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Cu(II) Heterochelates: Synthesis, Spectroscopic, Thermal and *in-vitro* Biological Studies

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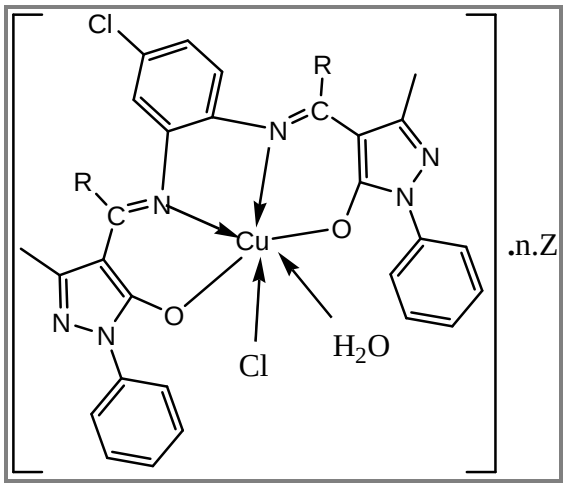
ABSTRACT

Novel organic based compound 4-Acyl pyrazolone derivatives and their thermal and biological activities were investigated. A new series of Bis-pyrazolone containing ligand and their Cu(II) based heterochelate were synthesis by various acyl chloride. The structure of bis-pyrazolone ligands were confirmed by ^{1}H NMR, IR, Elemental analysis and their heterochelates were confirmed by thermal studies (TGA and DSC) and FAB Mass spectroscopy. All the synthesized compounds were screened for their In-Vitro biological study against two Gram +ve (Bacillus cereus, Bacillus megaterium) and two Gram-ve (E. coli, E .aerogen) microorganism. The results confirmed that novel bis-pyrazolone based heterochelates have a great potential and significant for further investigation.

Graphical Abstract



The suggested structure of Heterochelate.

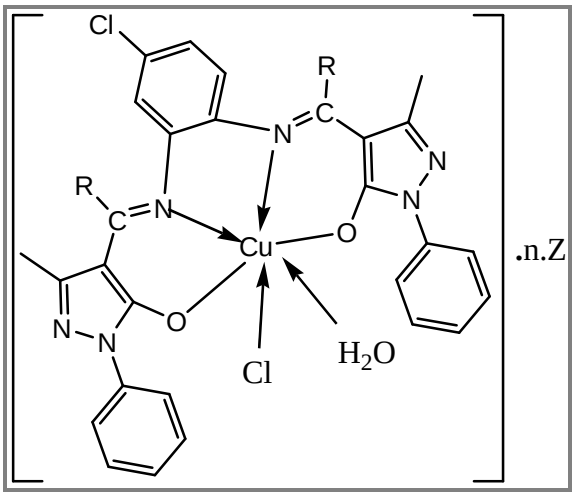
Keywords: Heterochelate, Biological Activity, Bis-pyrazolone, Novel Schiff base, Thermal Studies

INTRODUCTION

Copper complexes and clusters fascinating chemist for centuries, mostly because of the unique role these species play in both physical and biological research and applications [1]. Among the transition metal complexes Cu(II) complexes are considered the best alternative to cis platin because copper is biocompatible and exhibiting many significant roles in biological system. Several copper complexes contain pyridyl type ligands such as 1,10-Phenanthraline [2], were screened for their anticancer activity [3-5]. Sijman and co-workers [6] have develop the first chemical nucleus, Bis-1.10-Phenanthraline Cu(II) complex. Recently there has been a substantial increase in the design and study of DNA binding and cleavage properties of mixed ligand Cu(II) complex [7-10] and the development of new copper based metallodrugs.

The Chemistry of pyrazolone and its derivatives are particularly interesting because of their potential application in thermal [11], fluorescence [12], analytical [13] and biological studies [14, 15]. Further, more 4-Acyl pyrazolone derivatives have potential to form different type of coordination compounds due to the several electron rich donor centers [16, 17] and the tautomeric effect of enol form and keto form [18]. Complexes containing these ligands are known for almost every transition and main group metal [19].They are also known to show extensive solid state tautomerism and in the section of substituents with special conjugated system leads to them formation of compounds with intense stable color [20] Meanwhile the design of new bis pyrazolone based chelating ligand in coordination chemistry has been extensively investigated [21-30].

