Synthesis and Characterization of Co^{II}, Ni^{II}, Cu^{II} and Zn^{II} Cation Complexes with Tyrptophan. Investigation of Their Biological Properties

Triptofan-Co^{II}, Ni^{II}, Cu^{II} ve Zn^{II} Katyon Komplekslerinin Sentezi ve Karakterizasyonu. Bu Komlekslerin Biyolojik Özelliklerinin İncelenmesi

Research Article

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ABSTRACT

The complexes of Co^{II}, Ni^{II}, Cu^{II} and Zn^{II} metal cations with tryptophan amino acid were synthesized and characterized by FT-IR, TG/DrTG-DTA, UV-Vis spectroscopy and elemental analysis methods. The complexes were synthesized with high purity. The results of the elemental analysis indicated that the complexes contain two molecules of tryptophan as monoanionic bis-chelated ligands per mole formula unit that are coordinated acidic oxygen κ-O and amine grops κ-N and two moles coordinated aqua ligands in Co^{II}, Ni^{II} and Zn^{II} complexes, the Cu^{II} has just one mole aqua ligand so its geometry is square pyramidal. The others have octahedral geometry.

Lastly biological activities of complexes were investigated as anti-bacterial, anti-microbial and anti-fungal. The synthesized metal complexes were tested for antimicrobial activity by disc diffusion method. The results of these studies show the metal complexes to be more antimicrobial against one or more species. Also, total antioxidant capacity of the metal complexes were determined that of Zn(II)-trp and Ni(II)-trp complexes were found higher than other complexes.

Key Words
Amino acid complexes, Tryptophan-metal complexes,Thermal decomposition, Antimicrobial, Antioxidant

ÖZET

Triptofan amino asidi-Co^{II}, Ni^{II}, Cu^{II} ve Zn^{II} metal katyon kompleksleri sentezlenmiş ve FT-IR, TG / DrTG- DTA, UV-Vis spektroskopisi ve elementel analiz yöntemleriyle karakterize edilmiştir. Kompleksler yüksek saflıkta sentezlendi. Elementel analiz sonuçları, komplekslerin, koordine asidik oksijen κ-O ve amin grupları κ-N olan bir mol formül birimi için mono anyonik bis-şelatlayıcı ligand olarak 2 triptofan molekülü ve Co^{II}, Ni^{II} ve Zn^{II} komplekslerinde iki mol koordine su ligandı içerdiğini göstermektedir. Cu^{II} bir mol su ligandına sahiptir ve dolayısıyla geometrisi kare piramittir. Diğerleri oktahedral geometriye sahiptir.

Son olarak, komplekslerinin biyolojik aktiviteleri, anti-bakteriyel, anti-mikrobiyal ve anti-mantar olarak incelenmiştir. Sentezlenen metal kompleksleri disk difüzyon yöntemi ile anti-mikrobiyal aktivite için test edilmiştir. Bu çalışmaların sonuçları, metal komplekslerinin, bir veya daha fazla türe karşı daha fazla anti-mikrobiyal olduğunu göstermektedir. Ayrıca, metal komplekslerinin toplam antioksidan kapasitesinin Zn (II)-trp ve Ni (II)-trp kompleksleri için diğer komplekslerden daha fazla olduğu belirlenmiştir.

Anahtar Kelimeler
Amino asit kompleksleri, Triptofan-metal kompleksleri, Termal ayrışma, Antimikrobiyal, Antioksidan

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INTRODUCTION

The diversity of inorganic compounds and their applications in medicine encompass cancer chemotheraphy, arthritis, antimicrobial agents, metalloenzyme inhibitors, antimanic agents and many others [1]. Metal complexes of biologically important ligands are sometimes more effective than the free ligands [2]. It is well documented that heterocyclic compounds play a significant role in many biological systems, especially N-donor ligand systems being a component of several vitamins and drugs [3-6]. Moreover, the anti-bacterial and anti-microbial effect of some drug scould be enhanced when they are chelated to a metal. Therefore, for the preparation of effective anti-microbial species it is very important to gain knowledge about the structure and bonding relations of the complexes [7]. Co^{II}, Ni^{II}, Cu^{II} and Zn^{II} metal cations are recognized as essential elements that are distributed in biological systems including cells and body fluids. Also, copper exists in nuclei and plays a key role in determining DNA quaternary structure [8-10]. Tryptophan (IUPAC-IUBMB abbreviation: Trp or W; IUPAC abbreviation: L-Trp or D-Trp; sold for medical use as Tryptan is one of the 20 standard amino acids, as well as an essential amino acid in the human diet [11]. Plants and microorganisms commonly synthesize tryptophan from shikimic acid or anthranilate [12]. The isolation of tryptophan was first reported by Frederick Hopkins in 1901 through hydrolysis of casein. For many organisms (including humans), tryptophan is an essential amino acid [13-15]. This means that it cannot be synthesized by the organism and therefore must be part of its diet. Amino acids, including tryptophan, act as building blocks in protein biosynthesis. In addition, tryptophan functions as a biochemical precursor for the following compounds. In recent years metal(II) amino acids complexes have received much attention because they proved to be useful antibacterial agents nutritive supplies for humans and animals [16,17]. Complexes of transition metals with amino acids in proteins and peptides are utilized in numerous biological processes, such as oxygen conveyer, electron transfer and oxidation. In these processes, the enzymatic active site, which is very specific, forms complexes with divalent metal ions [18-20]. The coordination of amino acids to metal ions is well known, with strong binding to transition metals occurring via a chelate binding mode involving both carboxylate and amine groups [21].

