

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL STUDIES OF 1-(5-BROMO-2-HYDROXYPHENYL)-3-(4-BROMOPHENYL)-PROPANE-1,3-DIONE AND THEIR TRANSITION METAL COMPLEXES

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ABSTRACT

A new ligand 1-(5-bromo-2-hydroxyphenyl)-3-(4-bromophenyl)-propane-1, 3-dione have been synthesized from 5-bromo-2-hydroxyacetophenone and 4-bromo benzoic acid. Their transition metal complexes have been synthesized. 1, 3-dione or ligand co-ordinate with the transition metal ions through oxygen atoms. The stiochimetry ratio ligand to metal has been 2:1. The synthesized 1,3-dione and their transition metal complexes have been characterized by ¹H-NMR, ¹³C-NMR, IR, Elemental analysis, Powder XRD, TGA. Solution conductivity, Magnetic susceptibility and Antimicrobial screenings were also studied using Resazurin 96 well plate method. Tetracycline and Amphotericin B are used as standard drugs. The transition metal complexes showed moderate to excellent antimicrobial activity against all tested bacteria and fungi.

Keywords: 1, 3-dione, Metal-complexes, IR, Conductivity, Powder-XRD , Antimicrobial activity

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INTRODUCTION

The metal-based compounds are more biologically active than ligand. Transition metal series has an important role in pharmacology. Metal easily loses an electron to form charged ions which are soluble in biological fluids and interact with a biological molecule. The molecule 1,3-dione plays an important role in the biological system since they exhibit biological activities, such as antioxidants and antibacterial . In 1,3-dione the presence of two carbonyl group at 1, 3 position appear in the form of keto-enol tautomerism. The keto-enol tautomer equilibrium strongly shift towards enol form which is capable of forming a bond with metal ions. The metal complexes of 1,3-diketones are used as catalysts for olefin oxidation and epoxidation^{1,2}. In pharmaceutical industries, it is widely used as substrates for medicines as antidiabetic agents, antiulcer, gastroprotective drugs ,antiasthmatic and carcinogenic agents³⁻⁶. 1,3-diodes are also used in the synthesis of various heterocyclic compounds such as pyrazole, isoxazole , triazole , flavones , benzodiazepine and pyrimidine ⁷⁻¹². The complexes of Europium (III) have excellent luminescent property, as a chelating agent and extract for lanthanide ions¹³⁻¹⁵. Our research focus on the synthesis of new 1,3-diketone and their complexes and studied their properties and antibacterial properties against gram-positive- *B.subtilis* , *S.aureus* and Gram-negative- *E. coli*, *P. aerugenosa* and antifungal activity against *C. albicans*, *S. cerevisiae*.

EXPERIMENTAL

All chemical were used of analytical grade. All metal salts were used as nitrate (S.D Fine). 5-bromo-2-hydroxy acetophenone (Himedia), 4-Bromobenzoic acid (Spectrochem), dry pyridine (Spectrochem) were

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purchased and used without further purification. Distilled ethanol was used for recrystallization and synthesis of metal-complexes. Infrared spectra were recorded on Perkin Elmer spectrometer. The C, H and N analyses were carried out using a Euro-E 3000. The ^1H and ^{13}C NMR spectra were recorded in CDCl_3 using TMS as internal standard on a Jeol-400 MHz spectrometer. Magnetic susceptibility measurements were carried out at room temperature using Guoy balance. The TGA analysis was carried out by Ramp method using SDT Q600 V20.9 Build 20 instrument.

Synthesis of 2-acetyl-4-bromophenyl thiophene-2-carboxylate

To the mixture of 5-Bromo-2-hydroxy acetophenone (2.150 g, 0.01 mol) and 4-bromo benzoic acid (2.010 g, 0.01 mol), a dry pyridine (20 ml) and POCl_3 (1 ml) were added dropwise with constant stirring at 0°C . The reaction mixture was then continuously stirred for 5-6 hrs. After completion of the reaction (monitored by TLC), it was poured into HCl (1M) containing crushed ice. The solid obtained was filtered and washed with ice-cold methanol and then with distilled water. It was recrystallized from ethanol. Yield: 71%.

