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Metal Complexes of (E)-N-(2-ethoxyphenyl)-2-(mercapto-phenylamino-methylene)-3-oxo-butanamide (EPMPB): Preparation, Characterization and Biological Activity

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ABSTRACT

Some novel transition metal [V(V), Co(II), Ni(II), Cu(II) and Cd(II)] complexes of (EPMPB) have been synthesized and characterized. Complexes were isolated in solid state and characterized by elemental analyses, electronic spectra, thermal method (TGA and DTA), IR and X-ray powder diffraction. The elemental analysis confirms the assigned stoichiometries. The present paper describes synthesis and characterization of these complexes. The complexes are found to have striking structural features. Metal: Ligand ratio is found to be 1:1 for all metal complexes. Hence V(V), Co(II), Cu(II) and Cd(II) complexes are octahedral and Ni (II) complex is tetrahedral in geometry. The antimicrobial activities of the ligands and their complexes have been studied by screening the compounds against the bacteria *S. marcescens* (-ve), *P. eruginosa* (-ve), *E. coli* (-ve), *S. aurous* (+ve), *B. cereus* (+ve) and *M. luteus and also the fungi C. albicans* (-ve), *G. Candidum* (-ve), *A. flavus* (+ve), *F.oxysporium* (-ve), *S. brevicaulis* (+ve) and *T.rubrum* and results have been compared with the standard drug. . **Keywords:** Transition Metals, EPMPB, Preparation, Characterization and Antimicrobial Activities.

ARTICLE INFO

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1. Introduction

(E)-N-(2-ethoxyphenyl)-2-(mercapto-phenylamino methylene)-3-oxo-butanamide (EPMPB) as derivative of acetoacetanilide [1]. It is noticed that the preparation of International Journal of Chemistry and Pharmaceutical Sciences metal complexes of various transition metals with different derivatives of -ketoanilides compounds and their structural investigations have not been carried out much. It

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was therefore considered worthwhile to undertake this study systematically. It is of growing interest that the coordination compounds and metal chelates possessing nitrogen and oxygen donor atoms, show strong biological properties [2, 3].

Metals play a vital role in all living systems. Any malfunctioning of these metals can initiate a number of physiological abnormalities and symptoms of clinical disorders. Transition metal ions are responsible for proper functioning of different enzymes. Copper is one of the trace elements essential to the healthy life of humans and animals [4, 5]. Human diet usually includes 2 to 5 mg of copper per day. The adult body contains 100–150 mg, the muscle mass having 64 mg and the liver 18 mg of copper, [6]. Copper (II) usually forms stable complexes with N, O, and S donor ligands. For example, Cu (II) makes square planar complex with 4-methyl-imidazole [7].

Metal coordination complexes have been extensively used in clinical applications as enzyme inhibitors [8], antibacterial [9, 10], antiviral [11–13] and as anti-cancerous [14–16]. Different kinds of metals have been employed in these complexes including platinum, gold, vanadium, iron, molybdenum, cobalt, tin, gallium, copper and many others [15]. Metal complexes of adenine (A) have been shown to possess anticancer activity [16–20].

The present study investigates the physico- chemical properties of the complexes of chelating agents with transition metals on solid state and will be characterized from elemental analysis, magnetic, UV- visible Diffusive reflectance, IR, NMR, etc. This work aims to study the complex formation of EPMPB with V(V), Co(II), Ni (II), Cu(II) and Cd(II) in solid state using spectroscopic methods to throw some light on their compositions, structures, and analytical applications.

2. Materials and Methods Apparatus

All The pH measurements were carried out on VWR scientific model 2000 digital analyzer accurate total 0.01 pH unit. The C, H, N elemental analyses were done at the microchemical analysis Unit, Assiut University and. FT- IR spectra (400- 4000 cm⁻¹) were recorded as KBr discs using a Shmiadzu IR 479 spectrophotometer. Thermo gravimetric analysis of TGA was recorded on Shimadzu analyser 50 in a dynamic nitrogen atmosphere (100 ml/min) at a heating rate 10°C/min. X-ray diffraction data were collected at room temperature (~25°) on a Philips 1710 diffractometer at Assiut University. The patterns were run with cutarget and Ni filter (λ = 1.5418 N) at 40 KV and 30 mA in the range of 20= 40-60, 4-80 with scanning speed of 3.6 deg min⁻¹. Antimicrobial Activities were measured at Assiut University Mycological Center (AUMC).