Accordingly, in continuous to our earlier work we have synthesized a series of bis pyrazolone based ligands, these new types of chelating ligands have two donor sites centered at 5,5'-OH groups. Because of the presence of two active donor site they confirm various types of heterochelates with transition metal. Here, in present work we describe synthetic, spectroscopic, thermal and in-vitro bacterial studies of some novel Cu(II) heterochelates and the general structure is shown in figure1.



S. No	Ligand	R	nH_2O	ZCl
1	L_1	$-CH_3$	-	-
2	L_2	$-CH_2CH_3$	2.5 H_2O	-
3	L_3	$-CH_2CH_2CH_3$	4 H_2O	-
4	L_4	$-C_6H_5$	1 H_2O	3 Cl
5	L_5	$-C_6H_5NO_2$	4 H_2O	4 Cl

Figure 1. The suggested structure of Heterochelate.

MATERIALS AND METHODS

Materials: All the chemicals used were of analytical grade and used without further purification. The compounds l-phenyl-3-methyl-5-pyrazolone were purchased from Sigma Ltd (India). Acylchlorides were purchased from eualigens Fine Chemicals, India and used-without further purification.

Detection Methods: FT-IR spectra were recorded as KBr pallets on Nicolet-400D spectrophotometer. ^{1}H NMR spectra were recorded on Advance 400 Bruker FT-NMR instrument in DMSO-d_6 solvent. The FAB-mass spectrum of heterochelate was recorded with JEOL SX-102/DA-6000 mass spectrometer. Simultaneous TGA were obtained by a model 5000/2960 SDT. The experiment was performed in N_2 atmosphere at heating rate of 10°C min^{-1}.

General Procedure for Ligand: A 2:1 Molar ratio of above prepared intermediates with 4-Cl-OPDA in 50 mL of methanol heated for 3-4 h by adding catalytic amount of acetic acid and check reaction completion by TLC. Obtained product crystallized by 50 mL of methanol and washed with diethyl ether so primrose yellow solid was obtained. Final ligands are confirmed with ^{1}H NMR and IR spectroscopic technique.

4-Acylated bis-pyrazolone: M.F-$C_{30}H_{27}ClN_6O_2$ Yield 76%; M.P. 218°C; Green powder; FT-IR (KBr,cm^{-1}): 3437.15 ν(O–H), 3226.91 ν(N–H), 1624 ν(C=O), 1593 ν(C=N); ^{1}H NMR (400 MHz,DMSO-d_6): δ (ppm)=2.2-2.5 (3H, s, -CH_3); 2.2-2.5 (3H, s, -CH_3); 6.6-8.0 (Ar-H);(4H,m,Py-H). Elemental analysis found (%) C, 67.01; H, 5.12; N, 15.64; Cl, 6.63 O, 5.94 N, 15.59 calculated for $C_{30}H_{27}ClN_6O_2$: C, 66.85%; H, 5.05%; N, 15.59% Cl, 6.58% O, 5.94%.

4-Propiyonal bis-pyrazolone: M.F-$C_{32}H_{31}ClN_6O_2$ Yield 76%; M.P. 223°C; Green powder; FT-IR (KBr,cm^{-1}): 3408.22 ν(O–H), 3224.98 ν(N–H), 1624.06 ν(C=O), 1593.2 ν(C=N); ^{1}H NMR (400 MHz,DMSO-d_6): δ (ppm) = 1.03-1.08 (3H,s,-CH_3); 2.51-2.53 (3H,t,-CH_3);2.54-2.58(2H,q,-CH_2) 7.1-8.0 (Ar-H); (4H,m,Py-H). Elemental analysis found (%) C, 67.78; H, 5.51; N, 14.82; Cl, 6.25 O, 5.64 N,15.59 calculated for $C_{32}H_{31}ClN_6O_2$: C, 67.02%; H, 5.21%; N, 14.02 % Cl, 6.01% O, 5.21%.