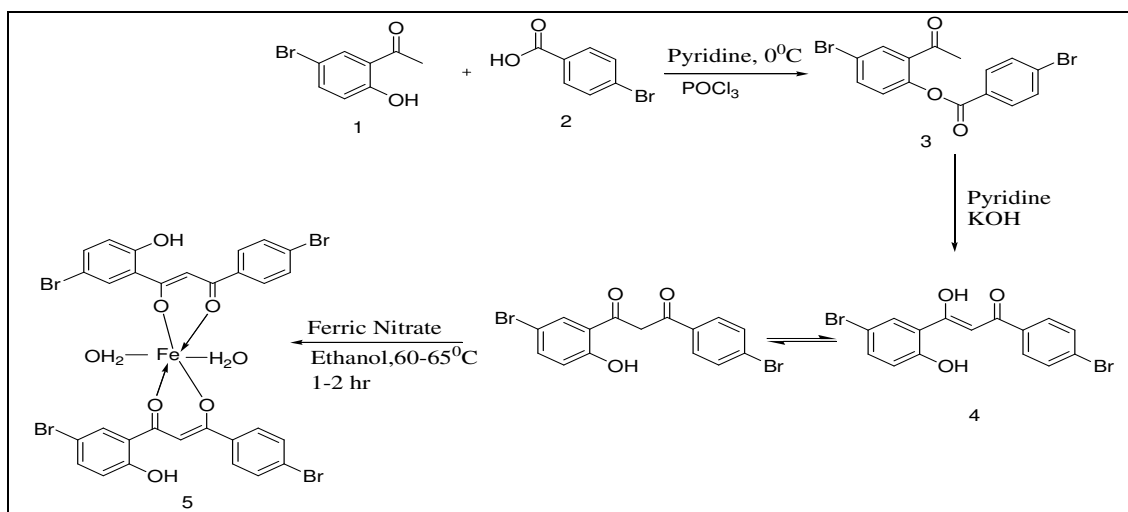
Synthesis of 1-(5-bromo-2-hydroxyphenyl)-3-(4-bromophenyl)-propane-1,3-dione

Compound 3 (3.980 g, 0.01 mol) was dissolved in dry pyridine (15 ml). To this powdered KOH (1.12 g, 0.02 mol) was added and the reaction mixture was continuously stirred for 3-4 hrs. After completion of the reaction (monitored by TLC), it was poured on ice cold water and acidified with HCl (1M). The pale yellow solid obtained was filtered off and recrystallized from absolute ethanol. Yield: 69%; mp: 148°C ; LC-MS: 393 (M-2) elemental analysis: calculated C= 45.26, H= 2.53. Found C= 44.89 H=2.86; ^1H NMR: 15.42 δ (s, 1H, enolic-OH), 11.98 δ (s, 1H, Phenolic -OH), 7.6 δ (s, 1H, =C-H ethylene); 6.81-7.83 δ (m, 7H, Ar-H); IR $\nu_{\text{max}}/\text{cm}^{-1}$ 1678 (ν (C=O) ketonic), 1587(ν (C=C), 1236 (ν (C-O) enolic), 3078(ν (-OH).

Bis-[1-(5-bromo-2-hydroxyphenyl)-3-(4-bromophenyl)-propane-1,3-dione]Fe(III) complex

A Mixture of Compound 4 (5 mmol) and 2.5 mmol of appropriate ferric nitrate was added in anhydrous 30 ml ethanol and the resulting mixture was refluxed at $60-65^\circ\text{C}$ for 1- 2 hour whereupon the complex precipitation occurs after the addition of alcoholic ammonia.