In the present study, we investigated the synthesis, spectroscopic and thermal properties of some new tryptophan complexes of Co^{II}, Ni^{II}, Cu^{II} and Zn^{II} metal cations. According to spectroscopic and thermal analysis data, their molecular structure were thought as octahedral for Co^{II}, Ni^{II}, Zn^{II} and square pyramidal for Cu^{II} complex. At the same time, we studied biological activation of their. The structure of ligand is shown in Figure 1.

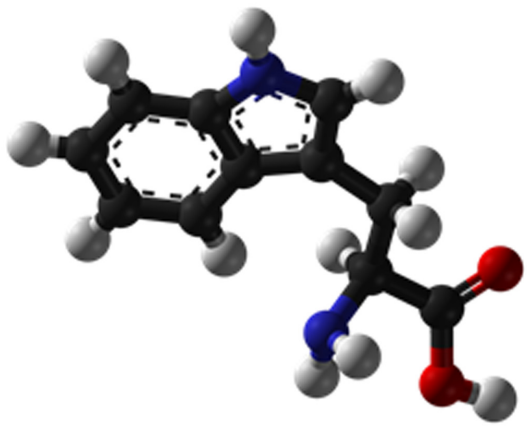


Figure 1. A view of the tryptophan amino acid.

MATERIALS AND METHODS

Preparation of complex

All chemicals used for synthesis were of reagent grade and $CoSO_4.5H_2O$, $NiSO_4.5H_2O$, $CuSO_4.5H_2O$, $ZnSO_4.5H_2O$, $NaHCO_3$ and tryptophan (trp) (Sigma-Aldrich) were used as received.

For the synthesis of metal(II)-tryptophan, firstly tryptophan sodium salt were prepared to the following equation;

$$2trp + 2NaHCO_3 \rightarrow 2Na\text{-}trp + 2CO_{2(g)} + 2H_2O$$

After removing of CO_2 gase, metal(II)-nitrate salt solutions were added to the main solution and stirred for two hours.

$$2Na\text{-}trp + M(NO_3)_2 \rightarrow [M(trp)_2(H_2O)_n)] + NaNO_{3(aq)}$$

M:Co, Ni, Cu, Zn; n:1,2

After three or four weeks, the obtained purple (Co^{II}), green (Ni^{II}), blue (Cu^{II}) and white (Zn^{II}) products were filtered off and dried in air atmosphere.

Biological activity methods

Antimicrobial studies: All the synthesized metal complexes were screened in vitro for their antimicrobial activity against Gram-positive bacteria (*Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 6538), gram-negative bacteria (*Pseudomonas aeroginosa* ATCC 27853 and *Escherichia coli* ATCC 25922) and fungus (*Candida albicans* ATCC 10231) strains using disc diffusion method. Bacterial cultures were grown at 37°C for 18-24 h in Nutrient Broth and fungus culture was grown 37°C for 18-24 h in Sabouraud Dextrose Broth. Culture suspensions were adjusted by comparing against 0.5 McFarland. Petri dishes with 20 ml of Mueller Hinton Agar (MHA) were prepared, previously inoculated with 100 µl of cultures suspension. Then paper discs (6 mm in diameter) containing 10 µl of substance to be tested (at a concentration of 5 mg/ml in DMSO) were placed at the edge of Petri plates containing MHA. Incubation of the plates was done at 37°C for 24-48 h. Reading of the results was done by measuring the diameters of the inhibition zones generated by the tested substances. DMSO was used as a negative control. Ampicillin and fluconazole were used as reference antibiotics for bacteria and fungi, respectively.

Minimum Inhibition Concentration (MIC): The prepared compounds were further used to determine minimum inhibitory concentration (MIC) in sterile tubes, based on broth micro dilution assay, which is an colorimetric method, uses the absorbance (optical density) of cultures in tubes. Total volume of each tubes was 1 mL, each tubes was filled with 800 µL of broth medium, 100 µL of test microorganism and 100 µl of compounds (Stock solution; 5 mg/mL). Then, serial dilution was among tubes. Tubes were incubated at 37 °C for 24 h. After incubation period, the tubes were read at 610 nm using spectrophotometer. So, minimum inhibitory concentration (MIC) values were defined as the lowest concentration of the extracts that inhibits the visible growth of the microorganisms.

Total antioxidant capacity (TAC): The total antioxidant capacity of the compounds was measured using a novel automated colorimetric measurement method for TAC developed by researchers [34]. The hydroxyl radical, the most potent biological radical, is produced by the Fenton reaction, and reacts with the colorless substrate O-dianisidine to produce the dianisyl radical, which is bright yellowish-brown in color in this method. Upon the addition of compounds, the oxidative reactions initiated by the hydroxyl radicals present in the reaction mix are suppressed by the antioxidant components of the compounds, preventing the color change and thereby providing an effective measure of the total antioxidant capacity of the compounds. The assay results are expressed as mmol Trolox eq./L.

$$Result = \frac{[(\Delta Abs\ Std_1) - (\Delta Abs\ sample)]}{[(\Delta Abs\ Std_1) - (\Delta Abs\ Std_2)]}\ x\ 20$$

ΔAbsorbance $Standard_1$=
(Second Absorbance of Std_1- First Absorbance of Std_1)
ΔAbsorbance $Standard_2$ =
(Second Absorbance of Std_2- First Absorbance of Std_2)
ΔCompound Absorbance=(Second Absorbance of Compound- First Absorbance of Compound).

