UNIVERSITY GRANTS COMMISSION

MINOR RESEARCH PROJECT- FINAL REPORT

"Biochemical studies of curcumin related 5-aryl-1 phenyl-4-pentene-1,3-diones and their metal complexes"

Dr.Mathew Paul Ukken

Associate Professor, Department of Chemistry

Christ College, Irinjalakuda – 680125

OCTOBER-2013

GENERAL INTRODUCTION

Metal complexes

One of the charming features of modern coordination chemistry is the ever growing academic, commercial and biological interest exhibited by metal complexes of organic molecules, both natural and synthetic. This is mainly due to the realization of vital role of metal complexes in biology and medicine, where much progress has been made during the last few decades[1-3]. Thus numerous highly efficient synthetic metal complexes which mimic the behavior of complex biomolecules are known and at present the study of such compounds are receiving much attention. Although the results obtained so far do not always parallel with those in nature, knowledge of the chemistry is being built up and the biochemical role of metal ions in natural ligand systems is to be better understood.

1,3-diketones are key structural units in many chelating ligands[4]. Similarly enolizable 1,3-diketones are important building blocks and their usefulness in preparations of the compounds such as pyrazole, isoxazole, triazole and benzopyran-4-ones has been well illustrated. Beta-diketonates form anions as a result of enolization and ionization after α-proton extraction by base. These beta-keto enolate ions form very stable chelate complexes with almost all metal ions[5]

However, it is pointed out that only very few reports are available on metal complexes of synthetic 1,3-dicarbonyls and related compounds. **The present study is an attempt in this direction. Therefore in this investigation a new series of unsaturated 1,3-diketones, in which only one of the keto group linked to an olefinic group and their metal complexes are considered.**

MATERIALS, METHODS AND INSTRUMENTAL TECHNIQUES

Materials

All the chemicals utilized in this study were AR grade purchased from Sigma Aldrich, USA. Melting points were determined by open tube capillary method and are uncorrected. Six different heterocyclic aldehydes like Indole-3-carboxaldehyde, Pyridine-2-carboxaldehyde and Thiophene 3-carboxaldehye, Imidazole-2-carboxaldehyde, Pyrrole-2 carboxaldehyde and Thiophene-2-carboxaldehyde were used along with 1,3 diketones like acetyl acetone and benzoyl acetone. Metal salts used for synthesis were Nickel(II) acetate tetra hydrate and copper (II) acetate mono hydrate. Commercial solvents were distilled and used for synthesis. Solvents purified by methods recommended by Weissberger[6] were employed for physical and physiochemical measurements.

Only compounds isolated analytically pure are reported in this thesis. All the compounds reported in this thesis are stable and have good keeping qualities. Compounds for recording spectra were recrystallised from proper solvents several times till chromatographically pure (tlc) materials are obtained.

Instruments

Instruments used in this investigation are

1) UV-1601 Schimadzu recording spectrophotometer

2) Thermo Nicolet, Avatar 370 FTIR spectrophotometer

3) Jeol/Sx-102(FAB) mass spectrometer

4) Flash EA 1112 series elemental analyser

5) Perkin Elmer Diamond TG/DTA

6) JES - FA200 ESR Spectrometer with X and Q band

7) Varian,Mercury Plus 300 MH_Z NMR spectrophotometer

8) Systronic pH meter

9) Gouy type magnetic balance

10) Deep freezer, Quene system

Methods

Elemental analysis

Carbon, hydrogen, nitrogen, oxygen, sulphur percentages reported are by micro analysis carried out at SAIF, IIT, Mumbai, India. It was based on the principle of "Dumas method" which involves the complete and instantaneous oxidation of the sample by "flash combustion". The combustion products are separated by a chromatographic column and detected by the thermal conductivity detector.

UV –Visible spectra

They were recorded from UV-1601 Schimadzu recording spectrophotometer using solution (10^{-3} M) of compounds in ethanol unless otherwise mentioned.

