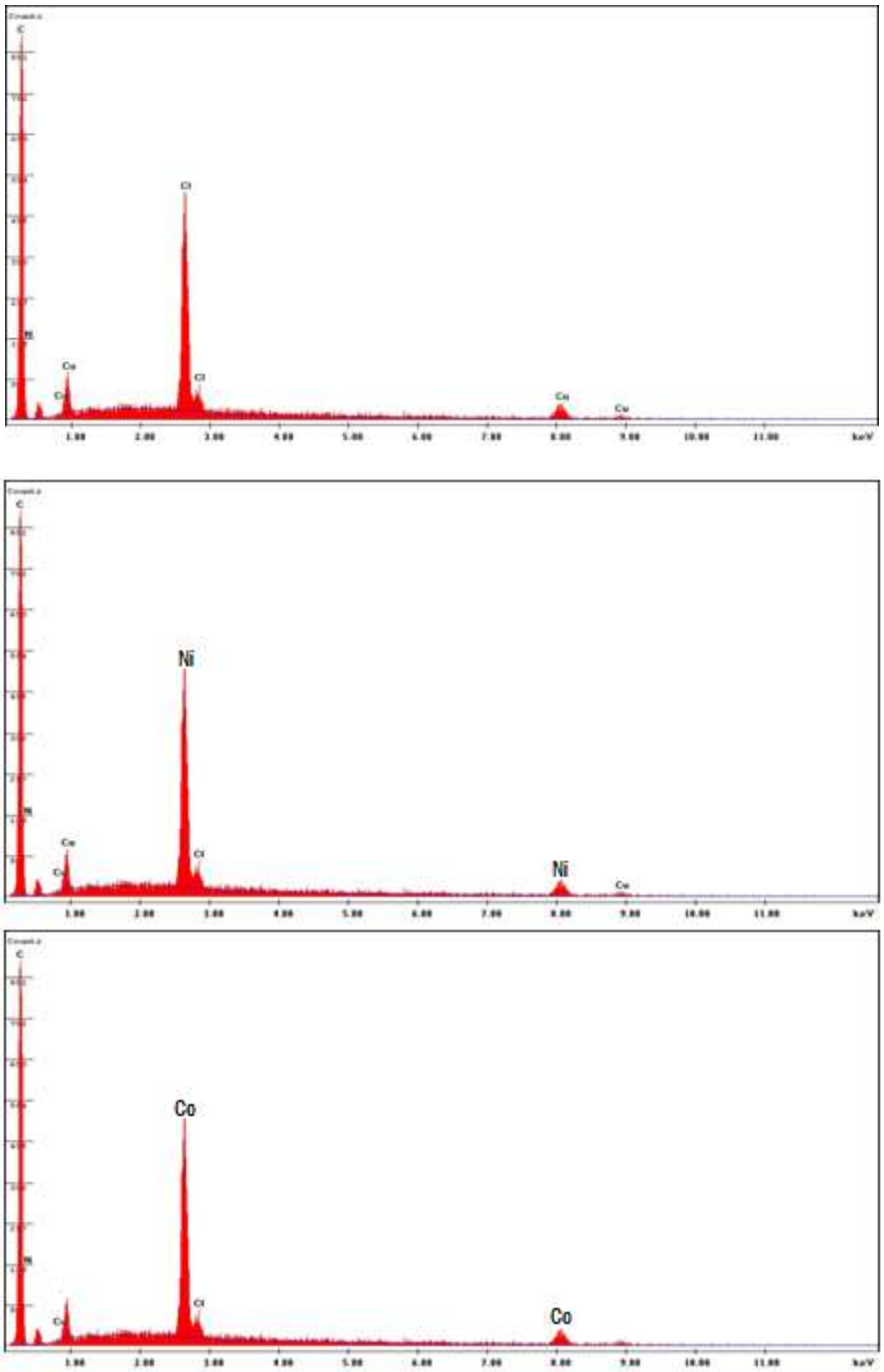


Fig.6. EDAX analysis of Cu, Ni, Co complex

3.6. Antibacterial results

In vitro antibacterial activity of the amino acid Schiff base ligand and their corresponding binuclear metal complexes was tested against Gram positive *S. aureus, B. subtilis* and Gram negative *E. coli, P. bacilli* bacteria. The well diffusion method was used in these assays and each experimental was performed in triplicate. The zone of inhibition value represents the mean value of three readings, which are shown in **Table 1.** The results show that all the syntheses compounds exhibit antibacterial activity and in many case, the copper complex are more potent in their inhibition properties than the free amino acid Schiff base ligand. This can be explained in terms of the greater lipid solubility and cellular penetration of the binuclear metal complexes [15]. It is clear that the coordination enhances the antibacterial activity and clearly indicates that the newly synthesized binuclear metal complexes in the present studies are more active against bacterial species.

