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Der Pharmacia Sinica, 2012, 3 (2):239-248

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Synthesis and antioxidant activity of Metal (II) complexes of isocoumarin derivatives

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ABSTRACT

The copper (II), cobalt (II) complexes of 4-alkyl-isocoumarin-3-carboxylic acid,4-alkyl-3-aroyl-isocoumarin has been synthesized and characterized by elemental analysis, thermal analysis followed by IR Spectra. Mononuclear structure for the complexes with isocoumarin derivatives and two water ligands per metal (II) ion is presented with the help of possible data. A study of antioxidant activity of cobalt and copper complexes of isocoumarin derivatives are reported here. Finally the metal ligand binding mode in the new Cu(II), Co(II) complexes of isocoumarin derivative is elucidated, and metal (II) complexes with isocoumarin ligands represent a novel class of antioxidant agents which deserves further attention to be used as bioactive agents.

Keywords: Isocoumarin, 3-carboxylic acid, 4-alkyl-3-aroyl isocoumarin, metal complexes, antioxidant activity.

INTRODUCTION

Oxygen heterocyclic compounds[1] specially coumarin / isocoumarin, has stimulated interesting research in biology, medicine and is found to be associated with diverse pharmacological activities, due to this reason these derivatives are of interest and have maintained important position in biological world[2-8].

Metal complexes play an essential role in agriculture, pharmaceutical and industrial chemistry[9]. The used metal complexes as therapeutic agents for treatment of different diseases have been extensively studied[10-14]. As they generally have different mechanism of activity from the organic compounds, the development of metal complexes provides an alternative route of novel drug[15].

Many researchers have proved that binding of a drug to metalloelement enhances its activity and in many cases the complex posses even more significant activity than the parent compound[16]. A number of coumarins have been investigated for complexing ability. In some cases metal complex of coumarins obtained revealed higher biological activity then their ligand.[17] This has motivated us to study metal binding properties of isocoumarin derivatives with different metal (II) ion and so its biological activity.

To the best of our knowledge and available literature on the subject no work appears to be done in the above field i.e having metal complex isocoumarin ligand.

The investigation of the binding properties of coumarin derivatives to different metal ions could help in understanding its isomer isocoumarin binding properties and factors controlling their biological activity[18]. 4-alkyl-isocoumarin-3-carboxylic acid and 4-alkyl-3-aroyl isocoumarin has been used rarely as a ligand in complexation reaction with copper (II), cobalt (II).The starting compound for this complexes were prepared by reported method in

our laboratory [19-20]. The mode of bonding of the ligand to Cu (II), Co(II) was elucidated by recording the IR spectra of complexes and compared with those of free ligand.

The biological studies of these complexes highlighted the potential of metal (II) complex with bioactive ligand as anti-oxidant activity. Ligands for the complexes were synthesized by condensing o-acetyl benzoic acid, bromoacetophenone / bromoacetyl malonate in presence of anhydrous K_2CO_3 in ethyl methyl ketone, which has previously been used in our earlier work[19-20]. Here we have co-ordinated different isocoumarin derivatives with cobalt (II), copper (II) ions, followed by IR, TGA interpretation.

Based on IR data and TGA analysis it was proposed that Cu & Co complexes are mononuclear with binding through carboxylate oxygen/carbonyl oxygen of two ligands and two water molecules, thus each metal atom is coordinated by 4 oxygen atom of ligands and two oxygen atoms from water at its apex forming a distorted octahedron geometry.[17]

MATERIALS AND METHODS

Chemistry

The reagents and the solvents used in this study were of analytical grade and were used without further purification. Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel GF254. IR were recorded on FTIR Perkin Elmer spectrophotometer. All the compounds gave satisfactory elemental analysis. 4-Methyl – isocoumarin-3-carboxylic acid[20] **1** and 4-Methyl-3-(4'-hydroxy-benzoyl) isocoumarin[19] **4** were prepared by literature method.

General procedure for the synthesis of 4-Methyl - isocoumarin-3-carboxylate metal (II) complex ***2-3 (Scheme I)***

4-Methyl isocoumarin-3-carboxylic acid (0.1g, 0.0005 mole) was dissolved in hot methanol by adding very dilute NaOH solution (1 ml, 0.001M) and stirred using magnetic stirrer for 5-10 minutes.$CoCl_2$ (0.02g, 0.00025 mole) salt was dissolved in hot methanol separately and added drop wise to ligand solution over 10 minutes, complex precipitates immediately and the solution was allowed to stir for 3 hours more. The precipitates formed were filtered and washed thoroughly with hot methanol and dried in air. The yield of the reaction was about 60.00%

General procedure for the synthesis of 4 – Methyl - 3-(4'-hydroxy-benzoyl) isocoumarin metal (II) complex ***5 (Scheme II)***

4-Methyl-3-(4'-hydroxy-benzoyl) isocoumarin (1.0g, 0.0035 mole) was dissolved in hot methanol by adding very dilute NaOH solution (1 ml,0.001 M) and stirred using magnetic stirrer for 5-10 minutes. $Cu(NO_3)_2$ (0.0458g,0.00025 mole) salt was dissolved in hot methanol separately and was added drop wise to ligand solution over 10 minutes, complex precipitates formed immediately and the solution was allowed to stir for 3 hours more. The precipitates obtained were filtered and washed thoroughly with hot methanol and was dried in air. The yield of the reaction was about 55.40%

Antioxidant Activity

Antioxidant activity was tested by estimating scavenging activity for nitrous oxide using Griess reagent[21] by test compounds.

