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SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIOXIDANT ACTIVITY OF A SUPRAMOLECULAR COPPER (II) COMPLEX OBTAINED FROM PYRIDINE-2, 6- DICARBOXYLIC ACID AND 3,5-DIAMINO - 1, 2, 4-TRIAZOLE.

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ABSTRACT

A supramolecular copper (II) compound**,** (HdatrzH)[Cu (Hdipic) (dipic)].3H_2O (**1**) **(**Hdatrz = 3,5-diamino-1,2,4- triazole, dipic = pyridine- 2,6-dicarboxylic acid) was synthesized and characterized by elemental analysis, Fourier transformed infrared spectroscopy (FT-IR), UV-Visible spectroscopy, mass spectrometry, proton nuclear magnetic resonance (^{1}H-NMR), thermal analysis, and magnetic susceptibility measurement. The room temperature magnetic susceptibility measurement showed a magnetic moment of 1.67 BM for compound **1**, deviating slightly from the spin-only magnetic moment value for Cu (II) ion. Thermogravimetric analysis revealed three decomposition stages for compound **1**. The compound showed no activity against all the tested microorganisms. Interestingly, compound **1** exhibited a significant radical scavenging activity (RSA).

INTRODUCTION

Supramolecular complexes have attracted increasing attention due to their fascinating and unconventional chemical and physical properties (Hu *et al*., 2014) that differ from those encountered by covalently linked backbones. Supramolecular complexes are discrete constructions that are often formed by combining soluble metal and ligand precursors, which spontaneously form metal-ligand linkages to produce a single thermodynamically favourable product. Because coordination bonds constitute the driving force for formation, this process is also known as coordination-driven self-assembly. The creation of supramolecular complexes via self-assembly by reversible and highly directional noncovalent interactions such as hydrogen bonds, π-π stacking, dipolar interactions, and Van der Waals forces is dynamic and has produced well-defined structures from simple molecules. As a result, these supramolecular complexes are promising candidates for future development of functional smart materials, similar to the assembling process of natural systems. (Chkiratea *et a*l., 2020).

Amongst the diverse multidentate ligands, compounds having the carboxylate functions have been widely utilized to generate stable transition metal coordination polymers and supramolecular architectures, essentially because of the flexible coordinating capability of the -COO moiety as well as the improved attraction of transition metal ions to O – donors of carboxylic acid. Several efforts have been made at exploiting proton transfer from carboxylic acids to both heterocyclic and substituted amine nitrogen (Moghimi *et al.*, 2002; Moghimi *et al.*, 2005; Moghimi *et al.*, 2007; Aghabozorg *et al.*, 2008a; Aghabozorg *et al.*, 2008b; Tabatabaee *et al.*, 2009, Pasdar *et al.*, 2011).

Herein we report the synthesis of a supramolecular compound by proton transfer approach from dipicolinic acid to 3,5-diamino-1,2,4-triazole and characterization of the synthesized compound **1** by elemental analysis, magnetic susceptibility, spectral studies, thermal analysis, antimicrobial, and antioxidant activities.

MATERIALS AND METHODS

Reagent-grade chemicals, obtained from commercial sources, were used throughout.

Physical measurements

Elemental analysis was achieved by using a Perkin-Elmer automated model 2400 Series II CHNS/O analyzer. Infrared spectra were recorded on a Shimadzu 8900 spectrophotometer within the range of 400- 4000 cm^{-1} by using KBr discs. Electronic spectra were recorded on a Hitachi U-3200 spectrophotometer between 190-450 nm using dimethylsulphoxide (DMSO) as solvent. The ^{1}H-NMR spectra of the ligands and metal complex with tetra-methylsilane (TMS) as internal standard, were recorded by using a Bruker Advance 400 MHz spectrophotometer in DMSO. All chemical shifts are accounted for on the δ scale compared to TMS.