Reagents and Materials

The solutions of V (V), Co(II), Ni(II), Cu(II) and Cd(II) ions (Merck and BDH) as nitrates were prepared and titrated complex metrically by EDTA [21]. Were obtained by dissolving the accurate weight of metal nitrate in the International Journal of Chemistry and Pharmaceutical Sciences

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appropriate volume of bi-distilled water. Stock standard solution of $(1 \times 10^{-3} \text{M})$ of (EPMPB) ligand was prepared by dissolving accurate weight of pure Ligand in ethanol and diluted with the same solvent to 10 mL volumetric flask (at 25°C). Sodium hydroxide (Merck) was prepared in bidstilled water as fresh solution. The universal buffer solution were prepared as recommended [22], and used to control the hydrogen ion concentration and ionic strength.

Preparation of (EPMPB) Ligand.

(E)-N(2-ethoxyphenyl)-2-(mercapto-phenylamino methyle ne) -3-oxo-butanamide (EMPMB) was synthesized [1], as follow: a Cold suspension of potassium hydroxide 0.01 mole in DMF 30mL was added the acetoacetanilide 0.01mole, followed by phenyl isothiocyanate 0.01 mole. The mixture was stirred for 5 h at room temperature. The reaction mixture was poured into ice-cold water and acidified by dilute HCl 10% v/v. The solid product formed was filtered off, washed with water, dried and crystallized from ethanol to give a compound characterized by elemental analysis, IR, UV-Vis spectra and thermal analysis.

Preparation of solid Complexes

The solid complexes were prepared by mixing equimolecular amounts of the lignad and metal salt in alcohol. The mixture was then stirred for about two hours. The solid complexes were isolated by addition of ether and then filtered immediately. Recrystallization of the solid complexes from ethanol/ether, to ensure the isolation of pure compounds was carried out. The solid complexes were then filtered off, washed and dried over P_2O_5 . Their structures were confirmed by elemental microanalyses IR, electronic absorption spectra, and thermogravimetric analysis and as well as x-ray powder diffraction analysis.

3. Results and Discussion

Microchemical analysis of L (EPMPB) and their metal complexes: The results of analysis of the solid metal complexes of L with of V(V), Co(II), Ni(II), Cu(II) and Cd(II) are illustrated in Table (1).

Infrared Spectra of Solid Complexes of (EPMPB)

The infrared spectra of investigated solid complexes, it's observed the influenced bands are shifts to lower and higher frequencies by complexation. The IR spectra in Fig.1 show the band in the range 3279, 3217 cm⁻¹ in the free ligand which corresponding to v (NH) group is shifted to higher and lower frequencies in the spectra of the complexes. this is due to coordination to V(V), Co(II), Ni(II), Cu(II)) and Cd (II) metal ions which is manifested by the appearance of bands at 3215cm⁻¹, (3218,3148) cm⁻¹, (3389, 3278) cm⁻¹ ¹, and (3466, 3277) (br) cm⁻¹, respectively. The two bands in the range 1666, 1623 cm⁻¹ in the IR spectra of (EPMPB) were attributed to stretching of v C=O which are shifted to lower and higher frequencies. This is due to coordination to the metal ions, at $(1628, 1667 \text{ cm}^{-1})$, $(1624, 1601 \text{ cm}^{-1})$, $(1602,1620 \text{ cm}^{-1})$, $(1721,1637 \text{ cm}^{-1})$ and $(1623,1601 \text{ cm}^{-1})$, for V(V), Co(II), Ni(II), Cu(II) and Cd(II) metal ions, respectively. On the other hand, the v(C=O) stretching vibrations appeared at lower frequencies in most cases. In spectra of the complexes relative to its position in the free ligands, in few cases, depending upon the nature of the

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metal ion, this band was found to be located at a slightly higher frequency. These changes indicate the involvement of the (C=O) group in coordination to the metal ion. The shift of v(C=O) band towards lower frequencies upon coordination to the metal ion indicates a decrease in the bond order of the carbonyl group. The shift of C=O band to higher frequencies, in some cases, can be ascribed to the ability metal ion to back donate electrons and hence increase the bond order of the C=O group in such cases. Two new bands appear for all chelates at 554-527 cm⁻¹ region corresponding to the stretching vM \leftarrow O metaloxygen band and 446-428 cm⁻¹ due to the stretching vM \leftarrow N metal-nitrogen band. The important IR bands are listed in Table 2.