2.0 ml of sodium nitroprusside (10 mM) in 0.5ml phosphate buffer pH 7.4 was incubated with 0.5 ml, 1000 ppm concentration of test compounds dissolved in a suitable solvent (DMSO) and tubes were incubated at 25^0C for 150 min. Control experiment was conducted with equal amount of solvent in an identical manner. After 150 mins, 1.0 ml of incubation solution was taken and diluted with 4.0 ml of Griess reagent (1.0 ml 1% sulfanilamide, 1.0 ml 5% o-phosphoric acid and 2.0 ml 0.1% N-naphthylethylenediamine dihydrochloride dissolved in distilled water). The absorbance of the chromophore formed during diazotization of nitrite with sulfanilamide and subsequent N-naphthylethylenediamine dihydrochloride was read at λ 546 nm after 30 mins. The experiment was repeated in triplicate. % NO scavenging was calculated using the following equation:

$$\% \text{ NO scavenging} = \frac{A_{control} - A_{test}}{A_{control}} \times 100$$

The results are given in Table III.

RESULTS AND DISCUSSION

The reaction of copper(II), cobalt(II) with isocoumarin 3-carboxylic acid afforded a bluish green, pink coloured complex respectively (**Scheme I**) and isocoumarinoyl derivative with Cu (II) form green complex (**Scheme II**) which were found to be quite stable in both solid state and in solution. All the complexes were insoluble in water but comparatively soluble in DMSO/DMF solvent, while the cobalt complex was found to be water soluble. The complexes formed does not show clear melting point and decompose at higher temperature (above 240^0C), which is a characteristic of complex formation. The metal estimation using gravimetry and titrimetry methods indicated the percentage of metal present in the complex, as well as ligand: metal (L:M) ratio . Experimentally, the L:M ratio found was 2:1,so it can be inferred that it is 2:1 metal complex.

The mode of bonding of ligands to M^{+2} was elucidated by recording the IR Spectra of the complexes as compared with free ligand.

The IR Spectra were recorded on solid state in KBr pellets in the range of 3800-400 cm^{-1} .A broad band characteristics of OH stretch of coordinated water was observed in the range of 3300-3450 cm^{-1},in the spectra of complexes (Fig. 2,3,7) .

Depending on the orientation of the two donor group C=O & COO^- in complexes **2,3**,**5**, difference in binding of the anions of isocoumarin – 3- carboxylic acid and 3- aroyl isocoumarin was found to be possible. Coordination of metal ion was confirmed through carbonyl oxygen and the carboxylate oxygen. (Scheme I & II)

In the IR Spectra of almost all the complexes the C=O stretching vibration associated with the carboxylate and carbonyl functional group of the ligand was shifted to a lower wavelength compared to that in the corresponding free ligand (Fig. 1) indicating that coordination to the M(II) ion has occurred via carbonyl oxygen and carboxylate oxygen (Table II). The C=O stretching vibration of the carbonyl function in the lactone ring of the free ligands appeared as a strong sharp band in the range 1683-1700 cm^{-1} (Fig. 6).In the spectrum of complexes **2** & **3**, the position of the band remained largely unchanged, suggesting that the lactone carbonyl oxygen is not involved in coordination to the metal where as in complex **5**, band shows sharp shift in IR showing involvement of lactone in complex formation.

Several new bands present in region of 510-600 cm^{-1} for **2**, **3** & **5** complexes were assigned to M-O stretching vibrations.

Upon complexation of **5**, the phenolic C-O stretching vibration change was not significant; suggesting that coordination of this oxygen atom is not involved in complexation (Scheme II) (Fig. 6).

Thermo gravimetric Analysis of Complexes

The thermo gravimetric curves of the complexes **2** & **3** are shown which indicate the water content of the complex.TGA shows presence of two water molecules per metal ion which are lost in one step process at relatively high temperature (160^0 - 190^0C,) (Fig. 5).This confirms that the two water molecules are coordinatively bonded to the metal ions with strong H-bond network holding water molecules in lattices.

The dry compound which is stable in small temperature range was the carbonates of the metal ion, which were not further decomposed. The TGA of ligand showed 82% of ash content after complete decomposition as shown in Fig. 5. Considering this into account, the experimental value found for the residue in complexes is equal to 24%, corresponds to the theoretical value. With the above discussion we propose the structure for complex **2** & **3** as shown in Scheme I consisting mononuclear molecule in which one copper atom **2** and cobalt atom **3** is joined with two carboxylic group of the isocoumarin – 3- carboxylic acid ligand and is also bonded to two water molecules. Thus, each copper and cobalt atom is co-ordinated by four oxygen atoms lying on its plane and the water oxygen atoms on its apex. Hydrogen bonded network could account for insolubility of complex. Again in 5 (Scheme II), copper atom is coordinated by aroyl carbonyl group, lactone and is bonded with two water molecules of 4-alkyl-3-aroyl isocoumarin ligand justifying the structure.

