

Synthesis, Characterization and Antimicrobial Studies of the Metal Complexes of β -Diketone

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ABSTRACT

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The ligand 1-(2-bromo-5-methoxyphenyl)-3-(2-hydroxyphenyl) propane-1, 3-dione (L) and its transition metal complexes have been synthesized. The ligand synthesized using 2-hydroxy acetophenone and 2-bromo-5-methoxy benzoic acid. Each metal complex synthesized by metal nitrate with β -diketone in the ratio 1:2 stoichiometry. The characterization were carried out by elemental analysis, UV-Visible spectroscopy, infrared spectroscopy, ¹H-NMR, ¹³C-NMR, magnetic susceptibility, molar conductance, powder XRD and TGA for structural formulae study. The synthesized β -diketones and their transition metal complexes have been screened for in vitro antibacterial, and antifungal activity using Resazurin 96 well plate method. This method is simple, sensitive, rapid, and reliable. It achieves more accurate minimum inhibitory concentration (MIC). The transition metal complexes and ligand showed moderate antimicrobial activity against all tested bacteria and fungi.

Keywords: Antimicrobial activity, Antioxidant, β -diketones, Metal-complexes, Magnetic susceptibility, TGA, XRD.

I. INTRODUCTION

In pharmaceutical industries metal containing drugs widely used. In particular transition metal series are more important in human body. Metal are easily loose electrons towards the molecules (ligands) forms co-ordinate bond and metal exists as positively ions soluble in biological fluids. Hemoglobin is an important constituent in blood contain Fe metal which give binding site for O₂. Cis-platin (cis-Pt(NH₃)₂Cl₂) is a first introduced in anti-cancer drug

contains platinum metal. Zn metal that regulate the function of genes in the nuclei of cells and component of insulin. Nickel (II) forms an important component in different enzymes, viz. urease, carbon monoxide dehydrogenase and hydrogenase¹.

The previous research found that 1, 3-diones showing antiviral, insecticidal, antibacterial, antitumor, antioxidant, HIV-1 Integrase (IN) inhibitors²⁻⁶. The β -diketones (1,3-diketone) are intermediate key for the synthesis of different hetero-cyclic compounds⁷⁻¹². In addition, 1,3-diketones (β -diketones) have also been

used as an anti sunscreen agent that filters U.V rays to protect from skin cancer¹³. 1, 3-dionemetal complexes are used as catalyst in reaction of olefin oxidation and epoxidation¹⁴⁻¹⁵. Europium (III)-diketonates have excellent luminescent property¹⁶. It is also used as chelating agent¹⁷ and extractants for lanthanide ions¹⁸. As a result, considerable efforts have been directed towards synthesis of beta-diketones and its metal complexes.

Here we report the synthesis of ligand and their metal complexes characterized by various spectral technique and also look the in vitro antibacterial screening was carried out by using micro titre plate based resazurin assay against Gram positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram negative (*Escherichia coli*, *Pseudomonas aeruginosa*) bacterial cultures. The antifungal susceptibility of ligand and its metal complexes was tested against *Candida albicans* and *Saccharomyces cerevisiae*. In micro titre plate based resazurin assay technique colorimetric indicator was resazurin.

II. EXPERIMENTAL

All chemicals were of reagents grade, purchased from commercial source and used directly. All metal salts were used as nitrate. Melting points were recorded by the open tube capillary method and are uncorrected. The progress of the reaction and the purity of compounds were monitored by thin-layer chromatography (TLC) analytical silica gel plates (Merck 60 F250). ¹H NMR and ¹³C NMR spectra were recorded on a Jeol-400 MHz instrument in CDCl₃ solution. Mass spectra were taken on a macro mass spectrometer by the electrospray ionization (ESI) method. The C, H and N analyses were carried out using a Euro-E 3000. Infrared spectra were recorded on SHIMADZU FT-IR spectrometer. The conductivity of metal-complexes measured by ELICO CM 180. The TGA analysis were carried out by Ramp method using SDT Q600 V20.9 Build 20 instrument.