The mass spectrum of the complex was obtained by the soft ionization technique; Electro spray ionization (ESI-MS) on QSTAR Excel MS/MS system. The thermal stability of the supramolecular complex was determined using SDT Q600 thermal analyzer attached to a computer and the sample was heated at the rate of 10^o C min^{-1} in an inert atmosphere of nitrogen. A Sherwood Scientific magnetic susceptibility balance was used for susceptibility measurement on the powdered sample. The magnetic balance was calibrated using $MnCl_2$, and diamagnetism adjustments were estimated from Pascal's constants.

Synthesis of $(C_2H_6N_5)^+[Cu(C_7H_4NO_4)(C_7H_3NO_4)]^-$. 3$H_2O$ (1)

Dipicolinic acid (1 mmol, 0.167 g) and 3,5-diamino-1,2,4-triazole (Hdatrz) (1 mmol, 0.099 g) were dissolved in a

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mixture of methanol/water solution (1:10 mL). The resulting solution was heated to 60°C with stirring. An aqueous solution (1 mL), containing 0.5 mmol (0.125 g) of $CuSO_4.5H_2O$, was added to the stirring solution. The greenish suspension was further stirred for 1 h and was filtered while hot. The filtrate was set aside at room temperature. Well-shaped blue crystals of the compound, suitable for X-ray diffraction analysis, were formed by slow evaporation of the solution after 5 days.

Antioxidant Activity Evaluation

The stable free radical, 1, 1-diphenyl-2-picrylhydrazyl radical (DPPH), reacted with the test sample **1** for 30 minutes at 37º C. The DPPH concentration was kept at 300 µM. The test sample was dissolved in DMSO, while DPPH was dissolved in ethanol. Subsequent to incubation, change in absorbance was recorded at 515 nm using of a multiplate reader (Spectra MAX-340, Molecular Devices, CA, USA). The ability of the test compound to forage radical activity was obtained as a percentage in comparison with a DMSO-treated control group. % Radical scavenging activity (RSA) was determined by the formula:

$$\text{DPPH Scavenging effect (\%)} = A_0 - A_1 \,/\, A_0 \, X \;\; 100$$

where, A_0 represents absorbance of the control and A_1 absorbance in the presence of the sample in DMSO (Molyneux, 2004). The actual decrease in absorbance, induced by the test compound, was compared with the positive controls. The IC_{50} value was determined using EZ-FIT computer software.

Superoxide Radical Scavenging Activity of Compound 1

The reaction mixture contained 0.2 mM β- nicotinamide adenine dinucleotide reduced form (NADH), 0.081 mM nitroblue tetrazolium (NBT) mM phenazine methosulphate (PMS) and test sample in 200 µL of 0.1 M phosphate buffer (pH 7.4). The NBT, NADH and PMS were primed in the same buffer. The test sample was dissolved in DMSO.

The reaction was carried out in 96-well microtitre plates (Molecular Devices, Spectramax 340, CA, USA) at ambient temperature and absorbance was considered at 560 nm (*de* Gaulejac *et al.*, 1999). The percentage ability of the sample to forage radical activity was determined in comparison with a DMSO-treated control group

% Radical scavenging activity was calculated using the formula:

$$\%\,\text{RSA} = 100 - \{(\text{OD Test compound} \,/\, \text{OD control}) \times 100\}$$

IC_{50} of the sample was determined by means of EZ-FIT computer software.

Cytotoxicity of compound 1

Cytotoxic activity of the compound was estimated in 96-well flat-bottomed micro- plates using the standard MTT (3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyl-tetrazolium bromide) colorimetric assay (Mosmann, 1983). For this purpose, PC-3 cells (Prostrate Cancer) / 3T3 Mouse fibroblast) were cultured in Dulbecco's Modified Eagle's Medium, supplemented with 5% of foetal bovine serum (FBS), 100 IU/mL of penicillin and 100 µg/mL of streptomycin in a 25 cm^3 flask, and kept in 5% CO_2 incubator at 37º C.