Infrared spectra

Infrared spectra of compounds were recorded from Thermo Nicolet, Avatar 370 FTIR spectrophotometer. The spectra were recorded from disc with KBr. Bands were calibrated using the nearest polystyrene bands.

^{1}H NMR spectra

^{1}H NMR were recorded using Varian, Mercury Plus 300 MH_Z NMR spectrophotometer (SAIF, IIT, Chennai). The spectra were recorded using MeOD as solvent and TMS as internal reference.

FAB mass spectra

Mass spectra were obtained from CDRI Lucknow. The spectra were recorded at room temperature using argon (6KV, 10mA) as the FAB gas and meta-nitrobenzyl alcohol as the matrix. The probable matrix peaks are located at m/z 136,137,154,289,307.

ESR spectra

ESR spectra were obtained from SAIF, IIT, Mumbai. The spectra of metal complexes were recorded by using JES - FA200 ESR Spectrometer with X and Q band, at 77K,in glassy state between 8.75-9.65GHz and caliberated with Diphenyl picryl hydrazil (DPPH) free radical for which g =2.0036 in DMF. The microwave power employed was 5Mw and field set up at 3000G.Scan time was 4 hours.

Thermal analysis

Thermal analysis was carried out by using Perkin Elmer Diamond TG/DTA (SAIF, IIT, Mumbai) at Vacuum (10^{-2} Torr) by using a heating range of 0.01-100º C/min.

Single-crystal X-ray diffraction

Single crystal X-ray diffraction studies were carried out at STIC (KUSAT) Kochi by using Bruker Kappa Apex II model X-ray diffractometer. Structure solution was carried out by using X Shell structure solution software.

Molecular weights

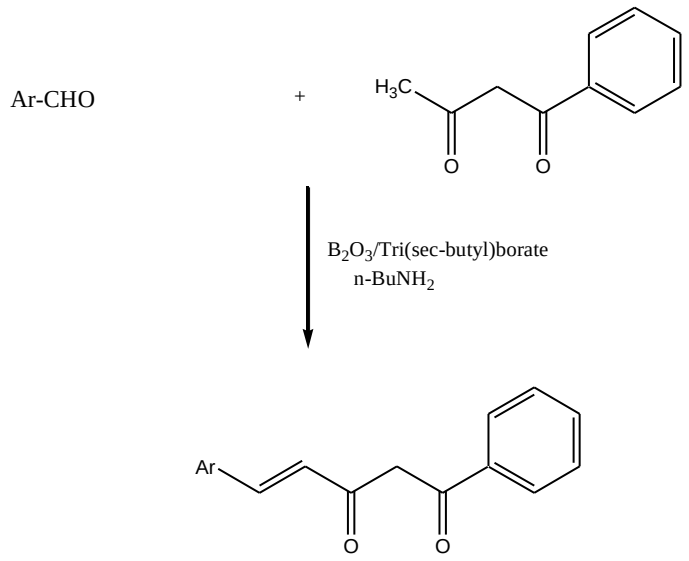
Molecular weights of compounds reported were determined by Rast's method[7] using naphthalene/camphor as medium.

EXPERIMENTAL

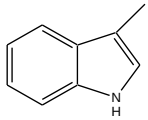
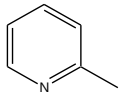
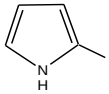
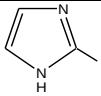
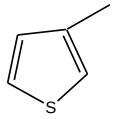
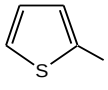
In this section synthesis and characterization of new series of 5-heteroaryl-1-phenyl-4-pentene-1,3-diones and their metal complexes are considered. The heteroaryl functions considered are indolyl, pyridinyl, pyrrolyl, imidazolyl and thiophenyl groups.

Synthesis of 5-heteroaryl-1-phenyl-4-pentene-1,3 diones

The compounds were synthesized by the condensation of heterocyclic aldehydes with benzoylacetone at room temperature in presence of tri(sec-butyl) borate,B_2O_3 and n-butyl amine as given below.(Scheme **5.1**).