A. Synthesis of 1-(2-bromo-5-methoxyphenyl)-3-(2-hydroxyphenyl) propane-1,3-dione (L):

The 2-hydroxy acetophenone (0.01 mol) and 2-bromo-5-methoxy benzoic acid (0.01 mol) was dissolved in dry pyridine (30 ml) and cooling the mixture at 0°C then POCl₃ (2-3 ml) was added drop wise with constant stirring maintain temperature below 5°C. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured on crushed ice and acidified with dil. HCl. The crimson colored solid (ester) product (3) was obtained. It was washed with water and filtered off and crystallized from alcohol. The ester (0.01 mol) dissolved in pyridine (25 ml) and add powdered KOH (1.12 g, 0.02 mol) and the reaction mixture stirred at room temperature for 5-6 hours which undergoes Baker-Venkataraman rearrangement. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured in dil. HCl in crushed ice. The yellow solid product obtained was washed with water and filtered off. The product crystallized from alcohol.

¹H-NMR: δ = 15.18 (s, 1H), 11.98 (s, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 8.9 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.18 (d, J = 3.1 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.93-6.88 (m, 2H), 6.73 (s, 1H), 3.84 (s, 3H)
¹³C-NMR: δ = 195.97, 177.06, 162.66, 55.66; IR: -1618 ν (C=O), 1581 ν (C=C), 1220 ν (C-O), 3280 ν (-OH) MS: m/z 346.9 (M - 1); Anal. calcd. for C₁₆H₁₃BrO₄: C, 55.04; H, 3.75; found: C, 55.18; H, 3.89; yield: 65%; M.P-106°C; Yield-66%.

B. Synthesis of metal complexes:

The ligand (L) 4 mmol dissolved in 35 ml of anhydrous ethanol and add 2 mmol of appropriate transition metal nitrate [Fe(III), Co(II), Ni(II), Cu(II), Zinc(II)] and stirred at 60-65°C for 2-3 hour. After the addition of alcoholic ammonia solution complex precipitation occurs and colored solid complex obtained was washed with ethanol and then crystallized by with ethyl acetate. The yield of the all metal complexes was in the range of 66-71%.

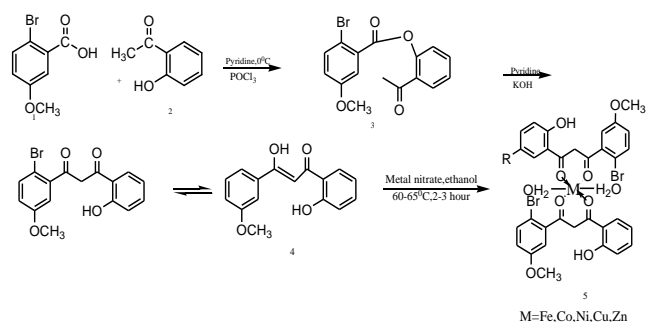


Fig 1.Synthesis of 1,3-dione and its metal complexes

III. RESULTS AND DISCUSSION

All the metal complexes were found to be highly stable at room temperature and readily soluble in dimethyl formamide and dimethyl sulfoxide other than common organic solvents. The results of elemental analysis confirmed stoichiometry of ligand to metal 2:1 for all metal complexes. The TGA data confirms two water molecules associated in the metal complexes reveals octahedral geometry.

1. IR spectra

The infrared spectral data of ligand (L) and their metal complexes are reported in Table 1. The carbonyl group ($>C=O$) stretching frequency of ligand (L) appearance at 1618 cm^{-1} . The appearance of frequency at 1581 cm^{-1} represents ($-C=C-$) double bond and the bond (C-O) appear at 1220 cm^{-1} . The metal complexes of ligand (L) show IR frequency of carbonyl group ($>C=O$) at $1617\text{--}1619\text{ cm}^{-1}$ which were nearly same or slightly lower than ligands (L)¹⁹. The slightly change in stretching frequency indicates that ligand (L) coordinated with the transition metal ions. Also a new band at $509\text{--}533\text{ cm}^{-1}$ observed due to metal–oxygen (M-O) bond vibrations in metal complexes which were absent in ligands²⁰. This confirms of metal ions coordinate with oxygen in complexes.

Table 1. FTIR (ν/cm^{-1}) data of ligand and metal complexes.

