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Binuclear Co(II), Ni(II) and Cu(II) acetate complexes derived from a novel Thiosemicarbazide:Preparation, characterization, DFT and *In vitro* cytotoxicity activity

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Abstract:A new series of binuclear complexes, Co^{2+}, $Ni^{2+}$and Cu^{2+} derived from N, N'-(2,2' malonylbis(hydrazine-1-carbonothioyl)) dibenzamide (H_4MHTS) in 1:2 (L:M) ratio was prepared and characterized. The complexes adopted the molecular formulae; $[Co_2(H_2MHTS)(OAc)_2].2H_2O$, $[Ni_2(H_2MHTS)(EtOH)_4(H_2O)_2]$ and $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$, respectively.IR data showed that H_4MHTS ligand acts as either dibasic $O_2N_2O_2$ hexadentate in Co^{2+} and Ni^{2+} complexes or neutral $O_2N_2S_2$ hexadentate. An octahedral environment was suggested for all complexes according to spectral and magnetic susceptibility. The low magnetic moment value of Co^{2+} complex confirms strong M-M interaction $\mu_{eff.}$ (3.69). DFT method we used to confirm the geometries of title compounds and evaluate other energetic parameters such as HOMO, LUMO, hardness, softness and electronegativity. Also, the thermal stability was examined by TG and DTG and the associated thermodynamic parameters of activation were determined using Coats-Redfern and Horowitz-Metzger methods. The data indicated that the thermal degradation process is slow, endothermic and non-spontaneous one. The *in vitro* cytotoxicity against cell lines, Mammary gland breast cancer (MCF-7) using doxorubicin as standard was examined revealing the potent activity of the thiosemicarbazide.

keywords: hexadentate, octahedral geometry, endothermic, magnetic moment, Kinetic**.**

1.Introduction

Thiosemicarbazides are potent intermediates for the synthesis of pharmaceutical and bioactive materials and thus, they are used extensively in the field of medicinal chemistry. The diversity of heterocycles generated from thiosemicarbazides is associated primarily with the fact that these compounds can exhibit properties of N(1),N(2)-, N(1),N(4)-, N(2),N(4)-, N(1),S-, N(2),S- and N(4),S-dinucleophiles [1].Also, thiosemicarbazides have been extensively utilized commercially as dyes, photographic films, plastic and in textile industry[2].Transition metal complexes derived from thiosemicarbazides have become of significant importance in industry and biology[3].Such metal complexes have revealed obviously the central role played by sulfur coordination in these compounds and consequently their “soft by acid-soft base” preference is [4].The real impetus toward developing the coordination chemistry of these potential ligands was probably provided by the remarkable antitumor [5], antiviral [6], and antimalarial [7,8] activity observed for some of these derivatives, which has since been shown to be related to their metal-complexing ability [9]. The mechanism of action of bis (thiosemicarbazide) cytotoxicity, in contrast to mono-thiosemicarbazides and their complexes, was not to stop the production of reactive oxygen species (ROS) [6,11–15], but rather to target hypoxic tissue. Because of their high hypoxia selectivity, these drugs are used extensively as radiopharmaceuticals.[16–19] Additionally, N'^{1},N'^{3}-dimethyl-N'^{1},N'^{3}-di (phenylcarbon othioyl)malonohydrazide, an anticancer medication chemically linked to elesclomol, demonstrated strong cytostatic [16].

Its Ni (II) and Pt (II) complexes exhibited significantly less activity than the Cu (II) complex against human leukemia K562 cells. The malonic acid dihydrazide derivatives possess greater flexibility than other dibasic acid dihydrazides like phthalic and oxalic This flexibility arises from the ability of free rotation around the CH_2–CO bond.[21] Malonic dihydrazide's interaction with several carbonyl compounds, aldehydes, and ketones has been widely documented [21–23], although thiosemicarbazide derivatives have hardly ever been investigated.

This suggests that a redox active metal is necessary for elesclomol to have its cell growth inhibitory effect.[20] Alternatively, the malonic acid derivatives of malonic acid dihydrazide attracted a lot of attention than their thiosemicarbazides derivatives although their phenyl and ethyl derivatives domstrated in vitro cytotoxicity activity against Hela cell and WISH cell line lines [15, 19].

