



## ECO-FRIENDLY SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF POTENTIALLY ACTIVE $\beta$ -DIKETONE LIGAND AND ITS TRANSITION METAL COMPLEXES

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### ABSTRACT

Diketones are key intermediates for the synthesis of core heterocycles such as isoxazole, pyrazole, flavones, triazole, pyrimidine and benzodiazepines. The  $\beta$ -diketone ligand and its transition metal complexes have been manufactured by ultrasound irradiation. The  $\beta$ -diketone is prepared by using Baker-Venkatraman rearrangement and characterized by physical, spectral and analytical data. The moieties  $\beta$ -diketone compound acts as bidentate ligand and co-ordinate with the transition metal atom through  $\beta$ -diketone system. The synthesized compounds have also been screened for *in vitro* antibacterial and antifungal activity.

**Keywords:**  $\beta$ -diketone, Baker-Venkatraman rearrangement, Metal complexes, Antimicrobial activity, IR, NMR, Mass.

### 1. INTRODUCTION

In the last few years,  $\beta$ -diketones and their metal complexes have been utilized as chelating ligands for lanthanides and transition metals [1].  $\beta$ -diketones are bidentate ligands with the probability of complexation along with nearly all the metal ions [2]. The chemistry of 1,3-diketones and its metal complexes has attracted the awareness of scientists for almost a century. Diketones are key intermediates for the synthesis of core heterocycles such as isoxazole [3], pyrazole [4], flavones [5], triazole [6], pyrimidine [7] and benzodiazepine [8].  $\beta$ -diketones are clinically important molecules since they exhibit some biological activities, such as antiviral, insecticidal, antioxidants, antitumor, anticancer [9] and antibacterial activities and are also key intermediates to various heterocyclic compounds. [10-13]. Metal 1, 3-diketonates have been used in the production of laser devices [14] and as NMR shift reagents [15].  $\beta$ -diketone and its metal complexes have been often used in multiple areas because of their unique structural features, chemical functionalities and electroluminescent materials [16] due to appropriate stability in heat and light.  $\beta$ -diketones have gained a lot of interest due to their high reactivity with to form chelates [17]. Some  $\beta$ -diketones are also used in UV sunscreen cosmetics that filter certain ultraviolet rays to protect skin [18].  $\beta$ -diketone in its

keto-enol form is also an important pharmacophores of HIV-1 integrase inhibitors [19].  $\beta$ -diketone and its metal complexes have been widely used in diverse areas because of their unique structural features, chemical functionalities, and toughness for light and heat as electroluminescence materials [20]. In present work, we have synthesized and studied some properties of 1-(5-chloro 2 hydroxyphenyl)-3-(4-nitrophenyl)-propane-1, 3-dione and its metal complexes. The title compound was synthesized from 5-chloro, 2-acetylphenyl, 4-nitro benzoate. by employing Baker-Venkataraman rearrangement [21]. The synthesized compounds were characterized by analytical techniques and screened for antibacterial study.

### 2. MATERIAL AND METHODS

All the solvents and reagents used were of A. R. grade. All the elemental analyses were done using the Perkin Elmer2400 CHN analyzer. Melting points were checked in open extended capillaries and were uncorrected. <sup>1</sup>H-NMR and <sup>13</sup>CNMR spectra were recorded on a Varian-NMR-mercury 300 using tetra methyl silane as an internal standard and CDCl<sub>3</sub> as solvent. UV/Vis spectra were recorded on spectrophotometer 166. Mass spectra were recorded on a Macro mass spectrometer and FT-IR spectra were taken using (KBr) disc on Bruker Spectrophotometer. The magnetic susceptibility of the

complexes was measured at room temperature using a Gouy's balance.

