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A *B*-keto ester as a novel, efficient, and versatile ligand for Ni(ii) and Co(ii) complexes and evaluation anti-bacterial activity

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Abstract
New versatile bi-dentate ligand α-acetyl-γ-butyrolactone was used for the synthesis of transition metal, complexes of Ni (II) and Co (II). Present communication describes Synthesis, Characterization and IR spectrum, elemental analysis, mass spectrum and UV visible and antimicrobial activity of the complex.

Keywords: A-Acetyl-γ-butyrolactone, nickel acetate and cobalt acetate monohydrate, structural analysis, biological activity

1. Introduction
A-Acetyl-γ-butyrolactoneis β ketoester, potentially reactive bis-electrophile, having ability to co-ordinate with metals due to presence of oxygen lone pair. The literature reports revealed that α-acetyl-γ-butyrolactone was used for the synthesis of various heterocyclic compounds having good biological activity. b-Ketoester is an important precursor used for the synthesis of multifunctional heterocyclic compounds, such as pyrazole [1, 3], isoxazole [3, 6] and triazole [7]. The heterocyclic compounds are alos used to treatment of coronavirus [8].

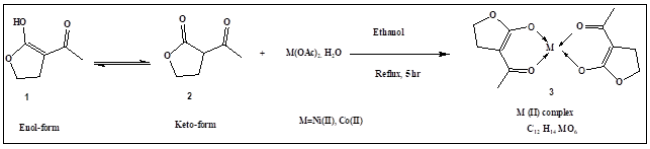
They are also used as chelating ligands for various lanthanide and transition metals in material chemistry [9, 11]. Owing to such an enormous application, the synthesis of 1, 3-diketones has gained considerable interest in recent years. The applications of 1,3-dicarbonyl compounds as ligand is well explored and are found to show great catalytic activities [12, 17]. On the contrary the chemistry of 1,3-keto ester is not much explored and there is huge scope to explore the chemistry of 1, 3-ketoester. There are only few reports available on use of cyclic 1,3-keto ester as a ligand for organic transformation which utilizes *in situ* in the preparation of metal complex [18]. There is tremendous scope in exploration of premade metal 1,3-keto ester complexes. The premade 1,3-keto ester metal complex will be stable, less-sensitive to water, easy to handle and having ability to exhibit catalytic and show medicinal properties. Considering all the above facts, we have prepared metal complex of α-acetyl-γ-butyrolactone with Ni (II) and Co (II), characterized and study its biological and catalytic activities discussed in current research.

2. Experimental
2.1 Material and methodology
All reagents were purchased commercially and were used directly without any further purification. The complex was characterized by IR, UV, HRMS, CHN analysis and physical constant.

IR spectra were recorded as KBr pellets on a Shimadzu FTIR-408 instrument. UV-visible spectra were recorded on Shimadzu 2450 UV-visible spectrophotometer. Mass spectra were recorded on a Shimadzu LC-MS: EI QP 2010A mass spectrometer with an ionization potential of 70eV. Elemental analyses were performed on Quest flash 1112 Series EA Analyzer at SAIF, Punjab University, Chandigarh. Melting points were determined on a Gallenkamp melting point apparatus. Reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F254 Merck plates using UV light (254 and 366 nm) for detection.

2.2 Synthesis of α-acetyl-γ-butyrolactone
α-Acetyl-γ-butyrolactone is prepared by condensation of γ-butyrolactone with an acetic ester in presence of strongly base. Enolate obtained was subjected to protonation. All these three reactants are continuously fed into the reaction mixture, where the ratio of acetic acid ester is 1.0-6.0 parts by moles, 0.9-1.6 parts by moles of strongly basic substance per part by moles of γ-butyrolactone. The reaction mixture obtained was removed from reaction zone and then it was protonated.