Thus, on continuation to our research program we aimed herein to focus on the synthesis, spectral characterization, and in vito cytotoxicity against breast cancer of new thiosemicarbazide and its corresponding Co^{2+}, $Ni^{2+}$and Cu^{2+} acetate complexes.

2. Materials and methods

2.1 Preparation of H_4MHTS

1.3 gm of malonohydrazide (5mmol) were added to 3 mL of benzoyl (10 mmol) in presence of 0.28 gm solid KOH (5mmol) and 15ml DMF. The reaction mixture was heated under reflux for 2 with stirring. Then, two drops of concentrated hydrochloric acid were added and a pale-yellow precipitate that formed was filtered off, washed several times with cold water and allowed to dry in a clean desiccator. over anhydrous$CaCl_2$. The product was tested by TLC, IR and ^{1}HNMR and the yield was %85 (1.98 gm); m.p.:200^0C.

2.1.1.H_4MHTS

$C_{19}H_{18}N_6O_4S_2$ (458.51): yield:85% yellow; m.p:200 %calc; C(49.77);H (3.96); N (18.33); Found C 50.15; .H 4.14; N 18.91;; FTIR (cm^{-1});1690ν(C=O)$_{hy}$;1673 ν(C=O)$_{benz}$; 3061ν(N^1H); 3222 ν(N^2H);3330 ν(N^4H)1263 ν(C=S); 792 δ(C=S).

2.2. Preparation of metal complexes

The corresponding metal acetate (1.0 mmol) was added to ethanolic solution of H_4MHTS (0.2751, 0.5mmol) in molar ratio (M:L=2:1) and heated under reflux for 2–3. The precipitates formed were filtered off, washed with ethanol followed by diethyl ether, dried in a vacuum desiccator over anhydrous$CaCl_2$ and checked by TLC, partial elemental analysis (C, H, N and S) as well as spectral tools (IR, UV-vis.,).The complexes are stable in air, soluble in dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) and non-electrolytes (1-18) [16]. Many trials were performed to isolate a single crystal but failed.

2.2.1 Co complex

$C_{23}H_{26}Co_2N_6O_{10}S_2$(728.48); yield:73%;brown;m.p:>300; Elemental Anal. %calc; C(37.92); H(3.60); N(11.54); M(16.18); Found C 37.02; H 3.11;N 11.17 M 17.7 FTIR (cm^{-1})1671ν(C=O)$_{benz.}$; 512 ν(M-O) ;449ν(M-N) ; 1603ν(C=N)*;1245ν(C-O)*.

2.2.2 Ni complex

$C_{27}H_{42}Ni_2N_6O_{10}S_2$(792.17);yield:80% Brown; m.p:>300; Elemental Anal. % Calc; C(40.94); H(5.34); N(10.61); M (14.82); Found C 41.10H 4.63; N 10.10; M 15.02;FTIR (cm^{-1}) 1645ν(C=O)$_{benz}$;3177ν(N^2H);3313ν(N^4H) ;1286ν(C=S); 799δ(C=S) ;524 ν(M-O); 475 ν(M-N) ; 1557ν(C=N)* ;1245ν(C-O) *.

2.2.3 Cu complex

$C_{27}H_{38}Cu_2N_6O_{16}S_2$(893.84); yield:68%brown;

.p:285; Elemental Anal. % calc ;C(39.28);H (4.29) ;N(9.40) M (14.22); Found C 39.48H 4.01N9.66M14.43 FTIR (cm^{-1}) 1675ν(C=O) $_{benz}$;1707ν(C=O)$_{Hyd}$;3064ν(N^1H); 153ν(N^2H); 3330ν(N^4H)1252ν(C=S);796δ(C=S);506 ν(M-O) ;475ν(M-N).