Scheme.5.1

Compound	Ar
5a	
2b	
5c	
5d	
5e	
5f	

Experimental

Synthesis of 5-heteroaryl-1-phenyl-4-pentene-1,3-diones

The compounds were prepared by the Claisen-Schmidt condensation of different heterocyclic aldehydes with benzoylacetone as reported [8-12]. 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, and extracted with ethyl acetate, the combined extracts were 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.

Synthesis of metal chelates of 5-hetero aryl-1-phenyl-4-pentene-1,3-diones

The Cu(II) and Ni(II) chelates of the diketones were prepared by the following general method[13-15]. 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.

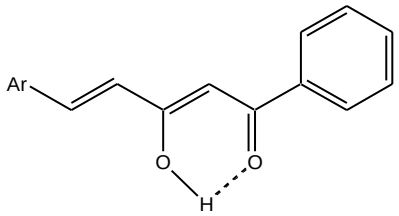
RESULTS AND DISCUSSION

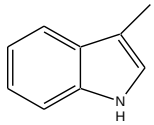
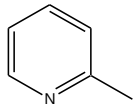
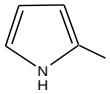
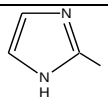
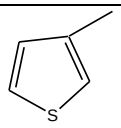
Characterisation of 5-Hetero aryl-1-phenyl-4-pentene-1,3-diones

UV, IR, ^{1}H NMR,Mass spectral details[16] of synthesized compounds were given in tables 5.1to 5.4

Table. 5.1

Synthetic details of the 5-Hetero aryl-1-phenyl-4-pentene-1,3-diones



Compounds	Aldehydes used for synthesis	Ar	Systematic name	Yield (%)
5a	Indole-3-carboxaldehyde		5-(1H-Indol-3-yl)-1-phenyl-pent-4-ene-1,3-dione	55 %
5b	Pyridine-2-carboxaldehyde		1-Phenyl-5-pyridin-2-yl-pent-4-ene-1,3-dione	54%
5c	Pyrrole-2-carboxaldehyde		1-Phenyl-5-(1H-pyrrol-2-yl)-pent-4-ene-1,3-dione	83%
5d	Imidazole-2-carboxaldehyde		5-(1H-Imidazol-2-yl)-1-phenyl-pent-4-ene-1,3-dione	78%
5e	Thiophene-3-carboxaldhyde		1-Phenyl-5-thiophen-3-yl-pent-4-ene-1,3-dione	60%
5f	Thiophene-2-carboxaldehyde		1-Phenyl-5-thiophen-2-yl-pent-4-ene-1,3-dione	79%

UV spectra

Table. 5.2

Physical ,analytical and uv spectral data of 5-Hetero aryl-1-phenyl-4-pentene-1,3 diones

Compound	M.P(°C)	Colour	Elemental analysis (%) calculated (found)				λ max nm
			C	H	N	S	
5a $C_{19}H_{15}NO_2$	158	Yellowish orange	78.87 (78.54)	5.23 (5.64)	4.84 (4.33)	---	385 224
5b $C_{16}H_{13}NO_2$	103	Reddish brown	76.48 (75.40)	5.21 (5.45)	5.57 (5.22)	---	392 227
2c $C_{15}H_{13}NO_2$	103	Black	75.30 (75.80)	5.48 (5.75)	5.85 (5.74)	---	417 232
5d $C_{14}H_{12}N_2O_2$	112	Reddish brown	69.99 (68.78)	5.03 (5.43)	11.66 (11.59)	---	410 228
5e $C_{15}H_{12}O_2S$	70	Brownish black	70.29 (70.81)	4.72 (4.76)	---	12.51 (11.85)	402 225
5f $C_{15}H_{12}O_2S$	143	Brownish black	70.29 (70.78)	4.72 (4.04)	---	16.51 (16.44)	403 225

Infrared spectra

Table.5.3

Characteristic ir data (cm^{-1}) of 5-heteroaryl-1-phenyl-4-pentene-1,3-diones (2a-f)