2.3 Synthesis of Ni (II) and Co (II) complex with α-acetyl-γ -butyrolactone
A solution of α-acetyl-γ-butyrolactone (2.15 mL; 20 mmol) 1 in 30 mL ethanol was stirred for 10 min, and then a solution of metal acetate monohydrate (nickel acetate /Cobalt acetate) (10 mmol) 2 in ethanol was added slowly at room temperature. The reaction mixture was stirred at reflux temperature for 5 hrs. After cooling to room temperature, the pale green and reddish pink collared complex 3 compound was filtered off, washed thoroughly with ethanol, followed by diethyl ether. The compound obtained was recrystallized from methanol and was finally dried under vacuum. Scheme 1



Scheme 1: Synthesis of Ni (II) and Co (II) complex of α-acetyl-γ-butyrolactone

3. Results and Discussion

3.1 Elemental analysis

The Ni (II) and Co (II) complexes are found to be stable in air. They are soluble in DMSO and DMF. The elemental analysis data for carbon, hydrogen and metal were determined and found and calculated values of percentage of elements are in good agreement. The metal content in both complexes were determined by Edax- complexes shows 1:2 metal to ligand ratio. The analytical data of complexes was calculated in Table 1. (Fig. 1,2)

Table 1: Analytical, physical data of lactone complexes

Complex	Colour % yield	M.P & Mol. Wt	Elemental analysis found (Calculated %)			
			C	H	M	O
$C_{12}H_{14}NiO_6$	Pale green (80%)	98 ºC 312.93	46.06 (44.66)	4.51	18.76 (16.69)	30.68 (37.63)
$C_{12}H_{14}CoO_6$	Reddish pink (80%)	240ºC 313.17	46.02 (32.40)	4.51	18.82 (24.02)	30.65 (35.90)

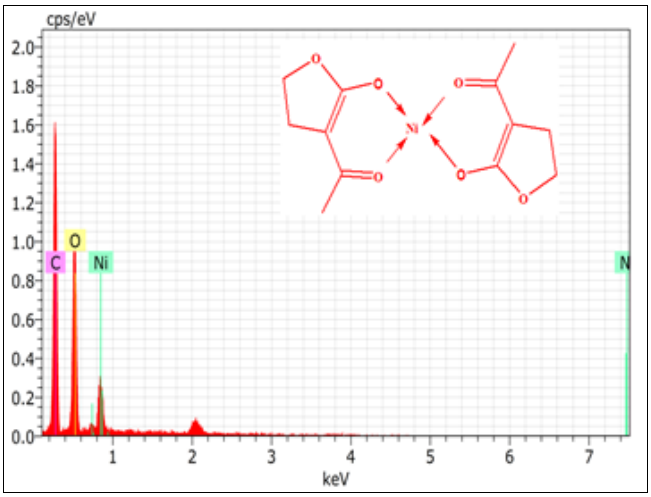


Fig 1: EDS of Complex $C_{12}H_{14}NiO_6$

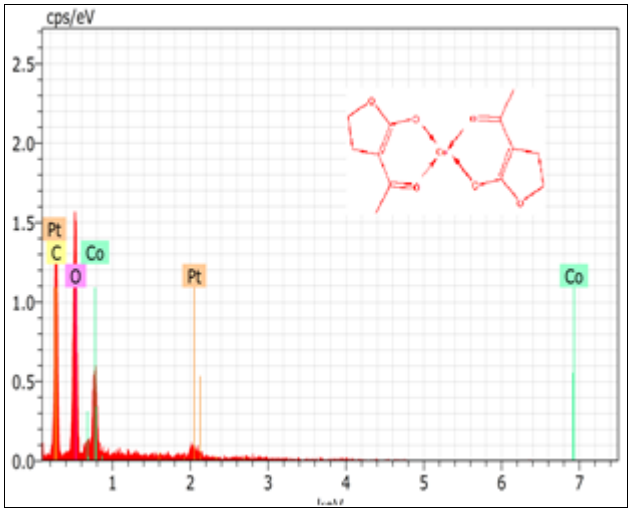


Fig 2: EDS of Complex $C_{12}H_{14}CoO_6$

3.2 Infrared Spectra

Scan IR spectra of lactone and complex showed different stretching, and bending frequencies, indicates that complexation of lactone with metals. The important IR spectra bands of lactone and metal complex along with their assignments. Lactone, α–acetyl-γ-butyrolactone shows a band at 1779 cm^{-1} indicates five-member cyclic ester group in ligand. The stretching frequency at 1726 cm^{-1} is attributed to carbonyl group. (Fig.3)

