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# Conventional and Ultrasonic synthesis of β-diketone with Mn(II), Fe(III), Co(II), Ni(II) and Cu(II) complexes and their antimicrobial screening

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## ABSTRACT

*1-(5-bromo-2-chlorophenyl)-3-hydroxy-3-(2-hydroxyphenyl)prop-2-en-1-one and its metal complexes have been synthesized by reaction with 5-bromo-2-chlorobenzoic acid, 2-hydroxyacetophenone and* $POCl_3$*. The ligand and its metal complexes were synthesized by conventional and ultrasonic methods. Synthesized beta-diketone shows keto-enol tautomerism by hydrogen bonding, hence acts as a chelating agent in the preparation of metal complexes. Synthesized compounds have been characterized by* $^1$*H-NMR,* $^{13}$*C-NMR, FTIR, LC-MS and elemental analysis. The structure of the metal complexes is found to be monoclinic and have been confirmed by XRD. Solution conductivity, magnetic susceptibility and antimicrobial screenings were also studied. The synthesized ligand and its metal complexes showed satisfactory antimicrobial activity.*

**Keywords:** Beta-diketone, metal complexes, Ultrasonic, magnetic susceptibility, antimicrobial screenings.

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## INTRODUCTION

β-diketones exist in the intramolecular hydrogen bonded keto-enol tautomerism hence form metal complexes, as enolic hydrogen atom can be replaced by a metal and a ketonic oxygen, thereby completing the chelate ring. β-diketones have many industrial and medicinal application hence are widely used. It possesses unique structural features and chemical functionalities and toughness for light and heat as electroluminescence [1-2]. β-diketones are versatile precursor for the synthesis of various heterocycles such as pyrazol [3], isoxazole [4], triazole [5], flavones [6], benzodiazepine [7] and pyrimidine [8]. β-diketones are important pharmacophores of HIV-1integrase (1N) inhibitor [9]. Cobalt is one of the major constituent of vitamin $B_{12}$ (Cobalamin) and plays a vital role in many biological activities, protects against brain atrophy or shrinkage associated with Alzheimer's disease and impaired cognitive function [10-11]. Many of cobalt containing compound possesses antineoplastic activity [12] and show efficient catalytic activity. β-diketones with different substituents and their complexes have been synthesized and their properties such as lewis acidity, standard molar enthalpies of formation, standard molar enthalpies of sublimation, vapour pressure and volatility have been studied [13]. β-diketones used in extraction processes of many metal ions [14]. Metal complexes have chelating ability and hence gained considerable interest in nucleic acid chemistry. The coordination behavior of β-diketones also has significant influences on the relative stabilities of the mixed ligand complexes as well as their use in biomedicine [15-18]. Cu(II) complexes have gain considerable importance as the antitumour candidate in recent years because copper is an essential micronutrient that participates in several biological processes like mitochondrial respiratory reactions, cellular stress response, antioxidant, etc., [19-20] and hence it may be less toxic than non-essential metals like platinum [21]. Nickel(II) forms an important component of various enzymes, viz. urease, carbon monoxide dehydrogenase and hydrogenase [22]. In view of the increasing interest in copper(II) and nickel(II) complexes [23–28], the free ligands and their complexes were analyzed for their DNA binding properties with calf thymus DNA and screened for both in vitro and in vivo antitumor activity against Dalton's lymphoma ascites cells. During the last two to three decades ultrasound irradiation method is extensively used by the researchers as an alternative source for organic synthesis as it accelerates the reaction. Acoustic cavitation is responsible for sonochemistry, another important application of sonochemistry to materials chemistry has been the preparation of biomaterials, most notably protein microspheres. Such microspheres have a wide range of biomedical applications, including their use as echo contrast agents for sonography, magnetic resonance imaging contrast enhancement, and oxygen or drug delivery.

## MATERIALS AND METHODS

### *2.1 Materials*

The analytical grade solvents and reagents were used for the synthetic work. Pyridine (Spectrochem), 5-bromo-2-chlorobenzoic acid (Spectrochem), Metal nitrates (Sigma aldrich) and 2-hydoxyacetophenone (Sigma aldrich) were purchased and used without further purification. Distilled ethanol was used for recrystallization and complex preparation.

