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METAL COMPLEXES OF HETEROCYCLIC UNSATURATED 1, 3- DIKETONES

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ABSTRACT: The present investigation is mainly on the synthesis, characterization and anti-microbial screening of certain new curcuminoid analogues containing imidazole, pyrrole and thiophene rings and their metal complexes. The ability of such heterocyclic β-dicarbonyl compounds and their metal ions to influence many of complex reaction upon which the vital processes of micro-organisms depends is the motivation behind the work. A series of 5- hetero aryl-1-phenyl-4-pentene-1,3-diones(1a-c) and their Cu (II), Ni (II) complexes of ML_2 stoichiometry were synthesized and characterized by UV, IR, mass and ^{1}H NMR spectroscopies. Analytical and spectral data suggest neutral bidentate coordination for unsaturated diketone with metals. Anti-microbial screening was carried out by using Kirby-Bauer disc plate method. All the ligands and their metal complexes showed significant anti-microbial action. Further complexation; seem to augment the antimicrobial activity of the compounds.

INTRODUCTION: Several synthetic metal complexes which mimic the behavior of complicated bimolecules are known and at present the study of such compounds are receiving much attention. One such example is curcuminoids, the active chemical component present in traditional Indian plant *curcuma longa* (turmeric). They are 1, 3-diketones in which the diketo function is directly attached to olefinic groups. Here all efforts were made to synthesize heterocyclic analogues of such β-dicarbonyl compounds and their metal complexes.

Very few literatures were available with the use of heterocyclic aldehydes for the synthesis of curcumin related compounds [1]. Pharmacological significance of hetero rings was the reason behind selecting different heterocyclic aldehydes like imidazole-2-carboxaldehyde, pyrrole-2-carboxaldehyde and thio phene-2-carboxaldhyde as one of the reactant to condense with benzoyl acetone.

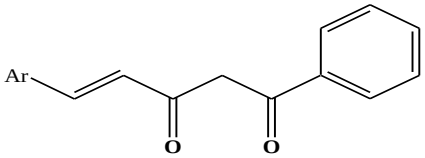
Transition metals like Cu(II), Ni(II) were used as metals for present work. The reaction proceeded via condensation of heterocyclic aldehydes with benzoyl acetone through boric anhydride mediated esterification [2]. These compounds were subjected to anti microbial tests against the test organisms; bacterial cultures *Staphylococcus aureus*, *Bacillus subtilis, Escherichia coli* and *pseudomonas aeruginosa* and fungal cultures *Candida albicans*, *Aspergillus niger* respectively.

MATERIALS AND METHODS: The chemicals required were obtained from Lancaster, Sigma and Aldrich chemical suppliers.UV spectra's were recorded in methanol solution (10^{-4}M) JASCO V-530 UV/VIS spectrophotometer.IR spectra(KBr pellets) were recorded on Schimadzu 81101A FTIR Spectrophotometer. Carbon and hydrogen percentages reported are by microanalysis and the metal percentage by using a Perkin-Elmer 2380 Atomic Absorption Spectrophotometer.

NMR on Jeol 400 NMR spectrometer,mass spectra on a Jeol/Sx-102(FAB) mass spectrometer. Micro analysis of the compounds was performed on a Perkin Elmer model 240 analyzer. Bacterial cultures *Staphylococus aureus*, *Bacillus subtilis, Escherichia coli* and *pseudomonas aeruginosa* and fungal cultures *Candida albicans*,*Aspergillus niger* were procured from National chemical laboratory,Pune.

Preparation of 5-hetero aryl-1-phenyl-4-pentene-1, 3-diones: The compounds (structure-I) were prepared by the condensation of three different heterocyclic aldehydes with benzoyl acetone as reported earlier for structurally related 5-aryl compounds [3, 4]. Benzoyl acetone (0.005 mol) mixed with boric oxide (0.005 mol) and dry ethyl acetate (5 ml) was stirred for *ca.* 1 h. The stirring was further continued for 1 h with slow addition of a solution of aromatic aldehyde(0.005) mol in dry ethyl acetate (5 mL), followed by tri-(sec-butyl)borate (0.01 mol) and N-butylamine (0.05 mL). After stirring for an additional period of *ca.*3 h. The solution was set aside overnight.