Exponentially budding cells were collected, added up with haemocytometer and thinned with a particular medium. Cell culture with concentration of $1x10^5$ cells/mL was primed and introduced (100 µL/well) into 96-well plates. After incubating all night, the medium was separated and 200 µL of fresh medium was added with varied concentrations of compound (1-100 µM). After 72 h, 50 µL MTT (2 mg/mL) was added to each well and incubated further for 4 hrs. Afterwards, 100 µL of DMSO was added to each well. The degree of MTT diminution to formazan inside cells was considered by assessing the absorbance at 570 nm, using a microplate ELISA reader (Spectra Max Plus, Molecular Devices, CA, USA). The cytotoxicity was recorded as concentration causing 50% growth inhibition of PC-3/ 3T3 cells.

Antimicrobial Activity

Antifungal and antibacterial activities of the free ligands and metal complexes were tested *in vitro* against five fungi (*Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani* and *Candida glabrata*) and six bacteria (*Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Shigella flexenari, Pseudomonas aeruginosa* and *Salmonella typhi*) by agar well diffusion method (Carron *et al*., 1987*)*. A concentration of 1 mg/mL of DMSO was used for antibacterial assay, while 200 µg/mL of DMSO was used for antifungal activity.

The test organisms (bacteria) were sub-cultured into sterile nutrient agar plates and labelled accordingly. Fungi were planted on sterile Sabouraud dextrose agar plates and labelled accordingly. Bacterial strains were incubated at 37º C for 24 hours and fungi at 28º C for 7 days. The dissolved ligands and metal complex were used to fill the holes on the seeded plates. The plates were kept warm at optimal temperature for 24 hours. Standard antibacterial (Imipenum) and antifungal (Muconazole and amphotericin) drugs, respectively, were used for comparison under similar conditions. The diameter of inhibition zones was measured in millimetres (mm).

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RESULTS AND DISCUSSION

Synthesis

The Cu (II) complex 1 was prepared by using 3,5-diamino-1,2,4- triazole as a proton acceptor and 2,6-pyridine dicarboxylic acid as a proton donor. The percentage yield based on copper was 51.67% and the melting point was greater than 240º C. X-ray crystal structure of the synthesized compound (Scheme 1) was reported (Yousuf *et al.*, 2011.

Scheme 1. Synthesis of the title compound

Elemental Analysis of the synthesized compound

Elemental analysis of synthesized compound 1 (Figure 1) revealed the number of carbon, hydrogen, and nitrogen atoms present in the compound. The calculated values of the elements present in the compound are in good agreement with the experimentally determined values as presented in Table 1.

Electronic spectra and magnetic moments

The absorption spectra of both the ligands and complex exhibit bands as presented in Table 1. Pyridine dicarboxylic acid showed a peak at 270 nm while 3,5-diamino-1,2,4-triazole showed a band at 208 nm. These are attributed to π-π^* transitions due to conjugated double bonds. The synthesized compound **1** showed bands at 193 and 286 nm. The transition at 193 nm is attributed to π-π^* and the absorption band at 286 nm is attributed to n-π^* transition.

Table 1. Elemental analysis (CHN) of the synthesized compound

Compound	% Carbon Found (Calculated)	%Hydrogen Found (Calculated)	% Nitrogen Found (Calculated)
(HdatrzH) [Cu(Hdipic) (dipic)].3H_2O	35.14 (34.97)	3.74 (3.46)	18.48 (17.85)

A room temperature magnetic moment of 1.67 BM was recorded for complex 1. This value is characteristic for a mononuclear copper (II) complex with S=1/2 spin state but is slightly less than the spin-only magnetic moment (1.73 BM) for one unpaired electron. The decrease in the magnetic moment may be due to hydrogen bonding (Laine *et al*., 1995).

Table 2. Electronic Transitions (nm) of ligands and complex and effective magnetic moment u_{eff} (B.M)

Compound	nm	Assignment	*μeff* (BM
H_2dipic	270	$\pi \rightarrow \pi^*$	-
Hdatrz	208	$\pi \rightarrow \pi^*$	-
$C_2H_6N_5$) [Cu (dipicH) (dipic)]·3H_2O	193	$\pi \rightarrow \pi^*$	1.67
	286	$n \rightarrow \pi^*$	