4-Butyryl bis-pyrazolone: M.F-$C_{34}H_{35}ClN_6O_2$ Yield 74%; M.P. 228°C; Green powder; FT-IR (KBr,cm^{-1}): 3423.65 ν(O–H), 3224.98 ν(N–H), 1627.92 ν(C=O), 1589.34 ν(C=N); ^{1}H NMR (400 MHz,DMSO-d_6): δ (ppm)=1.42-1.48 (3H,s,-CH_3); 1.54-1.58 (2H,m,-CH_2);2.38-2.41(3H,t,-CH_3);2.53-2.55(2H,t,-CH_2); 7.1-8.04 (Ar-H); (4H,m,Py-H). Elemental analysis found (%) C, 68.62; H, 5.93; N, 14.12; Cl, 5.96 O, 5.38 N, 15.59 calculated for $C_{34}H_{35}ClN_6O_2$: C, 68.02%; H, 5.43%; N, 14.01% Cl, 5.27% O, 5.03%.

4-Benzoyal bis-pyrazolone: M.F-$C_{40}H_{31}ClN_6O_2$ Yield 79%; M.P. 249°C; Red powder; FT-IR (KBr,cm^{-1}): 3408.22 ν(O–H), 3223.05 ν(N–H), 1627.92 ν(C=O), 1589.34 ν(C=N); ^{1}H NMR (400 MHz,DMSO-d_6): δ (ppm)=1.41-1.43 (3H,s,-CH_3); 6.71-7.38(Ar-H) (5H,s); 7.46-8.27 (Ar-H); (4H,m,Py-H). Elemental analysis found (%) C, 72.44; H, 4.71; N, 12.67; Cl, 5.35 O, 4.83 N, 12.67 calculated for $C_{40}H_{31}ClN_6O_2$: C, 71.93%; H, 4.41%; N, 12.61% Cl, 5.01% O, 4.34%.

4-Nitrobenzoyal bis-pyrazolone: M.F-$C_{40}H_{29}ClN_8O_6$ Yield 63%; M.P.263°C; Reddish brown powder; FT-IR (KBr,cm^{-1}): 3441.01 ν(O–H), 3116.97 ν(N–H), 1620.21 ν(C=O), 1577.77 ν(C=N); ^{1}H NMR (400 MHz,DMSO-d_6): δ (ppm) = 1.41-1.43 (3H,s,-CH_3); 6.75-7.42(Ar-H) (4H,s) 7.46-8.27 (Ar-H); (4H,m,Py-H). Elemental analysis found (%) C, 63.79; H, 3.88; N, 14.88; Cl, 4.71; O, 12.75; calculated for $C_{40}H_{29}ClN_8O_6$: C, 63.08 %; H, 3.31 %; N, 14.26 % Cl, 4.23% O, 12.02%.

General Procedure for Heterochelate: A general method has been adopted for the preparation and isolation of heterochelate. Hot methanolic solution of $CuCl_2.6H_2O$ (10 mmol) and solutions of respective Schiff bases (10 mmol) were mixed in1:1 molar ratio. The pH of the solution was adjusted by drop wise addition of 25% NaOH solution in water. The mixture was heated for 4-h at 70°C and

kept it overnight at room temperature. The obtained colored crystals were washed with water, methanol and finally with diethyl ether and dried in air.

RESULTS AND DISCUSSION

The structural investigation of all the prepared Schiff base ligands and heterochelates were carried out using elemental analysis, IR, ^{1}H NMR, FAB-Mass spectra and TGA analysis. The ^{1}H NMR data of Schiff base ligands are given in experimental section. The analytical and physical data of heterochelates are given in table 1. Heterochelates were sparingly soluble in methanol and completely soluble in DMF and DMSO. All the heterochelates were stable in air for extended period of time.