Compounds	$\nu(C=O)$	$\nu(C-O)$	$\nu(C=C)$	$\nu(M-O)$
L	1618	1220	1581	---
(L) ₂ -Fe	1618	1238	1581	522
(L) ₂ -Co	1617	1249	1585	533
(L) ₂ -Ni	1617	1213	1586	509
(L) ₂ -Cu	1619	1241	1585	523
(L) ₂ -Zn	1618	1249	1587	533

2. ¹H NMR and ¹³C NMR spectra

The ¹H NMR spectral data of the 1-(2-bromo-5-methoxyphenyl)-3-(2-hydroxyphenyl)propane-1,3-dione (L) show singlet at δ 15.18 ppm due to enolic proton, a singlet at δ 11.98 ppm due to phenolic proton adjacent to the carbonyl group which confirms the formation of β -diketone.

In the ¹³C NMR of ligand (L) 4, peak appeared at δ 195.97 ppm corresponds to carbonyl carbon (C=O) and enolic carbon (C-O) at δ 177.06 ppm. The signal at δ 96.08 ppm appeared shows methine linkage.

3. Magnetic Susceptibility and Molar Conductance

The molar conductance values recorded in $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$ at room temperature using DMSO as a solvent and results are recorded in Table 2. The molar conductance values were obtained in the range $18\text{--}42\ \Omega^{-1}\text{cm}^2\text{mol}^{-1}$. The conductance values of the metal complexes very low which indicate non-electrolytic in nature²¹. The magnetic susceptibilities values of all metal complexes indicates paramagnetic in nature except Zinc complexes were diamagnetic due to non-availability of unpaired electrons.

Table 2. Physical parameter of metal complexes.

Metal Complexes	Magnetic moment μ_{eff} (B.M)	Molar conductance	M. W.	Melting point	Elemental analysis (%)	
					Found/(Calcd.)	
					C	H
(L) ₂ Fe	5.81	39	790.23		48.12(48.64)	3.75(3.83)
(L) ₂ Co	3.22	42	793.32	221	47.99(48.45)	3.80(3.81)
(L) ₂ Ni	2.41	27	793.08	219	48.97(48.46)	3.59(3.81)
(L) ₂ Cu	1.11	18	797.93	277	47.61(48.17)	3.51(3.79)
(L) ₂ Zn	Dia	34	799.77	163	48.59(48.06)	3.61(3.78)

4. Powder XRD Studies

X-ray powder diffraction study basically used for phase identification of a materials and can provide information on unit cell dimensions. Single crystals of the metal complexes could not be possible therefore powder diffraction data used. The XRD data recorded in the range 10-80 (2 θ) values. Average particle size was calculated using Debye Scherrer's formula, $D = 0.9 \lambda / \beta \cdot \cos\theta$ where θ is the Bragg diffraction angle and β is the full width at half maximum (FWHM) ²². All metal complexes show monoclinic crystal system.

Table 3. Summary of XRD data of Metal Complexes

Parameter	(L) ₂ -Fe complex	(L) ₂ -Co complex
Temperature (k)	298	298
Wavelength	1.540598	1.540598
Radiation	Cu K α	Cu K α
Crystal System	Monoclinic	Monoclinic
a (Å)	6.014	9.32
b (Å)	26.3	13.21
c (Å)	6.99	12.49
α (°)	90.1	90
β (°)	116.7	102
γ (°)	91.2	90
Average Particle Size (nm)	8.476	7.989

5. Thermo gravimetric study of some metal complexes

Thermal gravimetric study used to evaluate the thermal stability of metal complex here some selected metal complexes was carried out at a heating rate of 10°C min⁻¹ under nitrogen atmosphere over the temperature range 25–600 °C. Thermo gravimetric analysis of bis-1-(2-bromo-5-methoxyphenyl)-3-(2-hydroxyphenyl) propane-1,3-dione Fe(III) complex shows some loss of weight (4.153%) at 179.18°C indicating that surface and coordinated water molecules are present in the complex²³⁻²⁴. A sudden weight loss (22.24%) from 179.18°C to 331.57°C due to loss of one phenyl ring with two hydroxy and one carbonyl group. Further, the weight loss (54.43%) from 331.57°C to 534.00°C corresponds to the decomposition of two phenyl ring and a propane-1, 3-dione moiety. On further heating above 534.00°C the weight remaining corresponds to that of only Ferric oxide.