2.3.DFT study

All calculations reported were computed using DMOL^3 program [16] in Materials Studio 7.0 package using (DFT semi-core pseudopods (dspp)) computations with the double numerical basis sets plus polarization functional (DNP) which was suggested by Kessi et al and the revised Perdew-Burke-Ernzerh of functionals

(RPBE)[17-19] to be more accurate when comparison with Gaussian basis sets of the same size

2.4. *In vitro* cytotoxicity

The MTT assay was employed for examination the cytotoxic activity of isolated compounds against two cell lines, *Epitheliod Carcinoma* (Hela) and *Human amnion* (WISH). According to the reported earlier, the procedure based on that mitochondrial succinate dehydrogenase in viable cells converted the yellow tetrazolium bromide (MTT) into a purple formazan derivative where the cell lines were cultured in RPMI-1640 medium with 10% fetal bovine serum and the relative cell viability in percentage was calculated. Doxorubicin was used as a standard anticancer drug [20].

3. Results and Discussion

3.1. IR spectra

The significant IR bands of H_4MHTS and its complexes (KBR discs) (4000-500 Cm^{-1}) are recorded in figure 1. The studied thiosemicarbazide can exist in three possible isomess *viz* keto- thione, enol-thione and keto-thiol (Scheme 1). The bands of strong intensities in the spectrum of the primary ligand *viz* H_4MHTS (Structure 1) at 1690 cm^{-1} and 1673 are attributable to stretching vibrations of (C=O) attached to benzene ring and that attached to N^1H group. The band at 1790 cm^- suffers a blue shift of ～15-19 cm^- upon involvement in coordination in Co(II) and Cu(II) complexes(Structures a & c). The band appeared at 1599 cm^{-1} is assigned to $\nu(C{=}C)_{phenyl}$ [20]. molecule not involved in chelation while the other suffers a shift to lower wavenumber due to participation in coordination which will be further supported by ^{1}HNMR spectrum of the ligand. [20]. The medium bands located at 1524, 1330 and 938 cm^{-1} assigned to thioamide I-IV vibrations have substantial contributions from ν(C-N), δ(C-H) and δ(N-H) and vibrations [21]. The bands at 3061, 3222 and 3330 cm^{-1} are due to $\nu(N^1H)$, $\nu(N^2H)$ and $\nu(N^4H)$ modes [22]. These bands undergo broadness In the IR spectra of metal complexes, that may arise from the overlap of the stretching vibrations of lattice water molecules with the ν(NH)'s [17]. The stretching and bending vibrations of C=S group are observed as strong bands at 1263 and 792 cm^{-1}, respectively [18]. The intense band at 1072 cm^{-1} is characteristic for ν(N-N). Also, the band at 3057 cm^{-1} is due to aromatic CH vibration and no band was observed in the region (2500-2650 cm^{-1}) in the IR spectrum characteristic for SH group suggested the obscure of possibility of keto/thiol tautomerism in the solid state. Finally, weak bands in the region 2884-2997 cm^{-1} is characteristic to aliphatic CH_2 group. On comparing the spectrum of the thiosemicarbazide and its metal complexes (Structures a-c) claryfied its coordinates as neutral or dibasic chelate. The following remarks can be drawn:

- Firstly, as a neutral $N_2O_2N_2$ hexadentate in $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$ complex (Structures c) coordinating each Cu atom through N^2H and (C=S) groups which confirmed by the shift of their bands to lower wavenumber and $(C{=}O)_{hydr}$ shift to higher wavenumber.

- Secondly, H_4MHTS binds as mononegative $O_2N_2O_2$ tridentate in $[Co_2(H_2MHTS)(OAc)_2].2H_2O$ complex in thione-enol form (Structure a) binding to each Co atom through $(C\text{-}O)_{hydr}$ that formed on enolization followed deprotonation upon coordination to metal ion, N^2H and $(C{=}O)_{benzoyl}$ [23]. This mode of chelation is supported by:

i) The blue shift of the band due to $\nu(C{=}O)_{benz}$.

ii) The disappearance of bands due to (C=O) and $\nu(N^1H)$ vibrations with simultaneous appearance of new bands at 1603 and 1245

cm^{-1}assignable to new ν (C=N)*and ν (C-O) bands support the suggested mode of chelation.

