Asian Journal of Chemistry; Vol. 30, No. 2 (2018), 398-402

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2018.21041

Synthesis, Characterization and Antimicrobial Screening of 1,3-Dione with their Metal Complexes

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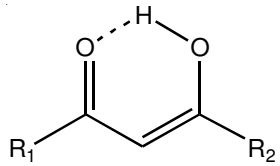
Received: 13 September 2017; *Accepted*: 28 November 2017; *Published online*: 31 December 2017; AJC-18713

1-(5-Bromo-2-hydroxyphenyl)-3-(thiophen-2-yl)-propane-1,3-dione and its metal complexes has been synthesized. The functionalized 1,3-dione potentially acts as bidentate ligand and coordinate with the transition metal ions through β-diketo system. The synthesized diketone and their transition metal complexes have been screened for *in vitro* antibacterial and antifungal activity using Resazurin 96 well plate method. The transition metal complexes showed moderate to excellent antimicrobial activity against all tested bacteria and fungi which constitutes a new group of compounds that can be used as potential metal derived drugs.

Keywords: 1,3-Dione, Metal complexes, Magnetic susceptibility, XRD, TGA, Antimicrobial activity.

INTRODUCTION

The research on various 1,3-dione and its metal complexes has wide scope in pharmaceutical industries. The functionalized 1,3-diones are potential antibacterial [1], antiviral [2], insectitial [3], antioxidant [4], antisunscreen activity [5], antitumor [6], HIV-1 Integrase (IN) inhibitors [7]. 1,3-Dione are key intermediate for the synthesis various heterocyclic compounds [8-10]. It is well known that the simplest form of 1,3-dione is pentane 2,4-dione or acetyl acetone in which two carbonyl group at 1, 3 position shows keto-enol tautomerism. The equilibrium in 1,3-dione is strongly shifted towards the enol form since formation of six membered stable ring and intramolecular hydrogen bonding. The enol form plays a vital role in formation of metal complexes with 1,3-diones.



General structure of enol form of 1,3-diones

1,3-Dione metal complexes are used as catalyst in reaction of olefin oxidation and epoxidation [11,12]. Europium(III)-diketonates have excellent luminescent property [13]. It is also used as chelating agent [14] and extractants for lanthanide ions [15].

In the present work, we have synthesized, characterized and screened for *in vitro* antibacterial and antifungal activities of the ligand, 1-(5-bromo-2-hydroxyphenyl)-3-(thiophen-2-yl)propane-1,3-dione and its metal complexes.

EXPERIMENTAL

All the chemical were used of analytical grade. All metal salts were used as nitrate (S.D. Fine). 5-Bromo-2-hydroxy-aceto-phenone (Himedia), 2-thiophenecarboxylic acid (Sigma Aldrich), dry pyridine (Spectrochem) were 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 ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a Bruker Avance DPX-400 spectrometer. The magnetic susceptibility was measured at room temperature using Guoy balance.

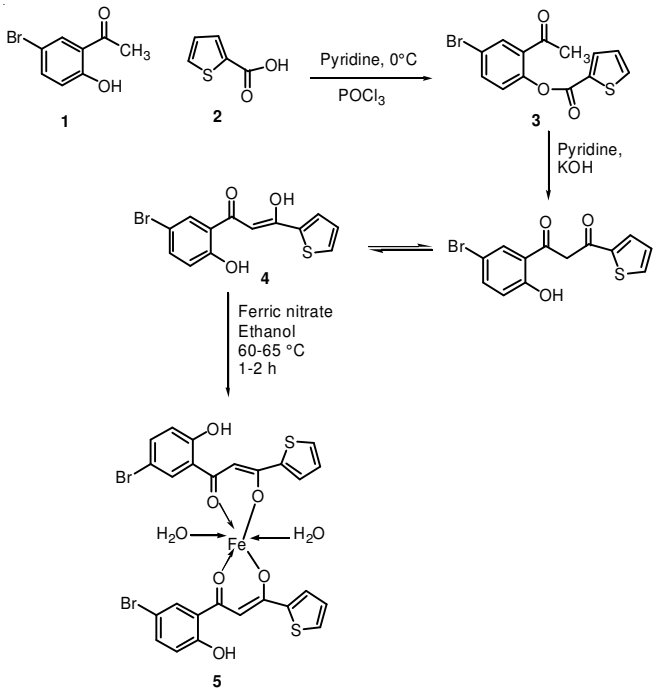
Synthesis of 2-acetyl-4-bromophenyl thiophene-2-carboxylate (3): To the mixture of 5-bromo-2-hydroxyaceto-phenone (2.150 g, 0.01 mol) and 2-thiophene carboxylic acid (1.281 g, 0.01 mol), dry pyridine (20 mL) and $POCl_3$ (1 mL) were added drop wise with constant stirring at 0 °C. The reaction mixture was then continually stirred for 5-6 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into HCl (1 M) containing of crushed ice. The solid obtained was filtered and washed with ice-cold methanol and

