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Synthesis, Spectroscopic Studies, Thermal Analysis and Molecular Docking of Chloramphenicol Metal Complexes as Anti-Prostate Cancer

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Abstract
Chloramphenicol metal complexes were synthesized, and examined utilizing IR, UV-Vis, ESR, magnetic susceptibility, and thermal analyses (TGA and DTA). Chloramphenicol complexes have a 1:2 (M:L) stoichiometry. According to IR data Chloramphenicol coordinates to metal ions as a bidentate ligand attached to the oxygen atom of hydroxyl groups. All complexes have octahedral geometry, according to magnetic moment values and electronic absorption spectra. $Cu(chloramphenicol)_2(H_2O)_2$ ESR measurements revealed isotropic spectrum. For the purpose of determining the decomposition mechanism and stability ranges, thermal studies of the ligands and their metal complexes were performed. Calculations are made for the thermodynamic parameters (E*), (H*), and (S*). A number of metal complexes of chloramphenicol were tested for their antimicrobial properties. The copper complex medication is molecularly docked with 6XXO prostate cancer protein.

Keywords
Complexes, Thermal analysis, Chloramphenicol, Biological activity, Coordination chemistry, Decomposition mechanisms, Molecular Docking

INTRODUCTION

Chloramphenicol is an antibiotic medication used for a number of bacterial infections **Fig. 1** which finds applications in a wide range of infections caused by Gram-negative and some Gram-positive organisms. It is the first-choice antibiotic in developing countries and is still widely used in industrialized countries for the treatment of serious bacterial infections [1,2]. Chloramphenicol is a bacteriostatic where It functions by inhibiting ribosomal activity and protein synthesis through prevention of the binding of aminoacyl-tRNA to the A site on the 50S subunits [3]. There was a previous work for chloramphenicol complexes which describes the synthesis and complexing ability of chloramphenicol with group 12 and 14 metal ions only Zn^{+2}, Cd^{+2}, Pb^{+2} and Sn^{+2}.where characterized only by IR , UV-visible and H-NMR [4]. The main purpose of this work is to study the complexing properties, biological activity, electron spin resonance of copper complex and thermal behavior of chloramphenicol ligand and its metal complexes. Chloramphenicol can form a six-membered

ring with metal ion during complexations which gives high stability to the formed complexes. Thermal analysis plays an important role in investigating the structure and the properties of metal complexes. The thermal decomposition mechanism is explained and the thermodynamic parameters are evaluated. Alaa E. Ali *et al.* reported the complexing properties and thermal behavior of some biologically active compounds [5-7]. Molecular docking of copper complex with prostate cancer protein .The pharmaceutical advantage is to provide a safe effective compound which can help to inhibit bacteria and inhibit prostate cancer and study of metal chelation effect.

EXPERIMENTAL

Metal ion content

Accurate weight 0.02 g of complexes, then digested by aqua-regia solution. The residue was dissolved in doubly distilled water. The metal contents were determined based on atomic absorption technique using model 6650 Shimadzu-atomic absorption spectrophotometer and examined complexmetrically with standard EDTA solution using the appropriate indicator as reported [8].

C, H, N, S and Cl contents

C, H, N and S contents, for all the synthesized complexes, were recorded on CHNS No. 11042023, at central lab, Cairo University. The analysis of chloride contents of the complexes were determined by applying the familiar Volhard method [8].

Uv.-Vis. electronic spectra:

The spectrophotometric measurements in ultraviolet and visible spectra regions were recorded by using a double beam spectrophotometer UV-530, Rev. 1.00, PC (JASCO Corp) mode covering the wavelength range 200-800 nm. Two quartz cells of 1 mm thickness were used, one for the test solution and the other for the blank.

Infrared spectra:

The infrared spectra of the ligands and their metal complexes were taken in potassium bromide disc using Perkin Elmer spectrophotometer, Model 1430 covering frequency range of 200-4000 cm^{-1}. Calibration of frequency reading was made with polystyrene film (1602 ± 1 cm^{-1}).

Electron spin resonance spectra (ESR):

X-band electron spin resonance spectra were recorded with a reflection spectrometer operating at (9.1-9.8) GHZ in a cylindrical resonance cavity with 100 KHZ modulation. The magnetic field was controlled with a (LMR Gauss meter). The g values were determined by comparison with DPPH signal.

Magnetic moment values:

Molar magnetic susceptibilities, corrected for diamagnetism using Pascal's constants were determined at room temperature (298 °K) using Faraday method. The instrument was calibrated with $Hg[Co(SCN)_4]$ [10].

Thermal analysis

Differential thermal analysis (DTA) and thermogravimetric analysis (TGA) of the ligand and their metal complexes were carried out using a Shimadzu DTA/TGA-50. The rate of heating was 10 °C/min. The cell used was platinum and the dry nitrogen rate flow over the samples was 10 ml/ min. The chamber cooling water flow rate was 10 l/h. Measurements were achieved by applying the baseline methods.