- Finally , in the binuclear complex,

$[Ni_2(H_2MHTS)(EtOH)_4(H_2O)_2]$ (Structure b) H_4MHTS chelates as binegative $O_2N_2O_2$ hexadentate coordinating two Ni atoms *via* enolized C-O, N^2H and new (C=N*) [23]. Also, the new bands that observed at 524 and

475 cm^{-1} assigned to ν(M-O) and ν(M-N) vibrations were taken as additional evidence for existing of the ligand in enol form and its coordination to the metal ion in binegative hexadentate fashion, via the deprotonated

enolized carbonyl oxygen and nitrogen atoms. The acetate group in the titled complexes coordinated either as bidentate ligand in $[Co_2(H_2MHTS)(OAc)_2].2H_2O$ complex or in monodentate manner in $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$complex revealed by the new bands appeared at (1644,1540 cm^{-1}) and (1671, 1480 cm^{-1}) attributed to the νas(OAc) and νs(OAc) vibrations, with (Δν difference ≈ 110 &191 cm^{-1}) [24], respectively matching with the reported values (Structure c). The two new bands assigned to the ν(M-O) and ν(M-N) at 506 and 475 [24], respectively, support the suggested mode of chelation.

3.2.NMR spectra

Figure 2 shows the ^1H NMR spectrum of the ligand, H_4MHTS in d6-DMSO where the peaks at 11.66, 11.18 and 10.00 ppm assignable to N^4H, N^2H and N^1H protons. These peaks disappear upon addition of D_2O (Figure 2b) suggesting they are easily exchangeable as they form hydrogen bonded with CO or CS, and so are shifted downfield. Thus, the appearance and disappearance of these signals confirms the existence of the ligand in keto form. In addition, the singlet signal observed at 3.57 are due to the protons malonyl CH_2 group. The peaks correspond to protons of benzene ring are observed as multiplet at δH:(7.49–7.96).

3.3. Electronic spectra

The electronic absorption spectra of compounds under study were displayed in DMF (Fig.3). The bands that observed at 41667, 34483 and 30395 cm^{-1} as broad ones in the absorption spectrum of H_4MHTS presumably arising from transitions {an overlap of the transitions due to those of benzene ring, carbonyl and thione groups} [24].These bands suffer a clear change upon complexation and appeared at 43290-40000 cm^{-1}, 34602-34013 cm^{-1} and 30581-31250 cm^{-1} indicating the chelation of central metal ion through the carbonyl and thione groups [24]. These three transitions bands of the ligand observed at (40816, 34602 and 31250 cm^{-1}), (43290, 34013 and 30581 cm^{-1}) and (40000, 34602 and 31250 cm^{-1}) for Co(II), Ni (II) and Cu(II) complexes, respectively

The spectrum of $[Co_2(H_2MHTS)(OAc)_2].2H_2O$, complex recorded in DMSO exhibited; new band at 16340 referred to transition of the new formed (C=N*) group [24]. A new broad band observed, in DMSO and Nujol mull, at 20450 cm^{-1}, with a shoulder at 16340 cm^{-1} and 15151 cm^{-1} were attributed to LMCT. The complex exhibited magnetic moment value, 3.69 B.M.The spectrum of $[Ni_2(H_2MHTS)(EtOH)_4(H_2O)_2]$, complex recorded in DMSO exhibited; new band at 34013 referred to transition of the new formed (C=N*) group [24]. and 16501 cm^{-1} were attributed to LMCT. magnetic moment value of The complex exhibited 2.98 B.M.The spectrum of $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$, complex recorded in DMSO exhibited; new band at 16892 and 14749.The complex exhibited magnetic moment value, 1.79 which found in the normal range of Cu(II) complexes regardless of their stereochemistry, 1.75-2.20 [24].(Co&Ni)the ligand field parameters ($10D_q$,B, β)were calculated and found to be (7103,771.12,79) and (12392,889.2,.85) respectively.