Thermo gravimetric analysis of bis-1-(2-bromo-5-methoxyphenyl)-3-(2-hydroxyphenyl)propane-1,3-dione Co(II) complex shows some loss of weight (5.018%) at 175.77°C indicating that surface and coordinated water molecules are present in the complex. A sudden weight loss (50.55%) from 175.77°C to 496.47°C due to loss of one phenyl ring with two hydroxy and one carbonyl group. Further, the weight loss (11.06%) from 496.47°C to 597.69°C corresponds to the decomposition of two phenyl ring and a propane-1, 3-dione moiety. On further heating

above 597.69°C the weight remaining corresponds to that of only Cobalt oxide.

6. Antimicrobial Activities

The antimicrobial activity of ligand and its metal complexes carried out by resazurin method which is developed by Drummond and Waigh in 2000²⁵. The resazurin method simple, sensitive, rapid, reliable and achieve more accurate minimum inhibitory

concentration (MIC). In this method resazurin used as an indicator and it was prepared by dissolving 270 mg tablet in 40 ml of sterile distilled water. The value of minimum inhibitory concentration (MIC) taken at color changes from purple to pink or colorless were recorded as positive. MIC value taken as color change occurs at lowest concentration as a average of three values of MIC for the test material and bacterial strain.

Table 4: MIC ($\mu\text{g/ml}$) determination using modified resazurin assay

Compounds	Antibacterial activity				Antifungal activity	
	Gram positive		Gram negative		<i>C.albicans</i>	<i>S.cerevisiae</i>
	<i>B.subtilus</i>	<i>S.aureus</i>	<i>E.coli</i>	<i>P.aerugenosa</i>		
L1	<50	<50	100	50	100	150
L2	100	50	100	50	150	150
(L1) ₂ Fe	50	50	100	50	150	150
(L1) ₂ Co	50	<50	50	50	100	150
(L1) ₂ Ni	50	<50	100	50	100	100
(L1) ₂ Cu	50	<50	100	50	150	100
(L1) ₂ Zn	50	<50	100	50	100	150
Tetracycline	2	1	4	1	-	-
Amphotericin B	-	-	-	-	1.25	1.25

7. 1,1-Diphenyl-2-picrylhydrazyl Assay (DPPH Assay)

The antioxidant activities of ligand and its metal complexes were examined according to DPPH method. In DPPH method stock solution of DPPH prepared in methanol. The percentage of inhibition was calculated. Ascorbic acid was used as a standard reference and dissolved in distilled water to make the stock solution with the same concentration of metal complexes. Control sample was prepared containing

the same volume and reference ascorbic acid; 95% methanol was used as blank and % scavenging of the DPPH free radical was measured using the following equation:

$$\% \text{ inhibition} = \left\{ \frac{A \text{ control} - A \text{ sample}}{A \text{ control}} \right\} \times 100$$

A control = absorbance of DPPH alone

A sample = absorbance of DPPH along with different concentrations of complexes.

Table 5:Antioxidant study of using DPPH method.

Concentration µg/mL	Ascorbic Acid	(L)	(L) ₂ Fe	(L) ₂ Co	(L) ₂ Ni	(L) ₂ Cu	(L) ₂ Zn
	% Inhibition	% Inhibition	% Inhibition	% Inhibition	% Inhibition	% Inhibition	% Inhibition
10	9.34	4.51	9.34	13.33	9.34	20.40	9.34
20	29.40	8.86	9.34	58.18	9.34	29.71	9.34
30	39.48	44.31	29.47	71.80	13.42	43.09	9.34
40	47.87	69.88	32.18	72.71	15.87	46.94	58.18
50	81.75	78.06	32.91	86.13	51.93	65.46	87.08

IV. CONCLUSIONS

The present research work, we synthesized new ligand and its transition metal complexes. In the metal complexes reveals that 1, 3-diones and metal 2:1stoichiometry ratio for all the prepared metal complexes. These complexes were characterized by various physicochemical and spectral analyses. It shows non-electrolytic nature and octahedral geometry with center of symmetry. Powder XRD study of complexes show monoclinic crystal system. The thermal stability were evaluated by TG method whose results revealed good thermal stability for the synthesized metal complexes. As per results, it can be seen that the newly synthesized ligands and its metal complexes shows considerable antimicrobial activity against all tested bacteria and fungi compared with antibiotics Tetracycline and Amphotericin B.

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