Chemicals

chloramphenicol pure drug was obtained from the Egyptian company Epico, while metal chlorides (Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)) from Sigma –Aldrich company.

Synthesis of complexes

3d transition elements (Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II)) chlorides are complexed with chloramphenicol ligand by a similar procedure [7]. The metal chloride and ligand are dissolved in adequate volumes of ethanol separately. The molar amount of the metal chloride salt is mixed with the calculated amount of the ligand using mole ratio (M:L) *viz*. 1:1. The reaction mixture is refluxed for about 2 hours then left over-night, where the precipitated complexes were separated by filtration, then washed several times with a mixture of $EtOH:H_2O$ and dried in a vacuum desiccator over anhydrous $CaCl_2$. The analytical results are given in Table 1.

Antimicrobial Activity

Preparation of the agar plate:

The sterile nutrient agar was poured aseptically as 40 ml portions into sterile Petri dishes (15 cm in diameter) onto a level surface to obtain a layer of about 4 mm thickness and the plates were then left to solidify. After solidification, the plates were incubated in inverted positions at 37° C for 18 h to be over dried before use.

Preparation of the inoculum:

Each tested organism was subcultured in 3 ml sterile nutrient broth and the resultant microbial growth was firstly compared with 0.5 'McFarland Opacity Standard' which was equivalent to approximately 108 CFU/ml and properly diluted; if necessary, to achieve the same turbidity of the standard. The turbidity standard "0.5 McFarland Opacity Standard" was prepared by transferring 0.5 ml of 1.175 % solution of barium chloride to 100 ml-graduated cylinder and completing to 100 ml with 1% sulfuric acid. This standard was placed in a tube identical to the one used for both culture, sealed then kept in the dark at room temperature and used within one month.

Procedure of the test:

Sterile cotton swabs were separately dipped into each of the adjusted organism cultures and excess inoculum was removed by pressing and rotating the swab firmly several times against the wall of the tube above the level of the liquid. The swab was streaked all over the surface of the nutrient agar in three dimensions at an angle of 60° to obtain an even distribution of the inoculum. The plates were then left to dry at room temperature for few minutes. A sterile cork porer (8 mm in diameter) is used to make wells in the solid nutrient agar plates, so that the distance between the edges of each two wells is not less than 24 mm. Fill each well with 75 µl of the test compound and another well with same volume of DMF as a vehicle control. Allow a period of free diffusion for 2 h , then incubate at 37° C for 18-24 h.

Reading and interpretation of Results:

After incubation, the diameters of inhibition zones around the wells were measured, to the nearest mm, in three different directions using a ruler and the average diameter was recorded and compared to that of the control.

Molecular docking study

A molecular docking study was conducted by the Molecular Operating Environmental module (MOE 2015.10) [9]. The 3D structure of the selected protein 6XXO was adopted from the protein data bank [10]. As docking initial steps, the protein structure was set up by removing water molecules and adding hydrogen atoms. Also, a site finder was used for the ligand-binding site prediction. Evaluation of the best binding pose between the investigated ligands and the receptor protein was based on the H-bond length and the scoring energy of the simulated docked complex [11].

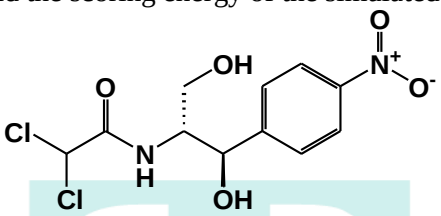


Fig. 1 Structure of chloramphenicol ligand *[2,2-Dichloro-N-[2-hydroxy-1-hydroxymethyl-2-(4-nitro-phenyl)-ethyl]-acetamide]*

Table 1 Elemental analysis, melting point formula, stoichiometries and color of chloramphenicol complexes

Complexes	Color	Calculated/(Found)%				
		C	H	N	M	Cl
$[Cr(chloramph)_2(Cl)(H_2O)]$	Violet	35.25 (35.22)	3.23 (3.25)	7.47 (7.47)	6.94 (6.95)	23.64 (23.62)
$[Mn(chloramph)_2(H_2O)_2]$	Yellow	35.94 (35.92)	3.56 (3.57)	7.62 (7.65)	7.47 (7.49)	19.29 (19.31)
$[Fe(chloramph)_2Cl(H_2O)]$	Drak brown	35.07 (35.09)	3.21 (3.22)	7.44 (7.49)	7.41 (7.46)	23.52 (23.55)
$[Co(chloramph)_2(H_2O)_2]$	Orange	35.75 (35.77)	3.55 (3.57)	7.58 (7.61)	7.97 (7.95)	19.18 (19.20)
$[Ni(chloramph)_2(H_2O)_2]$	Green	35.76 (35.77)	3.55 (3.57)	7.58 (7.68)	7.94 (7.96)	19.19 (19.21)
$[Cu(chloramph)_2(H_2O)_2]$	Brown	35.53 (35.55)	3.52 (3.55)	7.53 (7.57)	8.54 (8.56)	19.06 (19.08)
$[Zn(chloramph)_2(H_2O)_2]$	White	35.44 (35.46)	3.51 (3.52)	7.51 (7.52)	8.77 (8.79)	19.02 (19.05)
$[Cd(chloramph)_2(H_2O)_2]$	White	33.34 (33.36)	3.31 (3.33)	7.07 (7.09)	14.18 (14.20)	17.89 (17.91)
$[Hg(chloramph)_2(H_2O)_2]$	White	30.00 (30.03)	2.98 (2.96)	6.36 (6.38)	22.27 (22.28)	16.10 (16.12)