5a	5b	5c	5d	5e	5f	Probable Assignments
1631.78	1641.23	1620.44	1625.43	1647.35	1647.35	V C=O Chelated benzoyl
610.84	1610.33	1605.45	608.78	1602.21	1602.21	V C=O cinnamonyl
1575.72	1580.22	1544.15	1554.21	1579.70	1579.70	V C-C phenyl/alkenyl
1510.23	1478.54	1502.76	1510.12	1510.33	1510.33	V asym C-C-C chelate ring
1444.68	1442	1480.83	1460.78	1467.32	1467.32	V sym C-C-C chelate ring
1085.50	1057.56	1053.80	1064.67	1021.65	1021.65	β C-H chelate ring
950.36	931.40	999.38	972.43	940.33	940.33	V CH=CH trans
763.81	755.23	755.51	763.54	740.33	740.33	V C-H chelate ring

^{1}H NMR Spectra

Table 5.4

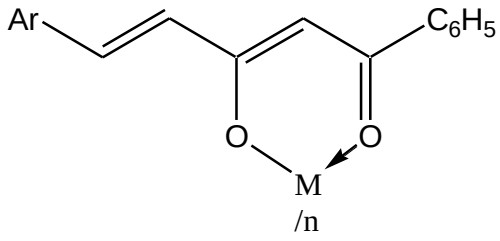
Characteristic ^{1}H nmr spectral data of 5-hetero aryl-1-phenyl-4-pentene-1,3-diones

chemical shift(δ ppm)						Probable assignment
5a	5b	5c	5d	5e	5f	
15.2	14.9	15.7	15.5	15.2	15.6	Enolic
7.2-7.5	7.5-8	6.6-6.8	6.8-7	7-7.2	6.8-7.1	Alkenyl
8-8.2	8.2-8.7	6-7.8	7.1-7.8	7.4-7.8	7.2-7.8	Aryl
4.9	4.9	5	5.1	4.8	4.9	Methine
9.9	--	4.7	13.4	--	--	NH

Mass spectra

Mass spectra of all the unsaturated diketones[30,146] showed intense molecular ion P $^+$/(P+1)$^+$ peaks in conformity with their formulation. Peaks due to (Ar-CH=CH-CO)$^+$, (P-C_6H_5)$^+$, (P-C_6H_5CO)$^+$, etc are characteristic of all the spectra.

Characterization of metal chelates of 5-heteroaryl-1-phenyl-4-pentene-1,3-diones



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

UV spectra

Table.5.6

Physical and analytical data of Cu(II) chelates of 5-heteroaryl-1-phenyl-4-pentene-1, 3-diones

Copper(II) chelate of (molecular formula)*	Yield (%)	M.P (° C)	Elemental analysis Calculated(found)					λ max (nm)
			C	H	O	N/S	M	
5a $(C_{19}H_{14}NO_2)_2Cu$	70	224	71.29 (71.12)	4.41 (4.46)	10.00 09.89	4.38 (4.66)	9.93 (9.87)	415 230
5b $(C_{16}H_{12}NO_2)_2Cu$	62	214	68.13 (68.22)	4.29 (4.32)	11.35 (11.28)	4.97 (4.86)	11.27 (11.32)	405 232
5c $(C_{15}H_{12}NO_2)_2Cu$	82	164	66.72 (65.56)	4.48 (4.56)	11.85 (11.93)	5.19 (5.97)	11.77 (11.98)	420 245
5d $(C_{14}H_{11}N_2O_2)_2Cu$	76	156	62.04 (62.72)	4.09 (4.43)	11.81 (11.45)	10.34 (9.19)	11.81 (12.21)	416 236
5e $(C_{15}H_{11}O_2S)_2Cu$	58	164	62.75 (62.72)	3.86 (3.88)	11.15 (11.17)	11.17 (11.11)	11.07 (11.12)	410 235
5f $(C_{15}H_{11}O_2S)_2Cu$	80	143	62.75 (63.21)	3.86 (4.01)	11.15 (11.02)	11.17 (10.19)	11.07 (11.57)	410 232