Structure Activity Relationship

Antioxidant activity of complex **2**, **3 & 5** was compared with ligand **1** & **4**. Cu and Co complexes where complexation was done via carboxylate was found to be excellent. Significant activity was found in both metal (II) complexes. However, where complexation was done via aroyl carbonyl **5**, activity was reduced; even it was less than ligand **4**. Here, complexation of metal ion with the carboxyl group of the ligand plays an important role than complexation with aroyl carbonyl (Table III).

Table I Physical data of Synthesised Compounds

Compound	Mol. Weight	Mol. formula	C (cal)	H (cal)
2	505.00	$C_{22}H_{18}CuO_{10}$	52.44 (52.27)	3.91 (3.56)
3	500.93	$C_{22}H_{18}CoO_{10}$	52.39 (52.80)	3.63 (3.60)
5	660.00	$C_{34}H_{28}CuO_{10}$	61.86 (61.81)	3.99 (4.24)

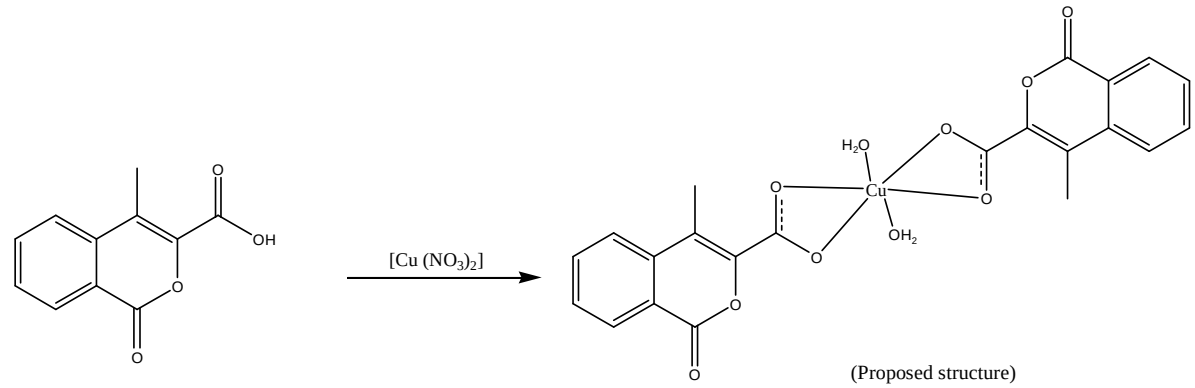
Table II Characterisation Data of Synthesised Transition Metals (II) Complexes

Comp.	IR (cm^{-1})	UV Absorption maxima(nm)	Metal Estimation		
			Theoretical	Obtained	Inference
1	1700 (C=O), 1736 (acid carbonyl), 3533 (-OH)	290	-	-	-
2	1653 (C=O), 1683 (acid carbonyl), 3435 (-OH), 516(M-O)	310	12.02	13.00	2:1 L:M Ratio
3	1630 (C=O), 1688 (acid carbonyl), 3239 (-OH), 610(M-O)	330	11.76	10.29	2:1 L:M Ratio
4	1650 (C=O), 1735 (Ketone carbonyl), 3600 (-OH)	310	-	-	-
5	1500(C=O), 1600 (Ketone carbonyl), 3200-3500 (-OH), 500 (M-L)	410	10.00	11.00	2:1 L:M Ratio

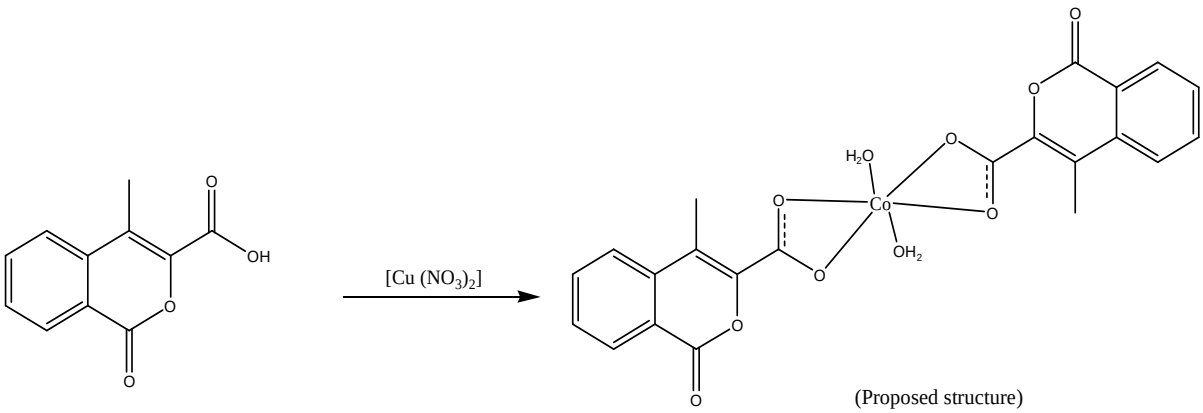
Table III Antioxidant activity Metal (II) Complexes

Compound	Absorbance	%NO Scavenging
1	-0.0085	109.60
2	-0.1811	309.00
3	-0.2483	381.20
4	-0.1604	155.04
5	-0.1885	146.84