Table 1. Analytical and physical data of Heterochelates

Sample No.	Compounds	Formula Weight	Color (%Yield)	Analysis (%) Found(Cal)					
				C	H	Cl	N	O	M
ML_1	$[Cu(L_1)Cl.H_2O]$ $C_{30}H_{27}Cl_2N_6CuO_3$	653.5	Yellow (78)	58.25 (58.02)	4.40 (4.29)	5.73 (5.65)	13.59 (13.51)	7.76 (7.71)	10.27 (10.13)
ML_2	$[Cu(L_2)Cl.H_2O].2.5\ H_2O$ $C_{33}H_{40}Cl_2N_6CuO_{3.1/2}$	727.3	Yellow (72)	59.44 (59.33)	4.83 (4.75)	5.48 (5.38)	13.00 (12.98)	7.42 (7.35)	9.83 (9.72)
ML_3	$[Cu(L_3)Cl.H_2O].4H_2O$ $C_{35}H_{47}Cl_2N_6CuO_7$	798.3	Dark Yellow (70)	55.11 (55.02)	6.21 (6.12)	4.65 (4.57)	11.02 (10.95)	14.08 (13.96)	8.33 (8.26)
ML_4	$[Cu(L_4)Cl.H_2O].H_2O.3Cl$ $C_{40}H_{33}Cl_5N_6CuO_4$	902.7	Reddish Yellow (67)	64.69 (64.61)	4.21 (4.13)	4.77 (4.69)	11.32 (11.24)	6.46 (6.34)	8.56 (8.48)
ML_5	$[Cu(L_5)Cl.H_2O].4H_2O.4Cl$ $C_{40}H_{37}Cl_6N_8CuO_{11}$	1082.2	Reddish Yellow (60)	57.69 (57.60)	3.51 (3.45)	4.26 (4.21)	13.46 (13.40)	13.45 (13.38)	7.63 (7.58)

^{1}H NMR spectra of ligands: The tautomerism of pyrazolone is a subject of considerable number of studies [**31, 32**]. The ^{1}H NMR studies of Schiff base ligands were carried out in DMSO-d_6 at room temperature. The data are represented in experimental section in case of ^{1}H NMR spectra of ligand two sharp singlet equivalent to one and two protons observed in the range of 12-13 δ ppm corresponding to -OH group [**33, 34**]. This Signal disappeared when a D_2O exchange experiment was carried out. Aromatic protons are observed in the range of 6.5-8.5 δ ppm and singlet's for methyl group in Schiff base ligands are observed in the range of 1.5 to 3.0 δ ppm. In case of the given NMR spectrum of L_1H (Figure 2), All the signals of -CH_3, aromatic protons and -OH group in NMR are respectively in repeated manner may indicate the presence of both keto and enol form. Also, the intensity of signal may helpful to define the percentage ratio of each form present in solution during

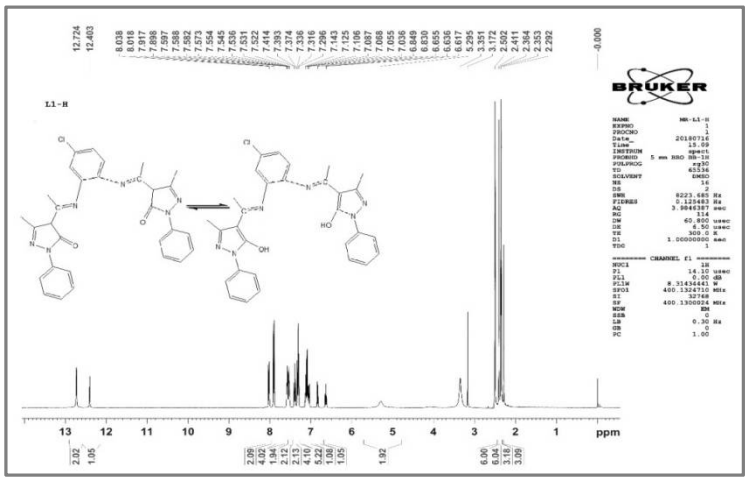


Figure 2. NMR spectrum of L_1.

the analysis. In some case signals of methyl group are overlapped with either solvent or moisture peak and all of these signals are closely spaced show it is difficult to assign each signal to a particular methyl group unambiguously [35]. On the basis of ^{1}H NMR spectroscopic data it is observed that Schiff base ligand exists in Keto-Enol form in solution state.