Hot *ca*.(60^{o}C) hydrochloric acid (0.4 M, 7.5 mL)was then added to the reaction mixture and again stirred for *ca* .1 h, before extraction with ethyl acetate, the washed extracts were combined, concentrated and the residual paste obtained was stirred with hydrochloric acid(2M,10 mL).The separated solid product was collected, washed with water, ethanol and dried under reduced pressure. The compounds were recrystalliized from hot benzene to get chromatographically (TLC) pure material. Structural details of 1(a-c) are presented in **table 1**.

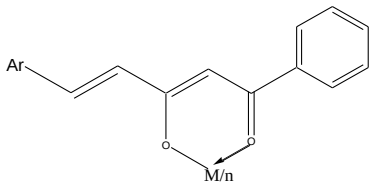


5-HETEROARYL-1-PHENYL-4-PENTENE-1, 3- DIONES (1)

TABLE 1:

Compound	Ar
1a	
1b	
1c	

Preparation of metal complexes: Cu(II), Ni(ii) chelates of diketones were prepared by the following general method [5]. To a refluxing ethanolic solution of the compound (0.002 mol, 20 mL),an aqueous solution of metal (II)acetate(0.001 mol, 5 mL) was added and the reaction mixture was refluxed for *ca*. 2 h. and the volume was reduced to half. The precipitated complex on cooling to room temperature was filtered, washed with water and dried in vacuum. The complexes were recrystalliised from hot methanol. The metal salts used were acetates of $Cu^{2+}$and Ni^{2+}.



M= Cu^{2+}, Ni^{2+} for n=2 (2)

Anti-microbial bio assay of ligands and its metal complexes: These three ligands and their metal complexes were assayed for their antimicrobial activities against six test organisms, namely, Bacterial cultures *Staphylococus aureus*, *Bacillus subtilis, Escherichia coli* and *pseudomonas aeruginosa* and fungal cultures *Candida albicans*, *Aspergillus niger*. Concentrations of 500μg/disc and 250 μg/disc were used for all the test compounds and results were compared with the standard drug ciprofloxacin (10 μg/disc) and fluconazole (20μg /disc) for anti bacterial and anti fungal screening respectively. Dimethyl formamide was used as the vehicle. The results were interpreted as per Kirby-Bauer method [6].

RESULTS AND DISCUSSION: The 5-hetero aryl-1-phenyl-4-pentene-1, 3-diones formed by above method were crystalline in nature with sharp melting points. The analytical data of ligands and their complexes were discussed here. The yield, melting points and the carbon, hydrogen percentages are presented in **Table 2**. These ligands formed stable complexes with Cu^{2+}, Ni^{2+}. They were crystalline in nature with sharp melting points. Carbon, hydrogen percentages are in agreement with ML_2 stochiometry. The electronic, IR, NMR and mass spectral data of complexes are compatible with the structure that would result when the chelated enol proton of the ligand is replaced by metal ion as in structure 2.

TABLE 2: ANALYTICAL AND PHYSICAL DATA OF 5-HETERO ARYL-1-PHENYL-4-PENTENE-1, 3-DIONES AND THEIR METAL COMPLEXES

Compound	Yield (%)	Mpt. (°C)	Elemental analysis (%) calculated (found)			λ_{max} (nm)
			C	H	M	
1a $C_{14}H_{12}N_2O_2$	78	112	69.99 (68.78)	5.03 (5.43)	--	410 228
1b $C_{15}H_{13}NO_2$	83	103	75.30 (75.80)	5.48 (5.75)	--	417 232
1c $C_{15}H_{12}O_2S$	79	98	70.29 (70.78)	4.72 (4.04)	--	403 225
1a$(C_{14}H_{11}N_2O_2)_2Cu$	76	156	62.04 (62.72)	4.09 (4.43)	11.81 (12.21)	416 236
1b$(C_{15}H_{12}NO_2)_2Cu$	82	164	66.72 (65.56)	4.48 (4.56)	11.77 (11.98)	420 245
1c$(C_{15}H_{11}O_2S)_2Cu$	80	143	62.75 (63.21)	3.86 (4.01)	11.07 (11.57)	410 232
1a$(C_{14}H_{11}N_2O_2)_2Ni$	81	160	62.60 (61.76)	4.13 (4.45)	10.93 (10.67)	414 235
1b$(C_{15}H_{12}NO_2)_2$ Ni	82	132	67.32 (66.78)	4.52 (4.44)	10.97 (10.44)	412 237
1c$(C_{15}H_{11}O_2S)_2$ Ni	78	135	63.29 (64.33)	3.89 (3.56)	10.31 (10.41)	414 238

The UV spectra of the compounds in 95% ethanol (10^{-3} M) showed two broad band's at *ca.* 410 and 225 nm respectively due to n→π* and π→ π* transitions. As expected these band shifted to higher wavelength compared to benzoyl acetone due to conjugation of the double bond to indole ring. In the metal complexes the former bond showed a bathochromic shift (5-16 nm) indicating the involvement of dicarbonyl function in complexation[7].