Infrared spectra

Table 5.7

Characteristic ir data (cm^{-1}) of copper complexes of the 5-hetero aryl-1-phenyl-4-pentene-1, 3-diones

Copper(II) complexes of						Probable Assignments
5a	5b	5c	5d	5e	5f	
1622.26	1630.05	1612.10	1610.32	1624.12	1624.12	ν C=O metal chelated benzoyl
1572.45	1585.49	1589.10	1590.78	1570.44	1586.05	ν C=O metal chelated cinnamonyl
490	488.96	450.54	453.73	470.33	460.33	ν M-O chelate ring

^{1}H NMR spectra

Characteristic ^{1}H NMR spectral data of Ni(II) complexes of 5-heteroaryl-1-phenyl-4-pentene-1, 3-diones

Table.5.8

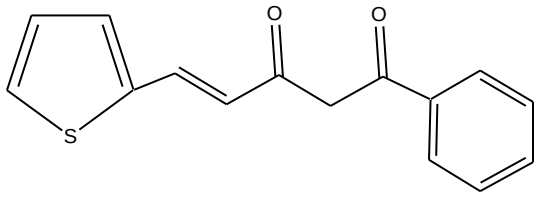
Ni(II) complexes						Probable assignment chemical shift(δ ppm)
5a	5b	5c	5d	5e	5f	
--	--	--	--	--	--	Enolic
4.9	5.1	5.1	5.1	5.1	5..0	Methane
10.1	--	4.8	13.4	--	--	NH

Mass spectra

The mass spectra of complexes show the step wise removal of aryl groups. The molecular ion peaks observed of these compounds were in agreement with ML2 stochiometry. The peaks due to $[ML]^{+}$,L^{+} and fragments of L^{++} are also detected in the spectraum.

X-ray diffraction study of of 5-hetero aryl-1-phenyl-4-pentene-1,3-diones

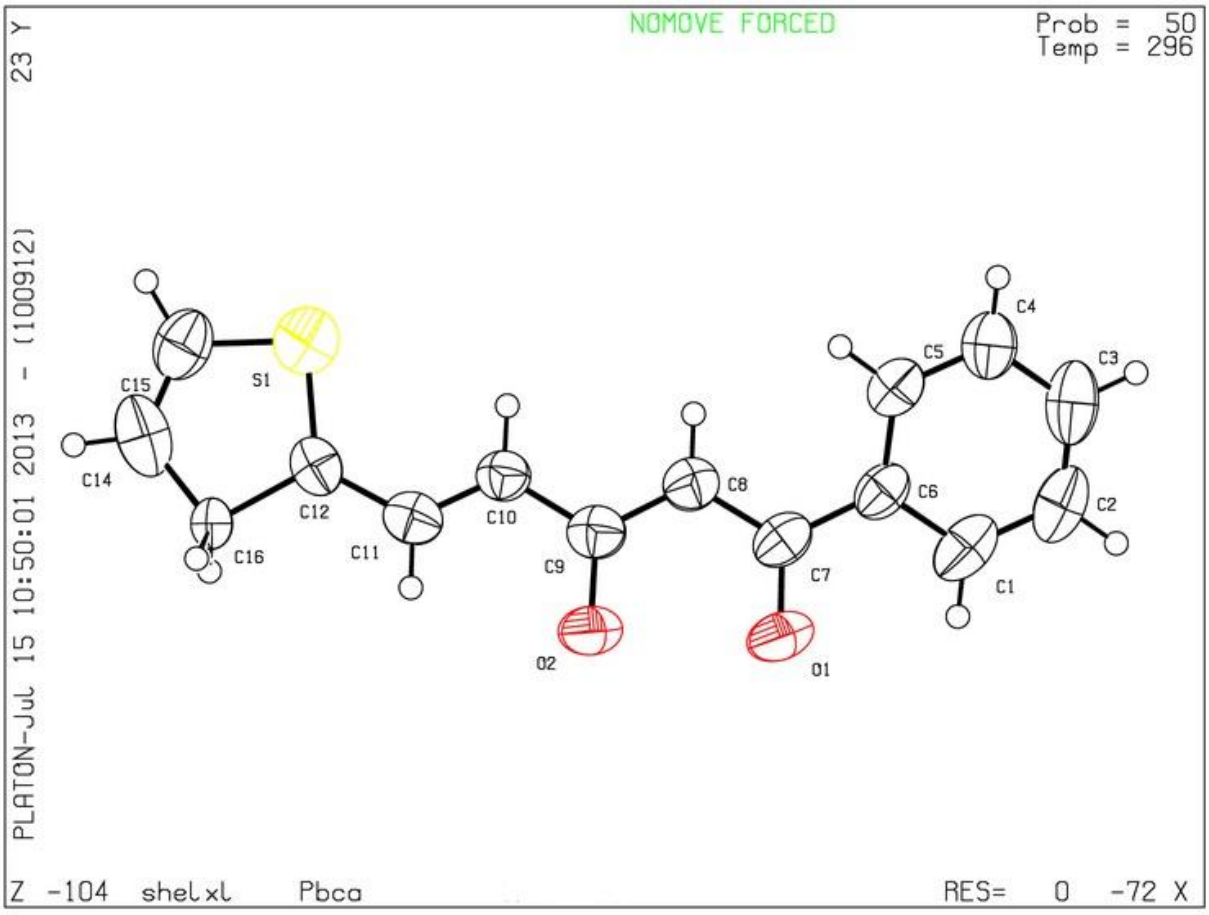
In the present study attempts were made to get single crystals of 5-heteroaryl-1-phenyl-4-pentene-1,3-diones and their metal complexes. However, crystals suitable for XRD studies were obtained only in the case of 5-hetero aryl-1-phenyl-4-pentene -1,3-diones. Out of which the details of single crystal XRD of 1-Phenyl-5-thiophen-2-yl-pent-4-ene-1,3-dione(**5f**) are given below[17].