### *2.2 Experimental Section*

#### *a) Conventional method*

*i) Synthesis of 2-acetylphenyl-5-bromo-2-chlorobenzoate (A):*

To a mixture of 5-bromo-2-chlorobenzoic acid (4g, 0.0169mol) and 2-hydroxyacetophenone (2ml,0.0169mol) was dissolved in pyridine (20ml) and $POCl_3$ (3ml, 0.0339mol) was added dropwise with constant stirring at 0°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. Obtained product was filtered and recrystallized by ethanol.

*ii) Synthesis of 1-(5-bromo-2-chlorophenyl)-3-hydroxy-3-(2-hydroxyphenyl)prop-2-en-1-one (L) (Base-catalyzed Bakervenkataraman Rearrangement):*

2-acetylphenyl-5-bromo-2-chlorobenzoate (4g, 0.0113mol) was dissolved in pyridine (15ml) and a powdered KOH (1.9g, 0.0339 mol) was added, and the reaction mixture was stirred at room temperature. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured on acidified crushed ice. The yellow product obtained was filtered and dried. Obtained product was recrystallized from ethanol. M.P: 114°C.

*iii) Synthesis of metal complexes:*

The complexes of Mn, Fe, Co, Ni and Cu were prepared as follows, 1-(5-bromo-2-chlorophenyl)-3-hydroxy-3-(2-hydroxyphenyl)prop-2-en-1-one (0.02mol) was dissolved in 20ml of ethanol and heated under stirring, to the hot solution of the ligand appropriate amount of transition metal nitrate (0.01mol) [Mn(II), Fe(III), Co(II), Ni(II), Cu(II),)] in same solvent was added. The resulting mixture was refluxed for five hours whereupon the complex precipitation occurs after the addition of alcoholic ammonia. The obtained solid was collected by filtration, washed with alcohol and then vacuum dried to obtain the product.

#### *b) Ultrasound Irradiation method*

*i) Synthesis of 2-acetylphenyl-5-bromo-2-chlorobenzoate A:*

5-bromo-2-chlorobenzoic acid (4g, 0.0169mol) and 2-hydroxyacetophenone (2ml, 0.0169mol) was dissolved in pyridine (15ml) and $POCl_3$ (3ml, 0.0339mol) was added dropwise at the temperature 0°C. The reaction mixture was irradiated by ultrasound for nearly 90 min and the progress of reaction was observed through TLC. After the completion of reaction, the reaction was worked up and the obtained product was recrystallized by ethanol. This method gives high yield and good purity of product than conventional method.

*ii) Synthesis of 1-(5-bromo-2-chlorophenyl)-3-hydroxy-3-(2-hydroxyphenyl)prop-2-en-1-one (L)*

2-acetylphenyl-5-bromo-2-chlorobenzoate (4g, 0.0113 mol) was dissolved in pyridine (15ml) and a powdered KOH (1.9g, 0.0339 mol) was added, and the reaction mixture was sonicated at room temperature. The progress of reaction was monitored by TLC. The reaction was completed within an hour with high purity and good yield.

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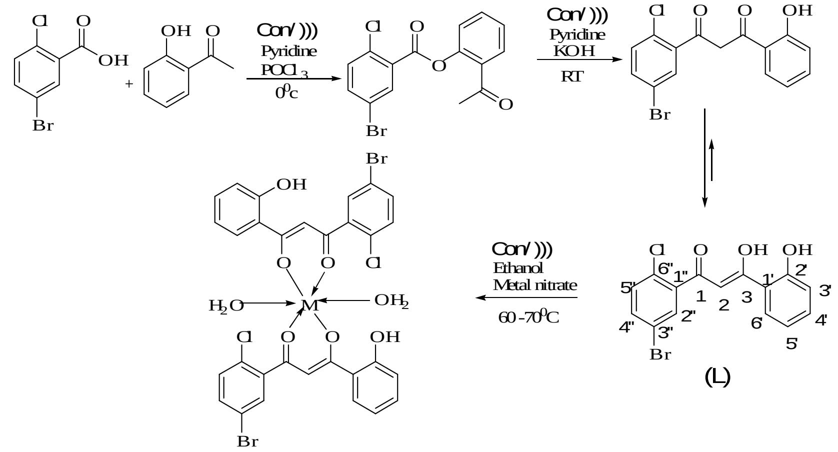
*iii) Synthesis of metal complexes:*