FT-IR Spectra

Significant infrared frequencies of the ligands and the Cu (II) complex **1** are given in Table 2. The spectra of the ligands and complex showed strong absorption bands in the range of 3445 -3373 cm^{-1}. The bands at 3445 and 3373 cm^{-1} are assigned to **υ**(OH) of acid in H_2dipic and water molecules for 1**,** respectively. The bands at 3313 (Hdatrz) and 3242 cm^{-1} in 1 are assigned to the υ(NH_2) vibrations of the uncoordinated triazole. The absorption bands due to υ(N-H) observed at 3118 cm^{-1} in the ligand, appeared at 3120 in complex 1. The relatively weak bands at 2918 cm^{-1} for H_2dipic, 2923 for Hdatrz and 2927 for 1 are due to stretching vibrations of aromatic C-H of the ligands.

The strong absorption bands at 1599 (H_2dipic), 1562 (Hdatrz), and 1585 cm^{-1} for compound 1 are attributed to υ (C=C) + υ(C=N) vibrations of the ligands. The characteristic absorption bands due to hydrogen-bonded carboxylic groups (COOH) of free H_2dipic at 1696 cm^{-1} (Çolaka *et al.*, 2010) disappeared from the spectrum of the complex. Observation of symmetric carboxylate bands (ν_sCOO) in the region 1373 cm^{-1} for 1 indicates that the carboxylic group of H_2dipic coordinated with the metal ion through deprotonation. Strong asymmetric (υ_{as}) vibrations in the free H_2dipic shifted to lower frequencies, that is 1631 and 1465 cm^{-1} for complex 1.

The difference between the asymmetric and symmetric vibrations of the carboxylate groups of the complex, $\Delta\upsilon$ = 258 cm^{-1} for 1, consistently proposes monodentate coordination of the carboxylate group to the metal ion (Cai, *et al*., 2011; Ilkimen and Canlıdinç, 2020)**.** The splitting of the asymmetric (ν_{as}) and symmetric (ν_s) COO^- bands imply that COO^- groups are bonded in different ways in the same molecule (Çolaka *et al*., 2010). The bands at 588 and 426 cm^{-1} for **1** are attributable to the Cu- O and Cu-N vibrations, respectively (Ilkimen *et al*., 2014).

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Table 3. Selected IR bands (cm^{-1}) of ligands and metal complex

Compound	**υ**(OH)	**υ(NH_2)**	**υ(N-H)**	**υ(C-H)**	**υ(CO)**	**$υ_{as}$(COO)**	**$υ_s$(COO)**	**υ(C=)+υ(C=N)**	**υ(M-O)**	**υ(M-N)**
H_2dipic	3445			2918	1696		1412	1599		
Hdatrz	3400	3313	3118	2923				1562		
Complex 1	3373	3242	3120	2927		1631, 1465	1373	1585	588	426

^{1}H –NMR Spectra

The ^{1}H-NMR spectrum of H_2dipic (Fig. 1) showed a resonance of -OH of carboxylic acid at δ 13.28 (br, s,2H) and a multiplet in the range δ 8.24– 8.13, (m, 2H, H_2dipic). The ^{1}H-NMR spectrum of Hdatrz (Fig. 2) has broad singlets for the protons of 3-NH_2 and 5-NH_2 groups, respectively. The signals at δ 4.76 (3-NH_2) and 5.50 (5-NH_2) correspond to the protons of amino groups of Hdatrz (Nakamoto, 1997). Another singlet, representing the proton of NH of the triazole ring, appeared at δ 10.69. A similar result has been reported (Chernyshev *et al*., 2005). In the ^{1}H-NMR spectrum of complex **1**, the resonance of –OH at δ 13.28 in free H_2dipic disappeared indicating that no free –COOH group exists in the complex. In the complex, resonance appeared at δ 8.21 for **1**, which indicates that –COO^- of $dipic^{2-}$ is coordinated with Cu (II) ions in **1** (Çolaka *et al*., 2010). The signal at δ 3.39 for **1**, suggests the presence of water molecules in the compound**,** and extensive hydrogen-bonding network which stabilizes the structure. The disappearance of the resonance of –OH of carboxylic acid at δ 13.28 and –NH of triazole at δ 10.69 indicates that the Hdatrz molecule is protonated in **1**.