### 2.1. Preparation of 5-chloro,2-acetylphenyl, 4-nitrobenzoate (1)

To the mixture of 5-chloro,2-hydroxyacetophenone (1.70g, 0.01mol) and 4-nitro benzoic acid (1.67g, 0.01mol), a dry pyridine (5ml) and POCl<sub>3</sub> (1ml) were added drop wise with constant stirring at 0°C. THE reaction mixture was then irradiated in ultrasound for 4-5hrs. After fulfillment of the reaction (monitored by TLC), the reaction mixture was immersed into 100ml HCl (1M) containing 50g of crushed ice and solid obtained was filtered and washed with 10ml ice-cold methanol and after that with distilled water. It was recrystallized from ethanol (Yield: 81%; MP: 113°C).

### 2.2. Preparation of 1-(5-chloro,2-hydroxyphenyl)-3-(4-nitrophenyl)propane-1,3-dione (2)

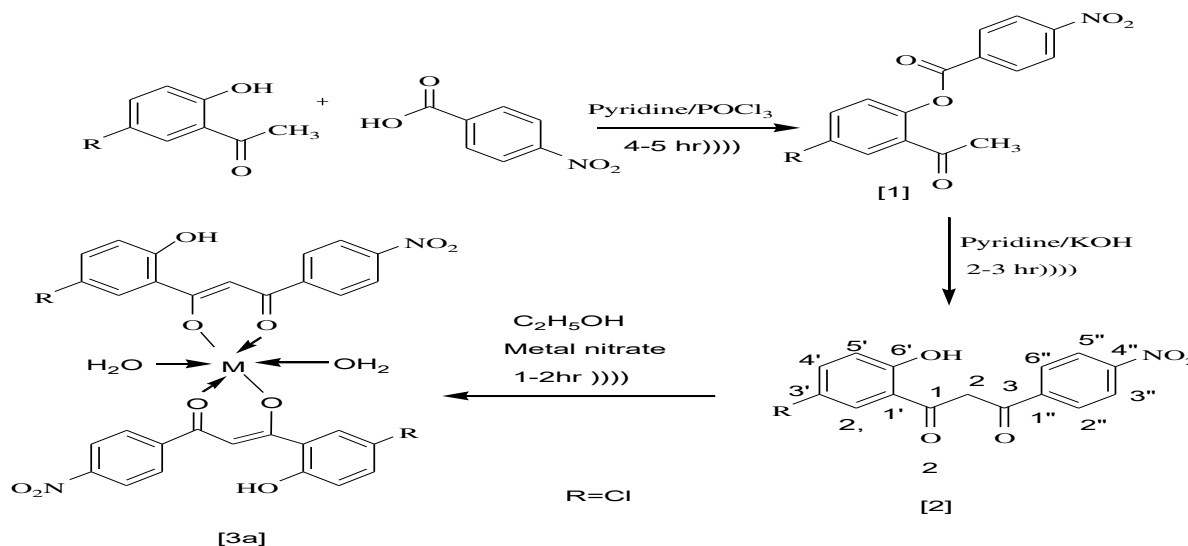
Compound 1 (3.19g, 0.01mol) was liquefied in dry

pyridine (10 ml). To this, powdered KOH (1.12 g, 0.02mol) was added and the reaction mixture was irradiated in ultrasound for 1-2 hrs. After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice cold water and conc. HCl was added till mixture acidified. The yellow coloured solid recovered was filtered off and crystallized by using absolute ethanol (Yield: 87%; mp:121°C).

### 2.3. Bis(-diketonato) Fe (III) complex(3a)

The mixture of compound 2 (6.39g, 0.02mol), anhydrous Fe (III) nitrate (4.04g, 0.01mol) and 20 ml anhydrous ethanol was added and irradiated for 1-2 hrs. under ultrasound. The solid precipitate was washed with hot ethanol and recrystallized from ethyl acetate. It gave brownish crystals of Fe (III)β- diketonate. (Yield: 84%; MP: 352°C).

A similar procedure was adopted to prepare Co (II), Ni (II), Cu (II), and Cr (III) complexes of 1-(5-chloro,2-hydroxyphenyl)-3-(4-nitrophenyl) propane-1,3-dione.