5f

Results and discussion

The labeling of atoms is indicated in fig.**5.1**. The unit cell dimensions reveal that the crystal system belongs to orthorhombic and with a space group Pbca **.**



Biological screening of 5-heteroaryl-1-phenyl-4-pentene-1, 3-diones and their metal complexes

It has been reported that these types of unsaturated dicarbonyl compounds possess several beneficial biological properties especially various medicinal applications. Further metal complexation enhances these properties significantly. In the present work two important

biological properties of compounds considered in section 1, namely antitubercular activity and antimicrobial activity were carried out and results are presented here.

Antitubercular screening of 5-heteroaryl-1-phenyl-4-pentene-1, 3-diones and their metal complexes by micro plate Alamar Blue assay

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[18-21]. This fostered the attempts to screen 5-heteroaryl-1-phenyl-4-pentene-1,3-diones and their Cu(II) metal complexes against tuberculosis, as they are less likely to show liver toxicity and nephrotoxicity upon long period of administration as drugs. Previously heterocyclic derivatives aroused a considerable attention in the antitubercular activities[22]. It was predicted that a structural analogue of curcuminoids in which phenolic group is replaced by heterocyclic ring would display novel molecular templates with interesting biological activities in animal models.

With the increased need for drugs to combat multi drug resistant tuberculosis (TB), there is an urgent need for rapid, low-cost, high-throughput assays for screening new drug candidates. Almar blue assay[23] is one such method which would also be useful for assessing activity against *Mycobacterium avium, Mycobacterium tuberculosis*, and related species[24]. The Alamar blue oxidation-reduction dye is a general indicator of cellular growth and/or viability; the blue, non fluorescent, oxidized form becomes pink and fluorescent upon reduction. Growth can therefore be measured with a spectrophotometer or determined by a visual color change[25].

Materials and methods

The antitubercular activity of compounds was evaluated against *M. tuberculosis* using Microplate Alamar Blue Assay (MABA) method. This method is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200 µl 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 was 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, 25 µl of freshly prepared 1:1 mixture of Alamar 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 the lowest drug concentration which prevented the colour change from blue to pink.