The IR spectra of the diketones show two prominent bands at *ca.*1647 and 1605 cm^{-1} respectively due to benzoyl and cinnamoyl ν(C=O) vibrations [8]. The observed position and intensity of bands indicate that the compounds exist entirely in the enol form and are enolised towards cinnamoyl function. However, the heterocyclic group and phenyl group may lower the carbonyl frequency. Thus the net effect is to lower the stretching of both carbonyl groups.

Therefore, it is difficult to assign precisely even the carbonyl stretching frequencies. The most striking feature in the IR spectra of complexes is the absence of any band in the region 1630-2000 cm^{-1} due to free or hydrogen bonded carbonyl groups. However in the spectra of all complexes, a new strong band appeared at at *ca.* 1580 cm^{-1} assignable to metal bonded carbonyl group.

This is further supported by the appearance of medium intensity bands at ca.450 and ca.463 cm^{-1} presumably due to ν (M-0) vibrations [9]. The important infrared bands and their assignments are given in **table 3 and 4.**

TABLE 3: CHARACTERISTIC IR DATA (cm-1) OF 5-HETERO ARYL-1-PHENYL-4-PENTENE-1, 3-DIONES

Ligands			Probable assignments
1a	1b	1c	
1625.43	1620.44	1647.21	ν C=O Chelated Benzoyl
1608.78	1605.45	1602.11	ν C=O Chelated Cinnamoyl
1554.21	1544.15	1579.34	ν C-C Phenyl
1510.12	1502.76	1503.52	ν asy C-C-C Chelate ring
1460.78	1480.83	1482.31	ν sym C-C-C Chelate ring
1064.67	1053.80	1021.68	β C-H Chelate ring
972.43	999.38	978.63	ϒ CH=CH Trans
763.54	755.51	740.32	ϒ C-H Chelate ring

TABLE 4: CHARACTERISTIC IR DATA (cm^{-1}) OF METAL COMPLEXES 5-HETERO ARYL-1-PHENYL-4-PENTENE-1, 3-DIONES

Compounds						Probable assignments
$(1a)_2Cu$	$(1b)_2Cu$	$(1c)_2Cu$	$(1a)_2Ni$	$(1b)_2Ni$	$(1c)_2Ni$	
1610.32	1612.10	1624.12	1615.44	1618.12	1610.45	V C=O Metal chelated Benzoyl
1590.78	1589.10	1586.05	1520.37	1524.78	1523.98	V C=O Metal Chelated Cinnamoyl
1505.45	1519.67	1516.05	1508.12	1510.43	1505.54	V asy C-C-C Chelating
1450.45	1454.26	1455.32	1455.14	1444.45	1442.43	V sym C-C-C Chelate ring
978.48	967.99	961.45	974.85	964.36	970.43	ϒ CH=CH Trans
453.73	450.54	460.33	448.56	456.52	463.69	V M-O Chelate ring

The ^{1}H NMR spectra of all unsaturated ligands displayed a one proton signal at *ca.* δ 15 ppm due to the intramolecularly hydrogen bonded enolic proton. Other signals appearing are in the range δ 7(methine protons), 6.8-7.5 (alkenyl protons) and 7.2-8.2 (aryl protons). In the H NMR spectra of metal complexes, the low field signal due to the enol proton of the ligand is absent indicating its replacement by the metal ion during complexation. The assignments of various proton signals observed are assembled in **Table 5 and 6.**

TABLE 5: ^{1}H-NMR SPECTRAOF (δ,ppm) OF 5-HETERO ARYL-1-PHENYL-4-PENTENE-1, 3-DIONES

Ligands			Probable assignements
1a	1b	1c	
15.5	15.7	15.6	Enolic OH
7.2	7.2	7.2	Methine
7.1-7.4	7.1-7.5	6.8-7.2	CH=CH
7.4-7.8	7.2-8.2	7.4-7.8	Aryl
7.1	7.7	7.2	Hetero aryl
13.4	5.0	---	NH