Scheme I

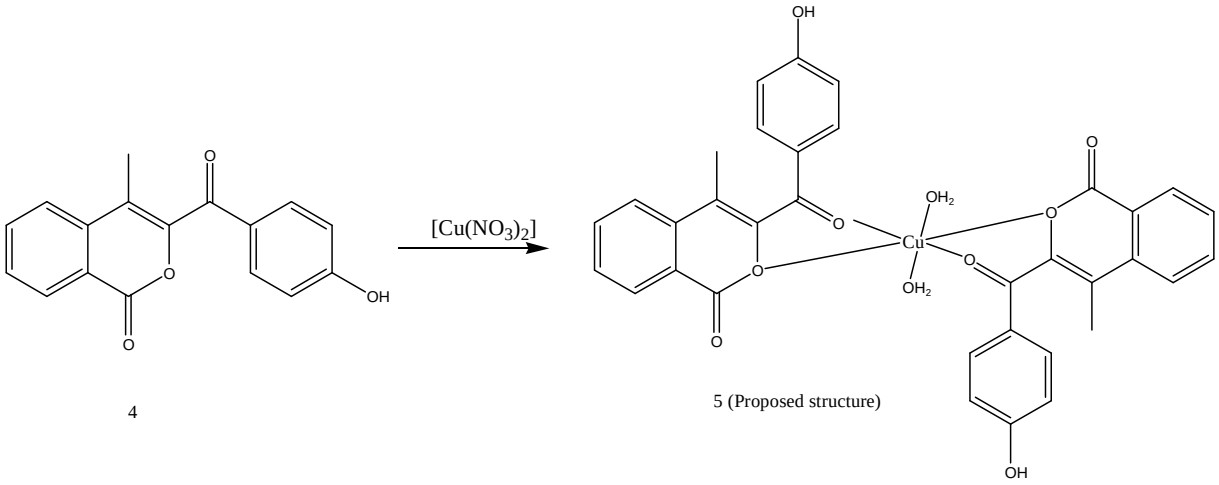


1 2 (Proposed structure)



1 3 (Proposed structure)

Scheme II



4

5 (Proposed structure)

