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Synthesis of some Novel Metal Complexes of 4-Hydroxy Benzopyran-2-Ones as Antimicrobial Agent

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Abstract

Complexes of 3-[{3-(3'-bromo phenyl)}-prop-2-enoyl]-4-hydroxy-6-methyl-2*H*-chromen-2-one with Cu(II), Ni(II), Fe(II), Co(II) and Mn(II) have been synthesized and characterized using elemental analysis, IR spectra and conductivity measurements. These studies revealed that they are having octahedral geometry of the type $[ML_2 (H_2O)_2]$. *In-vitro* antimicrobial activity of all synthesized compounds and standard drugs have been evaluated against four strains of bacterial culture and one fungus, which includes two gram +ve bacterial culture and two gram -ve bacterial culture, which show net enhancement in activity on co-ordination of metals with ligand but moderate activity as compare to standard drugs.

Keywords: Antimicrobial activity; Coumarin; Metal complexes; Structural study

Introduction

Coumarins contain the parent nucleus of benzo - α - pyrone and occur in plants of the families like Orchidaceae, Leguminaceae [1], Rutaceae, Umbellli-ferae and Labiatae. Some of the coumarins show distinct physiological photodynamic and bacteriostatic activities and placed for many diverse uses [2]. Their chelating characteristics have long been observed and the bacteriostatic activity seems to be due to chelation.

The complexes of metallic salts are more potent and less toxic in many cases as compared to the parent drug [3]. These metal complexes are found to be interesting due to their biological applications like antifungal [4], antibacterial [5] and anti tumor [6] activity.

Some chalcones derived from coumarin derivatives, possess significant antimicrobial activity [7]. Some 3-acetyl/acetoacetoacetyl-4-hydroxy benzopyran-2-ones have been reported as an anti-HIV agent [8]. So it was thought worthwhile to synthesize various novel metal complexes and to evaluate them for antimicrobial activity.

Materials and Methods

Some new chalcones(III) were synthesized by condensation of 3-acetyl 4-hydroxy-6-methyl-coumarin (II) with different aromatic aldehyde and it's metal complexes(IVa-e) have been prepared by refluxing metal salt solution and the alcoholic solution of ligand (III) in basic media. All the reactions are given in Figure 1.

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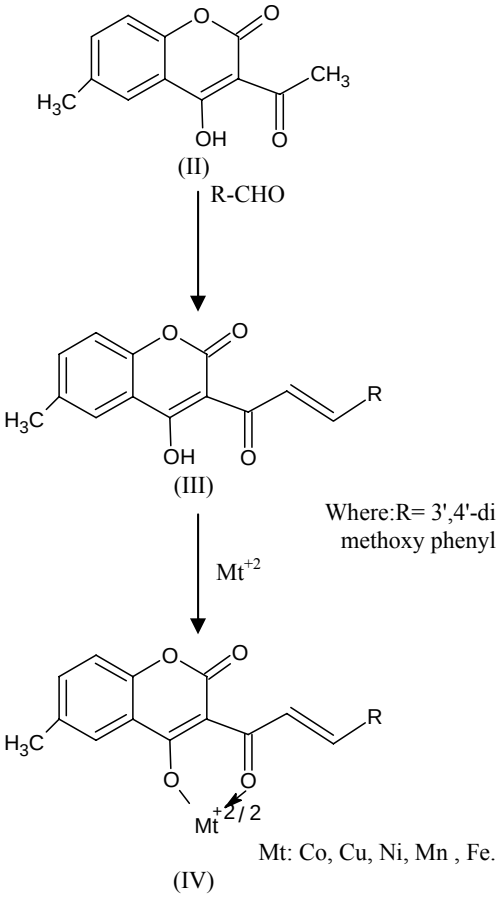

Figure 1.
Bis-(3-[{3-(Aryl substituted)}-prop-2-enoyl]-4-hydroxy-6-methyl-2H-chromen-2-one)Mt(II) complex
IVa : $Cu[L_2(H_2O)_2]$
IVb : $Ni[L_2(H_2O)_2]$
IVc : $Co[L_2(H_2O)_2]$
IVd : $Fe[L_2(H_2O)_2]$
IVe : $Mn[L_2(H_2O)_2]$

Experimental Protocols

Chemistry

All the reagents were of AR grade. All the melting points were determined in open capillary tubes and are uncorrected. Infrared spectra (KBr)(max, cm^{-1}) were recorded on a Shimadzu 435 –IR Spectrophotometer. The metal and anions are estimated using standard procedure [9]. Elemental analyses are quite comparable with their structure. Elemental analyses of metal complexes indicates that the metal: ligand (M:L) ratio is 1:2 for all the divalent metal ions. The conductivity of metal complexes was determined using Thoshniwal Conductivity Bridge.