The precipitated colored solid complex washed with ethanol and crystallized by using dichloromethane. Yield-68%. M.P $>300^\circ\text{C}$. Elemental analysis: calculated C=40.67, H=2.50 found C=41.03, H=2.85. Similarly, the complexes of Co(II), Ni(II), Cu(II) and Zn(II) were prepared.



Scheme-1: Synthesis Route of 1,3-Dione and its Metal Complexes

RESULTS AND DISCUSSION

The ligand 1-(5-bromo-2-hydroxyphenyl)-3-(4-bromophenyl)-propane-1,3-dione were synthesized from 5-bromo-2-hydroxyacetophenone and 4-Bromo benzoic acid using Baker-Venkataraman rearrangement. Their metal complexes synthesized by refluxing the metal nitrate with ligand in ethanolic solution for 1-2

hr. all metal complexes were in the solid state and highly soluble in dimethyl sulfoxide and dimethyl formamide. The ligand was soluble in all organic solvents. The results of elemental analysis confirmed stoichiometry of ligand to metal is 2:1 for all metal complexes. The study of TGA confirms two water molecules coordinated in the metal complexes which reveal octahedral geometry. The Spectral analysis data shows the confirmation of 1,3-dione and its metal complexes.

Molar Conductance and Magnetic Susceptibility

The molar conductance (Λ_M) values were obtained in mhos $\text{cm}^2 \text{mol}^{-1}$ at room temperature using DMSO as a solvent and results are recorded in Table-1. The Metal complexes showed their molar conductance values in the ranges 55–79 $\Omega^{-1} \text{cm}^2 \text{mol}^{-1}$ indicating their non-electrolytic nature¹⁶. All metal complexes were paramagnetic in nature except Zn-complex which showed diamagnetic in nature due to non-availability of unpaired electrons.

IR Spectra

The characteristic infrared spectral data of ligand (L) and their metal complexes are reported in Table-2. The carbonyl group ($>\text{C}=\text{O}$) of ligand (L) showed stretching frequency at 1678 cm^{-1} . The appearance of frequency at 1585 cm^{-1} is due to ($-\text{C}=\text{C}-$) double bond and the bond ($\text{C}-\text{O}$) appeared at 1249 cm^{-1} . The metal complexes show IR frequency of carbonyl group ($>\text{C}=\text{O}$) at $1637-1676 \text{ cm}^{-1}$ which were lower than IR frequency of ligand (L) 1678 cm^{-1} . This lowering stretching frequency indicates that the ligand (L) coordinated with the transition metal ion¹⁷. In addition new band at $503-528 \text{ cm}^{-1}$ was observed due to metal–oxygen (M–O) bond vibrations in metal complexes which were absent in ligand¹⁸. This confirms of metals ion coordinate with ligand via oxygen.

Table-1: Physical, Analytical Data of 1,3-Dione and its Complexes

Compound	M.W	M.P. ($^{\circ}\text{C}$)	Color	μ_{eff} (B M)	Molar conductance $\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$	Elemental Analysis Calculated(found)	
						% C	% H
Ligand	398.05	148	Yellow	--	--	45.26 (44.95)	2.53 (2.41)
Fe-Complex	885.95	>300	Brown	5.71	55	40.67 (40.79)	2.50 (2.53)
Co-Complex	889.04	>300	Yellow	3.54	79	40.53 (40.48)	2.49 (2.51)
Ni-Complex	888.80	>300	Green Yellow	2.84	58	40.54 (40.68)	2.49 (2.50)
Cu-Complex	893.65	>300	Green Yellow	1.41	56	40.32 (40.38)	2.48 (2.44)
Zn-Complex	895.50	>300	Pale Yellow	Dia	63	40.24 (40.56)	2.48 (2.69)

Table-2: IR studies of Complexes

Compound	IR Frequency (Wavenumber)				
	(C=O)	(C=C)	(C-O)	(OH)	(M-O)
Ligand	1678	1587	1236	3078	---
Fe(III)Complex	1676	1585	1251	3088	503
Co(II)Complex	1638	1585	1255	3072	528
Ni(II)Complex	1637	1583	1242	3074	528
Cu(II)Complex	1676	1579	1246	3116	526
Zn(II)Complex	1637	1587	1253	3074	528