M : Fe(III), Co(II) and Ni(II), however in case of Cu(II) and Cr(III) water of coordination is absent

Scheme 1. Synthesis of ligand and metal complexes

Table 1: Physical properties and elemental analyses of the ligand and its metal complexes

| Compound  | colour     | % yield | M.P. | Elemental Analyses found |            |            |         |
|---|------------|---------|------|--------------------------|------------|------------|---------|
|   |            |         |      | Carbon %                 | Hydrogen % | nitrogen % | Metal % |
| Ligand (L) (2)  | Yellow     | 87      | 121  | 56.32                    | 3.11       | 4.22       | -----   |
| [Fe(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ](3a) | Brown      | 84      | >300 | 50.51                    | 3.65       | 3.52       | 7.22    |
| [Co(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ](3b) | Rosewood   | 82      | >300 | 50.38                    | 3.61       | 3.58       | 7.67    |
| [Ni(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ](3c) | Brown      | 81      | >300 | 50.37                    | 3.63       | 3.53       | 7.66    |
| [Cu(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ](3d) | green      | 88      | >300 | 50.07                    | 3.60       | 3.61       | 8.21    |
| [Cr(L) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ](3e) | Dark brown | 83      | >300 | 50.81                    | 3.68       | 3.69       | 6.81    |

**Table 2: IR Spectra of  $\beta$ -diketone ligand and metal complexes ( $\text{cm}^{-1}$ )**

| Compound  | $\nu$ (C=O) | $\nu$ (C=C) | $\nu$ (-OH) | $\nu$ (-OH) coordinated $\text{H}_2\text{O}$ mole. | $\nu$ (M-O) |
|---|-------------|-------------|-------------|--|-------------|
| L (2)   | 1742.12     | 1648.20     | 3482.18     | -----  | -----       |
| [Fe(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3a) | 1687.80     | 1653.02     | 3438.16     | 3468.31  | 450.59      |
| [Co(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3b) | 1680.71     | 1642.80     | 3442.32     | 3446.30  | 457.67      |
| [Ni(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3c) | 1679.02     | 1667.85     | 3398.67     | 3459.91  | 468.17      |
| [Cu(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3d) | 1699.72     | 1639.82     | 3442.70     | 3468.93  | 458.19      |
| [Cr(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3e) | 1687.02     | 1637.08     | 3449.20     | 3471.03  | 443.53      |

### 3. RESULTS AND DISCUSSION

5-chloro, 2-acetylphenyl 4-nitro benzoate (1) underwent Baker-Venkataraman rearrangement to afford bright yellow needles of 1-(5-chloro, 2-hydroxyphenyl)-3-(4-nitrophenyl)-propane-1, 3-dione (2). The negative test for ester confirms that it is devoid of ester group. The elemental analysis and characteristic infrared spectral assignment of the compound is reported in Table 1 and Table 2 respectively. The structure was further confirmed by the other spectral analyses: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) $\delta$ : 15.89 (s, 1H, enolic -OH), 12.88 (s, 1H, OH), 4.76(s, 1H), 8.89(s, 1H), 8.84 (s, 1H), 7.10-8.17 (d, 2H), 7.26 (d, 1H), 6.92 (d, 1H), 7.02 (s, 1H); <sup>13</sup>C-NMR (300MHz, DMSO-d<sub>6</sub>),  $\delta$ 192.6(s, C-1, C=O), 90.8(s, C-2, -CH=), 178.1(s, C-3), 123.6(s, C-1'), 162.8(s, C-2'), 119.2(s, C-3'), 134.7(S, C-4), 127.1(s, C-5'), 130.6(s, C-6'), 121.1(s, C-1''), 128.8(d, C-2'', C-6''), 114.4(d, C-3'', C-5''), 160.9(s, C-4''), 63.5(s, C-7'', -CH<sub>2</sub>-), 14.1(s, C-8'', -CH<sub>3</sub>), Uv/vis (DMSO)nm: 360, 412. EC-MS: 343 (M+ 23).