then with distilled water. It was recrystallized from ethanol. Yield: 69 %.

Synthesis of 1-(5-bromo-2-hydroxyphenyl)-3-(thiophen-2-yl)propane-1,3-dione (4): Compound **3** (3.251 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 continually stirred for 3-4 h. After completion of the reaction (monitored by TLC), the mixture was poured on ice cold water and acidified with 1 M of HCl. The yellow colour solid product obtained was filtered off and recrystallized from absolute ethanol [16,17]. Yield: 72 %; m.p.: 93 °C; LC-MS: 324.8 (M^+) elemental analysis: calculated C, 48.02, H, 2.79. Found C, 48.31; H, 2.84; ^{1}H NMR: 15.59 δ (s, 1H, enolic-OH), 11.93 δ (s, 1H, phenolic -OH), 7.6 δ (s, 1H, =C-H ethylene); 6.81-7.81 δ (m, 6H, Ar-H); IR ν_{max}, cm^{-1}: 1618 ν(C=O) ketonic, 1220 ν(C-O) enolic.

Bis-[1-(5-bromo-2-hydroxyphenyl)-3-(thiophen-2-yl)-propane-1,3-dionate]-Fe(III) complex: A mixture of compound **4** (5 mmol) and 2.5 mmol of appropriate ferric nitrate added in anhydrous 30 mL ethanol and the resulting mixture was refluxed at 60-65 °C for 1-2 h where upon the complex precipitation occurs after the addition of alcoholic ammonia. The precipitated coloured solid complex washed with ethanol and crystallized by using dichloromethane (**Scheme-I**). Yield 67 %, m.p.: 348 °C, elemental analysis: calculated C, 42.19, H, 2.72 found C, 42.02, H, 2.85.

Similarly, the complexes of cobalt, nickel, copper and zinc were prepared by the same method.



Scheme-I: Synthetic route of 1,3-dione and its metal complexes

Antimicrobial activities: The antimicrobial activity carried out by Resazurin method which is developed by Drummond and Waigh [18]. This method is simple, sensitive, rapid, reliable and achieves 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. In this method, the microbial growth detected by small volumes of solution in microtitre plates without the use of a spectrophotometer. The medium was used for this assay isosensitest [19]. Using aseptic techniques single colony was transferred into a 100 mL bottle containing isosensitest broth, capped and placed in incubator overnight at 35 °C. after that using aseptic preparation and centrifuge, a clean sample of bacteria was prepared. The broth was settled down using centrifuge at 4000 rpm for 5-6 min. The supernatant was separate out in waste beaker. Using 20 mL of sterile saline the pellet was re-suspended by centrifuge at 4000 rpm for 5-6 min. The pellet was suspended in 20 mL of sterile saline and it is labeled. The optical density of labeled was recorded at 500 nm and serial dilutions were carried out by aseptic techniques upto 0.5-1.0 range of optical density. By using viability graph, the actual number of colony forming units was calculated. The plates were prepared in triplicate and placed in an incubator set at 37 °C for 18-24 h. The colour changes from purple to pink or colourless were recorded as positive. MIC values taken as colour change occur at lowest concentration. The average of three values of MIC for the test material and bacterial strain has been considered.

RESULTS AND DISCUSSION

The synthesized ligand and its transition metal complexes of 1-(5-bromo-2-hydroxyphenyl)-3-(thiophen-2-yl)propane-1,3-dione are stable at room temperature in the solid state. The ligand is soluble in all organic solvents but its metal complexes are highly soluble in dimethyl sulfoxide and dimethyl formamide. The synthesized metal complexes have 1:2 stoichiometric ratio of metal-ligand. Spectral analysis data shows the confirmation of 1,3-dione and its metal complexes.

