Synthesis, Characterization and Studies on d^{10} Metal Complexes Derived from Acyl Pyrazolones

Synopsis

Submitted to

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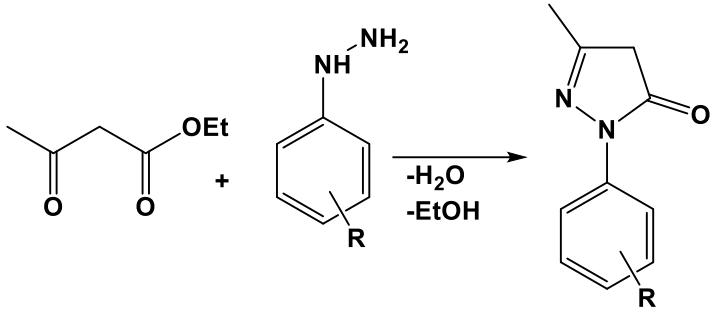
Chapter 1: Introduction

1.1 Pyrazolone

The pyrazolone synthesis was reported in 18th century by L. Knorr by the reaction between ethyl acetoacetate and substituted phenyl hydrazine.[1]



R= -H, -Cl, and -CH_3

Figure 1. Synthesis route of pyrazolone derivatives

1.2 Acyl Pyrazolone

In the synthesis of acyl pyrazolone, the reactants are the corresponding acyl chlorides and 1-phenyl-3-methylpyrazol-5-one.[2–5]

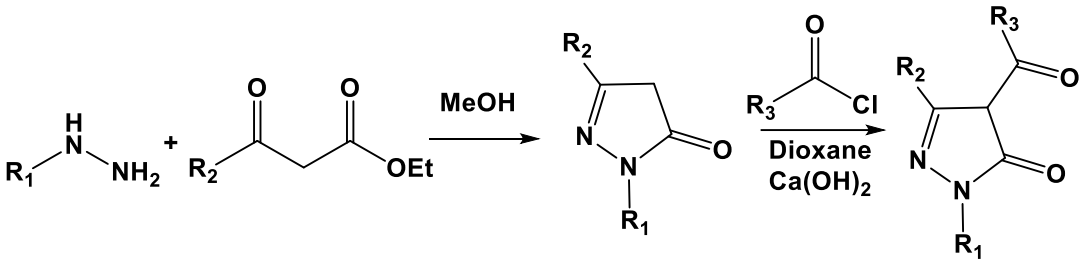


Figure 2. Syntheses of the acylpyrazolones (AP).

Acylationeasily occurs at C-4 position of the pyrazole ring in basic (calcium hydroxide) dioxane or THF at reflux. Subsequent treatment with acid aqueous solution affords the AP in high yield as a solid powder insoluble in water Acyl substitution has been much more explored, where a large number of groups, from alkyl to

1.3. 4-Acylhydrazone-5-pyrazolones

As the primary structural motif, pyrazolone is present in many bio-active compounds.

Schiff base ligands of pyrazolone can form multifarious complexes with a variety of metals, due to its enol–keto tautomerism and capacity to coordinate with metals in a series of deprotonated states such as dianionic and monoanionic forms.

In recent years, considerable attention has been paid to pyrazolone derivatives and its complexes in medicinal chemistry because of their easy preparation, stability, plasticity and strong bio-activity.[9–13]

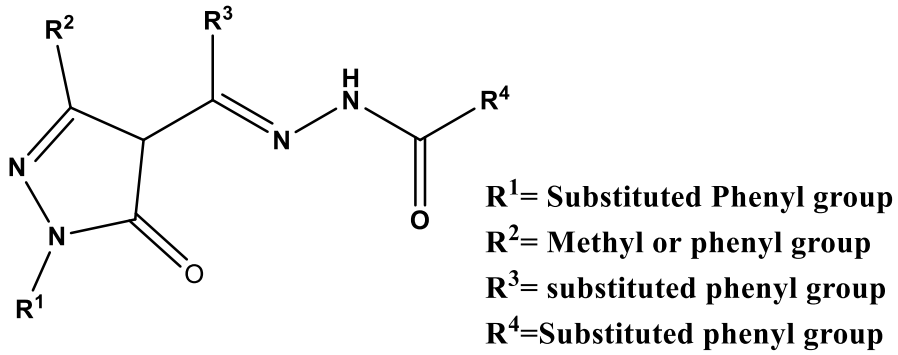


Figure 3. Generic structure of 4-acylhydrazone-5-pyrazolone.