RESULTS

Effective magnetic moments, elemental analysis data and compositions of the complexes are given in Table 1. The Bohr Magneton data are agreement with literature values for similar complexes. The complexes were synthesized with high purity. The results of the elemental analysis and FT-IR results indicated that the complexes contain two molecules of tryptophan as monoanionic bis-chelated ligands per mole formula unit that are coordinated acidic oxygen κ-O and amine grops κ-N.

Electronic Spectra

The electronic spectra showed two absorption bands attributed to *d–d* transitions at 17676 cm^{-1} ($^4T_{1g}\rightarrow{}^4T_{2g}$)(F) and 21800 cm^{-1} ($^4T_{1g}\rightarrow{}^4T_{1g}$)(P) and for Co^{II} complex. The electronic spectra of Ni^{II} complex showed three absorption bands for spin-allowed *d–d* transitions at 12120 cm^{-1} ($^3A_{2g}\rightarrow{}^3T_{1g}$) (P), 15690 cm^{-1} ($^3A_{2g}\rightarrow{}^3T_{1g}$) (F) and 25130 cm^{-1} ($^3A_{2g}\rightarrow{}^3T_{2g}$) (F), these transition bands are compatible with octahedral geometri for Ni^{II} complex. In the Cu^{II}

Table 1. Analytical data of complexes.

Complex	MW, g/mol	Yield	Contents found(calcd.) %			Color	m.p. °C	μ_{eff}. BM
			C	H	N			
$[Co(trp)_2(H_2O)_2]$ $C_{22}H_{26}CoN_4O_6$	501.39	91	51.94 (52.65)	4.07 (5.18)	11.28 (11.17)	purple	300 boz.	4,13
$[Ni(trp)_2(H_2O)_2]$ $C_{22}H_{26}NiN_4O_6$	501.15	76	52.27 (52.68)	5.12 (5.19)	10.76 (11.17)	green	358	2,94
$[Cu(trp)_2(H_2O)]$ $C_{22}H_{24}CuN_4O_5$	488.01	89	53.70 (54.09)	4.47 (4.92)	11.54 (11.48)	blue	266	1,60
$[Zn(trp)_2(H_2O)_2]$ $C_{22}H_{26}ZnN_4O_6$	507.86	82	53.33 (52.07)	4.52 (5.12)	11.07 (11.05)	white	323	Dia.

complex multiple absorption band is observed at about 10500–17500 cm^{-1} but they are overlapped. Because, octahedral complexes of Cu^{II} are observable distorted by Jahn–Teller effect and the structure of complex is to name pseudo-octahedral. It was to taken notice of top of the peak as absorption band and *d–d* transition at about 13470 cm^{-1} ($^2E_g \rightarrow {}^2T_{2g}$) for Cu^{II} complex. According to the magnetic susceptibility results, the Zn^{II} complexes are diamagnetic as expected so no peak was observed for *d-d* transitions. The high intesity peaks were detected at 28230 cm^{-1} for Co^{II} complex, 30880 cm^{-1} for Cu^{II} complex, 30250 cm^{-1} for Ni^{II} complex and 28945 cm^{-1} for Zn^{II} complex. These peaks are attributed to the metal → ligand charge transfer bands for Co^{II}, Cu^{II} and Ni^{II} complexes while it is the ligand → metal charge transfer for Zn^{II} complex. The results are agreeable to literature [22,23].

Infrared Spectroscopy

The FT-IR spectra of the complexes are shown in Figure 2 and their important stretching peaks are summarized in the Table 3. The strong and broad absorbtion band in the range of 3600-3000 cm^{-1} correspond to asymmetric and symmetric stretching vibrations of aqua molecules. At the range of 3392 cm^{-1} and 3161 cm^{-1} bands are belong to N-H stretches of NH_2 group of tryptophan. The weak bands at the range of 2936-2906 cm^{-1} are attributed to the CH_2 vibrations. In complexes, tryptophan ligands are coordinated to the metal ion as monodentate by carboxylic group. This claim about the products is supported by FT-IR spectra results. The $(COO^-)_{asym.}$ peaks are located at 1619 cm^{-1} for Co^{II}, 1605 cm^{-1} for Ni^{II}, 1625 cm^{-1} for Cu^{II} and 1622 cm^{-1} for Zn^{II} complexes. $(COO^-)_{sym}$ peaks are observed at 1459 cm^{-1} for Co^{II}, 1456 cm^{-1} for Ni^{II}, 1455 cm^{-1} for Cu^{II} and 1456 cm^{-1} for Zn^{II} complexes. The low intensity bands in the region of 600–400 cm^{-1} are attributed to M–N and M–O vibration [23-28].