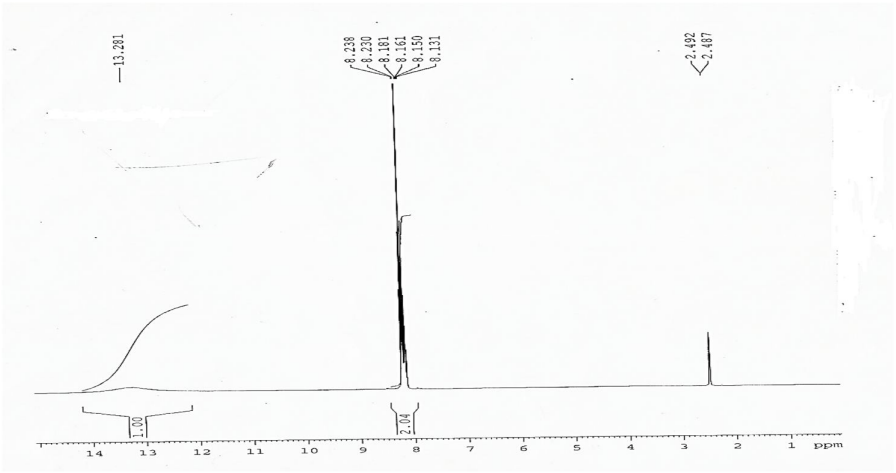

Figure 1. ^{1}H-NMR spectrum of pyridine-2,6-dicarboxylic acid (H_2dipic)

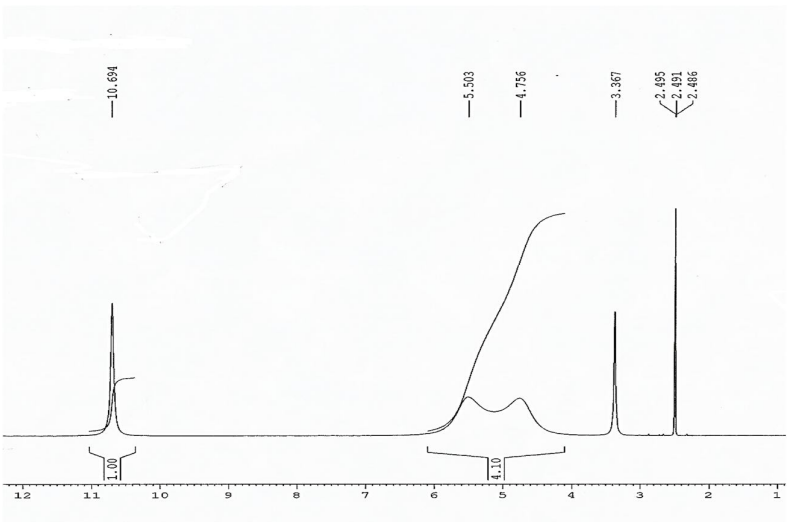

Figure 2. ^{1}H-NMR spectrum of 3,5-diamino-1,2,4- triazole (Had

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Mass Spectra

The electron ionization mass spectrometry (EI-MS) spectra of ligands exhibited molecular ion peaks $[M]^+$ at *m/z* = 99, and 168 for 3,5-diamino-1,2,4-triazole (Hdatrz) and 2,6-pyridine-dicarboxylic acid (H_2dipic), respectively. ESI-MS Spectra showed characteristic peaks for the complex. The $[M+H]^+$ peak at *m/z* = 495 indicates the presence of $C_2H_6N_5[Cu(C_7H_4NO_4)(C_7H_3NO_4)]$. Another peak at m/z = 395 indicates the loss of $C_2H_6N_5$ from $[M+H]^+$, a peak at *m/z* = 168 $[M+H]^+$ assigned to H_2dipic. No molecular ion peak appeared.