3.4. Thermogravimetric studies

TGA curves of H_4MHTS as well as its corresponding metal complexes are shown if figure 4 (a-d) and the data are recorded in table 1. Thermal degradation of H_4MHTS (Fig.4a) occurs through four steps. The first stage takes place in the temperature range(134-237^{0}C) with elimination of the fragment namely $C_3H_4N_2O_2$ with wt loss; 21.07% (Calcd. 21.83%). In the second stage, the fragment $C_{13}H_{12}N_2O_2$ is removed at 238-384^{0}C with wt loss; 49.82%

(Calcd. 49.78%) and in the third stage (385-684) the fragment $N_2CS_2H_2$ with wt loss; 23.71% (Calcd. 23.15%) was eliminated. The residual part that being left after complete degradation was 2C. On the other hand, the thermal degradation of $[Co_2(H_2MHTS)(OAc)_2].2H_2O$ H_4MHTS as a representative example takes place through five steps. The first stage in the range (25-102 ^{0}C) is corresponding to wt loss; 5.09% (Calcd. 4.95%) is attributed to loss of two water lattice molecules.

In the second stage, the fragment $2CH_3COOH$ is eliminated at 103-245^{0}C with wt loss;16.31% (Calcd.16.21%),in the third stage (246-396^{0}C) the fragment $C_{16}H_{12}N_2S_2$

with wt loss; 40.73%

(Calcd.40.69%) is removed while in the four stage (397-555^{0}C) fragment $C_2H_4N_4O_2$ with wt loss; 15.30% (Calcd.15.93%) is eliminated. The residual part was 2CoO+C.

3.5. Kinetic data

The kinetic and thermodynamic parameters of thermal degradation process using Coats-Redfern and Horowitz-Metzger models [25] have been evaluate and. The data obtained are represented graphically in figs. 5 &6. The high values of activation energy, E_a indicates the high stability of chelates because of their covalent bond character [25]. The sign of ΔG^* indicates all the decomposition steps are non-spontaneous and the positive values of enthalpy of activation, ΔH^* revealing the endothermic nature of the degradation process. Finally, ΔS^* has negative values indicating more ordered activated complex than the reactants or the reaction is slow [26].

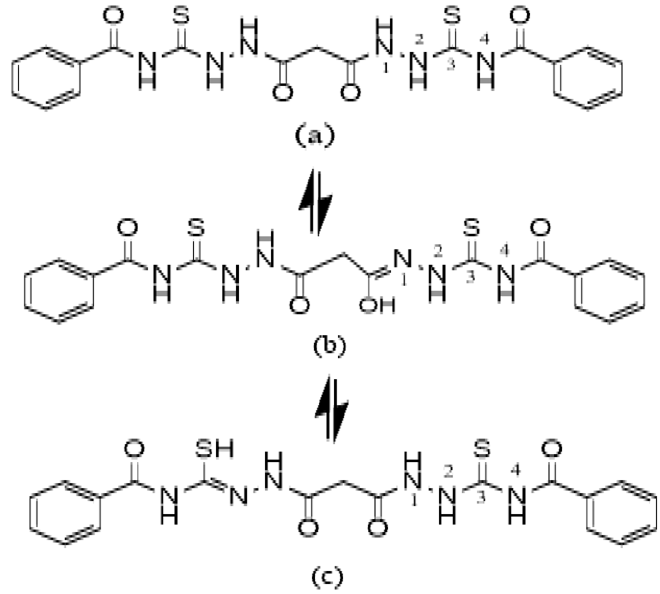
3.5.*In vitro* cytotoxicity

The well-known anti-cancer activity of bis(thiosemicarbazide)(H_4MHTS) and its complexes promoted us to examine the *in vitro* cytotoxic activities of the and its metal complexes against cell lines, Mammary gland breast cancer (MCF-7) using doxorubicin as standard. A glance at the data (Table 2) revealed that the potent activity of the ligand, IC_{50} 15.39±1.30 compared to the standard drug (doxorubicin :4.17±0.20)and the order is: H_4MHTS)> Co(II) complex> Ni(II) complex > Cu(II) complex; respectively [27]. This indicate that chelation did not enhance the activity with the exception of Co(II) complex. These results are consistent with those reported [15, 16]. This activity of Co(II) complex may referred to due to the unique electronic and structural properties of cobalt, which lead to a more potent induction of cell death mechanisms like apoptosis and pyroptosis. The cobalt complex's ability to effectively target breast cancer cells, while the Ni(II) and Cu(II) complexes may exhibit different levels of potency or be less selectivity which influences how the complexes interact with biological targets such as DNA and enzymes.