Thermogravimetric analysis of the compounds has been conducted in the 25-1000°C temperature range under nitrogen and the TG/DTG and DTA curves are given in Figure 3a-d. The observed mass losses for the dehydration and decomposition steps agree well with calculated values. While, the Cu^{II}

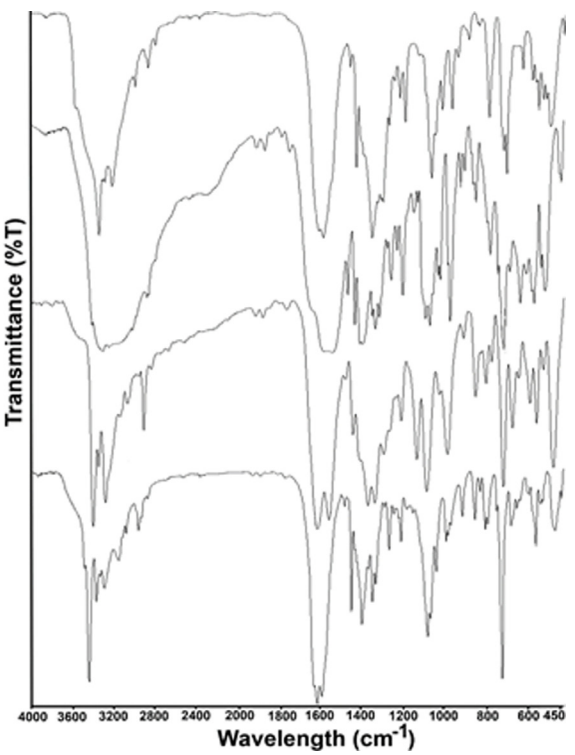


Figure 2. FT-IR spectra of the metal(II)- tryptophan complexes. (a) Co^{II}, (b) Ni^{II}, (c) Cu^{II}, (d) Zn^{II}.

Table 2. Some important FT-IR peaks of metal tryptophan complexes.

Groups	Co^{II}	Ni^{II}	Cu^{II}	Zn^{II}
$\nu(OH)_{H2O}$	3600-3000	3600-3000	3600-3000	3600-2900
$\nu(NH_2)$	3392,3266	3340,3161	3389-3271	3402
$\nu(NH_2)_{bending}$	1570	1562	1569	1596
$\nu(C=O)_{carbonyl}$	1625	1618	1625	1630
$\nu(COO^-)_{asym}$	1618	1605	1602	1610
$\nu(COO^-)_{sym}$	1459	1456	1455	1456
$\Delta\nu_{as\text{-}s}$	159	149	147	154
$\nu(CH_2)$	2920	2910	2906	2936
ν(C-N)	751,737	766-708	739,695	766,738
ν(M-N)	460	462	465	490
ν(M-O)	527	539	548	580

complex has one mole aqua ligand (this structure coordination number is five), the others structures have two moles coordinated water according to six coordination number. The metal cation complexes do not contain hydrated water. Firstly, aqua ligands remove from the structures and after than organic ligands two moles tryptophan molecules decompose by giving $CO/CO_2/NO/NO_2$. In the last stage one mole oxygen atom connected to metal cation give to metal oxides. As the decomposition residue remain metal oxide in the curable. The calculated and founded data of decomposition steps are compatible with each other (Table 2).

Mass Analysis

To deduce the thermal decomposition pathway for tryptophan complexes mass spectrum were recorded (Figures 4a-d) using direct insertion probe pyrolysis mass spectrometry method. The obtained pattern is relatively complex and exhibits a large number of peaks that belonging to the decomposition products of the complex and ligands. The decomposition peaks of tryptophan complexes are harmonic with probable molecular ion peaks of decomposition products. A schematic representation including the main fragmentation process for metal complexes are given Scheme 1a (for Co^{II}, Ni^{II}, and Zn^{II}) and Scheme 1b (for Cu^{II}).

Biological Activity

Although, antimicrobial activity of some of metal complexes has been reported earlier, antimicrobial activity of these complexes is yet to be reported. Therefore, different microorganisms have been chosen, and the antimicrobial effect of complexes on these microorganisms was determined according to the disc diffusion and minimum inhibitory concentration methods. According to other chemicals the Zn^{II} complex was found to be more effective on E. coli and C. Albicans bacteria. Overall, we look all of the metal complexes were determined to be more effective in yeast bacteria media (Figure 5). In addition, low doses of the metal complexes were found to be sufficient to inhibit yeast. It was needed high concentration doses of metal complexes to inhibit the E. Faecalis, S. Aureus and P. Aeroginosa bacteria. The antimicrobial properties of the high ones that are larger inhibition zone was much more effective. Minimum Inhibition Concentration (MIC) values, is seen to be effective in small doses. The results are summarized in Table 4 and 5.

The total antioxidant capacity (TAC) values of Zn(II)-trp, Ni(II)-trp, Co(II)-trp and Cu(II)-trp complexes were found 5.3, 3.21, 2.78 and 2.45 mmol Trolox equivalent/L, respectively (Table 6).