Results and discussion

The ligands 5a,5b,5c,5d and 5e and their Cu(II) complexes were tested for the *in vitro* anti-mycobacterial activity against *M. tuberculosis* H37Rv using the Alamar Blue assay method . The preliminary data indicate that the compounds 5a,5b ,5c,5d and 5e 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 metal complexes 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 enhanced antitubercular activity against *M. tuberculosis*. Hence, these compounds can be

considered as pharmacophore unit and can function as a novel antitubercular agent.. The results are shown in Table.**5.9**

Table 5.9

Anti tubercular activity of screened compounds

Compound code	Drug concentrations							
	100 µg/mL	50 µg/mL	25 µg/mL	12.5 µg/mL	6.25 µg/mL	3.125 µg/mL	1.6 µg/mL	0.8 µg/mL
5a	S	S	R	R	R	R	R	R
5b	S	S	S	S	R	R	R	R
5c	S	S	S	S	R	R	R	R
5d	S	S	S	S	R	R	R	R
5e	S	S	S	R	R	R	R	R
$(5a)_2Cu$	S	S	S	S	S	R	R	R
$(5b)_2Cu$	S	S	S	S	S	R	R	R
$(5c)_2Cu$	S	S	R	R	R	R	R	R
$(5d)_2$ Cu	S	S	S	S	S	R	R	R
$(5e)_2Cu$	S	S	S	S	S	R	R	R

S= Sensitive ,R= Resistant

Antimicrobial screening of 5-hetero aryl-1-phenyl-4-pentene-1, 3-diones and their metal complexes by Kirby-Bauer disc plate method

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 was grown on nutrient

agar and czepakdox agar respectively. Anti microbial screening was carried out by using Kirby-Bauer disc plate method. Concentrations of 500 μg /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 (20 μg /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[26].

Antimicrobial activity

The data (Table **5.10**) revealed that large number of synthesized ligands and their metal complexes possess comparable antibacterial and antifungal activities to that of standard drugs. The compound 5b is active against all the organisms in both 500 μg/disc *and* 250 μg/disc concentrations. Further copper complex of 5b 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[27]. They were thought to act by favoring the breakdown of permeability barrier of cell wall of micro organisms. 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.

Table.5.10

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	
	500 µg/disc	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc	250 µg/disc
5a	14	---	12	10	16	10	16	14
5b	13	12	12	10	14	12	17	13
5c	14	11	13	11	14	13	16	14
5d	14	12	12	10	16	12	15	14
5e	15	14	14	12	17	15	17	14
$(5a)_2Cu$	17	14	15	11	17	14	17	14
$(5b)_2Cu$	15	12	14	13	17	15	16	14
$(5c)_2Cu$	16	13	14	13	17	15	15	13
$(5d)_2Cu$	16	14	14	12	18	14	16	13
$(5e)_2Cu$	17	15	16	14	18	16	18	14
Ciprofloxacin (10 µg/disc)	20	16	20	16	---	---	---	---
Fluconazole (20µg/disc)	---	---	---	---	20	17	20	17

SUMMARY

5-heteroaryl -1-phenyl -4-pentene-1,3-diones was synthesized by the condensation of heterocyclic aldehydes and benzoylacetone. Cu(II) and Ni(II) metal chelates of diketones were also prepared. All the synthesized compounds were characterized by various spectral and analytical techniques. These studies revealed that the ligand exists in an intramolecularly hydrogen bonded enol form. Single crystal XRD studies strongly suggest that heteroaryl diketone may exist in diketo form depend upon nature of heteroaryl substitution in the crystalline state. Similarly 1:2 stoichiometry was found in the case of metal diketonates.. Further, as expected metal complexes showed significant antitubercular and antimicrobial activity when compared to corresponding diketones.

