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RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION OF SOME HETEROCYCLIC CURCUMIN ANALOGUES AND THEIR COPPER COMPLEXES AS ANTITUBERCULAR AND ANTIMICROBIAL AGENTS

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ABSTRACT

The present paper enlighten the synthesis, characterization and biological significance of a series of 5-hetero aryl -1-phenyl-4-pentene-1,3-diones(1a-c) and their Cu(II) complexes (1d-f) of ML_2 stoichiometry. The synthesis of the titled derivatives was achieved by the condensation of benzoyl acetone with various heterocyclic aldehydes through boric anhydride mediated mechanism in the N-butyl amine induced basic medium. . Boric anhydride act by blocking the middle methylene group of benzoyl acetone and facilitating the condensation of lateral methyl group of benzoyl acetone with aromatic aldehydes, hence preventing facile Knoevenagel type of condensation. Compound (1a-c) belongs to the class of 1, 3-dicarbonyl compounds in which the diketo function is directly attached to olefinic carbon, conferring complexing properties to the molecules. Analytical UV, IR, ^{1}H NMR and mass spectral data of metal complexes suggest, the intermolecularly hydrogen bonded enol proton was replaced by the metal atom to produce copper complexes of ligands(1a-c).All the six derivatives were screened for antitubercular and antimicrobial activities by micro plate Alamar Blue assay and Kirby-Bauer disc plate method respectively. Copper complexes of 1(a-c) have shown significant antitubercular and antimicrobial activity when compared with standard drugs.Further redox properties of metal when it is complexed with ligands were thought to be the reason for the increase sensitivity Cu (II) complexes as significant antitubercular and antimicrobial agents.

INTRODUCTION

Curcumin is a naturally occurring yellow pigment obtainable from the rhizomes of perennial herb Curcuma longa Linn. It has been shown to exhibit antioxidant, anti-inflammatory, antimicrobial and anti carcinogenic activities. They also claim to have hepatoprotective and nephroprotective activities and nephroprotective activities (Preetha et al., 2008). It has been revealed that the biological significance, especially medicinal importance of curcuminoids, is enhanced by complex formation with various inorganic species such as metal ions (John V.D and Krishnankutty K, 2010). However, poor water solubility and unsatisfactory pharmacokinetics of curcumin demand search for new curcumin analogues .Various works with present authors are available with regards to the study of synthetic analogues of this type of α β- unsaturated diketones and their metal complexes(Mathew .2002$_{a,b}$; Krishnankutty,2009) But it was interesting to notice that there were very few literatures are available with synthesis and use of curcumin and their synthetic analogues as antitubercular agents (Agrawal *et al.*,2008)

Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. The most important control measures in TB are the prevention and chemotherapy. But tuberculosis therapy has difficulties in controlling effectively the illness, due to inadequate adherence to treatment course caused by the length of time of medication and adverse reactions (Juan and Pere, 2012). This fostered our attempts to synthesize synthetic analogues of curcumin and their Cu (II) metal complexes against tuberculosis, as they are less likely show liver toxicity and nephrotoxicity upon long period of administration as drugs. The presence of conjugated β-diketone structure is suggested to be responsible for the pharmacological significance of curcumin related compounds. Previously heterocyclic derivatives aroused a considerable attention in the antitubercular activities (Subramaniam and Rao,2012) .It was predicted that a structural analogue of curcumin in which phenolic group is replaced by heterocyclic ring would display novel molecular templates with interesting biological activities in animal models. So, we here report the synthesis, characterization and biological screening of a series of 5-hetero aryl-1-phenyl-4-pentene-1, 3-diones and their Cu (II) chelates as significant compounds with antitubercular and anti microbial activities.

MATERIALS AND METHODS

The chemicals required were obtained from Lancaster, Sigma and Aldrich chemical suppliers.UV spectra's were recorded in methanol solution (10^{-3}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

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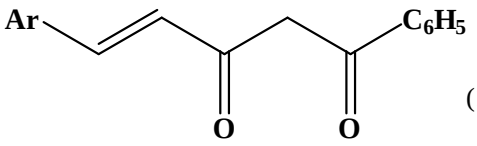
absorption spectrophotometer. NMR on Jeol 400 NMR spectrometer,mass spectra on a Jeol/Sx-102(FAB) mass spectrometer .

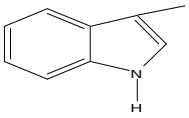
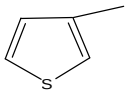
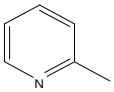
Preparation of 5-hetero aryl-1-phenyl-4-pentene-1, 3-diones

The compounds (structure-I) were prepared by the condensation of four different heterocyclic aldehydes with benzoyl acetone as reported earlier for structurally related 5-aryl compounds ((Mathew .2002$_{a,b}$; Krishnankutty,2009). Benzoylacetone (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°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 recrystalliised from hot benzene to get chromatographically (TLC) pure material.