Infrared Spectra: In order to study the binding mode of Schiff base (L_1 to L_5) to the Cu(II) ion in the heterochelates the IR spectra of Schiff base were compare with spectra of corresponding heterochelates. The Schiff base ligand in this investigation exhibits a broad band centered at 3408 to 3441 cm^{-1} this indicates the involvement of the 5-OH group in intramolecular H-bonding [36-39]. With the lone pair of azo methine it also suggests that the ligand exist in enol form of solid state. The Schiff base ligand (L_1 to L_5) shows a sharp and strong band of a υ(C=N) of the acyclic azomethine group at 1577 to 1593 cm^{-1}. The observed low energy shift of this band in the heterochelates and appearing at 1520 to 1565cm^{-1} suggest the co-ordination of azomethine nitrogen [40, 41]. The IR spectra of heterochelates shows a considerable negative shift of 15-20 cm^{-1} in υ(C=O) absorption of the pyrazolone group indicating a decrease in the stretching force constant of υ(C=O) as a consequence of co-ordination through the oxygen atom of the ligand. All of this data confirms the fact that (L_1 to L_5) behave as a dinegative bidentate ligand and forming a conjugate chelate ring with the ligand existing in the heterochelate in the enolic form.

Thermal Studies: Each decomposition process follows the trend

$$\text{Solid-1} \xrightarrow{heat} \text{Solid-2} + \text{Gas}$$

This process comprises of several stages.

The thermal fragmentation scheme for heterochelates $[Cu(L_n).Cl.H_2O].x.H_2O.y.Cl$ is as shown below

$$[Cu(L_n).Cl.H_2O].x.H_2O.y.Cl \xrightarrow{\substack{0-235\ ℃ \\ removal\ of \\ crystaline\ Cl+H_2O}} [Cu(L_n).Cl.H_2O] + x.H_2O.y.Cl$$

$$[Cu(L_n).Cl.H_2O] \xrightarrow{\substack{235-450\ ℃ \\ removal\ of \\ coordinate\ Cl+H_2O}} [Cu(L_n)]$$

$$[Cu(L_n)] \xrightarrow{\substack{450-750\ ℃ \\ removal\ of \\ ligand}} CuO$$

n	x(H_2O)	y(Cl)
1.	-	-
2.	2.5	-
3.	4	-
4.	1	3
5.	4	4

TG and DSC curves of heterochelates $[Cu(L_1).Cl.H_2O]$ are represented in figure 3. The decomposition of heterochelates $[Cu(L_1).Cl.H_2O]$ takes place in three stage. The thermal dehydration and dehalogenation of this heterochelates take place in a single step between 0 to 400℃ with mass loss of 63.48% (63.13%). 1 mol of coordinated H_2O and Cl molecule may remove in this stage. This process is accompanied by endothermic effect at 130.3℃ and 173.4℃ respectively. The second step which occurs in the temperature range of 400 to 550℃ corresponds to decomposition of some part of the L_1 ligand, the observed mass loss 23.72% (23.45%). The endothermic peak at 409℃ corresponds to this stage is given by DSC curve (Figure 3).

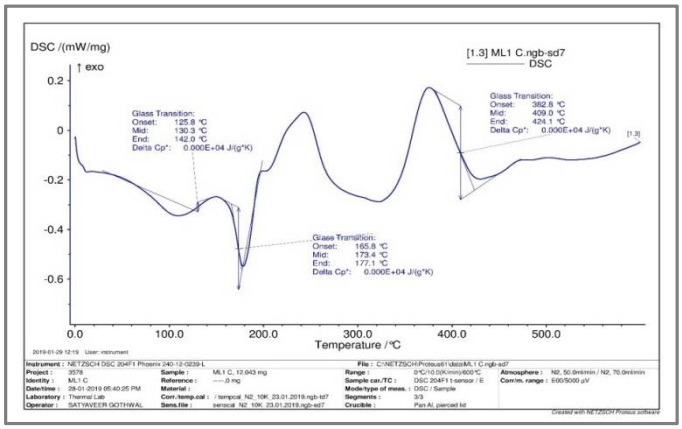


Figure 3. DSC curve of $Cu(L_1)Cl.H_2O$.