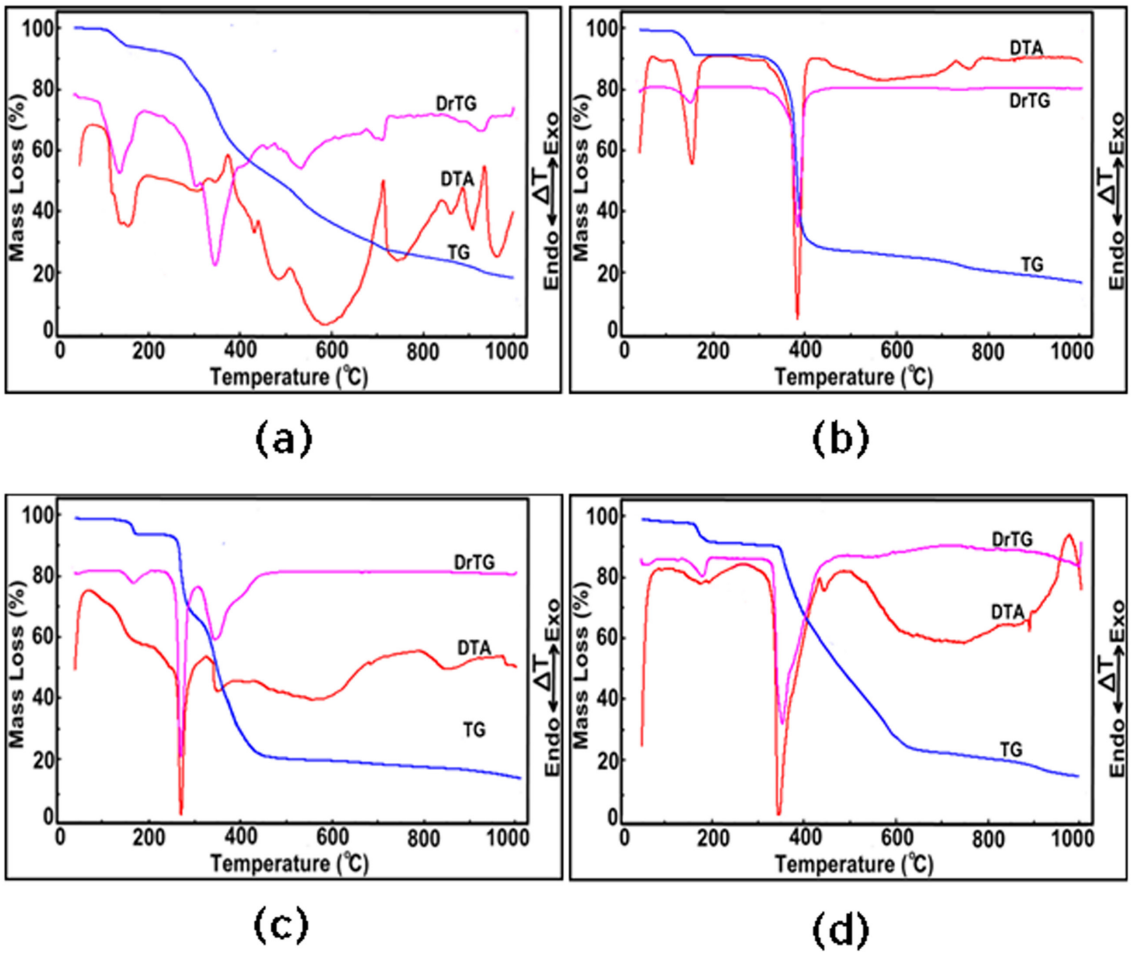
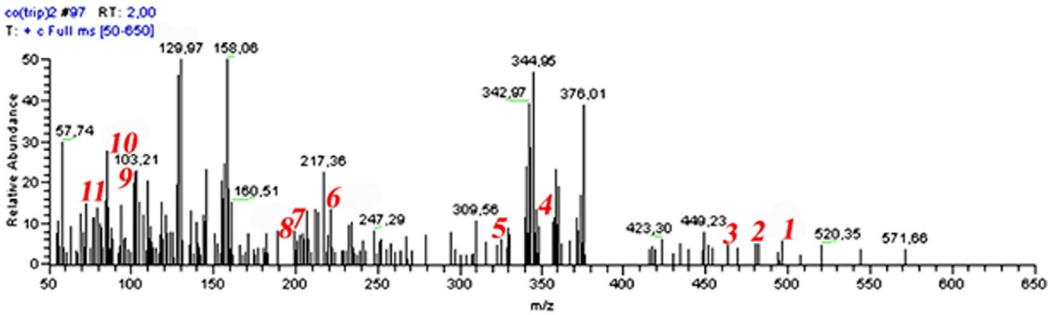


Figure 3. Thermal analysis curves of complexes. **(a)** Co^{II}, **(b)** Ni^{II}, **(c)** Cu^{II} and **(d)** Zn^{II}.

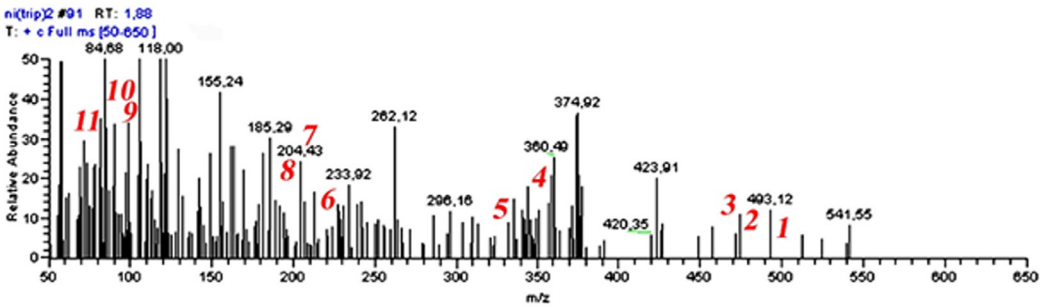
Table 3. Thermoanalytical results (TG/DrTG and DTA) for the metal complexes.