1.4. Zinc as a d^{10} Metal in the Complexation.

Coordination numbers of zinc are most commonly four to six, with three not quite so common, and two, seven and eight less often observed and more dependent on donor or ligand types.[14–16]

1.5. Zinc (II) Complexes in the Biological Activity.

Zinc compounds are receiving an increasing attention due to the numerous physiological roles of the zinc(II) complexes investigated in many fields (**binder complexes at DNA, Antitumor, antidiabetic insulin-mimetic and antibacterial or antimicrobial activities**).[14–21]

Zinc seems to play a role in the growth and survival of cells, moreover it displays a versatile coordination chemistry with diverse possible geometries while preserving the same oxidation state.[15]

Based on this facts, *we started to investigate the antimalarial potentials of Zn(II) complexes.* Here we did the evolution of *Insilico* and *Invitro* antimalarial activity of synthesized Zinc complexes.

Chapter 2

Part (a): Binary Mononuclear Zinc (II) Complexes of 4-acyl Pyrazolones: Synthesis, Characterization and Structural Features.

2.1. Syntheses of ligands

2.1.1. 4-(4-chlorobenzoyl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (L1)

3-methyl-1-phenyl pyrazolone-5-one (0.1 mole, 17.4gm) was dissolved in hot dioxane (80 ml) in a round bottom flask equipped with a mechanical stirrer, separating funnel and reflux condenser. Calcium hydroxide (0.2 mol, 14.81gm) was added to this solution, followed by 4-chloro benzoyl chloride (0.1 mol, 12.82 ml) added drop wise with precaution, as this reaction was exothermic. While this whole mass was converted into a thick paste. After the complete addition, the reaction mixture was refluxed for two hour and then it was poured into dilute hydrochloric acid (2 M, 200 ml). The colour crystals (HL^1) thus obtained were separated by filtration and recrystallized from Rectified spirit. M.P. 105ºC, Yield 70.85 %, Molecular formula: $C_{17}H_{13}ClN_2O_2$ (calc. M.W. 312.75). IR (KBr, cm^{-1}): 1558 (C=N, cyclic), 1589 (C=O, p-chloro benzoyl group); 1619(C=O, Pyrazolone ring); ^{1}H NMR ($CDCl_3$, 400MHz): δ *ppm* 2.1 (s) (3H, Pyrazolone C-CH_3), 7.5-7.6 (dd, 4H Ar C-H), 7.4-7.8 (m, 5H Phenyl of pyrazolone); ^{13}C NMR ($CDCl_3$, 400MHz) δ *ppm* 191, 161, 148, 138, 137, 136, 129.3, 129.1, 128.8, 127, 121, 103, 16.[21]

2.1.2. Synthesis of 4-(4-chlorobenzoyl)-2-(3-chlorophenyl)-5-methyl-2,4-dihydro-3H-pyrazol-3-ne (L2).

The synthesized ligand were reported in Shaikh et. al., 2019, [22]. (See Scheme 1) Yield: 58%. Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_2$(%): C, 58.81; H, 3.48; N, 8.07; Found(%): C, 58.57; H, 3.71; N, 8.15. M.w.: 347.20. M.P.: 105 °C.Λ_m ($S.cm^2.mol^{-1}$): 8.8.FTIR (KBr plates) υ (cm^{-1}): 1625(s) (C=O, amide of pyrazolone), 1590(m) (C=O, 4-chloro benzoyl), 966(s) (N-N of pyrazolone), 1486(m) (aromatic -C-C). ^{1}H NMR ($CDCl_3$) δ ppm: 2.14 (s, 3H, pyrazolone C–CH_3), 7.28-7.30 (m, 1H, m-chloro ph), 7.39-7.43 (m, 1H, m-chlorophenyl), 7.51-7.63 (m, 4H, *p*-chloro benzoyl), 7.83-7.85 (m, 1H, m-chloro ph), 7.963-7.968 (m, 1H, m-chloro ph). ^{13}C NMR ($CDCl_3$) δ ppm: 16 (-CH_3- pyrazolone), 103, 118, 120, 126, 128, 129, 130, 134, 135, 138, 138, 147 , 162 (C=O, amide of pyrazolone), 190 (C=O, 4-chloro benzoyl).