REFERENCES

1. S.J. Lippard and J.M.Berg, '*Principles of Bioinorganic Chemistry'*, University Science Books, California, 1994.
2. C.F.Bell, *'Principles and Applications of Metal Chelation'*, Oxford University, London, 1978.
3. G.Wilkinson (ed.in chief),'Comprehensive Coordination Chemistry', 1st edn., Vol.6, Pergamon, New York, 1987
4. N.V.Pooja, I.S. Javed and D. J.Harjit, *World Applied Sciences Journal.*, 2011, **14(8),** 1154.
5. K.C.Joshi and V.N.Pathak, *Coord. Chem. Rev.*,1977, **22,** 37.
6. A.Weissberger, P.S.Proskauer, J.A.Hiddik and B.E.Troops*,'Organic Solvents'*, Vol.3.Interscience, New York,1956.
7. F.G.Mann and B.C.Saunders,*'Practical Organic Chemistry'*, ELBS and Longman, London, 1975.
8. P.Venugopalan and K.Krishnankutty, *J.Indian Chem Soc.*,1997, **75**, 564
9. P.Venugopalan and K.Krishnankutty, *Synth.React.Inorg.Met.Chem*., 1998, **28(8),** 1313.
10. K.V.D.Babu and K.N.Rajasekharan, *Org.Prep.Proceed.Int.*,1994, 26**(6)**, 674.
11. P.U.Mathew, P.Venugopalan and K.Krishnankutty, *Asian J.Chem*., 2002, **14**, 1335.
12. P.U.Mathew and K.Krishnankutty, .*Asian J.Chem*., 2002, **14(2),** 949.
13. P.U. Mathew and K.Krishnankutty. *Asian J.Chem.*, 2002, **14,** 943.
14. K.Krishnankutty, B.U.Muhammed and P.U. Mathew, *Trade Science Inc. Inorganic Chemistry.*, 2009, **4(2**), 78.
15. V.D.John and K. Krishnankutty., *Main Group.Met.Chem*., 2010, **33(3),** 157.
16. B.U.Muhammed, K.Anjali and P.U.Mathew, *J.Iran.Chem.Res*., 2010, **3**, 71.

17. H.H.Tonnesen and M.Arvid and J.Karlsen, *Acta Chem.Scan*.,1982, **B36**, 475.

18. G.Sonia and T.K.Ravi, *Int.J.Pharm.Pharm.Sci*., 2011, **3**, 1491.

19. G,Sonia and T.K.Ravi, Med.Chem.Res., 2012

20. K.D.Thomas, A.V.Adhikari, I.H.Chowdhury, T.Sandeep, R.Mahmmod, B.Bhattacharya, E.Suresh, *Eur.J.Med.Chem*., 2011, 46, 4834

21. R. Subramaniam and G. Rao ,*Chem.Sci*., 2012, **66**, 1.

22. C.S. Maria, V.N.Marcus, C.P.Alessandria, L.F.Marcella, S.B.Raoni and C.M.Thais, *Arkivoc*., 2007, **(xv)**, 181.

23. L.Collins and S.G.Franzblau, *Antimicrob.Agents Chemother*., 1997, 41, 1004.

24. R. Subramaniam and G. Rao ,*Chem.Sci*., 2012, **66**, 1.

25. M.Bijo, E.M.Githa, G.Sonia, K.Anila, P.C.Neethu and K.Palanisami, *Bangladesh J. Pharmacol*., 2013, **8,** 242.

26. Mackie and McCartney, '*Practical Medical Microbiology'*, Churchill Livingstone, New York, 14th edition, 1996.

27. C.Mathewes and K.Mohanan, *Asian.J.Chem*., 2007, **19(4),** 2831.

ACKNOWLEDGMENT

I gratefully acknowledge the financial support of University of Grants Commission for completing this minor research project successfully.

I am much obliged to the Principal, Christ College, Irinjalakuda and the Head of Department of Chemistry for providing me the adequate facilities for the experimental studies.

I would like to acknowledge my gratitude to my colleagues of Christ College, Irinjalakuda for their valuable advice and timely help in completing the project.

Dr.Mathew Paul Ukken

Associate Professor, Dept.of Chemistry

Christ College, Irinjalakuda-680125