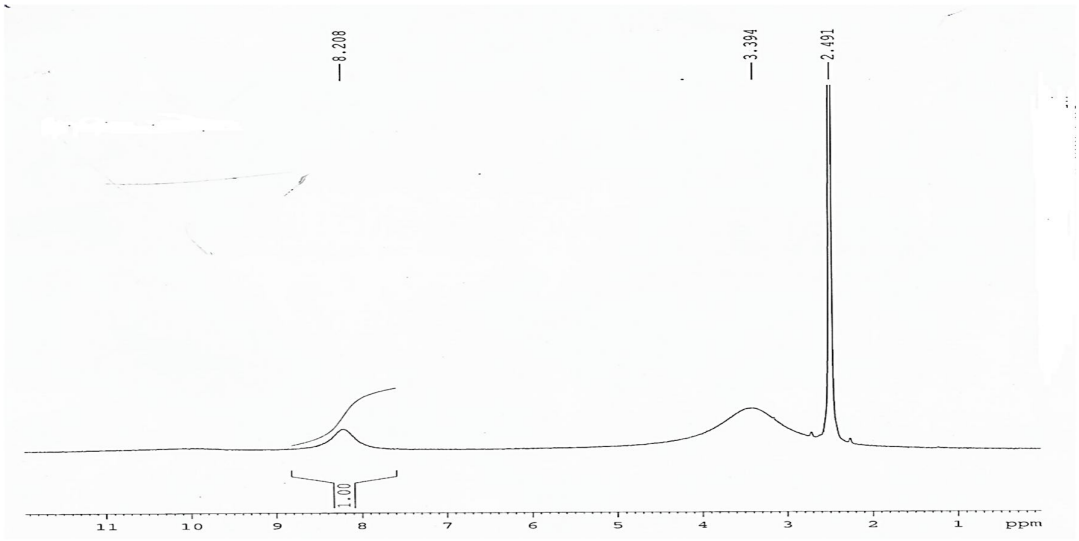

Figure 3. ^{1}H-NMR spectrum of $(C_2H_6N_5)[Cu(dipicH)(dipic)]\cdot 3H_2O$ (1)

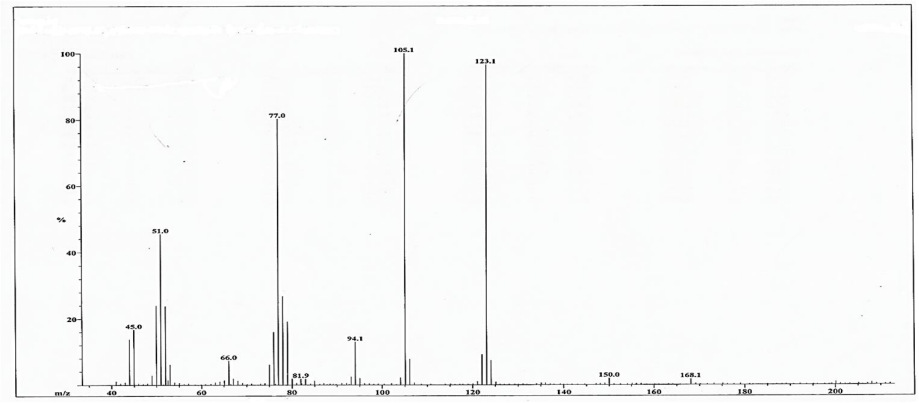

Figure 4. EI-MS Spectrum of pyridine-2,6- dicarboxylic acid (H_2dipic)

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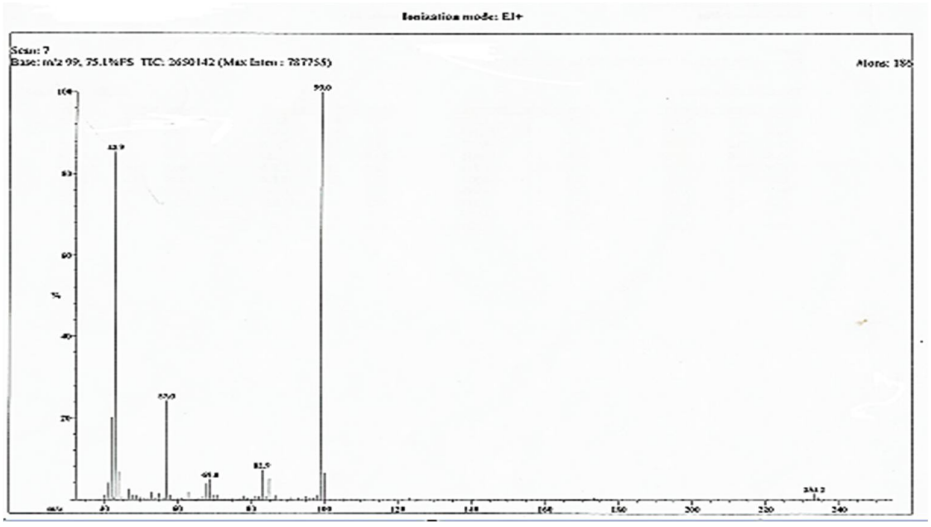