2.1.3. Synthesis of 4-(4-chlorobenzoyl)-5-methyl-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one (L3)

We have reported this ligand in Shaikh et al., 2019.[21] Yield: 65.5 %, Anal. Calcd for $C_{18}H_{15}ClN_2O_2$(%): C, 66.16; H, 4.63; N, 8.57, Found(%): C, 66.11; H, 4.71, N, 8.77. M.w.: 326.78. M.P.: 108ºC.Λ_m ($S.cm^2.mol^{-1}$): 10.1.IR (KBr, cm^{-1}): 1551(C=N, cyclic), 1590 (C=O, 4-chloro benzoyl group) 1625 (m) (C=O, Pyrazolone ring); ^{1}H NMR ($CDCl_3$, 400MHz): δ *ppm* 2.1 (s, 3H, Pyrazolone

C-CH_3), 2.38-2.39(m, 1H, -CH-cyclic), 2.4 (s,3H, CH_3-Ar) , 7.28-7.30 (d, 2H, aromatic, *J*=8Hz), 7.50-7.52(m, 2H, aromatic), 7.60-7.62 (d, 2H, p-chloro benzoyl-, *J*=8Hz),7.72-7.74(d, 2H, p-chloro benzoyl-, *J*=8Hz); ^{13}CNMR ($CDCl_3$, 400MHz) 16(-CH_3, pyrazolone), 21(-CH_3 toluyl), 30, 103, 121, 128.7, 129, 130, 131, 135, 136, 138, 147, 160(C=O, amide of pyrazolone), 191(C=O, 4-chloro benzoyl).[21] Synthesis of ligands summarized in **Scheme 1**.

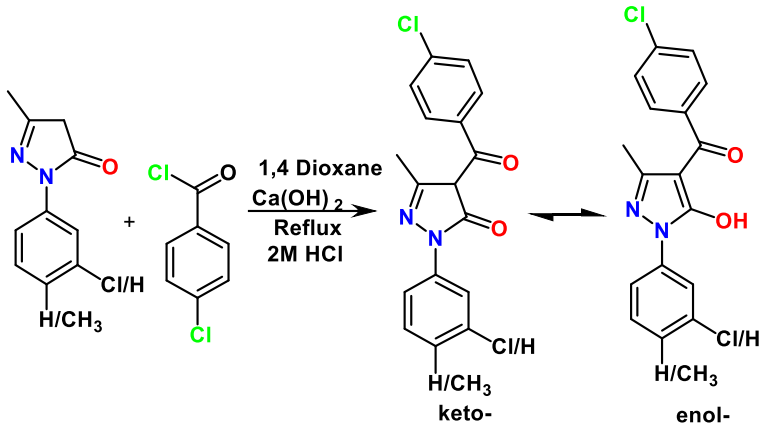


Figure 4. Synthesis route of ligands L1-L3.

2.2. Synthesis of Binary Zinc (II) complexes 1-3.

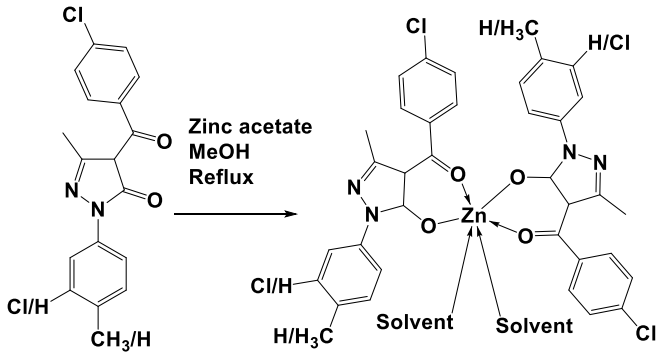


Figure 5. Synthesis route of binary Zinc (II) complexes **1-3** of 4-acyl pyrazolone.(In the complex **1** coordinated solvent is Methanol, in complex **2** and **3** coordinated solvent is water.)

2.2.1. [Zn(L1)$_2$(CH$_3$OH)$_2$] (Complex 1)