Fig. 1 - IR: Ligand 1

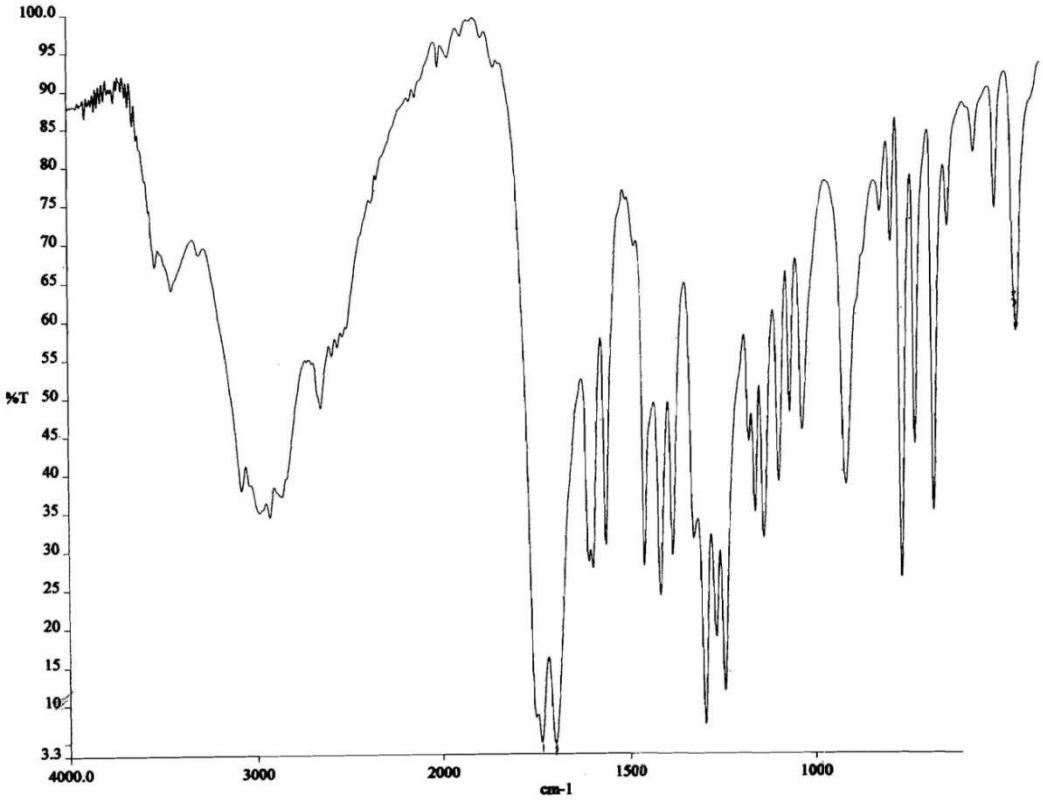


Fig. 2 - IR: Complex 2

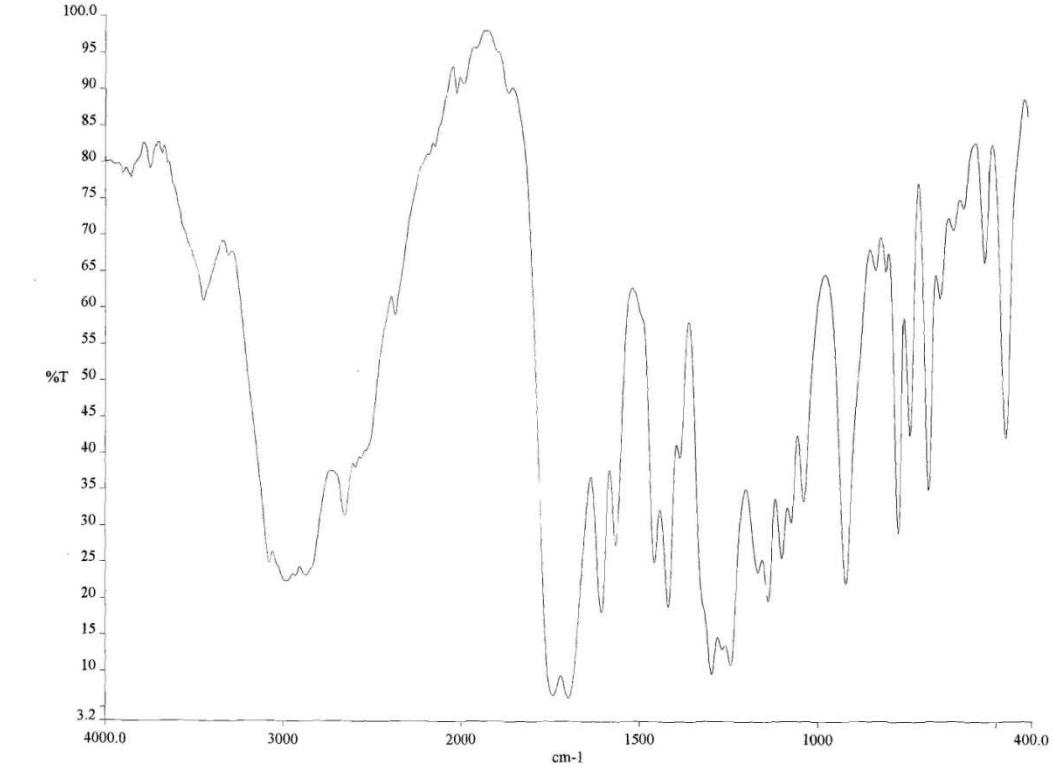


Fig. 3 - IR: Complex 3

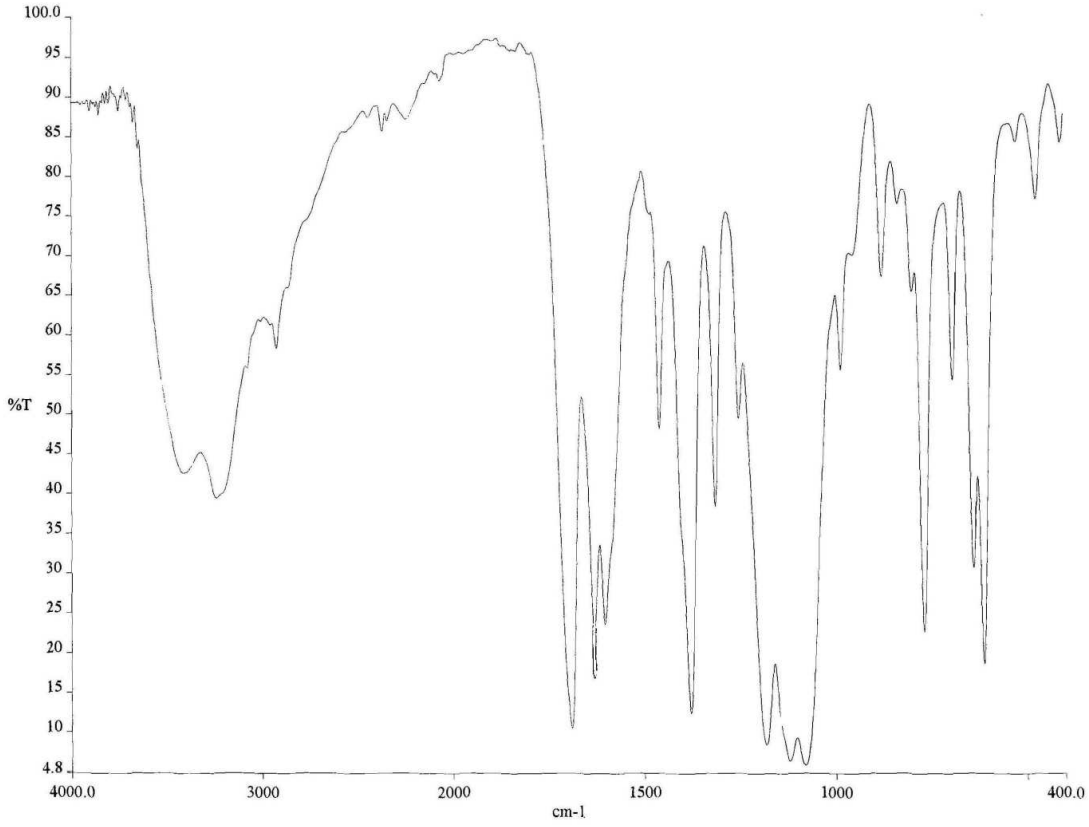


Fig. 4 - Thermogravimetric curve: Ligand 1

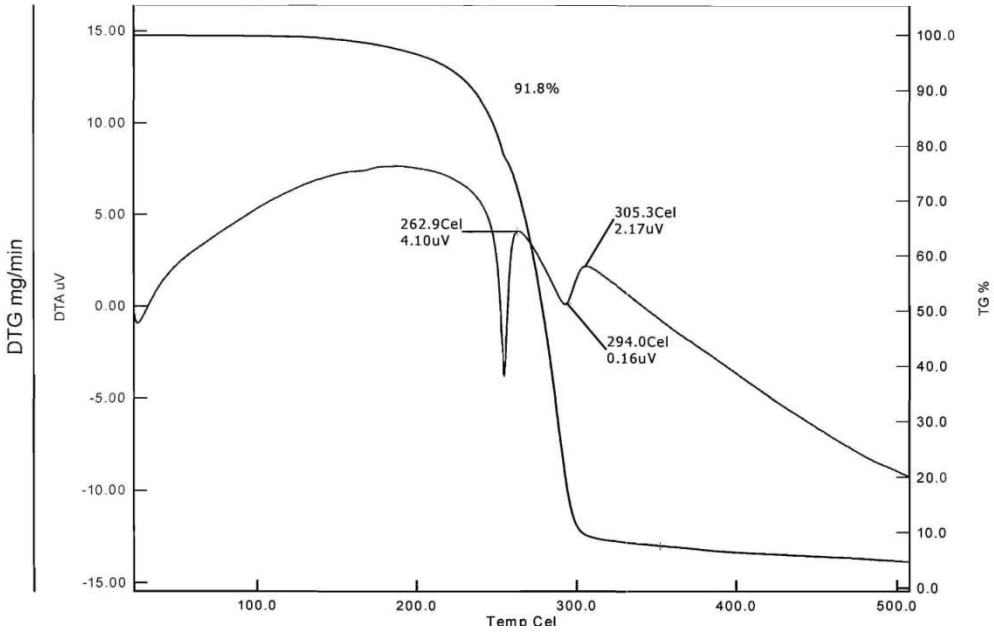