Figure 5. EI-MS spectrum of 3,5-diamino-1,2,4- triazole

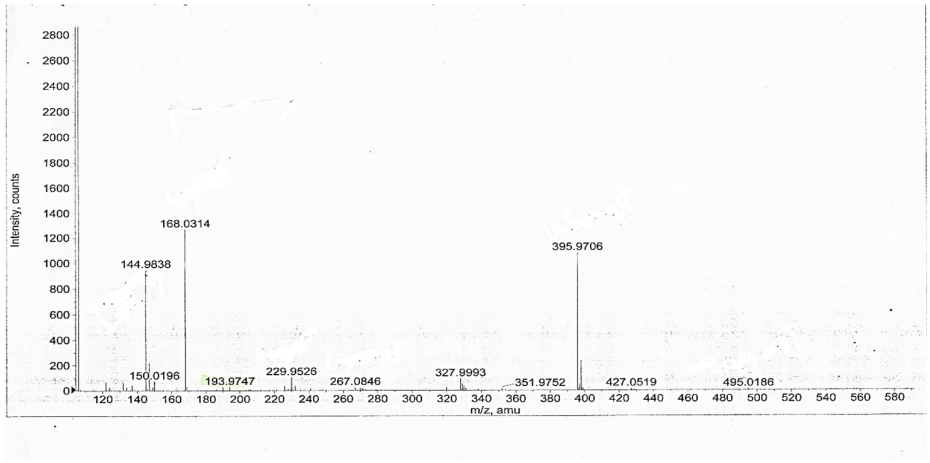

Figure 6. ESI-MS Spectrum of $C_2H_6N_5)[Cu(dipicH)(dipic)]\cdot 3H_2O$ (**1**)

Thermal analysis

Thermal analysis was performed to study the stability of the complex. The DSC-TGA curves for complex **1** are shown in Figure 7. Complex **1** reveals three phases of weight loss.

The initial phase of weight loss from 100-197° C (DSC_{max} = 150° C) is related to the endothermic removal of three crystal water molecules (found 10.62, calculated 9.84%). The second phase is related to the breakdown of the one protonated $HdatrzH^+$ and $dipicH^-$ in the range 197.62-358.31° C (found 49.98, calculated 48.50%). The third stage between 358.31 – 1201° C is attributed to the loss of the residual $dipic^{2-}$ with the release of CO (found 24.80, calculated. 24.97%).

Total weight loss (found 85.37, calculated 83.31%).

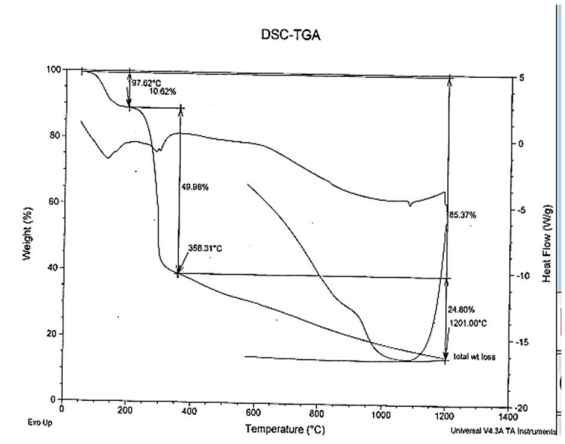

Figure **7.** Thermal analysis curves for complex (**1**) **(**$C_2H_6N_5$) $[Cu(C_7H_4NO_4)\ (C_7H_3NO_4\ )].3H_2O$

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Table 3. Results of DPPH (1, 1-diphenyl-2-picrylhydrazyl) Radical Scavenging Assay.