Magnetic susceptibility and molar conductance: The magnetic susceptibility observed at room temperature. All the metal complexes paramagnetic in nature except Zn-complex show diamagnetic in nature. Molar conductance (Λ_M) values of metal complexes were obtained at room temperature at 1×10^{-3} M DMSO solution. The studies show negligible molar conductance values of metal complexes in range 0.008-0.012 ohm^{-1} cm^2 mol^{-1} results showed in Table-1 clear that all the metal complexes are non-electrolytic in nature [20].

IR spectra: The characteristic infrared spectral data of ligand (L) and their metal complexes are reported in Table-1. The carbonyl group (>C=O) of ligand (L) stretching frequency appearance at 1618 cm^{-1}. The appearance of frequency at 1587 cm^{-1} due to (-C=C-) double bond and the bond (C-O) appear at 1220 cm^{-1}. The metal complexes shows IR frequency of carbonyl group (>C=O) at 1596-1615 cm^{-1} which were lower than IR frequency of ligand (L) 1618 cm^{-1}. This lowering stretching frequency indicates that the ligand (L) coordinated with the transition metal ion. In addition, new band at 519-527 cm^{-1} observed due to metal-oxygen (M-O) bond vibrations in metal complexes which were absent in ligand 4. This confirms of metals coordinate with ligand *via* oxygen.

Electronic absorption spectra: UV spectra were taken at 1×10^{-3} M DMSO solution. Electronic absorption spectra studies reveals that only charge transfer transitions were observed in all metal complexes therefore geometry of the

TABLE-1
MAGNETIC, CONDUCTANCE, INFRARED AND ELECTRONIC SPECTRA

Compound	Magnetic moment μ_{eff} (BM)	Molar conductance (ohm^{-1} cm^2 mol^{-1})	IR (cm^{-1})					ν (cm^{-1})
			ν(C=O)	ν(C=C)	ν(C-O)	ν(OH) coordinated H_2O molecule	ν(M-O)	
Ligand	–	–	1618	1587	1220	–	–	25873, 38535
Fe(III) complex	5.86	0.012	1610	1572	1227	3672	525	26212, 31347, 38314
Co(II) complex	3.49	0.008	1606	1580	1230	3679	525	25641, 38461
Ni(II) complex	2.45	0.012	1615	1585	1241	3564	527	24420, 25706, 38535
Cu(II) complex	1.39	0.011	1596	1596	1210	3584	519	25873, 38240
Zn(II) complex	Diamag.	0.010	1597	1597	1229	3351	522	24183, 27397, 38461

complexes is octahedral geometry with center of symmetry which is Laporte forbidden transition therefore weak *d-d* transitions were not observed only charge transfer transitions occurs in metal complexes. Wavenumber of electronic absorption spectra as shown in Table-1.

^{1}H NMR and ^{13}C NMR spectra: The ^{1}H NMR spectral data of the 1-(5-bromo-2-hydroxyphenyl)-3-(thiophen-2-yl) propane-1,3- dione (L) shows singlet at δ 15.59 ppm due to enolic proton, a singlet at δ 11.93 ppm due to phenolic proton adjacent to the carbonyl group which confirms the formation of β-diketone. In the ^{13}C NMR of ligand **4**, peak appeared at δ 193.33 ppm corresponds to carbonyl carbon (C=O) and enolic carbon (C-O) at δ 173.62 ppm. The signal at δ 91.67 ppm appeared shows methine linkage.

Powder X-ray diffraction: The XRD study was performed with Cu as anode material, K_α (Å) = 1.540598 and the generator settings 30 mA, 40 KV in the range 10-80°. The high intensity peaks of the diffraction pattern were indexed and analyzed by the powder-X software. The XRD pattern of L-Co and L-Zn complexes shows monoclinic crystal system. The average crystallite size for the above mentioned complexes was found to be 15.6 and 9.01 nm, respectively. The value of unit cell dimension of Co(II) complex were a = 8.818 Å, b = 7.585 Å, c = 19.26 Å and α = 90°, β = 90°, γ = 120°. Unit cell volume = 1114.13.