In the previous researches about chloramphenicol metal complexes 2011 Pranay et al. prepared only Nickel and cobalt with chloramphenicol in different molar ratio in presence of vanadium oxide anion. However M. jemeric prepared a solution copper complex of chloramphenicol not a solid complex [12].

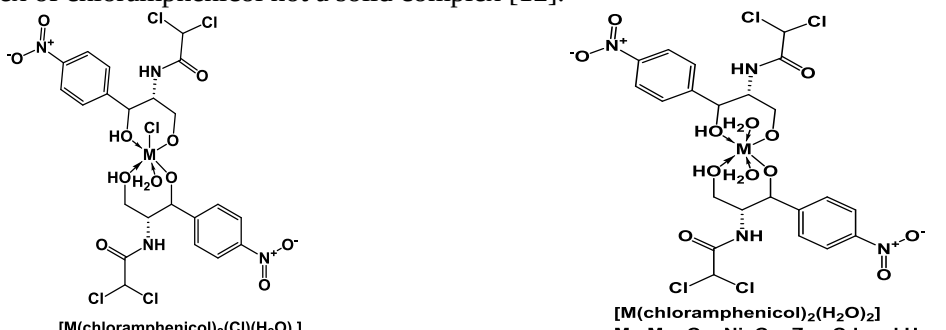


Fig. 2 Proposed structures of chloramphenicol complexes.

RESULTS AND DISCUSSION

IR spectra of chloramphenicol and its metal complexes

All the prepared complexes contain water. In general, water in inorganic salts may be classified as lattice or coordinated water [5]. There is, however, no definite border line between the two. The former term denotes water molecules trapped in the crystalline lattice, either by weak hydrogen bonds to the anion or by weak ionic bonds to the metal, or by both, whereas the latter denotes water molecules bonded to the metal through partially covalent bonds [13]. Generally, lattice water absorbs at 3652-3352 cm^{-1} (asymmetric and symmetric OH stretching) . From IR spectra of chloramphenicol metal complexes, one can notice that: The broad bands at 3297-3290 cm^{-1} in the systems could be assigned to ν_{O-H} involved in hydrogen bond, due to the presence of coordinated water molecules in all prepared complexes [14-16]. It seems from the elemental analysis of the complexes and thermal analysis that all complexes contain water molecules in their structures. This is evident by ν_{OH}, Table 2. However, coordinated water in these complexes is indicated by the appearance of metal-oxygen bands attributable to rocking modes at 402-421 cm^{-1} region [17]. The complexation is confirmed through IR bands of free ligand chloramphenicol and the metal complexes where the spectra of chloramphenicol coordinated water appeared as bands between 3353 and 3652 cm^{-1} with peak maxima at 3652 cm^{-1}. In metal complexes of chloramphenicol, some very prominent peak shifting has been observed along with change in intensities of several important peaks indicating chloramphenicol has undergone complexation reaction with metals as shown in Table 2 where the coordination through the secondary alcoholic OH group. In the far IR spectra, the bonding of oxygen is provided by the presence of bands at 402 cm^{-1} (M-O) [18].

Table 2 Fundamental infrared bands (cm^{-1}) of chloramphenicol and its metal complexes

Compound	ν_{OH} of H_2O	ν(C=O)	ν_{M-N}	ν_{M-O}
Chloramphenicol	3350	1653	-	-
$[Cr(chloramphenicol)_2(Cl)(H_2O)]$	3652	1652	-	402
$[Mn(chloramphenicol)_2(H_2O)_2]$	3498	1654	-	405
$[Fe(chloramphenicol)_2Cl(H_2O)]$	3495	1653	-	404
$[Co(chloramphenicol)_2(H_2O)_2]$	3592	1652	-	404
$[Ni(chloramphenicol)_2(H_2O)_2]$	3593	1651	-	405
$[Cu(chloramphenicol)_2(H_2O)_2]$	3428	1653	-	404
$[Zn(chloramphenicol)_2(H_2O)_2]$	3496	1652	-	408
$[Cd(chloramphenicol)_2(H_2O)_2]$	3597	1653	-	421
$[Hg(chloramphenicol)_2(H_2O)_2]$	3350	1654	-	420