The metal nitrate in ethanol were mixed separately with ethanolic solution of the ligand in 1:2 stichometry (Metal: Ligand) and the resulting mixture solutions were sonicated at 60–70°C for about one hour in sonicator. After the addition of alcoholic ammonia complex precipitation occurs, the solid metal complexes thus separated were then washed with ethanol and dried in vacuum desiccator.



**Scheme:** Synthesis of the b-diketone (L) and its metal complexes
M= Mn, Fe, Co, Ni and Cu

**Table1. The comparative results of conventional and ultrasonic methods**

| Compound | Conventional | Ultrasonication | Yield % | | M.P/decomp. Temp. (°C) |
|---|---|---|---|---|---|
| | Time (min) | Time(min) | Conventional | Ultrasonication | |
| A | 175 | 90 | 71 | 90 | 110 |
| L | 75 | 55 | 72 | 88 | 114 |
| $[Mn(L)_2](H_2O)_2$ | 190 | 110 | 69.7 | 83 | >300 |
| $[Fe(L)_2](H_2O)_2$ | 186 | 95 | 66.5 | 76.6 | >300 |
| $[Co(L)_2](H_2O)_2$ | 172 | 105 | 72.8 | 82.3 | >300 |
| $[Ni(L)_2](H_2O)_2$ | 170 | 84 | 73.8 | 86.1 | >300 |
| $[Cu(L)_2](H_2O)_2$ | 160 | 75 | 75.7 | 89.5 | >300 |

### *2.3 Characterizations*:

Melting points were determined in open glass capillaries and were uncorrected. The elemental analyses were carried out using EuroVector EA 3000 Elemental Analyser, $^1$HNMR and $^{13}$CNMR were recorded on a Bruker's AVANCE-III 400MHz FT-NMR spectrometers by using tetramethylsilane as an internal standard and $CDCl_3$ as solvent, FTIR were recorded using (KBr) disc on Shimadzu. The magnetic susceptibility was measured at room temperature using a Guoy balance. Molar conductivities of metal complexes were measured at room temperature by using Equiptronics Digital conductivitymeter (EQ-660). Synthesis was carried out by conventional as well as by ultrasound irradiation method. Ultrasound assisted synthesis were carried out in Citizen ultrasonic sonicator.

## RESULTS AND DISCUSSION

The ultrasound irradiation method is very useful to carry out chemical reactions, ecofriendly, atom economy, simple setup and easy handling. The prepared metal complexes were coloured, stable to air and soluble in polar solvent like DMSO and DMF. The result of elemental analysis show 1:2 (metal:ligand) stoichiometry for all the prepared metal complexes. The presence of two coordinated water molecules appears to be hexa-coordinated of metal atom and the probable geometry is octahedral, Magnetic study reveals that the complexes of Mn, Fe, Co, Ni and Cu were paramagnetic in nature. The molar conductance of the metal complexes of $10^{-3}$M solution in DMF was found in the range 8 to 15cm$^{-1}$ mol$^{-1}$, which indicates that these complexes are nonelectrolytes.