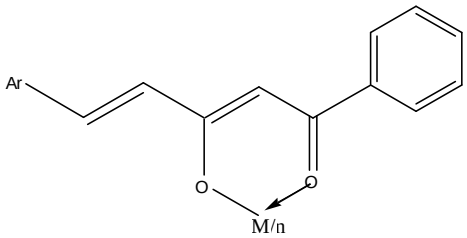
(1)

5-Aryl-1-Phenyl-4-Pentene-1,3-diones

Compounds	Ar
1a	
1b	
1c	

Preparation of Metal Complexes

Cu(II) chelates of diketones were prepared by the following general method. To a refluxing ethanolic solution of the compound (0.002 mol, 20 mL),an aqueous solution of metal (II)acetate0.001 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+}.



M= Cu^{2+} for n=2

(2)

Antitubercular Activity of ligands and its metal complexes

The antitubercular activity of compounds evaluated against *M. tuberculosis* using Microplate Alamar Blue Assay (MABA) method (Maria *et al.,* 2007). This method is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200µl of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to minimize evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.8 µg/mL. Plates were covered and sealed and incubated at 37^{o}C for five days. After the specified period, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue colour in the well was interpreted as no bacterial growth, and pink colour was scored as growth. The MIC was defined as lowest drug concentration which prevented the colour change from blue to pink.

Anti microbial bio assay of ligands and its metal complexes

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 .Bacterial and fungal culture were grown on nutrient agar and czepak dox agar respectively.Anti microbial screening was carried out by using Kirby-Bauer disc plate method(Prescott *et al.*,1990;Collins and Lyne,1970) . Concentrations of 500µg/disc and 250 µg/disc were used for all the test compounds and results were compared with the standard drug ciprofloxacin at 10 µg/disc and fluconazole (20µg /disc) for anti bacterial and anti fungal screening respectively by using dimethyl formamide as the vehicle. The results were interpreted as per Kirby-Bauer method.

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. For convenience, the analytical data of only ligands and their Cu complexes were discussed here. The yield, melting points and the carbon, hydrogen percentages are presented in Table-1.

These ligands formed stable complexes with Cu^{2+},Ni^{2}+,Co^{2+}, They were crystalline in nature with sharp melting points. Carbon, hydrogen percentages are in agreement with ML_2 stoichiometry. 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.

the involvement of dicarbonyl function in complexation. (Nakamoto. 1976).

Table 1 Analytical and physical data of 5-hetero aryl-1-phenyl-4-pentene-1, 3-diones

Compound		Yield (%)	m.p (^{0}C)	Elemental analysis % calculated(found) C	H	N	O	S	λ Max
1a	$C_{19}H_{15}NO_2$	55	158	78.87	5.23	4.84	11.06		385
				(78.54)	(5.64)	(4.33)	(11.49)		224
1b	$C_{15}H_{12}O_2S$	60	70	70.29	4.72		12.48	12.51	402
				(70.81)	(4.76)		(12.58)	(11.85)	225
1c	$C_{15}H_{12}NO_2$	54	103	75.61	5.08	13.43	5.88		392
				(75.40)	(5.45)	(13.22)	(5.93)		227

Table 2 Analytical and physical data of metal chelates of the 5 –hetero -aryl-1-phenyl-4- pentene-1,3-diones

Metal chelates	Yield (%)	mp (^{0}C)	Elemental analysis (%) C	H	M	λ max (nm)
1d $(C_{19}H_{14}NO_2)_2Cu$	70	224	71.29	4.41	9.93	415
			(71.12)	(4.46)	(9.87)	230
1e $(C_{15}H_{11}O_2S)_2Cu$	58	164	62.75	3.86	11.07	410
			(62.72)	(3.88)	(11.12)	235
1f $(C_{15}H_{11}NO_2)_2Cu$	62	214	68.13	4.29	11.27	405
			(68.22)	(4.32)	(11.32)	232

Table-3 Characteristic Ir Data (Cm-1) Of 5-Hetero Aryl-1-Phenyl-4-Pentene-1, 3-Diones

Compounds			Probable assignments
1a	1b	1c	
1631.78	1647.35	1641.23	ν C=O Chelated Benzoyl
1610.84	1602.21	1610.33	ν C=O Chelated Cinnamoyl
1575.72	1579.7	1580.22	ν C-C Phenyl
1510.23	1510.33	1478.54	ν asy C-C-C Chelate ring
1444.68	1467.32	1442.00	ν sym C-C-C Chelate ring
1085.5	1021.65	1057.56	β C-H Chelate ring
950.36	940.33	931.40	γ CH=CH Trans
763.81	740.33	755.23	γ C-H Chelate ring