Electronic spectral and magnetic studies

The electronic absorption spectra for the violet chromium complex $[Cr(chloramphenicol)_2(Cl)(H_2O)]$ showed three bands at 288, 410, 460 nm due to $^4A_{2g} \rightarrow {}^4T_{2g}$ (F), $^4A_{2g} \rightarrow {}^4T_{1g}$(F) and $^4A_{2g} \rightarrow {}^4T_{1g}$(p) transitions, respectively [7]. So, complex have octahedral geometries [19]. Such O_h geometry is further deduced from the μ_{eff} values which equals, 4.8 B.M. [13], However, the yellow electronic absorption spectrum of manganese-complexes, $[Mn (chloramphenicol)_2(H_2O)_2]$, gave two bands , 382, 446 transition, where the first band is assigned to $^6A_{1g} \rightarrow {}^4A_{1g}$, while the second is due to $^6A_{1g} \rightarrow {}^4T_{2g}$ transition where its room temperature μ_{eff} value of 5.7 B.M. typified the existence of O_h configuration . The brown electronic absorption spectra of iron-complex $[Fe(chloramphenicol)_2Cl(H_2O)]$ gave bands at 359, 423, 489 nm. These bands are due to CT ($t_{2g} \rightarrow \pi^*$) and CT ($\pi \rightarrow e_g$). Its room temperature μ_{eff} value of 5 typified the existence of O_h configuration. The electronic absorption spectra of $[Co(chloramphenicol)_2(H_2O)_2]$, gave bands at 289, 480, 516 nm bands are assigned to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ transition with magnetic moment value equal to 5.85 B.M. typified the existence of the complex in O_h geometry. The green electronic absorption spectra for Nickel-complexes, $[Ni(chloramphenicol)_2(H_2O)_2]$ showed three bands at 248, 330, 550 nm due to $^3A_{2g} \rightarrow {}^3T_{1g}$(p), $^3A_{2g} \rightarrow {}^3T_{1g}$ (P) transitions of octahedral geometry, further deduced from the μ_{eff} values which equals, (2.9) B.M. [7]. The copper complex $[Cu(chloramphenicol)_2(H_2O)_2]$, exhibited bands at 290, 425 nm with μeff = 1.8 B.M. The latter broad band is assigned to the $^2E_g \rightarrow {}^2T_{2g}$ (D) transition assignable to octahedral environment. Zn(II), Cd(II) and Hg(II) complexes exhibited only high intensity bands, Table 3, which is assigned to ligand → metal charge transfer. Owing to the d^{10}-configuration of Zn(II), Cd(II) and Hg(II), no d-*d* transition could be observed and therefore the stereochemistry around these metals in its complexes cannot be determined from ultraviolet and visible spectra [6]. However, by comparing the spectra of these complexes and those of similar environments, an octahedral geometry is suggested for these complexes. IR, electronic absorption spectra and magnetic moment values are concluded the proposed structures which are shown in Fig. 2.

Table 3 Nujol mull electronic absorption spectra λ_{max} (nm), room temperature effective magnetic moment values (μ_{eff}, 298 K) and geometries of chloramphenicol metal complexes

Complex	λ_{max} (nm)	μ_{eff}	Geometry
$[Cr(chloramphenicol)_2(Cl)(H_2O)]$	288, 410, 460	4.90	O_h
$[Mn (chloramphenicol)_2(H_2O)_2]$	382, 446	5.70	O_h
$[Fe(chloramphenicol)_2Cl(H_2O)]$	359, 423, 489	5.00	O_h
$[Co(chloramphenicol)_2(H_2O)_2]$	289, 480, 516	5.85	O_h
$[Ni(chloramphenicol)_2(H_2O)_2]$	288, 330, 550	2.90	O_h
$[Cu(chloramphenicol)_2(H_2O)_2]$	290, 425	1.80	O_h
$[Zn(chloramphenicol)_2(H_2O)_2]$	280	diamagnetic	O_h
$[Cd (chloramphenicol)_2(H_2O)_2]$	288	diamagnetic	O_h
$[Hg(chloramphenicol)_2(H_2O)_2]$	265	diamagnetic	O_h

Electron spin resonance of copper complex

At the room temperature an isotropic nature of [Cu(chloramphenicol)$_2$(H_2O)$_2$] complex polycrystalline X-band ESR spectral pattern, with g_s = 1.16 and value of A = 69 (Fig. 3). The presence of ESR signals at g < 4 may assign the spin-spin interaction between the Cu atoms show the diametric nature of complex.