Therefore, further *in vivo* biological assessment and mechanisms of action research are required.

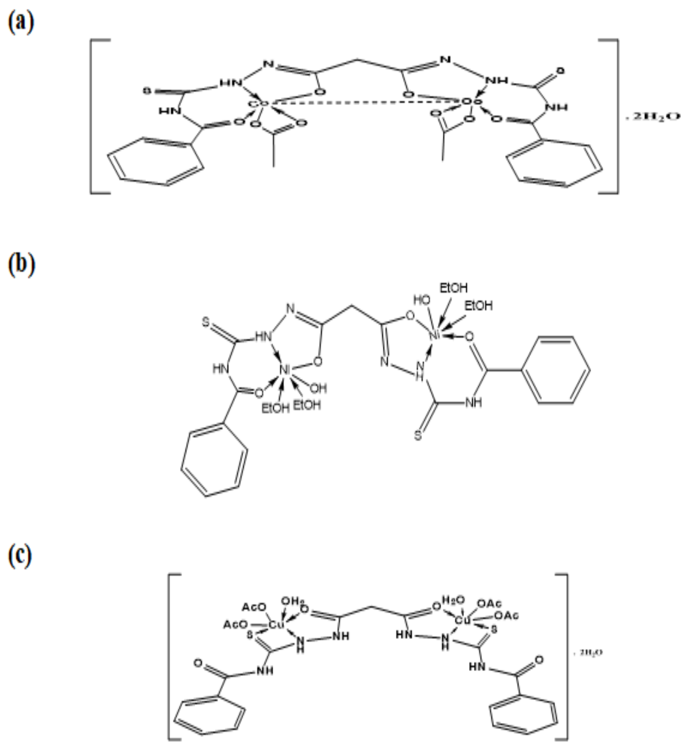
3.6.Geometry optimization

The molecular structures of all compounds are demonstrated in Figure 7.



N,N'-(2,2'-malonylbis(hydrazine-1-carbonothioyl))dibenzamide **(**H_4MHTS).

Scheme 1. Possible isomerism of H_4MHTS:(a) Keto-Thione, (b) Enol-Thione and (c) Keto-Thiol.



Scheme 2: Structures of metal complexes: (a) Co(II) complex; (b) Ni complex(II) and (c) Cu(II) complex.

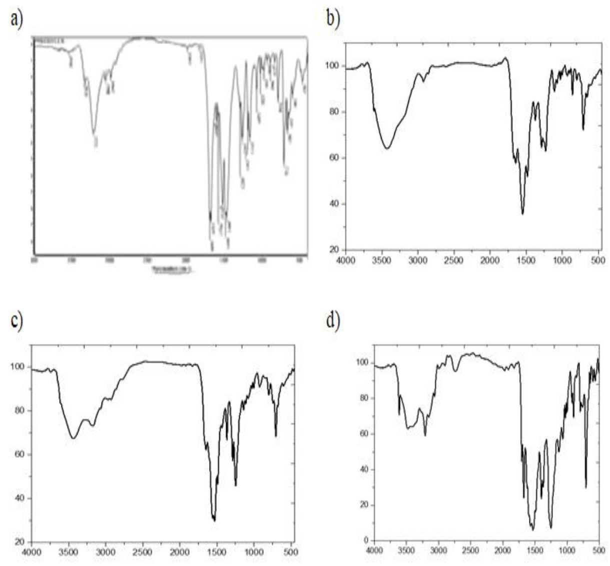


Figure 1.IR spectra of: a) H_4MHTS, b) $[Co_2(H_2MHTS)(OAc)_2].2H_2O$, c)$[Ni_2\ (H_2MHTS)(EtOH)_4(H_2O)_2]$ and $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$.

Figure 2. ^{1}HNMR spectrum of H_4MHTS (in d_6 DMSO).