3.1.1. 3-[{3-(3'-bromo phenyl)}-prop-2-enoyl] -4-hydroxy-6-methyl-2H-chromen-2-one (III).

This compound was prepared according to the reported method [10].

A mixture of 3-acetyl-4-hydroxy-6-methyl coumarin (2.52 g, 0.01 mole); 3'-bromo benzaldehyde (0.025 mole) and piperidine (1 ml) were added into ethanol (50 ml). The reaction mixture was refluxed on water bath for 4 h, cooled and solid was separated. Then it was crystallized from suitable solvent, reddish yellow coloured compound was obtained yield 74%, m.p. 210°C. Found: C, 54.22%, H, 3.37%, Br,20.77% for $C_{19}H_{13}O_4Br$ required C, 54.10%, H, 3.22%, Br,20.68%.

3.1.2. Bis [3-[{3-(3'-bromo phenyl)}prop-2-enoyl] 4-hydroxy-6-methyl-2H-chromen-2-one] copper(II) complex $[Cu(C_{19}H_{12}O_4Br)_2(H_2O)_2]$ (IVa)

Copper chloride solution (10.0 ml., 0.1 mole) diluted to 50 ml. and excess of ammonium hydroxide was added to get the pH between 10.5-11.0. It was refluxed with excess of alcoholic solution of 3-[{3-(3'-bromophenyl)} prop-2-enoyl]4-hydroxy-6-methyl-2H-chromen-2-one (a) (0.1mole) on a water bath for half an hour when *cinnamon brown* precipitates of copper complex were obtained. The precipitates were filtered, washed with distilled water and dried at 100°C. The complex was crystallized from DMF (ethanol). Yield: 63% Found: C,52.56%, H, 3.22%, Cu, 7.32% for $[Cu(C_{19}H_{11}O_4Br)_2(H_2O)_2]$ required C, 52.50%, H, 3.16%, Cu, 7.25%.

Similarly other metal complexes were prepared. The complexes did not show clear melting point. They charred at temperature above 290°C.

3.2. Conductivity

The conductivity of metal complexes was determined using Thoshniwal Conductivity Bridge. It was dissolved in DMF and conductivity was measured.

Conductivity of the DMF along was measured and solution of the complexes in DMF with different concentration was measured.

The molar conductivity was calculated using the formula.

$$\text{Molecular conductivity} = \frac{1000 \times K}{C}$$

Where, K = Conductivity of the sol. of the complexes in DMF. C = Concentration of the complexes (10^{-3} M). The conductivity data are presented in (Table 1) and the data indicates that the complexes are non-electrolyte in nature [11].

Table 1. Elemental and metal analysis of metal (II) complexes

Sr.	Molecular Formula	Mole.	% of Carbon		% of Hydrogen		% of Bromine		% of Metal		Conductivity
		Weight	*Calcd.*	*Found*	*Calcd.*	*Found*	*Calcd.*	*Found*	*Calcd.*	*Found*	
IVa	$Cu[C_{19}H_{12}O_4Br]_2(H_2O)_2$	867.54	52.56	52.40	3.22	3.10	18.24	18.10	7.32	7.20	7.50
IVb	$Ni[C_{19}H_{12}O_4Br]_2(H_2O)_2$	864.71	52.73	52.60	3.23	3.10	18.50	18.30	6.78	6.60	9.10
IVc	$Co[C_{19}H_{12}O_4Br]_2(H_2O)_2$	864.93	52.72	52.60	3.23	3.10	18.49	18.30	6.81	6.70	8.90
IVd	$Fe[C_{19}H_{12}O_4Br]_2(H_2O)_2$	859.85	53.03	52.90	3.72	3.60	18.60	18.50	6.49	6.30	11.00
IVe	$Mn[C_{19}H_{12}O_4Br]_2(H_2O)_2$	860.93	52.96	52.80	3.25	3.10	18.58	18.40	6.38	6.20	10.80

3.3. IR Spectral Analyses

The Infrared spectra of the metal complexes were recorded on Shimadzu 435-IR Spectrophotometer between 4000-400 cm^{-1}.

The examination of the IR spectra of all the complexes reveals that

(I) All the IR spectra have identical bands at their respective positions.