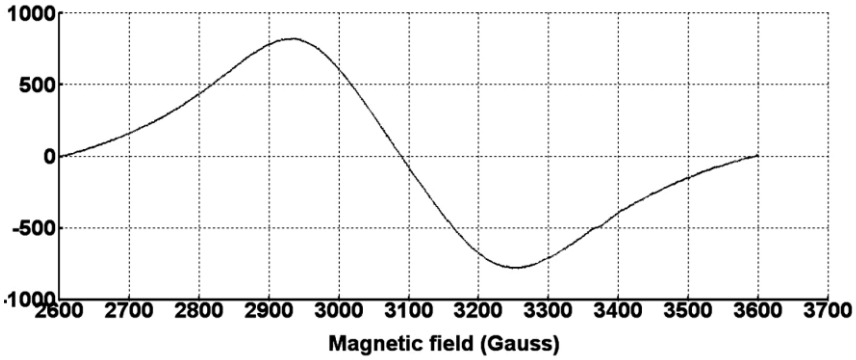
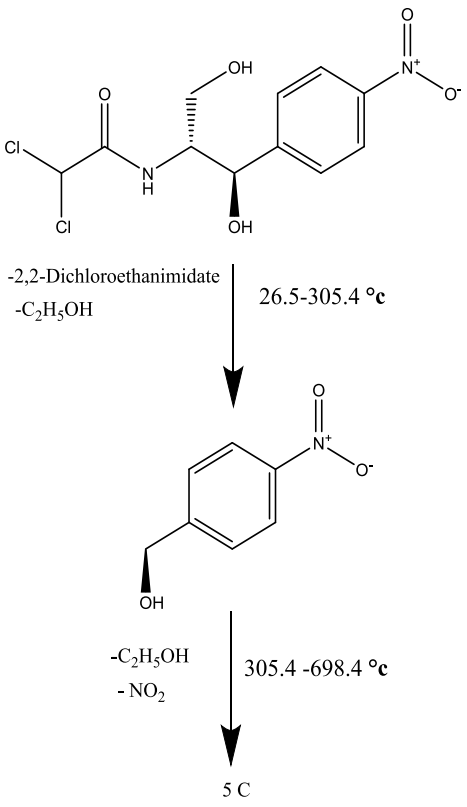


Fig. 3 ESR spectra of [Cu(chloramphenicol)$_2$(H_2O)$_2$]

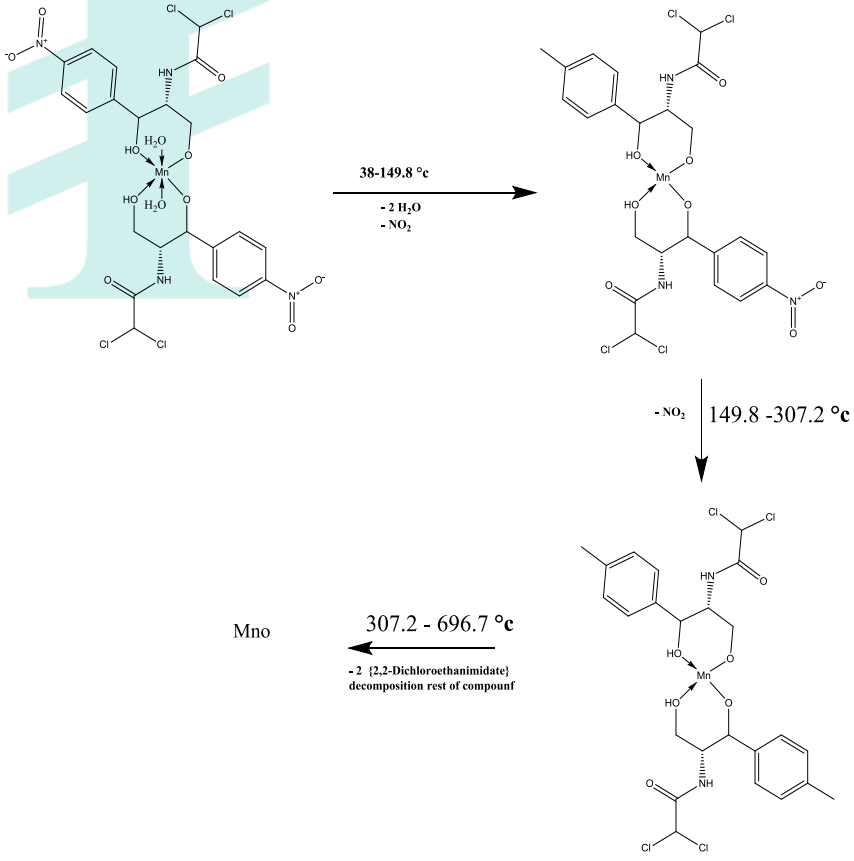
Thermal analysis investigations

The DTA sheet of chloramphenicol have four peaks at 88.3, 431.4, and 585.7 °C with activation energies 85.96, 95.42, 96.77 and 56.62 kJ/mole, respectively. The orders of reactions were 0.701, 2.02 and 1.067, respectively. All peaks are of the first order type except second peak is of second order type. All peaks are endothermic, except for last one show exothermic type (Scheme 1).