Table 4 Characteristic ir data (cm^{-1}) of copper (ii) chelates of 5-hetero aryl-1-pheny l-4-pentene-1, 3-diones

Copper (II) chelates			Probable assignments
1d	1e	1f	
1622.26	1624.12	1630.05	ν C=O Metal Chelated Benzoyl
1572.45	1570.44	1585.49	ν C=O Metal Chelated Cinnamoyl
1514.48	1516.05	1524 .05	ν C-C Phenyl
1392.87	1350.32	1398.98	ν asy C-C-C Chelating
1285.72	1270.00	1286.52	ν sym C-C-C Chelating
1096.57	1025.33	1174.65	β C-H Chelate ring
965.96	950.33	968.27	ν CH=CH Trans
490	470.33	488.96	ν M-O Chelate ring

Table 5 ^{1} H NMR Spectral data of 5- hetero aryl-1-phenyl-4-pentene-1, 3-diones

Chemical shift (ppm)			Assignments
1a	1b	1c	
15	15.2	15	Enolic
7—8.2	6.85-7.2	7.2-7.4	Alkenyl
7.37-7.86	7.45-7.81	7.45-7.81	Aryl
9.9	----	----	NH
7.1-7.4	7.2-7.3	7.28-7.75	Methine
7	7.2	8.8	Hetero aryl

The UV spectra of the compounds in 95% ethanol (10^{-3}M) showed two broad bands *ca.* 402 and 224 nm respectively due to carbonyl and olefinic functions. In the metal complexes former bands showed a bathochromic shift (5-15 nm) due to

The IR spectra of the diketones show two prominent bands at *ca.*1647 and 1610 cm^{-1} respectively due to chelated benzoyl and chelated cinnamoyl (C=O) vibrations[13]. The observed position and intensity of bands indicate that the compounds

Table 6 ^{1}H NMR Spectra of (δ,ppm) of copper (ii) chelates of 1a

Copper (II) chelate of	Probable assignements
1a	
----	Enolic OH
9.9	NH stretching
5.1	Methine
7.2-8.3	Alkenyl
7.4	Aryl
7.5	Hetero aryl

Table7 Mass spectral data of ligands and their copper (ii) complexes

Compound	Mass spectral data(m/e)
1a	290.1, 258.1, 170.06, 143.9,112.9, 88.9
1b	256.4 ,215, 179 ,137.2, 108.8
1c	252.1, 210.0, 173, 147.1,105
1d	640.33, 453.9, 358.6.290.170.7, 137.1
1e	573.6, 521.4, 341.1, 256 ,170.9,119.1
1f	564.09, 521.4, 435.2, 379.1, 270, 186.

exists entirely in the enol form and are enolised towards cinnamoyl function as in structure 1.Several medium intensity bands seen in the region 1600-1500 cm^{-1}.The intense and broad band observed in the region 3500-2400 cm^{-1} undoubtedly due to existence of strong intramolecular hydrogen bonding in these compounds (Bellamy. 1980),

In the spectra of metal complexes,bands in the region 1650-1635 cm^{-1} almost disappeared but instead two new bands appeared at *ca.* 1620 cm^{-1} and 1570 cm^{-1} of appreciable intensity due to metal chelated carbonyl groups.Several medium intensity bands appeared in this region due to aromatic and alkenyl (C=C) vibrations. This is further supported by the appearance of medium intensity bands at ca.470 and ca.490 cm^{-1} presumably due to (M-0) vibrations. Thus IR data strongly support structure 2 of the complexes. Since metal complexes have very similar spectral bands only the characteristic IR bands of copper (II) complexes are tabulated in table-4.

The^{1}H NMR spectra of all unsaturated ligands displayed a one proton signal at *ca.* δ 15.2 ppm due to the intramolecularly hydrogen bonded enolic proton. Other signals appearing are in the range δ 7.1-7.75(methine protons), 6.8-8.2 (alkenyl protons) and 7.3-7.8 (aryl protons).

In the ^{1}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 (Muhammed *et al.*2010). The integrated intensities of the aryl and alkenyl protons agree well with the [ML_2] stoichiometry of the complexes as in structure 2.The assignements of various proton signals observed are assembled in Table-5 and table -6.