In the <sup>1</sup>H NMR Spectra it gave characteristic peak at  $\delta$ 15.89 which corresponds to enolic proton and at  $\delta$ 12.88 which is being due to phenolic proton adjacent to carbonyl group. It confirms the formation of  $\beta$ -diketones. The compound in enolic form is extra stable than that of ketonic form and in the <sup>13</sup>C-NMR spectra it gives characteristic peaks at  $\delta$ 192.6, 90.8 and 178.1 confirms the formation of  $\beta$ -diketone. The complex of synthesized compound (2) gives brown coloured Fe (III) diketonate (3a) whose structure was then confirmed by spectral analysis. IR (KBr) $\text{cm}^{-1}$ :1687.80 (C=O), 3438.16 (-OH), 450.59(M-O). The C=O bond in complex (3a) shifted to lower frequency (1687.80) as compared to that of free ligand which indicates the coordination of metal atom with the carbonyl group of diketone. Likewise, other transition metal complexes were prepared by the same method. All the above evidences were further supported by the emergence of new bands at 443.57-468.17  $\text{cm}^{-1}$  due to the metal-oxygen vibrations. In the spectra of the transition metal

complexes only these new bands were observed. The ligand and its metal complexes are quite stable. All the complexes were insoluble in water but soluble in acetone, DMSO and DMF.

The complex of synthesized compound 2 gives brown colored Fe (II)  $\beta$ -diketonate 3a in high yield. The complexes are non-electrolytic in nature [23]. The magnetic susceptibility measurements of all the complexes were carried out at room temperature by the Gouy's method. (Hg[Co(NCS)<sub>4</sub>]) was used as reference material. The magnetic moments ( $\mu_{\text{eff}}$ ) of all the complexes have been reported in table 3.

**Table 3: Magnetic moments ( $\mu_{\text{eff}}$ ) of the complexes**

| Compound  | Magnetic moment $\mu_{\text{eff}}$ (BM) | Molar conductance $\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-2}$ |
|---|---|---|
| [Fe(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3a) | 6.31                                    | 65.1  |
| [Co(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3b) | 4.41                                    | 24.6  |
| [Ni(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3c) | 2.72                                    | 51.4  |
| [Cu(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3d) | 2.13                                    | 27.1  |
| [Cr(L <sub>2</sub> ) (H <sub>2</sub> O) <sub>2</sub> ] (3e) | 3.65                                    | 26.2  |

#### 3.1. Antimicrobial activity

The antibacterial screening of synthesized compounds was carried out by paper disc diffusion [24] method at 100ppm against Gram +ve bacteria; *B. subtilis*, *S. aureus*, and *E. coli* as Gram-ve bacteria. The synthesized ligands and their transition metal complexes were tested at the concentration 100ppm in DMSO and compared with known antibiotics viz streptomycin. The antifungal activity of the compounds was assayed using fungal species *F. Oxysporum* and *Aspergillus niger*. Also, standard antibacterial streptomycin was screened under similar condition for comparison. *Escherichia coli*, *B. subtilis*, & *staphylococcus aureus* determined by paper disc diffusion method [24] are presented in table 4. The activity of known antibiotic viz. streptomycin is comprised with the activity of ligand and its metal complexes. The

consequence of the *in vitro* fungicidal activity of the compounds against *F.oxysporum* and *A. niger* are given in same table no. 4, in which the outcomes of the control are also introduced. From table 4, it is evident that complexes having more antibacterial as well as antifungal activity as compared to free ligand [25]. Also regarding to standard, all the synthesized complexes and ligand were found to be fairly active. This may be explained by the chelation theory [26, 27]; according to which, chelation reduces the polarity of the central metal atom because groups and possible  $\pi$ -electron delocalization within the whole chelating ring. This chelation increases the lipophilic nature of the central atom, which favors the penetration of the complexes through the lipid layer of the cell membrane [28] and blocking of metal binding sites on the enzymes of the

micro-organism. It was observed from antibacterial screening studies that the metal chelates have higher activity than the corresponding free ligand and control against the same microorganisms under identical experimental conditions, which was consistent with earlier reports [29]. The antifungal data reveals that the metal complexes show enhanced activity as compared to free ligand and the inhibition increased as the concentration increased. It was found that these complexes show strong antifungal activity at lower concentration as similar to earlier reported literature [30].