Fig. 5- Thermogravimetric curve: Complex 2

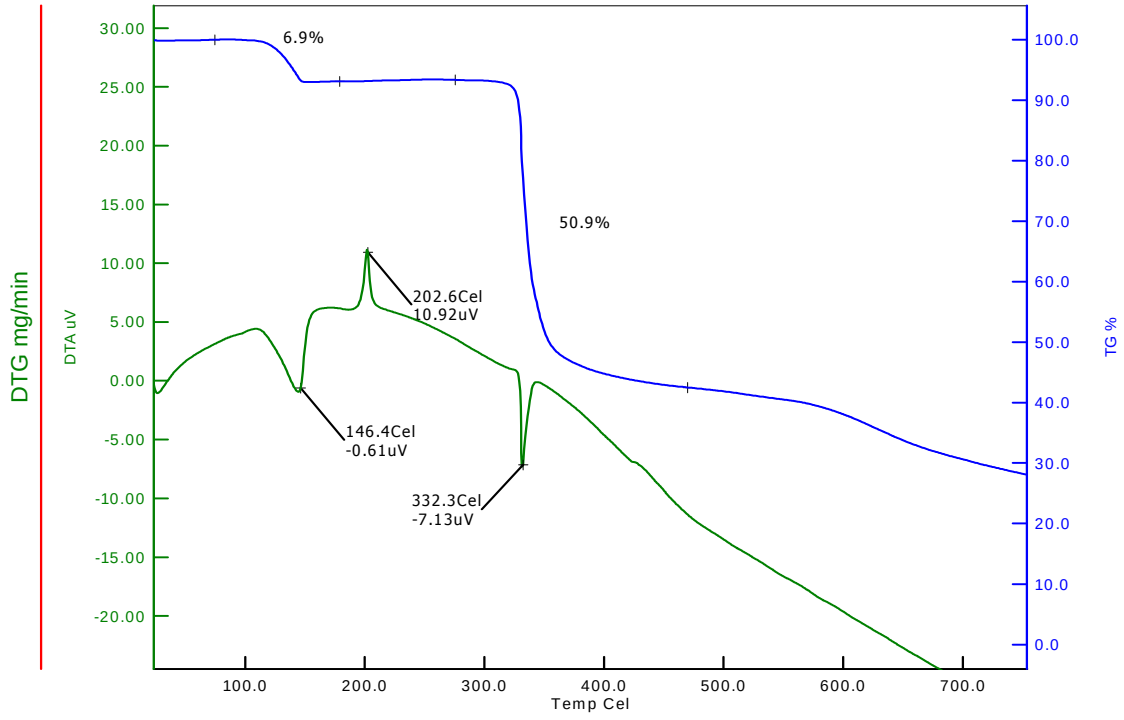


Fig. 6 - IR: Ligand 4

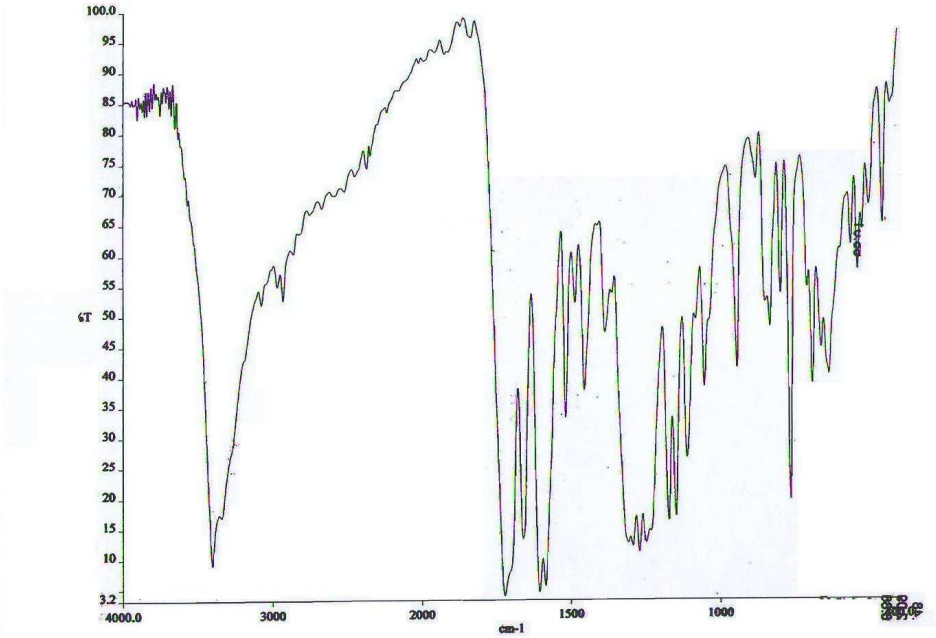


Fig. 7 - IR: Complex 5

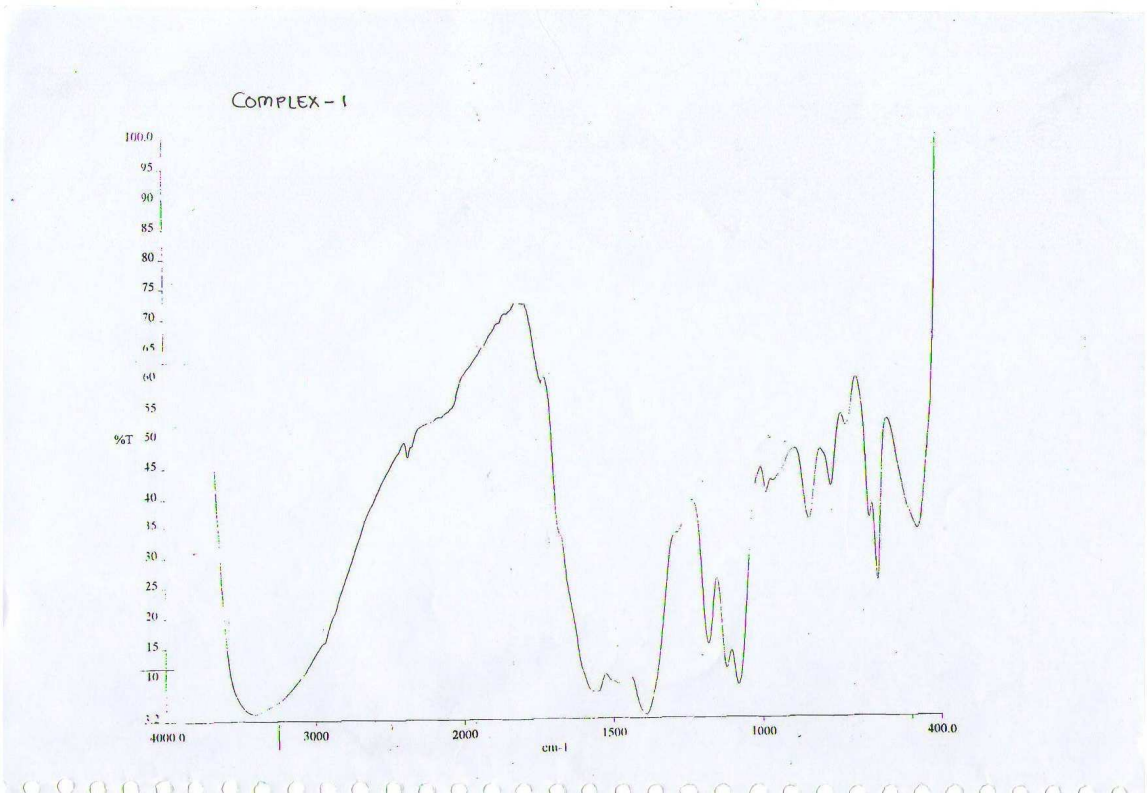


Fig. 8 - Thermogravimetric curve: Ligand 4

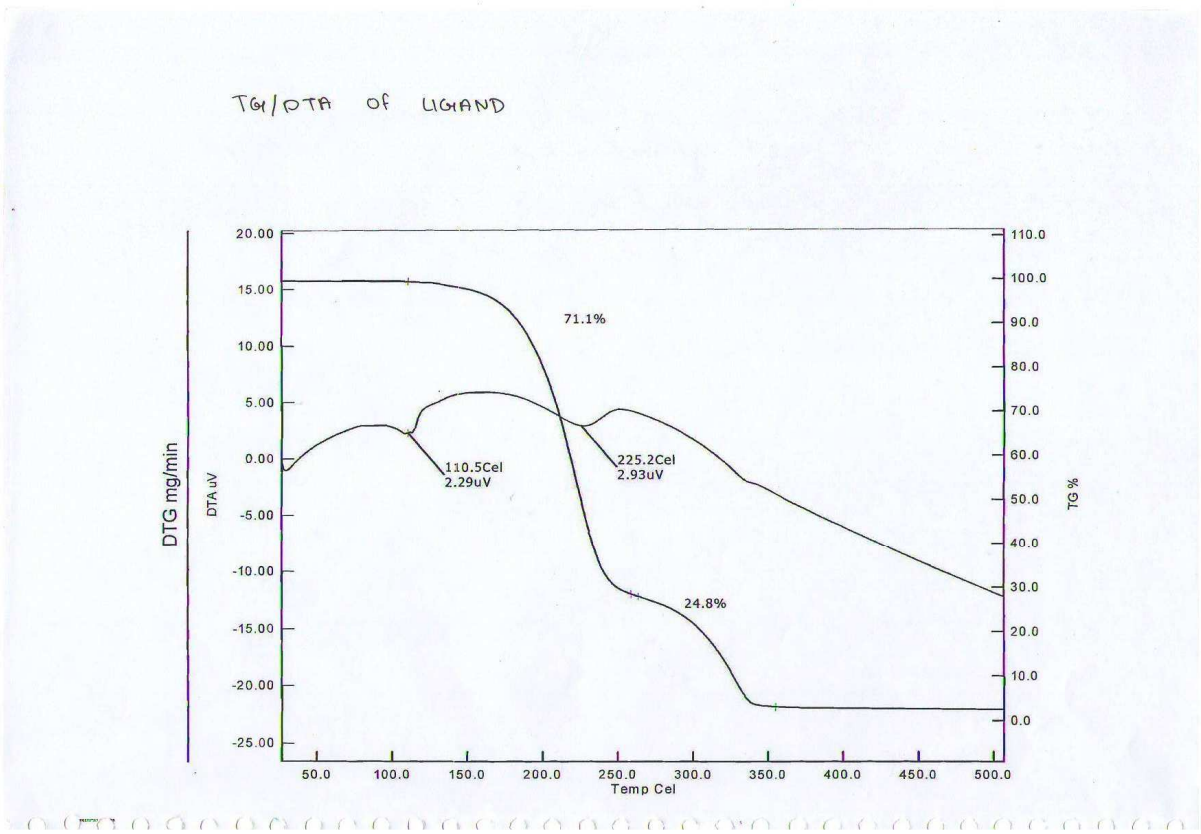