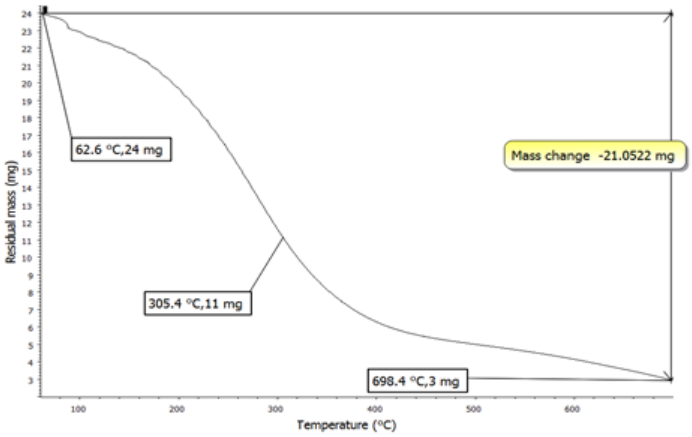
For an example [Mn (chloramph)$_2$(H_2O)$_2$] complex have well defined three peaks at 87, 23.5 and 480.7 °C with activation energies 24.03, 31.67 and 66.04 kJ/mole, respectively and the orders of reactions are first order. All peaks are endothermic except for last one show exothermic type. The TGA data confirmed these results which it gave three peaks, in the following Scheme 2. While Pranay et al. 2011 shows the decomposition of Nickel and cobalt in two steps. First step weight loss 300- 430 K, which indicates the loss of loosely, bound water of crystallization. The second step in the thermogram shows the loss of ligand molecules of the complex, which occurs between 440-910 K. The metal oxide is formed in the both case.



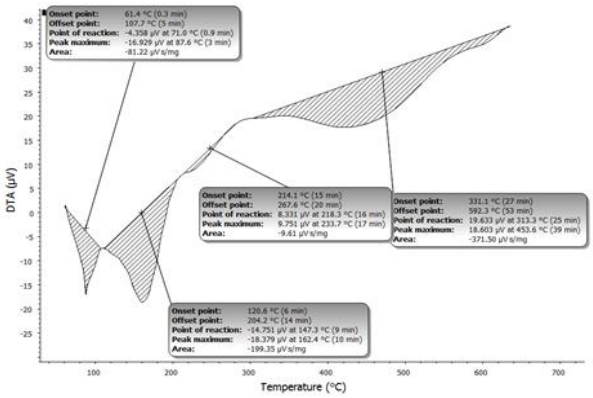
Scheme 1 Thermolysis of chloramphenicol



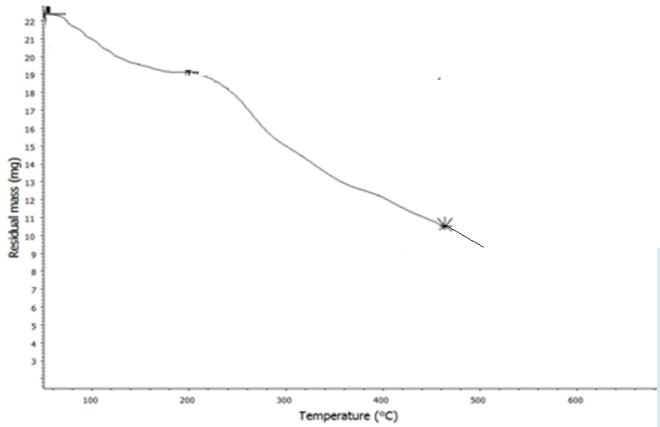
Scheme 2 Thermolysis of [Mn(chloramph)$_2$(H_2O)$_2$]



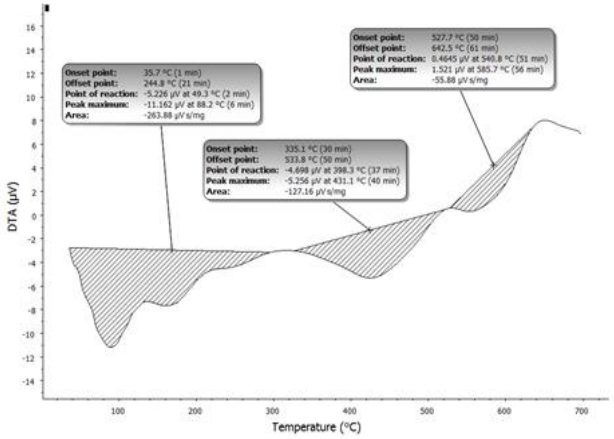
TG of chloramphenicol



DTA of chloramphenicol



TG of [Mn (chloramph)$_2$(H_2O)$_2$]



DTA of [Mn (chloramph)$_2$(H_2O)$_2$]