### *3.1 $^1$H-NMR, $^{13}$C and Mass spectral data of the Ligand(L)*

**$^1$H-NMR**(400MHz, $CDCl_3$)δ**:** 6.76 (s, 1H, vinylic), 6.88 – 7.83(m, 7H, Ar-H), 11.90 (s, 1H Ar-OH), 15.14 (s, 1H enolic-OH).**$^{13}$C-NMR**(400MHz, $CDCl_3$)δ**:** 196.20 (s C-1, C=O), 98.33 (C-2, -CH=), 174.13 (s, C-3), 118.72 (s, C-1'), 162.77 (s, C-2'), 118.90 (s, C-3'), 128.86 (s, C-4'), 119.40 (s, C-5'), 126.42 (s, C-6'), 136.47 (s, C-1''), 133.08 (s, C-2''), 120.78 (s, C-3"), 134.60 (s, C-4"), 131.21 (s, C-5"), 132.33 (s, C-6"). **LC-MS (ESI$^-$)** at m/z 352.9 .

**Table2. Analytical, physical data, magnetic moment and molar conductance values of the compounds**

| Ligand/Complex | F. W. | Magnetic moment $\mu_{eff}$(B.M) | Molar conductance | Elemental Analysis | | | |
|---|---|---|---|---|---|---|---|
| | | | | Carbon % | Hydrogen% | Oxygen% | Metal% |
| L | 353.6 | --- | --- | 49.445 | 2.820 | 13.221 | ---- |
| $[Mn(L)_2](H2O)_2$ | 796.14 | 5.87 | 15.2 | 45.126 | 2.324 | 15.812 | 7.447 |
| $[Fe(l)_2](H_2O)_2$ | 797.05 | 5.51 | 8.59 | 45.105 | 2.551 | 15.863 | 7.522 |
| $[Co(L)_2](H_2O)_2$ | 800.14 | 3.3 | 10.20 | 44.221 | 2.275 | 16.118 | 7.157 |
| $[Ni(L)_2](H_2O)_2$ | 799.9 | 2.69 | 12.10 | 44.997 | 3.132 | 16.093 | 7.985 |
| $[Cu(L)_2](H_2O)_2$ | 804.75 | 1.27 | 14.04 | 44.922 | 3.008 | 16.021 | 7.112 |

### *3.2) FTIR spectra of the ligand and metal complexes:*

The IR spectra of free ligand and its metal complexes were made for comparison. The free ligand as expected exhibits keto-enoltautomerism [29]. The IR spectral data of ligand and its metal complexes are listed in table 3. The spectral band for ligand (i.e for keto carbonyl) appears at 1629 cm$^{-1}$ (ν C=O), the shifting of the same band to lower frequency in all the metal(II) complexes indicates the coordination of carbonyl group to the central metal ion. The spectral band appear in the range 1514-1577cm$^{\backslash -1}$and 1211-1240cm$^{-1}$are assigned to stretching vibrations of ν(C=C) and ν(C–O) [30–32]. The new band appeared in the 515 – 522 cm$^{-1}$ region are assigned to ν(M-O) bond. The band at around 3543-3655 cm$^{-1}$ indicates the existence of coordinated water in all the complexes.

**Table 3. IR spectra of free ligand and its metal complexes**

| Compound | ν(C=O) | ν(C=C) | ν(C–O) | ν(OH) of $H_2O$ | M–O |
|---|---|---|---|---|---|
| L | 1629 | 1577 | 1211 | ----- | ----- |
| $[Mn(L)_2](H_2O)_2$ | 1602 | 1539 | 1242 | 3616 | 516 |
| $[Fe(L)_2](H_2O)_2$ | 1605 | 1514 | 1242 | 3610 | 515 |
| $[Co(L)_2](H_2O)_2$ | 1602 | 1537 | 1244 | 3607 | 516 |
| $[Ni(L)_2](H_2O)_2$ | 1581 | 1535 | 1244 | 3655 | 516 |
| $[Cu(L)_2](H_2O)_2$ | 1614 | 1541 | 1240 | 3543 | 522 |

## POWDER XRD STUDIES

The X - ray diffraction (powder pattern) of the complexes was made with the help of X-ray diffractometer with Cu as anode material, the generator settings 30mA, 40KV in the range 5° - 80°. The indexing and calculation of unit cell parameters were performed using powder-X software and the powder diffraction of metal complexes K, L, M, and N shows well defined crystalline peaks (fig.1). The indexing method yields the Miller indices (*hkl*), the unit cell parameters and average particle size (table 4). The XRD pattern of K, L, M & N complexes shows monoclinic crystal system. The average crystallite size for the above mentioned complexes was calculated using Debye Scherrer's formula [33]:

$$D = 0.9\lambda/\beta.\cos\theta$$

Where, constant 0.9 is the shape factor, λ is the X-ray wavelength of Cu Kα radiation (1.5406 Å), θ is the Bragg diffraction angle and β is the full width at half maximum (FWHM).