The complex of Ni (II) showed shifting of these two carbonyls to 1543. cm^{-1} and 1419 cm^{-1}. A new M-O band stretching frequency at 562cm^{-1} in spectra of Ni (II) complex confirms the co-ordination between metal and oxygen. (Fig.4). This indicated that coordination of ester oxygen and carbonyl oxygen with metal ions. A new M-O band stretching frequency at 540cm^{-1} in spectra of Co (II) complex confirms the co-ordination between metal and oxygen. (Fig.4). The complex of Co (II) showed shifting of these two carbonyls to 1535. cm^{-1} and 1420 cm^{-1}. This indicated that coordination of ester oxygen and carbonyl oxygen with metal ions. A new M-O band stretching frequency at 540cm^{-1} in spectra of Co (II) complex confirms the co-ordination between metal and oxygen. (Fig.4)

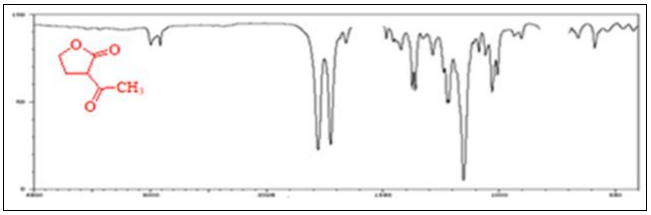


Fig 3: IR Spectrum of α-acetyl-γ-butyrolactone

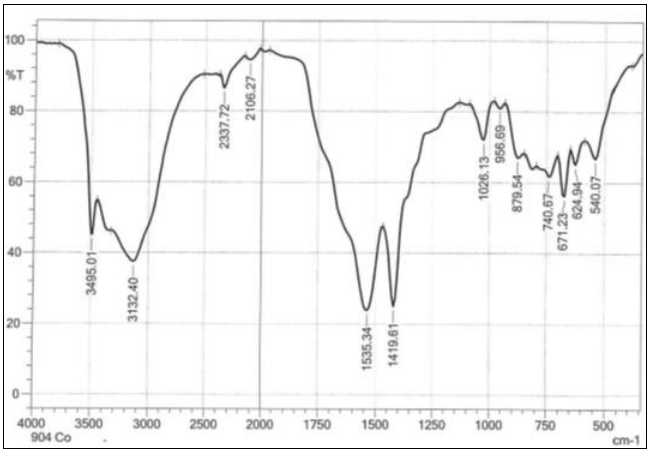


Fig 4: IR spectrum of Ni (II) complex of α-acetyl-γ-butyrolactone

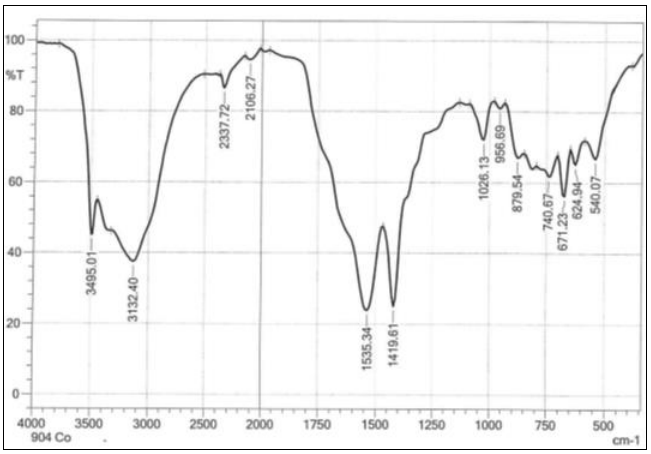


Fig 5: IR spectrum of Co (II) complex of α-acetyl-γ-butyrolactone

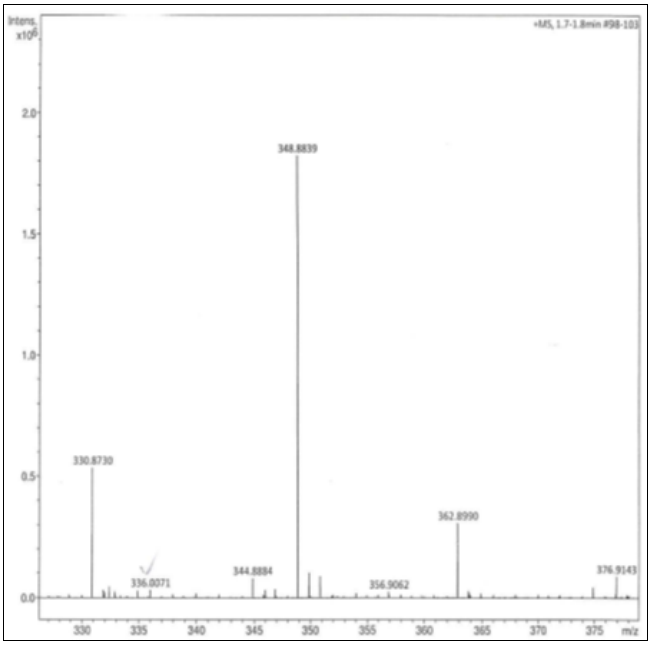


Fig 6: Mass spectrum of Ni (II) complex of α-acetyl-γ-butyrolactone