The screening data of the amino acid Schiff base ligand and its binuclear metal complexes show that the former has greater activity than the latter from the biochemical point of view. On com- paring the results in general, it may be concluded that the metal complexes have greater inhibiting power than the free amino acid

Schiff base ligand against all the microbes. Although it is difficult to make out an exact structure-activity relationship between the antimicrobial activity and the geometry of these binuclear metal complexes, it can possibly be concluded that the chelation enhance the biological activity of the metal complexes. The variation in the toxicity of different antibacterial agents against various organisms depends on either the impermeability of the cell or differences in site of action or ability to cause mutations in the microorganism [16]. Though the results suggest that the amino acid Schiff base ligand have a remarkable property, their binuclear metal complex of copper inhibit the growth of microorganisms to a greater extent because of biocompatibility of copper.

Table .1. Disc diffusion method results of the synthesized amino acid Schiff base ligand and its Schiff base metal complexes.

Compounds	Zone of inhibition (mm) ; Concentration in mg/ L															
	S. aureus				B. suptilis				E.coli				P. bacilli			
	10	20	30	40	10	20	30	40	10	20	30	40	10	20	30	40
L	10	15	20	30	9	14	19	25	7	12	19	28	11	20	30	38
Cu	12	18	22	32	16	19	24	32	17	26	34	42	19	26	35	42
Co	15	20	26	35	17	22	22	34	17	30	40	46	22	28	37	46
Ni	14	22	27	36	16	23	27	38	17	32	41	50	18	30	38	47

3.7. Anticancer activity

The anticancer activity of the amino acid Schiff base ligand and its Cu, Co and Ni complexes were tested against MCF-7 cancer cell linesin the concentration of 10, 25 and 50 µM. After 24 h of treatment, and the cell viability were performed by using the Trypan blue exclusion method. Among the synthesized compounds, we noticed that the inhibitory effects of Cu(II) complex shows more activity than the other metal complexes and the free amino acid Schiff base ligand.

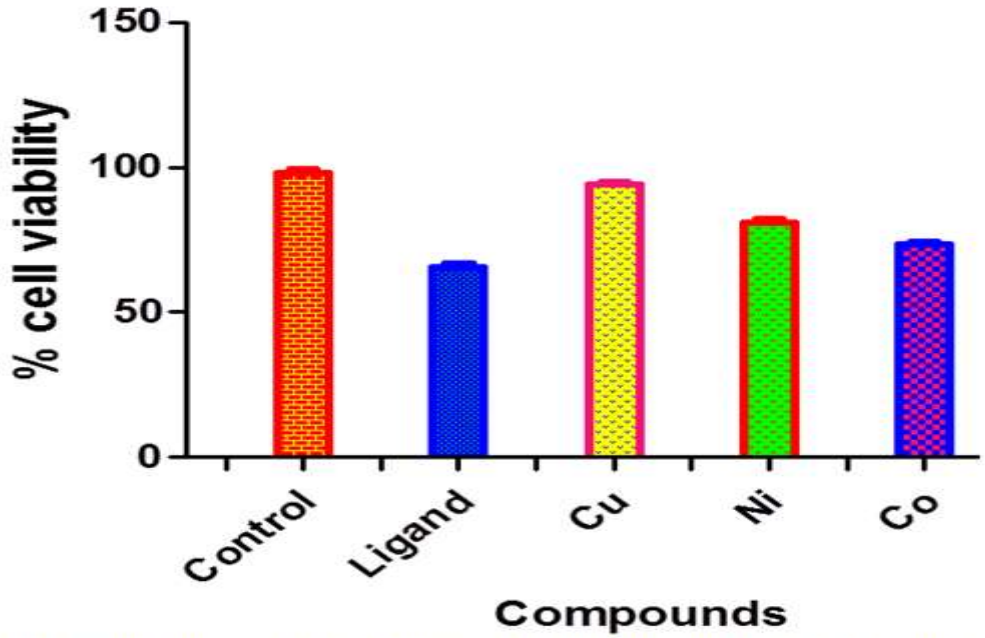


Fig. 7. Anticancer activity of amino acid Schiff base and their metal complexes

IV. Conclusion

A new series of amino acid Schiff base binuclear metal complexes were prepared in very good yields. Based on various physical, chemical and structural investigations, it was concluded that the amino acid Schiff base ligand act as tridentate and trans square planar geometry has been suggested for the synthesized amino acid Schiff base binuclear metal complexes. Furthermore, the current study strongly demonstrates that these amino acid Schiff base binuclear metal complexes are more effective antibacterial agents than the parent ligand. Selectivity is observed in the activities of amino acid Schiff base copper complex over particular microorganisms, which is very important for the future pharmaceutical applications in order to avoid the side effects, so we can conclude that the amino acid Schiff base binuclear metal complexes synthesized and tested look very promising.

Acknowledgements

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