Complex	Temp. Range (°C)	DTG $_{max.}$ (°C)	Removed Group	Mass Loss %		Total Loss %		Decomp. Product	Color
				Found	Calc.	Found	Clac.		
$[Co(trp)_2(H_2O)_2]$									purple
1	110-180	143	2 H_2O	7.62	7.18			$[Co(trp)_2]$	
2	201-922	305,352,490, 593,738,907	2 trp	75.63	77.78	84.84	85.05	CoO	black
$[Ni(trp)_2(H_2O)_2]$									green
1	117-166	152	2 H_2O	7.14	7.18			$[Ni(trp)_2]$	
2	293-912	391,585,752	2 trp	76.13	77.82	84.22	85.09	NiO	black
$[Cu(trp)_2(H_2O)]$									blue
1	111-173	161	H_2O	4.21	3.50			$[Cu(trp)_2]$	
2	233-901	281,362,592, 850	2 trp	77.63	79.92	82.78	83.70	CuO	black
$[Zn(trp)_2(H_2O)_2]$									white
1	152-198	182	2 H_2O	6.82	7.10			$[Zn(trp)_2]$	
2	311-927	351,438,673, 891	2 trp	75.12	76.79	82.46	83.95	ZnO	black

(a)



(b)



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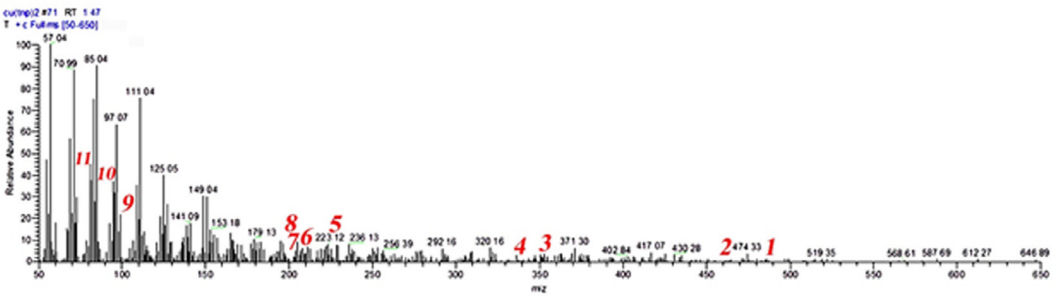


(d)

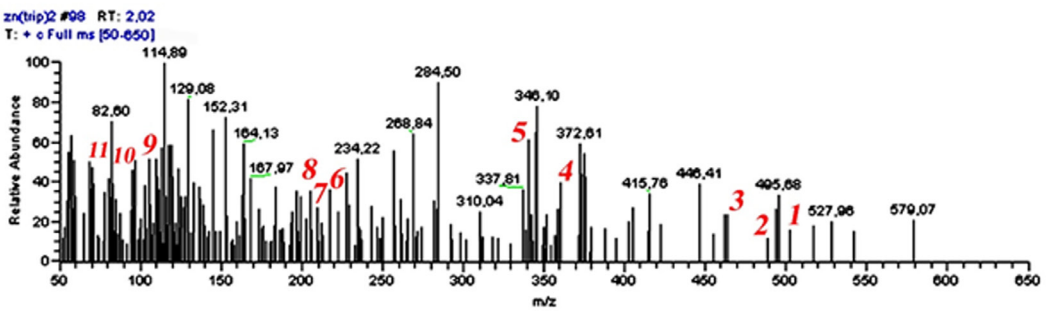
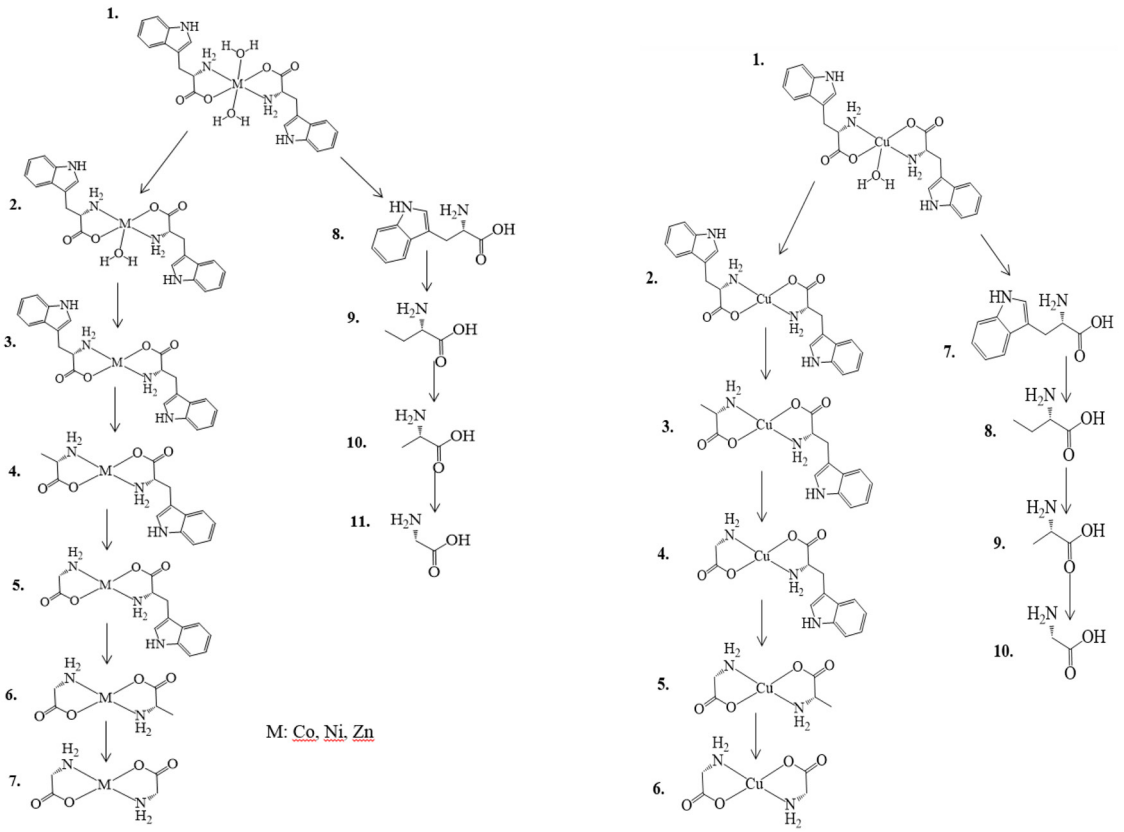