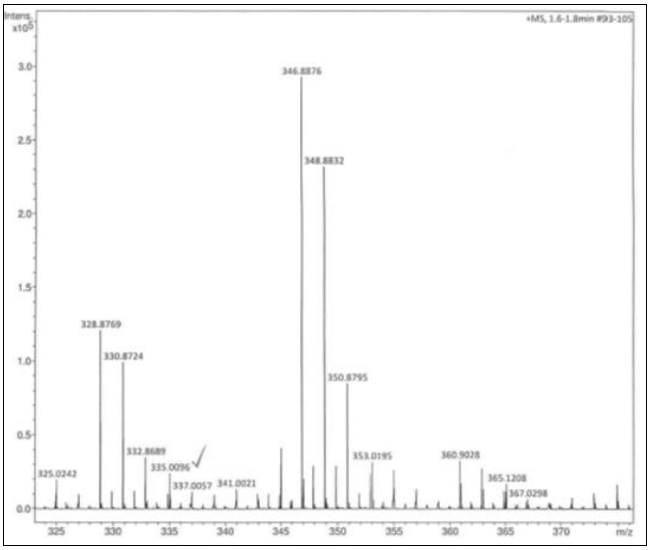


Fig 7: Mass spectrum of Co (II) complex of α-acetyl-γ-butyrolactone actone

3.3 Mass Spectra

The mass spectrum of the Ni (II) complex were recorded showed molecular ion peak at MS (m/z=335.8696, M^+ for Ni (II) complex $C_{12}H_{14}NiO_6$, 312.93 +22.989(Na) =335.919 which agrees with molecular weight of the Ni (II) complex 317. (Fig.6). The mass spectrum of the Co (II) complex were recorded showed molecular ion peak at MS (m/z=336.00, M^+ for Co (II) complex $C_{12}H_{14}CoO_6$, 313.17+22.989(Na) =336.159 which agrees with molecular weight of the Co (II) complex. (Fig.7)

3.4 Electronic Spectra Ni & Co

The spectra of complex shows shifting in wavelength. The Ni (II) complex shows stretching at 203 nm,335 nm,380 nm and 665 nm which indicates $1A_{1g} \rightarrow {}^1A_{2g}$ and ${}_1A_{1g} \rightarrow {}^1B_{1g}$ transitions in metal complex; which is a feature of square planar geometry [19-22] Fig. 8. The electronic spectra of Co (II) complex shows the bands at 295 nm,400 nm and 570 nm which were assigned to ${}^4T_{2g} \rightarrow {}^4T_{1g}$ and ${}_4T_{2g} \rightarrow {}^4A_{2g}$ C.T. transitions. These transitions are accordance with square planar geometry [19-22] fig. 9