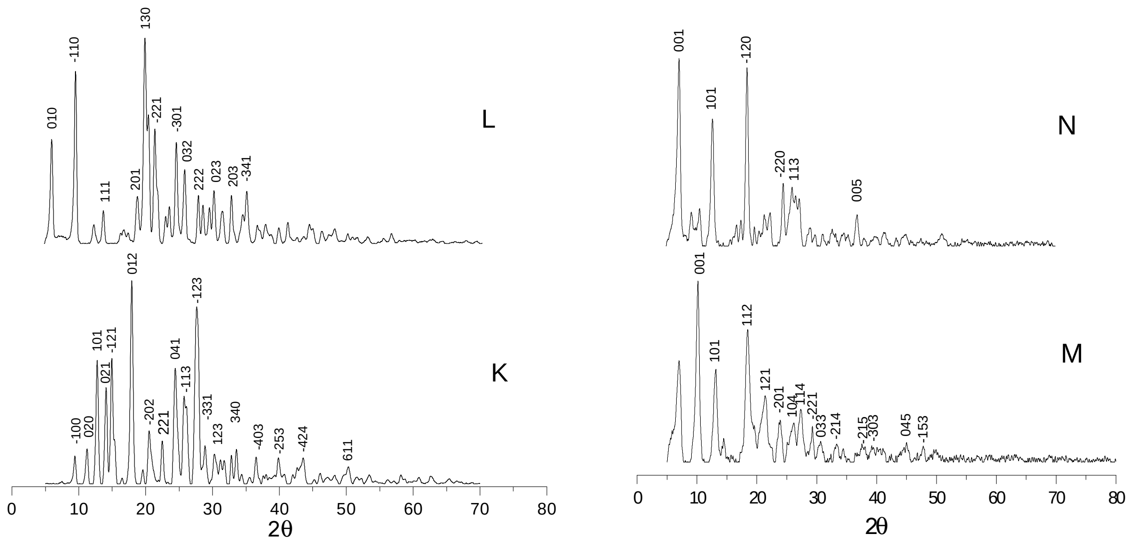


**Figure (1) XRD Patterns: K = $[Cu(L)_2](H_2O)_2$, L = $[Ni(L)_2](H_2O)_2$, M=$[Mn(L)_2](H_2O)_2$, N=$[Co(L)_2](H_2O)_2$**

**Table 4. XRD data and refinement parameters of K, L, M and N metal complexes**

| Parameters | | K | L | M | N |
|---|---|---|---|---|---|
| Temperature (k) | | 298 | 298 | 298 | 298 |
| Wavelength(A°) | | 1.540598 | 1.540598 | 1.540598 | 1.540598 |
| Radiation | | Cu Kα | Cu Kα | Cu Kα | Cu Kα |
| Crystal system | | Monoclinic | Monoclinic | Monoclinic | Monoclinic |
| Unit cell dimension | a(A°) | 11.6912 | 11.307 | 7.5795 | 9.500 |
| | b(A°) | 15.5434 | 14.5489 | 10.5795 | 11.193 |
| | c(A°) | 10.7214 | 9.7457 | 15.5452 | 12.210 |
| α(°) | | 90 | 90 | 90 | 90 |
| β(°) | | 101 | 94 | 92 | 96 |
| γ(°) | | 90 | 90 | 90 | 90 |
| Average particle size(nm) | | 19.1253373 | 20.3075965 | 12.01007 | 16.8346247 |

## Antimicrobial activity

In this research work Mn(II), Fe(III), Co(II), Ni(II) and Cu(II) metal complexes of the 1-(5-bromo-2-chlorophenyl)-3-hydroxy-3-(2-hydroxyphenyl)prop-2-en-1-one have been prepared to explore their antibacterial and antifungal properties. The antimicrobial analysis was done on petri-plates containing solidified 20ml Muller Hinton agar medium. These plates were inoculated with 20-24 hour culture of bacterial and fungal strains. The antimicrobial activity was assayed by measuring the diameter of the inhibition zone formed in terms of mm.