The powder X-ray diffraction analysis of Zn(II) complex exhibited some sharp peaks while no sharp peaks were observed for Co-complex indicating their amorphous nature (Fig. 1). Also, the value of unit cell dimension of Zn(II) complex were a = 6.847 Å, b = 8.310 Å, c = 24.12 Å and α = 90°, β = 90°, γ = 120°. Unit cell volume = 932.54 (Fig. 2).

Thermogravimetric analysis of metal complexes: Thermal decomposition of selected metal complexes was carried out at a heating rate of 10 °C min^{-1} under nitrogen atmosphere over the temperature range 28-1000 °C. Thermogravimetric analysis of cobalt complex shows some loss of weight between 60 and 185 °C indicating that surface and coordinated water molecules are present in the complexes [21,22]. A sudden weight loss from 200 to 300 °C due to loss of one phenyl ring with two hydroxy and one carbonyl group. Further, the weight loss from 377 to 420 °C corresponds to the decomposition of two phenyl ring and a propane-1,3-dione moiety. On further heating up to 600 °C, the weight remaining corresponds to that of cobalt oxide (Fig. 2).

Thermogravimetric analysis of zinc(II) complexes shows some loss of weight between 70 and 233 °C indicating that coordinated water molecules are present in the complexes. A sudden weight loss from 357 to 450 °C due to loss of one phenyl ring with two hydroxyl and one carbonyl group. Further, the weight loss from 450 to 520 °C corresponds to the decomposition of two phenyl ring and a propane-1,3-dione moiety. On further heating up to 600 °C the weight remaining corresponds to that of zinc oxide (Fig. 2).

The antimicrobial activity data shows that ligand and its transition metal complexes shows considerable antimicrobial activity compared with standard drug (Table-2).

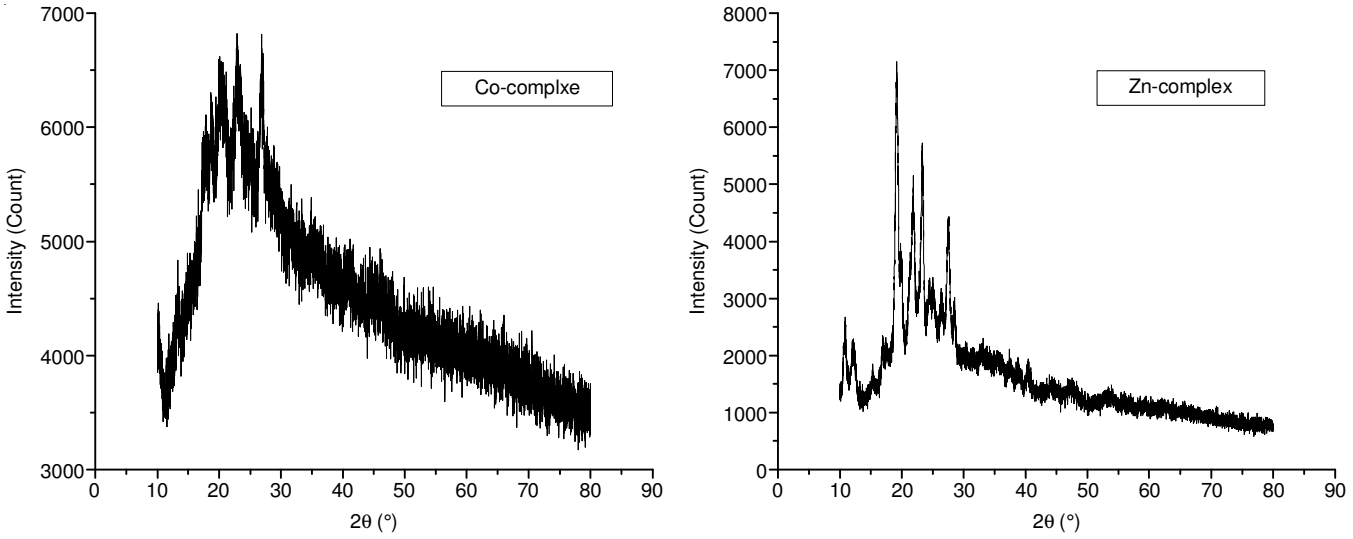


Fig. 1. Powder XRD patterns of Co-complex and Zn-complex (using Origin Software)