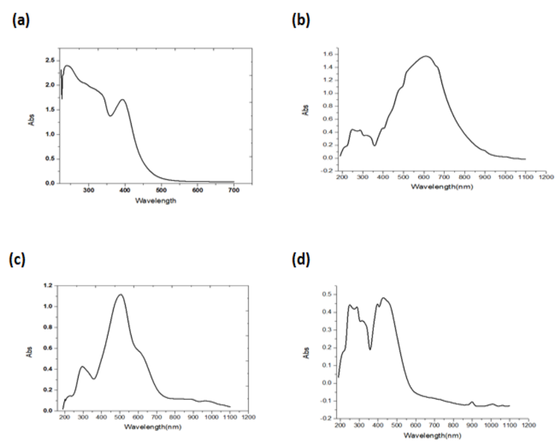


Fig 3. Electronic spectra of : a) H_4MHTS, b) $[Co_2(H_2MHTS)(OAc)_2].2H_2O$, c) $[Ni_2\ (H_2MHTS)(EtOH)_4(H_2O)_2]$ and $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$.

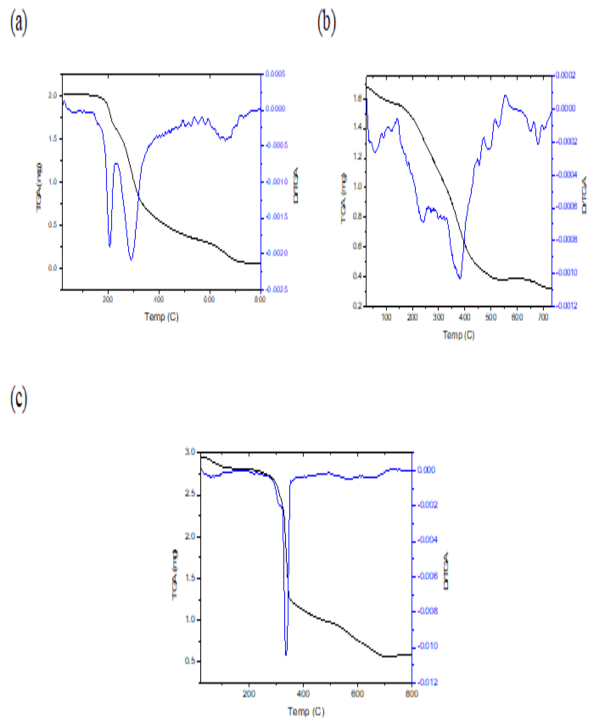


Fig. 4. TGA, and DrTG thermal analysis curves of : a) H_4MHTS, b) $[Co_2(H_2MHTS)(OAc)_2].2H_2O$, and c) $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$.

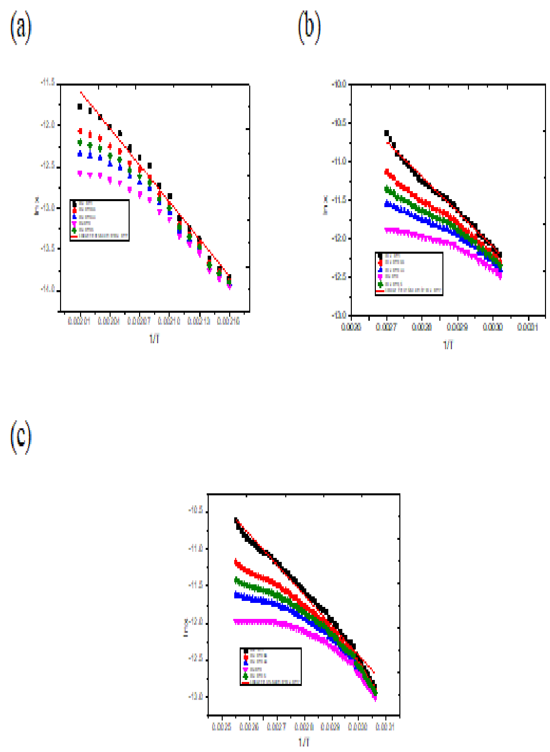


Figure 5: Coats-Redfern plots of the first degradation step for a) H_4MHTS, b) $[Co_2(H_2MHTS)(OAc)_2].2H_2O$,and c) $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$.