The third stage is related to the decomposition of related part of L_1 Ligand and estimated amount of CuO in temperature range of 550 to 750°C accompanied by mass loss 12.16% (12.11%). The overall mass loss observed is 98.76% as compare to theoretical value 98.69%. From the above discussion proposed octahedral structure of heterochelate can be assumed as shown in figure 1 and thermodynamic data of heterochelate are reported in table 2 and TGA curves of Cu(II) heterochelates are shown in figure 4.

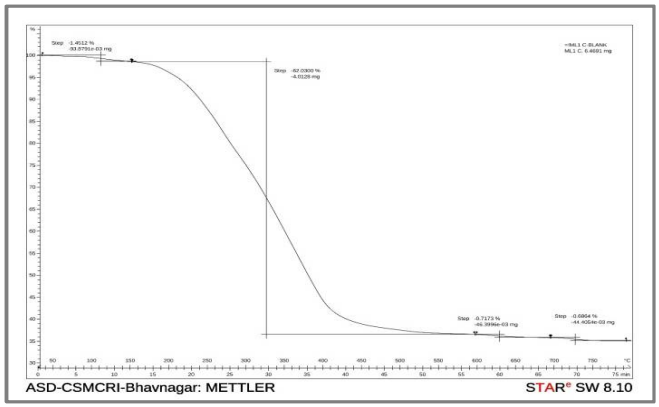


Figure 4. TGA Analysis of $[Cu(L_1)Cl.H_2O]$.

FAB Study: The recorded FAB mass spectrum figure 5 and the molecular ion peak for the heterochelate $[Cu(L_1)Cl.H_2O]$ were used to confirm the molecular formula. The proposed fragmentation pattern is shown in scheme (1). The first peak at m/z=653 represents the molecular ion peak of heterochelates. Scheme (1) demonstrates the possible degradation path way for the investigated heterochelates. The primary fragmentation of the heterochelate take place due to the loss of coordinated H_2O and Cl molecule from the species **(a)** to give species **(b)** with peak at m/z=600.

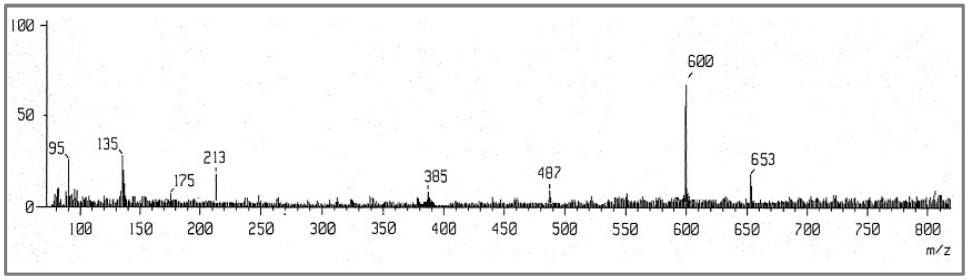
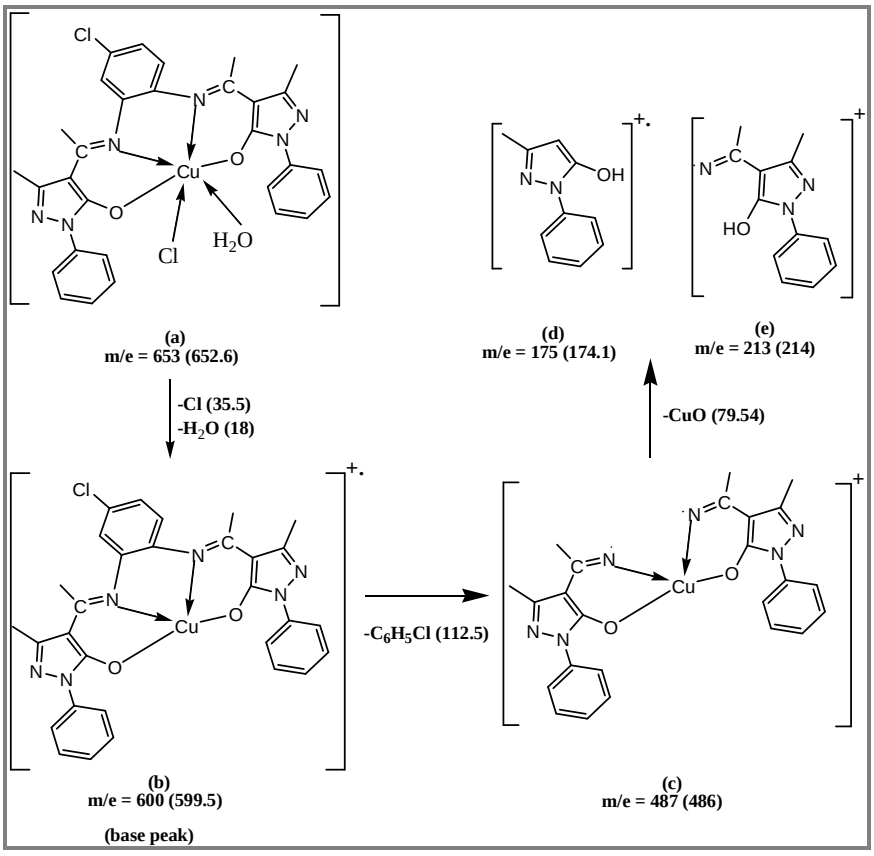