Fig. 4 TGA of chloramphenicol and its Mn-complex

Table 4 DTA analysis of chloramphenicol and its metal complexes

Complex	Type	Tm (°K)	E_a kJ mol^{-1}	n	α_m	$\Delta S^{\#}$ kJ K^{-1} mol^{-1}	$\Delta H^{\#}$ kJ mol^{-1}	Z S^{-1}	Temp. (°C) TGA	Wt. Loss % Calc	Wt. Loss % Found	Assignment
Chloramphenicol	Endo	88.2	6.34	1.17	0.60	-0.29	-32.6	0.006	26.5 -305.4°C	54.16	54.18	Loss of {2,2-dichloroethanimidate} and C_2H_5OH
	Endo	431.5	294.49	1.16	0.60	-0.27	-57.9	0.168	305.4 – 698.4 °C	87.5	87.6	Loss of C_2H_5OH, NO_2
	Exo	585.7	158.77	1.74	0.52	-0.29	-109.7	0.050				
[Mn (chloramphenicol)$_2$(H_2O)$_2$]	Endo	87	24.049	1.38	0.57	-0.28	-35.3	0.023	38- 149.8°C	12	12.11	Dehydration of $2H_2O$ and loss of NO_2
	Endo	232.5	31.685	1.18	0.60	-0.29	-77.4	0.014	149.8-307.2°C	36.5	36.7	Loss of NO_2
	Exo	480.7	66.501	1.11	0.61	-0.30	-142.2	0.016	307.2-696.7°C	52.5	52.6	Loss of 2-{2,2-dichloroethanimidate} loss of rest of compound.
[Cu(chloramphenicol)$_2$(H_2O)$_2$]	Endo	87	11.700	1.23	0.59	-0.29	-42.3	0.009	36.6-169.6 °C	4.2	4.2	Dehydration of $2H_2O$
	Endo	189.8	81.600	1.36	0.57	-0.28	-74.0	0.038	169.6-477.7 °C	12.6	12.7	loss of NO_2
	Endo	519.7	82.482	0.77	0.67	-0.29	-116.2	0.025	477.7 -697.9 °C	30.25	30.32	Loss of $NO_2$and dichloroacetylradical
[Zn(chloramphenicol)$_2$(H_2O)$_2$]	Endo	189.8	192.62	1.36	0.57	-0.26	-20.28	0.023	36.6-169.6 °C	29.16	29.18	Dehydration of $2H_2O$, dichloroacetylradical and NO_2
	Endo	519.7	39.25	1.33	0.57	-0.29	-57.49	0.130	169.6 -499 °C	54.16	54.21	Loss of -{2,2-dichloroethanimidate} and NH_3
[Cd (chloramphenicol)$_2$(H_2O)$_2$]	Endo	80.9	61.91	1.73	0.52	-0.27	-30.39	0.06	36.6-369.6 °C	28.69	28.69	Dehydration of $2H_2O$, loss of 2,2-dichloroethanimidate, and $2NO_2$
	Endo	210.7	76.80	1.30	0.58	-0.28	-58.12	0.04	369.6 -672 °C	53.16	53.18	Loss of 2,2-dichloroethanimidate and loss NO_2
	Exo	480.4	210.58	1.74	0.52	-0.28	-70.82	0.10				

Pranay et al 2011 shows only the decomposition of Nickel and cobalt in two steps without thermodynamic parameter.

Biological Activity

Most of the metal complexes have higher activity than the free ligands such increased activity of the metal chelates could be explained on the bases of overtones̛ concept and chelation theory. In this study, five microorganisms representing different microbial categories, two Gram-positive (*Staphylococcus Aureas* ATCC6538P and Bacillus subtilis ATCC19659), two Gram negative (*Escherischia coli* ATCC8739 strain and *Pseudomonas aeruginosa* ATCC9027) bacteria were used Table 5. The study included, ligand and two complexes of different metal ions (Zn and Cu). Four different broadly antibiotics (Ciprofloxacin and Clotrimazole) are used in this study as references. $[Zn(chloramph)_2(H_2O)_2]$ and $[Cu(chloramphen)_2(H_2O)_2]$complex showed activity in the same range of chloramphenicol for *Escherischia coli*, *Staphyllococcus aureus* and *Bacillus subtilis*.