Table 1: The temperature range and weight loss of each decomposition steps for H_4MHTS, $[Co_2(H_2MHTS)(OAc)_2].2H_2O$,and $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$.

Complex	Step	Temp.Range,°C	Removed species	Wt. Loss (%)	
				Found	Calcd
H_4MHTS	1st	134-237	$-C_3H_4N_2O_2$	21.07	21.83
	2nd	238-384	$-C_{13}H_{12}N_2O_2$	49.82	49.78
	3rd	385-684	$-N_2CS_2H_2$	23.71	23.15
	Residue	685-800	2C	5.69	5.24
$[Co_2(H_2MHTS)(OAc)_2].2H_2O$	1st	25-102	$-2H_2O$	5.09	4.95
	2nd	103-245	-2(HOAc)	16.31	16.21
	3rd	246-396	$-C_{16}H_{12}N_2S_2$	40.73	40.69
	4th	397-555	$-C_2H_4N_4O_2$	15.30	15.93
	Residue	556-800	2CoO+C	22.22	22.45
$[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$	1st	23-124	$-2H_2O$	4.33	4.03
	2nd	125-327	$-2H_2O$+2(HOAc)	18.27	17.24
	3rd	328-365	-2(HOAc)+$C_{12}H_{10}$+2CO	36.81	36.73
	4th	443-655	$-C_3H_8N_6S_2$	20.36	21.51
	Residue	656-800	2CuO+2C	21.62	20.48

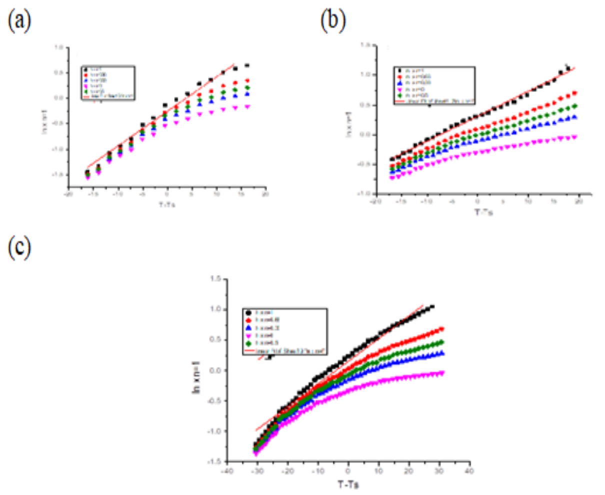


Figure 6: Horowitz-Metzger equation plots of the first degradation step for for a) H_4MHTS, b) $[Co_2(H_2MHTS)(OAc)_2].2H_2O$,and c) $[Cu_2(H_4MHTS)(OAc)_4(H_2O)_2].2H_2O$.

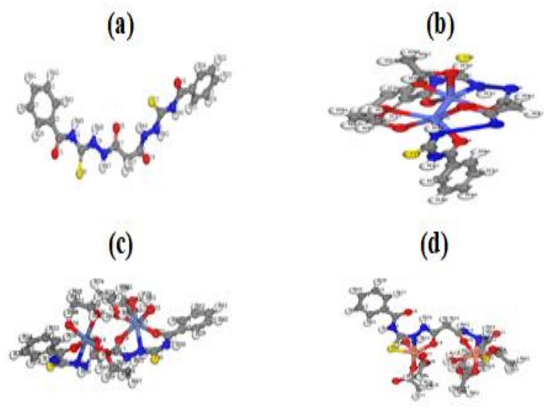


Figure 7. Molecular modelling provided with the atoms number of (a) H_4MHTS, (b) Co(II) complex, (c) Ni(II) complex and (d) [Cu(II) complex.

****: Standard.**

Table 2: Cytotoxic activity of H_4MHTS and its metal complexes against *Epitheliod Carcinoma*) using MTT assay.

No.	Compound.	In vitro Cytotoxicity IC_{50} (µM)*
		MTT
**	DOX	4.17±0.20
1	H_4MHTS	15.39±1.30
2	Co (II) complex	25.78±2.00
3	Ni (II) complex	40.60±2.9
4	Cu(II) complex	46.21±3.2

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