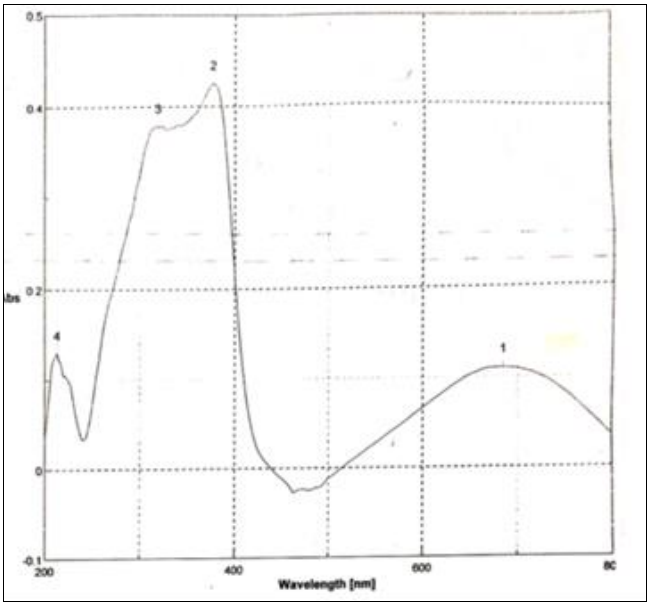


Fig 8: UV Ni (II) complex of α-acetyl-γ-butyrolactone

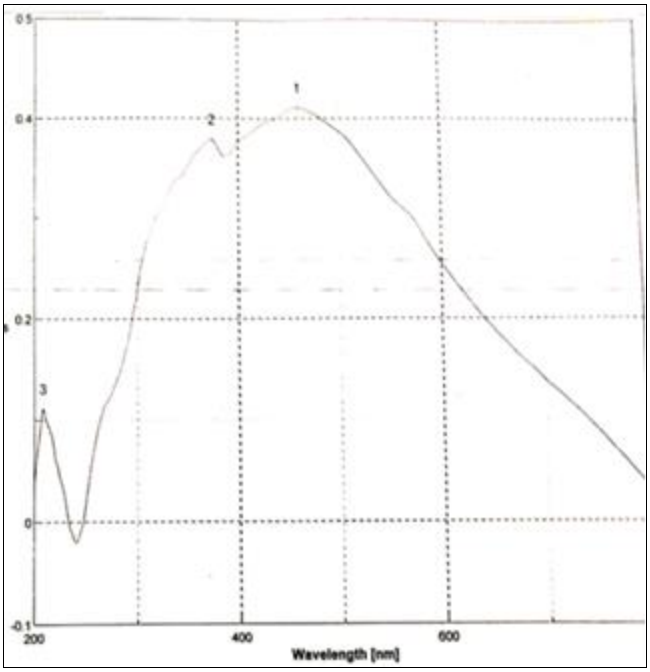


Fig 9: UV Co (II) complex of α-acetyl-γ-butyrolactone actone

4. Biological Activity

4.1 Antimicrobial Assay

The antimicrobial assay evaluation of the recently synthesized 3-aminothiophene-2-carboxylate derivatives was done using agar well plate method [40]. The antibacterial and antifungal assays were performed in Muller-Hinton broth and Crazek Dox broth [40]. The standard strains used for the antimicrobial assay was procured from Microbial Culture Collection, Pune, India.

Antimicrobial evaluation was performed using the bacteria reseeded in Muller-Hinton broth for 24 hr at 37ºC and fungi reseeded in Crazek Dox broth for 48 hr at 25ºC. The antibacterial activity of tested samples were studied in triplicate against gram positive bacteria *Staphylococcus aureus* (ATCC 29737) and gram negative bacteria

Escherichia coli (ATCC 25922). The same samples were tested for antifungal activity in triplicate against *Candida albicans* (MTCC 277) and *Aspergillus niger* (MCIM 545). The compounds were dissolved in DMSO at desired concentrations of 40, 20, 10 µg/ mL. DMSO was loaded as negative control. Gentamicin (10 µg/ mL) and Fluconazole (20 µg/ mL) were used as standards for evaluating the antibacterial and antifungal activity. The zone of inhibition (mm) was determined from the diameter of the zone of inhibition using calliper. The lowest concentration that showed invisible growth after spot subculture was considered as Minimum Inhibitory Concentration (MIC µg/mL) value for each sample after 24 hr incubation period at 37ºC. (MIC µg/ mL) value for each sample were determined using MH agar plates by pouring the molten agar in unique sized petri dishes as per National Committee for Chemical Laboratory Standards (NCCLS, M7-A5, January 2000).