Compound	Conc [mM]	IC_{50} ± SEM [μM]	%RSA
(HdatrzH)[Cu(Hdipic)(dipic)].3H_2O (**1**)	0.5	33.9±1.39	91
Ascorbic acid	0.5	40.5±1.2	96
Butylated hydroxyanisole (BHA)	0.5	44.6 ±0.7	95

DPPH Scavenging Activity

The radical scavenging activity of the complex was measured as the capability of the test compound to scavenge DPPH, a stable free radical. The DPPH radical has an unpaired electron which is accountable for the absorbance at 515 nm, as well as for the visible deep purple colour. Once DPPH accepts an electron contributed by an antioxidant compound, the DPPH is decolourized. The extent of decolourization can be quantitatively calculated from the changes in absorbance. Evaluation of the antioxidant activity of the metal complex, relative to that of ascorbic acid and butylated hydroxyanisole (BHA) is presented in Table 3. The complex showed considerable inhibition of DPPH radical scavenging activity, with an IC_{50} value of 33.9 ± 1. 39 μM for **1**, as compared to the standards 40.5±1.2 (ascorbic acid) and 44.6 ±0.67 (BHA).

Table 4. Superoxide Anion Scavenging Activity of Complex 1.

Compound	Conc. (Mm)	IC_{50} SEM [μM]	% RSA
HdatrzH) [Cu(Hdipic)(dipic)]. 3H_2O (**1**)	0.5	0.3707± 0.0057	99
Quercetin (Standard)	0.5	94.24± 1.1	100

Table 5. Cytotoxicity of Complex 1.

Compound	IC_{50} ± SEM [μM]
HdatrzH)[Cu(Hdipic)(dipic)].3H_2O (**1**)	>30
Cycloheximide (standard drug)	0.26±0.1

Superoxide Radical Scavenging Activity

Complex **1** (HdatrzH) [Cu (Hdipic)(dipic)].3H_2O exhibited a considerable superoxide scavenging activity (99%), with a 50% inhibition (IC_{50}) value of 0.3707±0.0057 μM as compared to the standard quercetin with RSA of 100% and IC_{50} value of 94.2± 1.1 μM. This may well be attributed to a large ligand field strength of the chelating primary ligand $(dipic)^{2-}$ (Collman *et al*., 1980)

Cytotoxicity Test

The result of the cytotoxicity test for compound **1** is presented in Table 5. The 50% growth inhibition value recorded indicates that compound **1** is non-cytotoxic against 3T3 cell line.

Antimicrobial activity

Although many metal complexes containing dipicolinic moiety have been reported to show antimicrobial activity (Çolaka *et al*.,2009; Çolaka *et al*., 2010; Cai *et al*., 2011) with micro-gram (μg) concentrations of ligands and complexes, the ligands and metal complex evaluated in this study showed no antifungal and antibacterial activity.

The lack of activities in these compounds at low concentrations may be attributed to the inability of the ligands and complex to form bonds with the cell constituents of the microorganisms (John *et al*., 2004).

CONCLUSION

A new compound, $(C_2H_6N_5)[Cu(C_7H_4NO_4)(C_7H_3NO_4].3H_2O$ (**1**) was prepared and characterized by elemental analysis, spectroscopic techniques (IR, UV-Vis, ^{1}H NMR, ESI-MS), thermal analysis, and magnetic susceptibility measurement. In compound **1**, the H_2dipic ligand acted as a *bis*- tridentate ligand through the nitrogen atoms of the pyridine ring and the oxygen atoms of the carboxylate, while the protonated 3,5-diamino-1,2,4-triazole served as a counter ion. The compound showed no antimicrobial activities at minimum concentrations. Interestingly, the compound exhibited a significant radical scavenging activity (RSA). It is concluded that the compound prepared and characterized in this study can be exploited as a possible candidate for the treatment of oxidative stress-induced ailments.

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