¹H NMR and ¹³C NMR Spectra

The ¹H NMR spectral data of the 1-(5-bromo-2-hydroxyphenyl)-3-(4-bromophenyl)-propane-1,3-dione (L) shows singlet at δ 15.42 ppm due to an enolic proton, a singlet at δ 11.98 ppm due to phenolic proton adjacent to the carbonyl group which confirms the formation of 1,3-dione.

In the ¹³C NMR, the peak appeared at δ 194.55 ppm corresponds to carbonyl carbon (C=O) and enolic carbon (C-O) at δ 177.20 ppm. The signal appearing at δ 92.30 ppm show methine linkage.

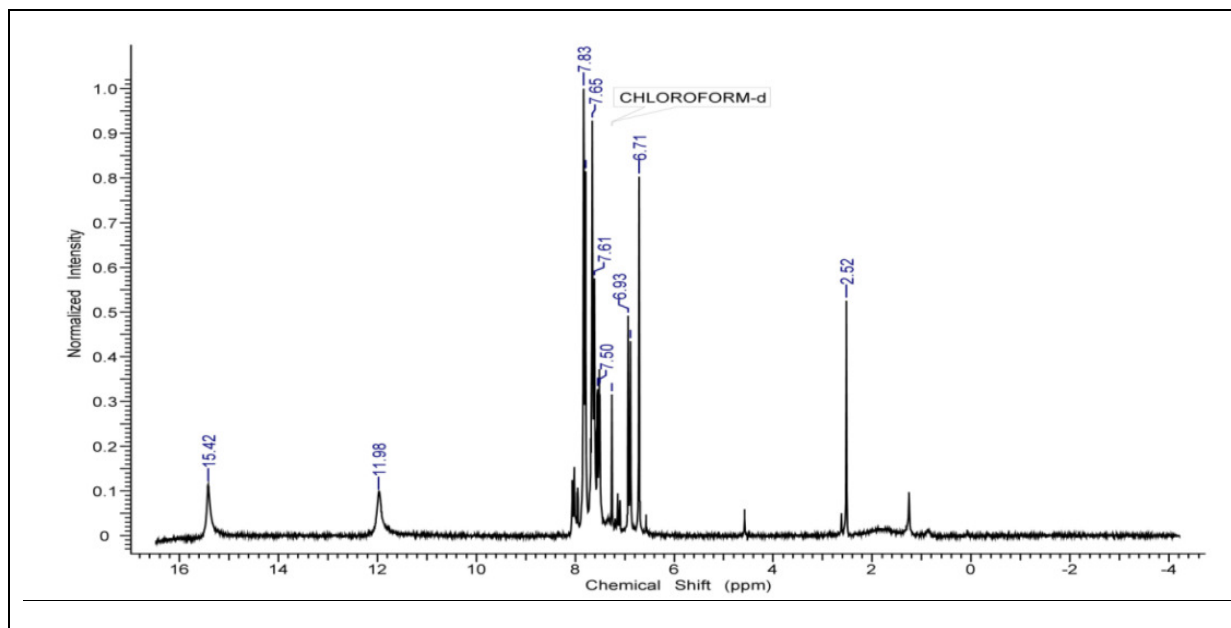


Fig.-1: ¹H NMR of the 1-(5-bromo-2-hydroxyphenyl)-3-(4-bromophenyl)-propane-1,3-dione

Powder XRD Studies

The powder XRD of the some selected metal complexes provides structural information. The study of the XRD was performed with Cu as anode material, K-alpha [\AA] = 1.540598 and the generator settings 30 mA, 40 KV in the range 10^0 - 80^0 . The high-intensity peaks of the diffraction pattern were indexed and analyzed by the Powder-X software. The XRD pattern of L-Co & L-Ni complex shows a monoclinic crystal system. The average crystallite size for L-Co & L-Ni complexes were found to be 9.3134 nm & 11.4974 nm respectively and it 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)¹⁹.