The antibacterial analysis was done by using Agar diffusion method. The wells were filled with 250 and 500 ppm concentration of the sample and incubated at 37 °C for 24 hours. Antibacterial activity of ligand and its metal complexes were tested in vitro against bacteria such as *S. aureus, S. typhi* and *E. coli* at 250 and 500ppm control plates with standard Gentamicin (for bacteria) and solvent were maintained. The results of the tested compounds against bacteria are shown in table 5. In vitro antibacterial activity of ligand and some of the metal complexes are moderately active as compared with standard gentamycin. Among the synthesized metal complexes Cu(II) complexes showed excellent bacterial activity.

The antifungal activity of the synthesized compound were tested by using disc diffusion method against the fungi such as *Saccharomyces cerevisiae* and *Candida albicans* at 10ppm and Amphotericin B used as standard in solvent DMSO. The results of the tested compounds against fungi are shown in table 6. In vitro antifungal activity of metal complexes compared to standard Amphotericin B among the synthesized metal complexes Ni(II) complex showed excellent antifungal activity against *C. albicans* and *S. cerevisiae*.

The metal complexes shows more antimicrobial activity than ligands due to the enhanced lipophilicity of the complexes, which leads to the breakdown of permeability barrier of the cell and thus retards the normal cell process in bacteria. With respect to standard, among the tested compounds some them were found moderately active.

**Table 5. Antibacterial screening of ligand and its metal complexes**

| Compound | *S. aureus* | | *S.typhi* | | *E.coli* | |
|---|---|---|---|---|---|---|
| | 250ppm | 500pp | 250ppm | 500ppm | 250ppm | 500ppm |
| L | 9 | 10 | 11 | 12 | 10 | 13 |
| $[Mn(L)_2](H_2O)_2$ | ---- | ---- | ---- | ---- | ---- | ---- |
| $[Fe(L)_2](H_2O)_2$ | ---- | ---- | ---- | ---- | ---- | ---- |
| $[Co(L)_2](H_2O)_2$ | 10 | 11 | 12 | 14 | ---- | 14 |
| $[Ni(L)_2](H_2O)_2$ | 13 | 16 | 13 | 15 | 12 | 16 |
| $[Cu(L)_2](H_2O)_2$ | 24 | 35 | 17 | 26 | 18 | 20 |
| Gentamycin | 26 | 27 | 26 | 30 | 29 | 31 |

**Table6.Antifungal screening of ligand and its metal complexes**

| Compound | *Saccharomyces cerevisiae* 10ppm | *Candida albicans* 10ppm |
|---|---|---|
| L | 9 | 7 |
| $[Mn(L)_2](H_2O)_2$ | ---- | ---- |
| $[Fe(L)_2](H_2O)_2$ | ---- | ---- |
| $[Co(L)_2](H_2O)_2$ | 9 | 9 |
| $[Ni(L)_2](H_2O)_2$ | 11 | 10 |
| $[Cu(L)_2](H_2O)_2$ | 7 | 6.5 |
| Amphotericin B | 5 | 2 |

## CONCLUSION

In the present work we have been synthesized the ligand and its metal complexes by conventional and ultrasonic methods to compare the reaction time and yield of the product. The synthesized compounds were characterized by various analytical techniques. The synthesized β-diketone ligand binds with the metal ions in a bidentate manner with oxygen as the donor sites. 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 suggests the nonelectrolyte nature of complexes. The XRD pattern indicates the crystalline nature of the complexes. From antimicrobial study it is suggested that the synthesized ligand and its metal complexes may be good candidate for antimicrobial studies.

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