Table 8 Antitubercular activity of synthesized compounds

		compound code concentration(μg/ml)							
	100	**50**	**25**	**12.5**	**6.25**	**3.125**	**1.6**	**0.8**	
1a		S	S		R	R	R	R	R
1b		S	S	S	R	R	R	R	R
1c		S	S	S	S	R	R	R	
1d	[Cu (1a) $_2$]	S	S	R S	S	S	R	R	R
1e	[Cu (1b) $_2$]	S	S	S	S	S	R	R	R
1f	[Cu (1c) $_2$]	S	S	S	S	S	R	R	R

*S=Sensitive, R=Resistant

Table 9 Anti microbial l activity (diameter inhibition zone in mm) of the ligands and their Cu complex

	Diameter of zone of inhibition in mm							
Compound	***Staphylococus aureus*** **NCIM 2079**		***Escherichia coli*** **NCIM 2063**		***Aspergillus niger*** **NCIM 596**		***Candida albicans*** **NCIM 3102**	
	500 μg/disc	250 μg/disc	500 μg/disc	250 μg/disc	500 μg/disc	250 μg/disc	500 μg/disc	250 μg/disc
DMF	---	---	---	---	----	----	----	----
1a	14	---	12	10	16	10	16	14
1b	15	14	14	12	17	15	17	14
1c	13	12	12	10	14	12	17	13
1d [Cu (1a) $_2$]	17	14	15	11	17	14	17	14
1e [Cu (1b) $_2$]	17	15	16	14	18	16	18	14
1f [Cu (1c) $_2$]	15	12	14	13	17	15	16	14
Ciprofloxacin (10 μg/disc)	20	16	20	16				
Fluconazole (20μg/disc)					20	17	20	17

which is also evident from the lowering of benzoyl carbonyl stretching frequency. A medium intensity band at *ca*.931 cm^{-1} possibly arising due to newly formed trans -CH=CH- double bond absorption. The important infrared bands and their assignments are given in table-3.

Mass Spectea

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 FAB

mass spectra of the Cu(II) complexes showed molecular ion peaks corresponding to $[CuL_2]$ stoichiometry.Peaks correspond to $[CuL]^+$,L^+ and fragments of L^+ are also present in the spectra. Another important factor is the presence of large number of fragments containing copper in the 3:1 natural abundance of ^{63}Cu and ^{65}Cu isotopes.

Antitubercular activity

The synthesized ligands and their Cu(II) complexes in the present study were tested for the *in vitro* anti-mycobacterial activity against *M. tuberculosis* H37Rv using the Alamar Blue assay method . Our preliminary data indicate that the compounds (1a-c) possessing a heterocyclic ring system in the side chain attached through olefinic linkage to the dicarbonyl moiety were active against *M. tuberculosis* at a higher concentration (12.5µg/ml) whereas the compounds (1d-f)prepared by complexing the ligands with copper metal showed promising activity at a minimum concentration of 6.25 µg/ml. It was interesting to observe that the replacement of the enolic hydrogen with Cu (II) has shown promising antitubercular activity against *M. tuberculosis.* Hence, these compounds can be considered as pharmacophore unit and exploited further to obtain novel antitubercular agent. .The results are shown in Table 8.

Antimicrobial activity

The data (table-8) revealed that large number of synthesized ligands and their metal complexes possess comparable anti bacterial and anti fungal activities to that of standard drugs. In ligands compound 1b is active against all the organisms in both 500 µg/disc *and* 250 µg/disc concentrations.Further copper complex of 1b has shown significant anti microbial activity as expected.

It is observed that Cu complexes of all the derivatives show more antitubercular and antimicrobial activity than ligands. This can be explained on the basis of chelation theory Mathewes and Mohanan. 2007). Chelation reduces the polarity of the metal ion considerably, mainly because of the partial sharing of its positive charge with donor groups and possible electron π delocalization on the whole chelate rings. The lipids and polysaccharides are some important constituents of cell wall and membranes, which are preferred for metal ion interaction. In addition to this, cell wall also contains many amino phosphates, carbonyl and cysteinyl ligands which maintain the integrity of the membrane by acting as a diffusion barrier and also provides suitable sites for binding. Chelation can considerably reduce the polarity of the metal ion, which in turn increases the lipophilic character of the chelate, and the interaction between metal ion and the lipid is favoured. This may lead to the breakdown of the permeability barrier of the cell, resulting in interference with the normal cell process.

CONCLUSION

During the present work three ligands and their Cu(II)complexes were prepared. Out of 6 derivatives screened all the ligands and its complexes shown significant antimicrobial and antitubercular activities. As expected, copper complexation found to increase the sensitivity of the compounds as drugs. It was also found that there is good correlation existing between antitubercular and antimicrobial activities of titled compounds. It suggests that this class of compounds may be selectively targeted to *M. tuberculosis* and microbial growth, also considering that they were not cytotoxic to host cells at the same concentration and could be a fine starting point to find new lead compounds. We watched further work can be done on synthetic analogue of curcumin based copper complexes to check its toxicity and side effects.

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