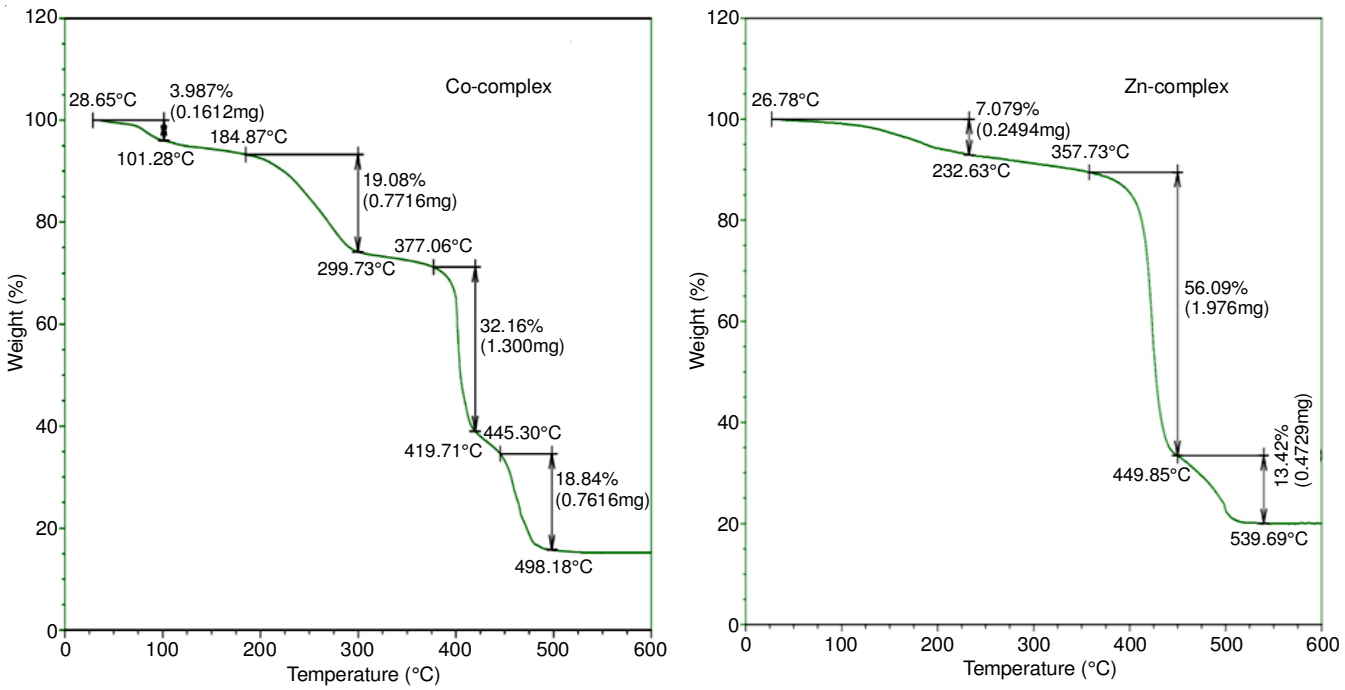


Fig. 2. TGA of Co(II) complex and Zn(II) complex

TABLE-2
MIC (µg/mL) VALUES DETERMINATION USING MODIFIED RESAZURIN ASSAY

Compounds	Antibacterial activity				Antifungal activity	
	Gram-positive		Gram-negative		*C. albicans*	*S. cerevisiae*
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*		
L	50	< 50	100	50	100	100
L-Fe	100	< 50	100	50	200	100
L-Co	< 50	< 50	100	50	100	50
L-Ni	100	< 50	100	100	150	150
L-Cu	50	< 50	100	100	150	100
L-Zn	50	< 50	100	50	100	150
Tetracycline	2	1	4	1	-	-
Amphotericin B	-	-	-	-	1.25	1.25

Conclusion

In the present work, we have synthesized a new ligand and its metal complexes by conventional method. The synthesized compounds were characterized by various analytical techniques. The synthesized β-diketone ligand coordinate with the metal ions by oxygen atom as donor sites. Magnetic studies revealed the paramagnetic nature of complexes.

ACKNOWLEDGEMENTS

The authors are thankful to the Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad and Principal, Kalikadevi Arts, Commerce & Science College, Shirur (ka), India for providing the laboratory facilities.

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