Structure of (EPMPB) - Metal ion complex Where M=V(V), Co(II), Ni(II), Cu(II) and Cd(II)

Thermogravimetric Analysis of (EPMPB) -Metal ion Complexes:

Thermogravimetric analysis curves (TGA) of two representatives compounds such as [CoL (H₂O)₄] Cl₂ .2H₂O and [Ni L (H₂O)₂]Cl₂.2H₂O in the temperature range from ambient to 800 at heating rate 15°C/min. The thermogram of [Co L (H₂O)₄]Cl₂.2H₂O complex is given in Figure (2). The thermogram reveals that the complex decomposes completely up to 780°C, with mass losses on four steps. Final residue is Co(II) oxide, which is a stable product. The first step amounted to 17.9% in the temperature range 60-225°C; this can be attributed to the elimination of the four coordinated water molecules and two crystalline water molecules. The second step in the temperature range 230-285°C the mass loss reaches 12.01% is in accordance with the loss of two HCl molecules. The mass loss in the third step corresponds to 22.2% in the temperature range 290 -460°C, which may be attributed to the removal of the non-coordinated part of ligand 2ethoxyaniline. The final step from 470-685°C, with a mass loss of 35.90% corresponds to the decomposition of the coordinated part of the ligand 2-(Mercapto-phenylamino) methylene)-3-oxobutanal. The structure of the metal complex can be represented as follows:



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The [Ni L $(H_2O)_2$]Cl₂.2H₂O complex thermogram reveals that the complex decomposes completely up to 750°C, with mass losses occurring in three steps and the final residue is the Nickel (II) oxide, which is a stable product. The first step amounted to 12.23% in the temperature range 60 -205°C that can be attributed to the removal of two coordinated and two crystalline water molecule. The second step amounted to 23.90% in the temperature range 210-280°C which may be attributed to the removal of the noncoordinated part of ligand 2-ethoxyaniline. The final step amounted to 36.96% in the temperature range between 215-700°C. The proposed structural of complex based on the results discussed in this paper located as follows



Figure 2: Thermogravimetric analysis curve of Co (II) - (EPMPB) complex

X-Ray Powder Diffraction:

The X-ray diffraction pattern for Co (II)- (EPMPB). Complex is shown in Fig.3 indicates it's crystalline. But for Cu(II) & Ni(II) with (EPMPB) complexes X-ray diffraction pattern reveals it's crystalline - amorphous.



Figure 3: X-ray powder diffraction for Co (II) – (EPMPB) complex.

Antimicrobial Activity studies

Antibacterial activity: The results of antibacterial activity of (MPMPB) ligand and their Cu (II) and Co(II) solid binary complexes. The organisms selected for the studies were Serratia marcescens (-ve), Pseudomonas eruginosa (ve), Escherichia coli (-ve), Staphylococcus aurous (+ve), Bacillus cereus (+ve) and Micrococcus luteus. The antibacterial activity was evaluated by the inhibition zone technique. The results of antibacterial screening of L and their Cu (II) and Co (II) binary complexes at concentration of all samples are 2%. Cu (II) binary complexe was more antibacterial activity than the parent ligand. Co(II) with (EPMPB) L complex do not show any significant effect, but show highest antibacterial activity was against Bacillus cereus (+ve). Binary complexes of Cu (II) and Co(II) with (EPMPB) they show antibacterial activity less than chloroamphenicol as antibacterial standard.

Antifungal activity: The antifungal activity of ligand (EPMPB) and their Cu(II) and Co(II) solid binary

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complexes were carried out against pathogenic fungi, namely Candida albicans (-ve), Geotrichum Candidum (ve), Aspergillus flavus (+ve), Fusarium oxysporium (-ve), Scopulariopsis brevicaulis (+ve) and Trichophytin rubrum by radial growth methods. The solution of the test compounds was prepared as 2% for all samples. The linear growth of the fungus was recorded by measuring the diameter of the fungus colony after 24 h and the percentage inhibition was calculated as 100(C-T)/C, where T are the diameter of the fungus colony in the control and text plates, respectively. The results of antifungal activity of the ligand and Cu (II), Co(II) binary complexes are compared with the conventional fungicide clotriamaxazole as antifungal standards. Co (II) showed no significant effects except the highest antifungal activity to Candida albicans (-ve). The antifungal screening data, reveal that the Cu (II) binary complexes are more fungi toxic than the parent ligand. The toxicity increased with increasing concentrations.