Figure 4. Solid Probe GC-Mass Spectroscopy patterns. (a) Co^{II}, (b)Ni^{II}, (c)Cu^{II} and (d)Zn^{II} complexes.



Scheme 1. Mass spectral fragmentation pattern of the metal complexes. (a) Co^{II}, Ni^{II} and Zn^{II}; (b) Cu^{II} complexes.

Table 4. In vitro antimicrobial activity results of synthesized metal complexes.

Metal Complexes	Antimicrobial activity (Zone of inhibition in mm)				
	E.faecalis	S. aereus	E. coli	P.aeroginosa	C.Albicans
Co(II)-Thr	2.0±0.50	-	2.00±0.50	-	13.50±1.50
Ni(II)-Thr	-	-	3.0±1.00	-	4.50±1.50
Cu(II)-Thr	-	-	1.00±0.25	8.0±1.50	3.00±1.00
Zn(II)-Thr	1.5±0.50	-	2.50±1.00	7.5±1.00	14.00±2.00
Standard[a]	9.50±2.00	7.00±1.00	10.50±2.50	8.75±2.25	-
Standard[b]	-	-	-	-	10.50±1.50
DMSO	-	-	-	-	-

Standard[a]: Gentamycin; Standard[b]: Flucanozole; -:No inhibition

Table 5. Minimum inhibition concentration results of synthesized metal complexes.

Metal Complexes	Minimum inhibition concentration (mg/ml)				
	E.faecalis	S. aereus	E. coli	P.aeroginosa	C.albicans
Co(II)-trp	> 5	> 5	0.625	>5	< 0.156
Ni(II)- trp	> 5	> 5	>5	>5	< 1.25
Cu(II)- trp	> 5	>5	2.5	>5	0.156
Zn(II)- trp	> 5	> 5	< 0.625	>5	0.078

The concentration range of complexes was 5 to 0.0097mg/ml.

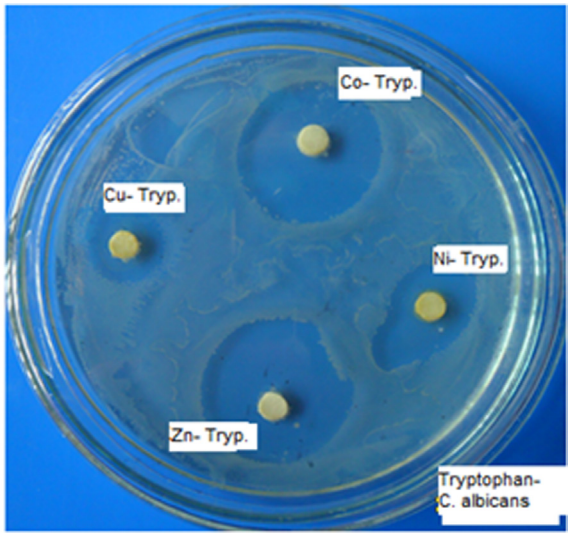


Figure 5. Inhibition zones of the metal complexes in bacterial media.

Despite having a certain total antioxidant capacity of all metal complexes, total antioxidant capacity of Zn(II)-trp complex was found higher than other complexes. And also, total antioxidant capacity of Cu(II)-trp complex determined lowest than other complexes.

DISCUSSION

The electronic transitions and Bohr Magneton data of complexes are compatible with literature. The complexes contain two moles of coordinated water, Cu^{II} complex except. The Cu^{II} complex includes just one mole of coordinated water. They haven't got any hydrated water. Dehydration of complexes occur in the range of 166-198°C. The experimental values for the mass loss of the dehydration stage are well consistent with the calculated values. The results indicate that metal–water bond strength is almost the same for all of the water molecules. After the dehydration process, decomposition stages of the anhydrous complexes are related to the release of organic part of complexes. Previous studies showed that the organic ligand-metal complexes decompose by releasing $CO/CO_2/NO/NO_2$ [24-28]. In complexes, tryptophan ligands are coordinated to the metal ion as bidentate. This claim about the products is supported by FT-IR spectra results. The shift (Δ) between of the $\nu_{asym.}$ and $\nu_{sym.}$ bands of COO^- groups are for all of the complexes almost identical (149-170 cm^{-1}) and more than for the sodium salt tryptophan amino acid (133 cm^{-1}) [29] that monodentate carboxylate group exists [23-28].