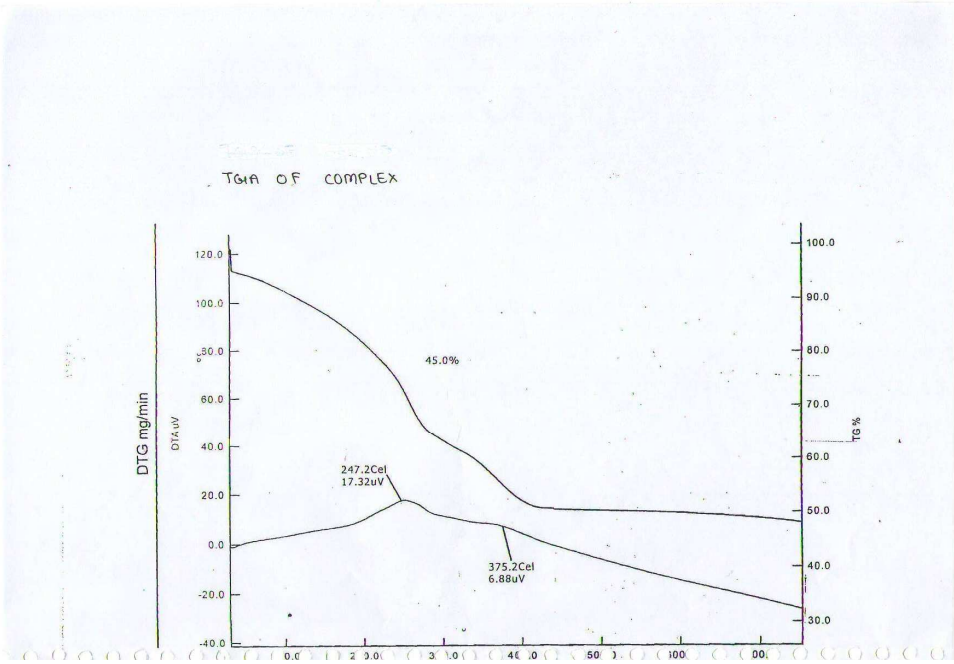


Fig. 9 – Thermogravimetric curve: Complex 5



CONCLUSION

In conclusion, we have synthesized metal (II) complexes of 4-alkyl - isocoumarin – 3- carboxylic acid **2** & **3** and 4 – alkyl – 3- aroyl isocoumarin **5**. Metal complexes of isocoumarin derivatives obtained revealed higher biological activity than the corresponding ligands.

Acknowledgement
Authors are grateful to The Head, Department of Chemistry, The M. S. University of Baroda, Gujarat, for providing all the facilities to carry out this research work.

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