Table 1: Microchemical anal	vsis data of L (EPMPB) and	their metal con	oplexes
Lable I: When other anal	Join and of L (Li mi D) unu	then metul con	ipienes.

Compound	Colour	M.wt	C%	Н%	N%	S%
			Calc. (found)	Calc. (found)	Calc. (found)	Calc. (found)
(EPMPB) L	Crystal	356.4	64.03	5.65	7.86	8.99
$C_{19}H_{20}N_2O_3S$	Yellowish		(63.58)	(5.61)	(7.80)	(8.93)
NH ₄ [V L (H ₂ O) ₄] 2H ₂ O	Black	533.4	42.78 (42.20)	6.80 (6.19)	7.88 (7.17)	6.01 (5.66)
[CoL (H ₂ O) ₄] Cl ₂ .2H ₂ O	Greenish	594.34	38.39 (38.12)	5.44 (5.38)	4.71 (4.68)	5.39 (5.35)
[Ni L (H ₂ O) ₂]Cl ₂ .2H ₂ O	Yellowish	558.11	40.89 (40.60)	5.05 (4.60)	5.01 (4.98)	5.74 (5.70)
[Cu L (H ₂ O) ₄]Cl ₂	Brown	562.9	40.54 (40.26)	5.01 (4.89)	4.98 (4.88)	5.70 (5.40)
[Cd L (H ₂ O) ₄]Cl ₂	White	611.8	37.30	4.61	4.58	5.24
	Greenish		(37.03)	(4.45)	(4.55)	(5.10)

Compound		^NH	^C=O		€MÆO	€MÆN
(EPMPB) L		3217	1666	1623	-	-
NH ₄ [V L (H ₂ O) ₄] 2H ₂ O	3215	-		1667	527	436
[CoL (H ₂ O) ₄] Cl ₂ .2H ₂ O		3148	1624	1601	527	436
[Ni L (H ₂ O) ₂]Cl ₂ .2H ₂ O		3278		1602	527	436
$[Cu L (H_2O)_4] Cl_2$	3432	-	1721	1637	538	428
[Cd L (H ₂ O) ₄] Cl ₂	3466	3277	1623	1601	527	432

Table 3: Antibacterial, Fungicidal	screening data for (EPM	PB) ligand and their Cu (II).	, Co (II) metal ion complexes
, ,	0	, ,	

Antibacterial,	Type of Antibacterial and	Ligand	Cu (II)	Co (II)	Control
Antifungal	Antifungal	0	complex	complex	
	Serratia marcescens (-ve)	0	13	0	18
	Pseudomonas eruginosa (-ve)	0	13	0	13
Antibacterial	Escherichia coli (-ve)	0	18	0	34
	Staphylococcus aurous (+ve)	0	18	0	22
	Bacillus cereus (+ve)	0	20	12	30
	Micrococcus luteus	0	18	0	20
	Candida albicans (-ve)	0	14	12p.i	17
	Geotrichum Candidum (-ve)	0	13	0	24
Fungicidal	Fusarium oxysporium (-ve)	0	13	0	14
	Aspergillus flavus (+ve)	0	8	0	24
	Scopulariopsis brevicaulis (+ve)	0	13	0	24
	Trichophytin rubrum	0	0	0	36

p.i = Partial inhibition. Control = Chloroamphenicol as antibacterial standard, Clotriamazole as antifungal standard



Figure 1: Infrared spectra of the free ligand (EPMPB) L and its metal complexes. (a) Free ligand (L), b) V(V)-L complex , c) Co(II)-L complex, d) Ni(II)- L complex and (e) Cu(II)-L complex

4. Conclusion

The coordination was taking place through the N-H of group of 2-mercapto-phenylamino and oxygen atom C=O the ligand with the metal atom. Also metal to ligand ratio was found to be 1:1. For all complexes shows the presence of vM \leftarrow O and M-N bonds. All these experimental data suggest tetrahedral structure for the Ni (II) complex and octahedral structures for V(V), Co(II), Cu(II) and Cd(II) complexes.

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