Figure 5. FAB Mass Spectrum of $[Cu(L_1)Cl.H_2O]$.

Further degradation yields species **(c)** with loss of C_6H_5Cl. Species **(c)**further degrade to species **(d)** and **(e)** with loss of CuO. The sharp peak (base peak) observed at m/z=600 represent the stable species **(b)** with 98.0% abundance. The measured molecular weight for all the suggested degradation steps was with expected value [42].

Table 2. Thermo Analytical Results of Heterochelates

S. No.	Heterochelates	Temp. Range	Mass Loss (%) Obs. (Cal.)	Analysis
1	$[Cu(L_1)Cl.H_2O]$	0-400 400-550 550-750	63.48 (63.13) 23.72 (23.45) 12.16 (12.11)	Along with co-ordinated -Cl and -H_2O,some part of ligand may loss Ligand molecule may loss and remaining Cu. Remaining Cu may present as CuO
2	$[Cu(L_2)Cl.H_2O].2.5H_2O$	0-180 180-350 350-750	6.57 (6.41) 7.71 (7.21) 73.55 (72.89)	2.5 H_2O crystalline molecule may loss Cl.H_2O Co-Ordinated molecule may loss Leaving CuO residue
3	$[Cu(L_3)Cl.H_2O].4H_2O$	0-175 175-380 380-750	10.15(10.02) 7.40 (7.14) 68.84 (68.67)	4 H_2O crystalline molecule may loss Cl.H_2O Co-Ordinated molecule may loss Leaving CuO residue
4	$[Cu(L_4)Cl.H_2O].Cl_3.H_2O$	0-220 220-430 430-750	13.42(13.10) 6.77(6.21) 65.35(65.02)	Crystalline -Cl and -H_2O molecule may loss Cl.H_2O Co-Ordinated molecule may loss Leaving CuO residue
5	$[Cu(L_5)Cl.H_2O].Cl_4.4H_2O$	0-235 235-450 450-750	24012(23.98) 6.08(5.98) 55.56(55.26)	Crystalline -Cl and -H_2O molecule may loss Cl.H_2O Co-Ordinated molecule may loss Leaving CuO residue



Scheme 1. The Suggested Fragmentation pattern of $[Cu(L_1)Cl.H_2O]$.