Table 5 The antifungal activity of the free ligands and its complexes against some reference strains expressed in absolute activity (AU)

Biological compounds	***Candida albicans***		***Escherischia coli***		***Pseudomonas aeruginosa***		***Staphyllococcus aureus***		***Bacillus subtilis***	
		Cpd.		Cpd.		Cpd.		Cpd.		Cpd.
$[Cu(chloramph)_2(H_2O)_2]$	8	14	8	12	8	8	8	12	8	11
$[Zn(chloramph)_2(H_2O)_2]$	8	16	8	14	8	8	8	14	8	17
Chloramph	8	12	8	12	8	8	8	12	8	11
Ciprofloxacin	9	30	9	30	9	30	9	30	-	-
Clotrimazole	-	-	-	-	-	-	-	-	10	17

DOCKING RESULTS

The best docked pose of designed drug $[Cu(chloramph)_2(H_2O)_2]$ with 6XXO , where 6XXO is responsible for prostate cancer Fig. (4) shows an excellent electrostatic and hydrogen bond between ligand and receptor interaction distances were ≤ 3.5 A in most cases, which indicates the presence of typical real bonds which means high binding affinity . For example, the nearest interaction is observed via H-donors with 6XX0 (2.30A) and $[Cu(chloramph)_2(H_2O)_2]$ With plant score 566.89 and Moldock score 4648 , five torsions of designed drug with different amino acids(Arg38, Ala 47, Glu 62 and Glu 46) were observed which demonstrating their higher inhibition for protien prostate cancer . Fig. (5) representing the 2D structure of docked designed drug with amino acids. Fig. (6) representing the energy map of docked designed drug with amino acids [20-21].

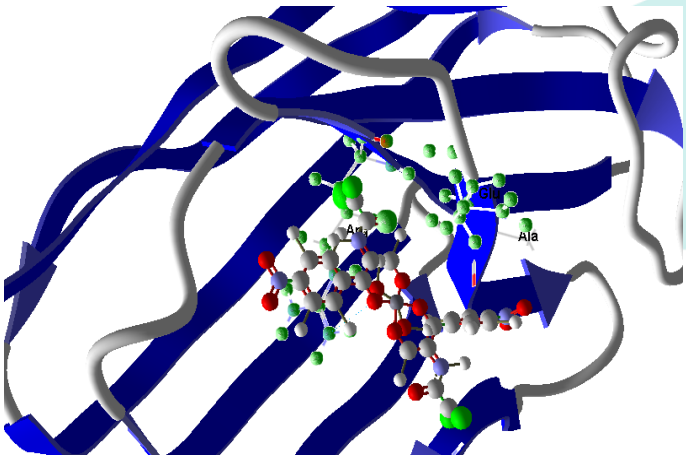


Fig. 4 Virtual Molecular docking of the best docked $[Cu(chloramph)_2(H_2O)_2]$ with with 6XXO protein

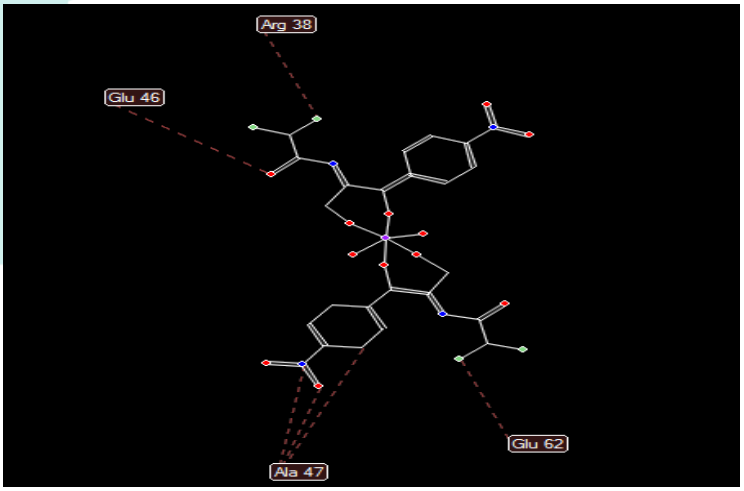


Fig. 5 2D structure of Molecular docking of $[Cu(chloramph)_2(H_2O)_2]$ with 6XX0 protein

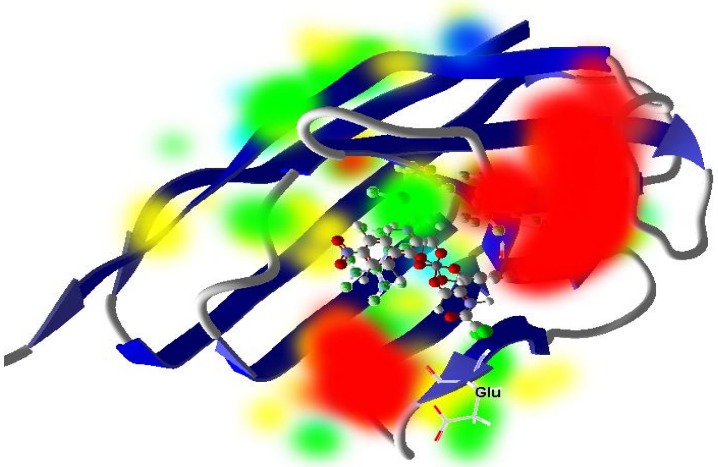


Fig. 6 2D energy map of $[Cu(chloramph)_2(H_2O)_2]$ with 6XX0 protein

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

RELEVANT CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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