In the present work we have been synthesized the ligand and its metal complexes by ultrasound irradiation method and we found that ultrasound irradiation method gives high yield and good purity of product [31].

**Table 4: Antimicrobial screening of ligand and its metal complexes**

| Compounds  | Conc. (ppm) | Antibacterial activity (Inhibition in mm) |         |                   | Antifungal activity (Inhibition in mm) |                    |
|--|-------------|---|---------|-------------------|--|--------------------|
|  |             | Bacillus subtilis                         | E. coli | Staphyloc. aureus | Aspergill. niger                       | Fusarium oxysporum |
| L (2)  | 100         | 7   | 7       | 7                 | 7                                      | 7                  |
| [Fe(L <sub>2</sub> )(H <sub>2</sub> O) <sub>2</sub> ] (3a) | 100         | 8   | 8       | 8                 | 9                                      | 9                  |
| [Co(L <sub>2</sub> )(H <sub>2</sub> O) <sub>2</sub> ] (3b) | 100         | 12  | 16      | 18                | 16                                     | 14                 |
| [Ni(L <sub>2</sub> )(H <sub>2</sub> O) <sub>2</sub> ] (3c) | 100         | 12  | 12      | 10                | 10                                     | 9                  |
| [Cu(L <sub>2</sub> )(H <sub>2</sub> O) <sub>2</sub> ] (3d) | 100         | 22  | 20      | 22                | 22                                     | 20                 |
| [Cr(L <sub>2</sub> )(H <sub>2</sub> O) <sub>2</sub> ] (3e) | 100         | 13  | 8       | 8                 | 9                                      | 8                  |
| Streptomycin   | 100         | 7   | 7       | 8                 | 8                                      | 7                  |

In the present work 1-(5-chloro, 2-hydroxyphenyl)-3-(4-nitrophenyl)-propane-1, 3-dione (2) was prepared by employing Baker-Venkataraman transformation and its transition metal complexes were also synthesized. Their structures were clarified on the basis of spectral analysis such as elemental analysis, IR, UV/vis, NMR and mass. The spectra revealed that the prepared compounds possess characteristic peaks due to the presence of enolic proton and phenolic proton adjacent to carbonyl group and magnetic moment of complexes were measured at room temperature and from the observed magnetic moment value of Fe (III) complex is 6.31BM, Co (II) complex is 4.41BM, Ni (II) complex is 2.72BM, Cu (II) complex is 2.13BM and Cr (III) complex is 3.65 BM we concluded that complexes has been octahedral geometry [32-33].

These synthesized compounds were screened for *in vitro* antibacterial and antifungal activity and found to be promising candidates as new antibacterial agents.

#### 4. CONCLUSION

In the present work we have synthesized the ligand and its metal complexes by ultrasound irradiation method. The synthesized compounds were characterized by various analytical techniques. The synthesized  $\beta$ -diketone ligand binds with the metal ions in a bidentate manner with oxygen as the donor sites. Based on the physicochemical and spectral data discussed above, octahedral geometry for Fe(III), Co(II), Ni(II), Cu(II) and Cr(III) complexes are proposed. The IR spectra of ligand and complexes were made comparison and to study the mode of coordination, magnetic study reveals the paramagnetic nature of complexes. Solution conductivity suggest the non-electrolytic nature of complexes. From antimicrobial study it is suggested that the synthesized ligand and its metal complexes are biologically active and showed enhances antimicrobial activities compared to standard. In future current studies is also applicable as anti-inflammatory as well as anti-oxidant agent.

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## Conflict of interest

None declared

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