(II) Most of the bands appeared in the spectra of ligand are observed at the similar position in the IR spectra of metal complexes.

(III) Only the discernible difference in the IR spectra of metal complexes has been appeared. The band between 3200 - 3400 cm^{-1} due to - OH group in the spectra of ligands is less broader in the spectra of all the metal complexes. This might be due to complexation of metal ion. The less broadness might be due to water molecules associated with complex formation.

(IV) In addition the IR spectra of complexes showed new bands between 590-500 cm^{-1} assigned to metal-ligand vibration (M-O).

Pharmacology

The antimicrobial activity was assayed by Cup-plate agar diffusion method [12] by measuring inhibition zones in mm. *In vitro* antimicrobial activity of all synthesized compounds and standard drugs have been evaluated against four strains of bacteria which includes two Gram +ve bacteria such as *Staphylococcus aureus, Bacillus megaterium* and two Gram-ve bacteria such as *Escherichia coli, Proteus vulgaris* and one fungi *Aspergillus niger.* The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.04 ml (40 µg/ml) solution of sample in DMF.

The plates were incubated at 37°C for 24 h. and the control was also maintained with 0.04 ml of DMF in similar manner and the zones of inhibition of the bacterial/ fungal growth were measured in millimeter and recorded in Table 3.

The antibacterial activity was compared with standard drugs; namely, amoxycillin, ampicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug griseofulvin.

Most of the compounds inhibit the growth of the above organism, which cause diseases in many plants. Hence such type of compounds may find as agricultural and garden bactericides and fungicides.

Results and Discussion

Antimicrobial activity of the synthesized compounds and standard drugs is given in (Table 3). From the Table it is clear that the zone of inhibition area is much larger for the metal chelates than the ligand. The increase in antimicrobial activity is due to faster diffusion of metal complexes as a whole through the cell membrane or due to the combined activity effect of the metal and ligand [13].

The antimicrobial activity of tested compounds against different strains of bacteria and fungi is shown in Table 3. From Table 3 it can be concluded that all the compounds have displayed maximum activity against *P. vulgaris*. The compounds IVb and IVe are highly active against *E. coli*. The compounds IVb and IVc also showed very good activity against *B. megaterium*, while compounds IVa and IVc showed good activity against *S. aureus*. From the data of anti fungal activity it is observed that almost all the compounds are highly active against *A. niger* except compound IVc, which exhibits moderate activity.

In comparison to standard drug Ciprofloxacin the compounds are less active, while other drugs have parallel activity.

Such increased activity of the metal complexes can be explained on the basis of Overtone's concept [14] and Tweedy's chelation theory [15].

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Table 2. IR Spectral data of metal (II) complexes

Sr.	Metal complexes	Frequencies cm^{-1}						
		Alkane $-CH_3$	*Aromatic* -CH	*Ketone* -C=O	*Alkene* CH=CH	*M-O Band*	*Ether* C-O-C	*Halogen* C-Br
IVa	$Cu[C_{19}H_{12}O_4Br]_2(H_2O)_2$	2928 2834 1443 1383	1511 1249 832	1650 1710	1609	590-500	1112	785
IVb	$Ni[C_{19}H_{12}O_4Br]_2(H_2O)_2$	2920 2858 1456 1384	1562 821 1222	1697 1715	1612	590-500	1130	781
IVc	$Co[C_{19}H_{12}O_4Br]_2(H_2O)_2$	1922 2853 1460 1375	1554 1222 833	1689 1715	1584	590-500	1138	782
IVd	$Fe[C_{19}H_{12}O_4Br]_2(H_2O)_2$	2920 2850 1418 1376	1584 1223 819	1669 1710	1608	590-500	1137	778
IVe	$Mn[C_{19}H_{12}O_4Br]_2(H_2O)_2$	2933 2858 1464 1383	1562 1227 821	161 1732	1602	590-500	1072	782

Table 3. Microbiological evaluation of synthesised compounds

Organism	Compounds						Standard drugs				
	III	IVa	IVb	IVc	IVd	IVe	Ampicillin	Amoxycillin	Ciprofloxacin	Erythromycin	Griseofulvin
E. coli	18	21	18	24	22	23	16	17	26	22	0
P. vulgaris	18	20	25	19	20	22	24	21	28	18	0
B. mega	20	19	22	21	19	20	20	22	23	10	0
S. aureus	21	20	19	22	18	18	25	29	24	22	0
A. niger	19	20	24	18	19	21	0	0	0	0	21

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