TABLE 6: ^{1}H-NMR SPECTRAOF (δ,ppm) OF METAL COMPLEXES 5-HETERO ARYL-1-PHENYL-4-PENTENE-1, 3-DIONES

Compounds						Probable assignments
$(1a)_2Cu$	$(1b)_2Cu$	$(1c)_2Cu$	$(1a)_2Ni$	$(1b)_2Ni$	$(1c)_2Ni$	
---	---	---	---	---	---	Enolic OH
5.3	6.7	5.6	5.2	6.5	5.5	Methine
6.6-6.8	5.6-6.6	5.7-6.6	6.6-6.7	5.6-6.6	5.7-6.4	CH=CH
7.3	7.1-7.2	7.1-7.2	7.2	7.2	7.1-7.2	Aryl
7.1	6.1-6.6	7.0-7.2	7.3	6.2-6.5	7.0-7.2	Hetero aryl
13.4	5.0	---	13.4	5.0	----	NH

Mass spectra of all the unsaturated diketones showed intense molecular ion $P^+/(P+1)^+$ peaks in conformity with their formulation. Peaks due to $(Ar\text{-}CH{=}CH\text{-}CO)^+$, $(P\text{-}C_6H_5)^+$, $(P\text{-}C_6H_5CO)^+$,etc are characteristic of all the spectra. The mass spectrum of complexes shows the step wise removal of aryl groups. The molecular ion peeks obtained from these compounds were in agreement with ML_2 stochiometry. The anti bacterial and anti fungal activity of ligands and their metal complexes were illustrated in **table 7**.

TABLE 7: ANTI MICROBIAL ACTIVITY OF 5-HETERO ARYL-1-PHENYL-4-PENTENE-1, 3-DIONES AND THEIR METAL COMPLEXES

Compound	Diameter of zone of inhibition in mm							
	Staphylococus aureus NCIM 2079		*Escherichia coli* NCIM 2063		*Aspergillus niger* NCIM 596		*Candida albicans* NCIM 3102	
	500µg/disc	250µg/disc	500µg/disc	250µg/disc	500µg/disc	250µg/disc	500µg/disc	250µg/disc
1a	17	14	16	14	15	12	16	14
1b	19	15	18	15	19	14	17	14
1c	17	13	16	13	17	13	17	15
$(1a)_2Cu$	19	15	18	15	17	14	19	13
$(1b)_2Cu$	21	18	22	18	20	17	22	18
$(1c)_2Cu$	19	14	18	16	19	15	19	16
$(1a)_2Ni$	18	14	17	14	17	13	18	14
$(1b)_2Ni$	21	16	20	16	18	15	18	16
$(1c)_2Ni$	20	14	21	17	19	16	20	16
Ciprofloxacin (10 µg/disc)	24	20	24	20	---	---	---	---
Fluconazole (20µg/disc)	---	---	---	---	24	21	24	20

The data (**table 8**) revealed that large number of synthesized ligands and their metal complexes possess comparable anti bacterial and anti fungal activities comparable to that of standard drugs. Amoung the compounds, 1b, which contain Pyrrole substitution found to be highly active against all six strains studied.In many cases metal complexation increased the activity of the unsaturated diketones. Amoung the complexes, Cu (II) complexes are found to be highly active. This can be explained on the basis of chelation theory [10]. They thought to act by favoring the breakdown of permeability barrier of cell wall of micro organisms.

CONCLUSION: Three heterocyclic synthetic analogues of curcumin and their Cu, Ni complexes were obtained in this research as a result of experiments. The existence of the unsaturated diketones in the intramolecularly hydrogen bonded enol form has been well demonstrated from their analytical and spectral data.Analytical and spectral data of metal complexes with Cu(II) and Ni(II) showed the monobasic bidendate coordination, in which the intramolecularly hydrogen bonded enolic proton is replaced by metal cation.

Anti microbial studies reveal that the compounds possesses significant activity against all the tested organisms. Further compound 1b and its Cu complex were found to be highly active. The present study proves that the title compounds may find application for therapeutic purposes in human diseases provided they are non toxic to human body.

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