The Ni (II) and Co (II) Complex showed moderate antibacterial activity against Gram positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* with MIC 40 µg/mL when compared with standard drug Gentamicin (10 µg/mL). (Table 2)

Table 2: Antimicrobial activity of complexes- *Zone of inhibition (mm*)

Comp. No.	Conc. (µg/ml)	*Zone of Inhibition (mm)*			
		S. aureus	***E. coli***	***A. niger***	***C.albicans***
		ATCC 25923	**ATCC 25922**	**MCIM 745**	**MTCC 277**
Ni (II) Complex	80	21 ± 0.7	23 ± 0.6	25 ± 0.7	29 ± 0.8
	40	19 ± 0.9	20 ± 0.8	21 ± 0.3	26 ± 0.5
	20	17 ± 0.2	17 ± 0.3	17 ± 0.5	21 ± 0.7
Co (II) Complex	80	19 ± 0.8	20 ± 0.4	27 ± 0.7	26 ± 0.3
	40	16 ± 0.7	17 ± 0.7	24 ± 0.4	23 ± 0.6
	20	12 ± 0.3	14 ± 0.5	21 ± 0.2	20 ± 0.3
DMF		09 ± 0.4	10 ± 0.3	10 ± 0.6	11 ± 0.3
Gentamicin	10	21 ± 0.7	24 ± 0.5	-----	-----
Fluconazole	20	-----	-----	23 ± 0.4	26 ± 0.6
Gentamicin (10 µg/ mL) and fluconazole (20 µg/ mL) Inhibition Zone = 8-13 mm: slight activity, 14-19 mm: moderate activity, >20 mm: excellent activity					

Table 3: Antimicrobial activity of complexes- *Minimum Inhibitory Concentration (MIC*-µg/ml)

Comp. No.	***Minimum Inhibitory Concentration (MIC*-µg/ml)**			
	S. aureus	***E. coli***	***A. niger***	***C.albicans***
	ATCC 25923	**ATCC 25922**	**MCIM 745**	**MTCC 277**
Ni (II) Complex	40	40	40	20
Co (II) Complex	40	40	20	20
Gentamicin	10	10	-----	-----
Fluconazole	-----	-----	20	20
Gentamicin (10 µg/ mL) and fluconazole (20 µg/ mL), MIC in µg / mL) = 20 µg / mL: excellent activity; 40 µg / mL: moderate activity; 80 µg / mL: slight activity				

Similarly, the Ni (II) Complex showed excellent antifungal activity against *Candida albicans* with MIC 20 µg/mL and moderate antifungal activity against *Aspergillus niger* with MIC 40 µg/mL on comparison with standard drug Fluconazole (20 µg/mL). The Co (II) Complex showed excellent antifungal activity against *Aspergillus niger* and *Candida albicans* with MIC 20 µg/mL on Similarly, the Ni(II) Complex showed excellent antifungal activity against *Candida albicans* with MIC 20 µg/mL and moderate antifungal activity against *Aspergillus niger* with MIC 40 µg/mL on comparison with standard drug Fluconazole (20 µg/mL). The Co (II) Complex showed excellent antifungal activity against *Aspergillus niger* and *Candida albicans* with MIC 20 µg/mL on comparison with standard drug Fluconazole (20 µg/mL). (Table 3)

Statistical Analysis

The standard deviation value was calculated using ANOVA method and expressed in terms of ± SD. It has been observed that differences below 0.0001 levels ($p \leq 0.0001$) were considered as statistically significant [23].

5. Conclusion

The novel Nickel (II) and Cobalt (II) complexes of α-acetyl- γ- butyrolactone were synthesized as a ligand and were well characterized using various analytical tools viz. IR,UV, HRMS, elemental analysis, EDS These complexes were tested for Antimicrobial activity activities by agar disc diffusion method and showed truly biological activities, showed comparable activity with standard used.

6. Acknowledgement

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