The value of unit cell dimension of Co(II) complex were $a = 14.51 \text{ \AA}$, $b = 8.21 \text{ \AA}$, $c = 13.55 \text{ \AA}$ and $\alpha = 90^0$, $\beta = 90^0$, $\gamma = 120^0$. Also, the value of unit cell dimension of Ni(II) complex were $a = 7.42 \text{ \AA}$, $b = 10.11 \text{ \AA}$, $c = 18.26 \text{ \AA}$ and $\alpha = 92^0$, $\beta = 91^0$, $\gamma = 120^0$.

Thermo Gravimetric Study of Metal Complexes

Thermal gravimetric studies of selected metal complexes were carried out at a heating rate of $10^\circ\text{C min}^{-1}$ under nitrogen atmosphere over the temperature range 25–1000 $^\circ\text{C}$. Thermogravimetric analysis of Co(II) complex showed some loss of weight between 193.81 $^\circ\text{C}$ and 265.44 $^\circ\text{C}$ indicating that surface and coordinated water molecules are present in the complexes²⁰⁻²¹. A sudden weight loss (35.61%) from 265.44 $^\circ\text{C}$ to 410.72 $^\circ\text{C}$ was due to the loss of one phenyl ring with two hydroxy and one carbonyl group. Further, the weight loss (42.88%) from 410.72 $^\circ\text{C}$ to 599.37 $^\circ\text{C}$ corresponds to the decomposition of two phenyl ring and a propane-1, 3-dione moiety. On further heating above 599.37 $^\circ\text{C}$ the weight remained constant corresponding to the formation of cobalt oxide.

Thermogravimetric studies of Ni(II) complex showed some loss of weight between 94.46 $^\circ\text{C}$ and 212.16 $^\circ\text{C}$ indicating that surface and coordinated water molecules are present in the complexes. A sudden major weight loss (56.54%) from 212.16 $^\circ\text{C}$ to 413.46 $^\circ\text{C}$ was due to the loss of one phenyl ring with two hydroxyl and one carbonyl group. Further, the weight loss from 413.46 $^\circ\text{C}$ to 521.26 $^\circ\text{C}$ corresponds to the

decomposition of two phenyl ring and a propane-1, 3-dione moiety. On further heating up to 600°C no change was observed due to of zinc oxide. The thermal stability properties evaluated by TG methods revealed good stability for the synthesized metal complexes.

Antimicrobial Activities

The antimicrobial activity of ligand and its complexes carried out by Resazurin method which is developed by Drummond and Weigh in 2000²². This method is simple, sensitive, rapid, reliable and achieves more accurate minimum inhibitory concentration (MIC). Resazurin acts as an indicator and it is prepared by dissolving 270 mg tablet in 40 ml of sterile distilled water. The microbial growth detected by very small volumes of solution in microtitre plates without the use of a spectrophotometer. Isosensitest medium was used for this assay²³. The color changes from purple to pink or colorless were recorded as positive. MIC values taken as color change occurred at the lowest concentration. The average of three values of MIC for the test material and bacterial strain has been considered.

Table-3: MIC ($\mu\text{g/ml}$) Values Determination.

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

CONCLUSION

In the present work, we have synthesized the new ligand (L) and its metal complexes by a conventional method. Spectral data confirmed the synthesis of ligand and its complexes. The metal complexes were soluble in DMSO and DMF. XRD study of both (L)₂-Co & (L)₂-Ni complexes showed a monoclinic crystal system. TGA study revealed high thermal stability of metal complexes. Water molecules also coordinated in metal complexes. The antimicrobial activity results show that ligand and its transition metal complexes show considerable antimicrobial activities as compared to standard drugs

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