Zone of Inhibition: A stock solution of 10 mg mL^{-1} was made by dissolving compound in minimum amount of DMSO and making it up to the mark with double distilled water. The medium was made up by dissolving bacteriological agar (20 g) and Luria broth (20 g; SRL, India) in 1-liter distilled water. The mixture was autoclave for 15 min at 120°C and then dispensed into sterilized Petri dishes, allowed to solidify and then used for inoculation. The target microorganism cultures were prepared separately in 15 mL of liquid Luria broth medium for activation. Inoculation was done with the help of micropipette with sterilized tips; 100 µL of activated strain was placed onto the surface of an agar plate and spread evenly over the surface by means of a sterile, bent glass rod. Then two wells having diameter of 10 mm were made using a sterilized borer in each plate. Application of disks Sterilized stock solutions (10 mg mL^{-1}) were used for the application in the well of earlier inoculated agar plates. When the disks were applied, they were incubated at 30°C (Gram+ve) and 37°C (Gram-ve) for 24 h. The zone of inhibition was then measured (in mm) around the disk shown in figure 6 The control experiments were performed with only the equivalent volume of solvents without added test compounds and the zone of inhibitions was measured (in mm) shown in table 3 [**43**].

Table 3. Antimicrobial Effects of The Ligands and Their Heterochelates

S.No	Compounds	Gram+ve		Gram-ve	
		Bacillus Cerus	*Bacillus Megaterium*	*E. Coli*	*E. Aerogen*
1	L_1	5	4	7	5
2	L_2	7	5	10	6
3	L_3	4	6	**10**	6
4	L_4	8	8	8	7
5	L_5	8	8	6	6
6	CuL_1	12	19	13	13
7	CuL_2	13	16	14	11
8	CuL_3	15	19	**16**	10
9	CuL_4	14	14	10	14
10	CuL_5	17	17	12	11

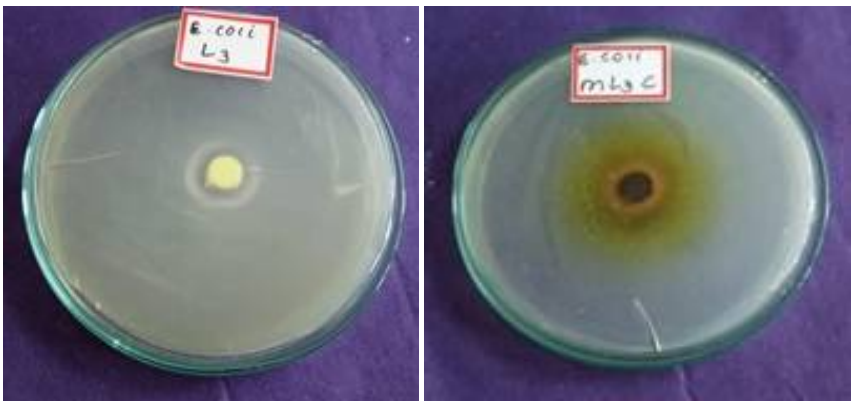


Figure 6. Zone of inhibition(mm) of Ligand and its Heterochelates.

APPLICATION

All the synthesized ligands namely L1-L5 and their heterochelates ML1-ML5 (where M = Cu) where screened against the bacterial strains. The antimicrobial screening data (Table no 3) shows that heterochelate exhibit more inhibitory effects towards gram +ve and gram -ve bacteria then the parent ligand. The ligands (L_3) and heterochelates (CuL_3) are much powerful bactericides against *E.coli*. The increased activities of the heterochelates as compared to ligands can be explained on the basis of overtone concept [**44**] and chelation theory [**45**].

CONCLUSION

The design and synthesis of new bis pyrazolone ligand have been successfully demonstrated FT-IR and ^{1}H NMR Spectral studies reveal that ligand exists in tautomeric enol form both in solid and solution state with intramolecular H-bonding. We have synthesized a series of some novel Cu(II) heterochelates with bis-pyrazolone derivative and characterize their properties. All the synthesized compounds were screened for their bioassay. The heterochelates exhibit strong activities against Gram+ve (*Bacillus cerus*, *Bacillus megaterium*) and Gram-ve *(E. coli*, *E. aerogen*) organisms in comparison with ligand. The heterochelates were more active against one or more bacterial strain introducing a novel class of metal based bactericidal agents.

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