Table 6. Total antioxidant activity (TAC) results of synthesized metal complexes.

Metal Complexes	TAC(mmol Trolox eq./L.)
Zn(II)-trp	5.63
Ni(II)-trp	3.21
Co(II)-trp	2.78
Cu(II)-trp	2.45

According to the thermal stability of non-hydrated complexes follow the order ;

$$Co^{II} < Cu^{II} < Ni^{II} < Zn^{II}$$

This order is followed Pearson's arrangement of 2+ ions of metals.

The decomposition steps and products of metal-tryptophan complexes were investigated by mass spectral analysis. Decomposition products of tryptophan ligands were obtained using molecular ion peaks and they are compatible with thought steps.

According to spectroscopic and thermal analysis data, suggested molecular formulas were shown Figure 6 and Figure 7.

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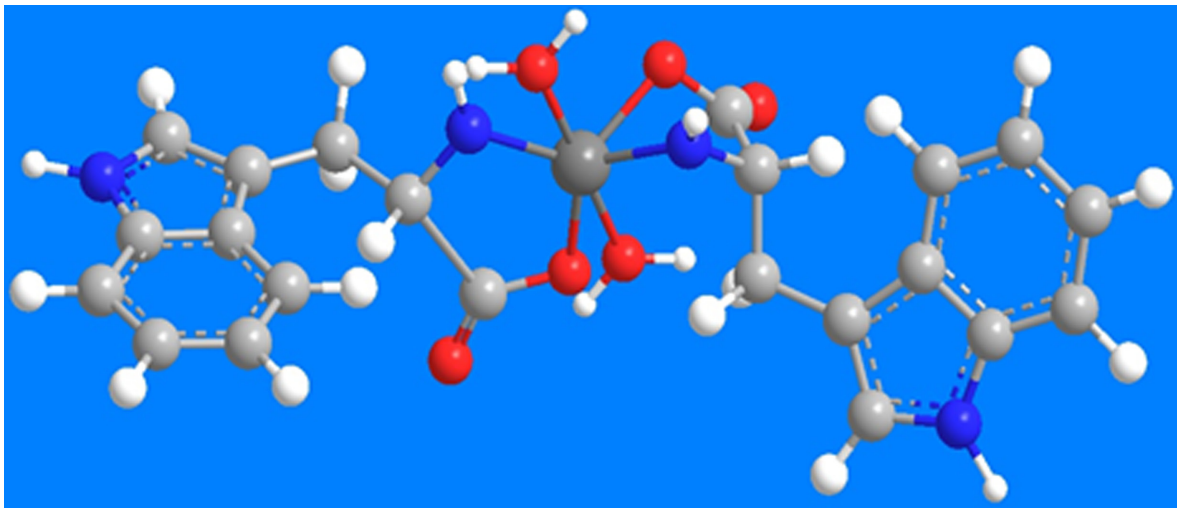

Figure 6. Suggested molecular structure of $C_{22}H_{24}N_4O_5$-Co, Ni and Zn complexes.

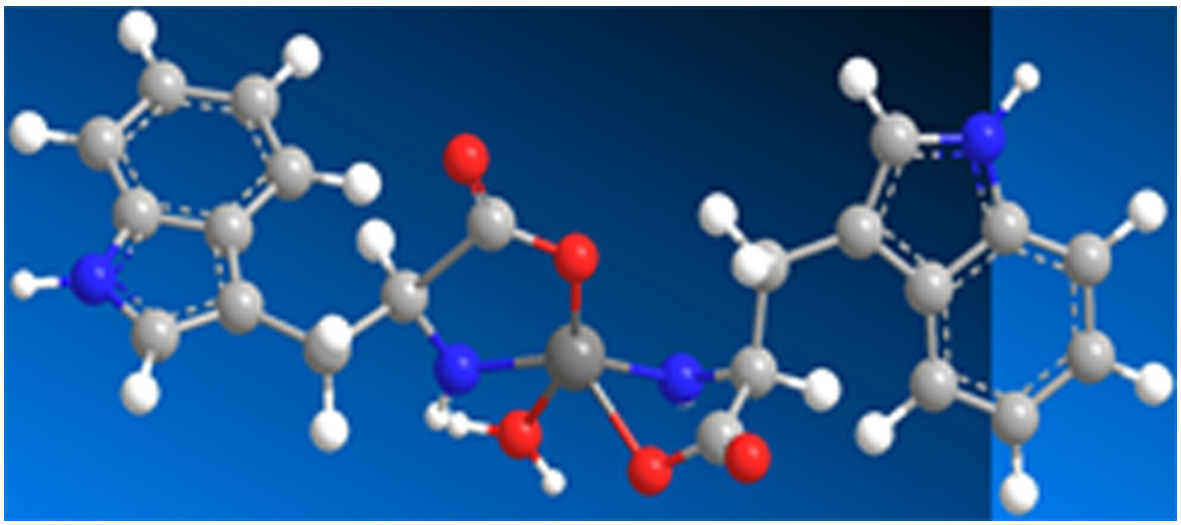

Figure 7. Suggested molecular structure of $C_{22}H_{24}N_4O_5Cu$ complex.

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