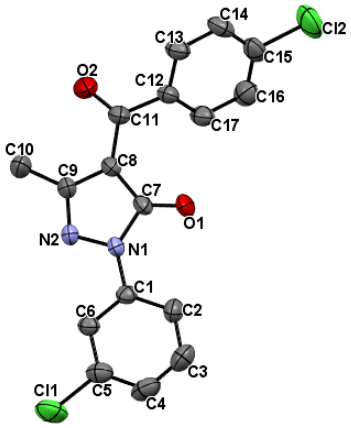
The complex was synthesized by the following method. The metal salt Zinc acetate dihydrate ($Zn(CH_3COO)_2$•$2H_2O$) (0.219 gm, 0.001 mol) was dissolved in methanol and the solution was added to methanolic solution of the ligand (HL^1) (0.625gm, 0.002 mol). After complete addition, the mixture was refluxed about for 3 hours. The reaction mixture was then filtered and was washed with MeOH and hot water and dried in air. It was recrystallized from $CHCl_3$+MeOH at low temperature. M.P. >200 ºC, Yield 78 %, Molecular formula: $C_{36}H_{32}Cl_2N_4O_6Zn$ (calc Molecular Weight: 752.95); IR (KBr, cm^{-1}): 3109 (co-ordinated CH_3-OH), 1613 (C=O p-chloro benzoyl group), 1494 (C=N cyclic), 1457 (C-O, pyrazolone ring), 505 (Zn-O); ^{1}H NMR (DMSO-d6) δ *ppm* 1.6 (s, 3H pyrazolone CH_3-), 7.53-7.42 (dd, 4H, p-chloro benzoyl), 7.9-7.1(Ar-H, phenyl of pyrazolone).[21]

2.2.2. $[Zn(L2)_2(H_2O)_2]$ (complex 2) and $[Zn(L3)_2(H_2O)_2]$ (complex 3)

The complex 2 and 3 were synthesised by the previous method which is used in complex 1.

2.3. Crystallographic Data of Ligands and complexes

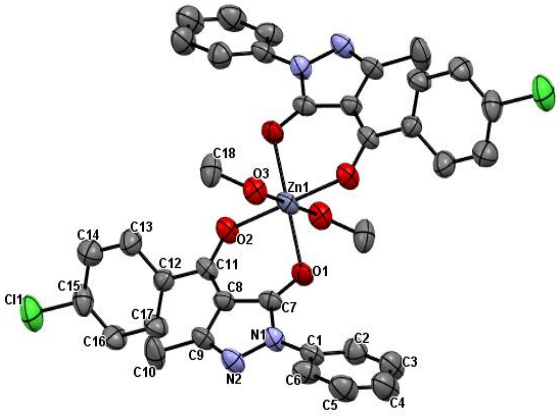
2.3.1. Crystal feature of Ligand L2.



O1-C7 (1.243 Å) and O2-C11 (1.222 Å) bond length indicating double bond. Double bond between N2-C9 (1.314 Å), C9-C8 (1.391 A) and C8-C7 (1.427 A) having double bond and single bond respectively. C9-N2 (1.314 A) and N2-N1 (1.366 A) both have single bonds.[5]

Figure 6. Atom numbering scheme of L2

2.3.2. Crystal features of Complex 1.



In the complex, the zinc atom occupies a distorted octahedral environment (OH), formed by four oxygen atoms [O(1), O(2)] supplied by one pyrazolone ligand (Symmetry code: (i) 12-X,-Y,2-Z).

Figure 7. *ORTEP* diagram of complex 1. H-Atoms are omitted for clarity.

2.4. Thermogravimetric analysis

Binary complexes show first degradation at up to 100 °C due to the coordinated solvent molecules in the complexes. Second degradation start after 360 due to pyrolysis of acyl pyrazolone in all complexes. Complex **2** and **3** contain water molecule in complex and complex **1** having coordinated MeOH molecule in the complex.[21]

2.5. Electronic spectral Study

All complexes were completely soluble in DMSO. In the complexes Uv/Vis spectra, the first intense band is attributed to a ligand-centered (LC) π–π* transition localized on the aromatic rings of the ligand.

There is no d-d transition in all complexes due to d^{10} metal. Compounds bearing the coordinated acyl pyrazolone ligands, show an intense band at around 275-280 nm, and LMCT band at around 350-360 nm.[21]

2.6. Conclusion

The 4-acyl pyrazolone ligands have been prepared by the acylation of pyrazolone derivatives with 4-chloro benzoyl chloride. Ligands have been characterized by **IR, X-ray crystal study, ^{1}H NMR, and ^{13}C NMR spectroscopy.** Binary Zn(II) complexes of these ligands have been synthesized and fully **characterized by metal estimation, molar conductance, UV/Vis, FTIR, Thermogravimetric analysis, ^{1}H NMR, and single crystal X-ray study**.

Chapter 2

Part (b): Ternary Mixed Ligand Zinc(II) Complexes of 4-Acyl Pyrazolone with 2,2'-Bipyridine and 1,10'-Phenanthroline: Synthesis, Characterization and Structural Features.

2.2.1. Synthesis of the ternary mixed ligand Zn(II) complexes

2.2.1.1. Synthesis of complex 4 $[Zn(L1)_2(bpy)]$

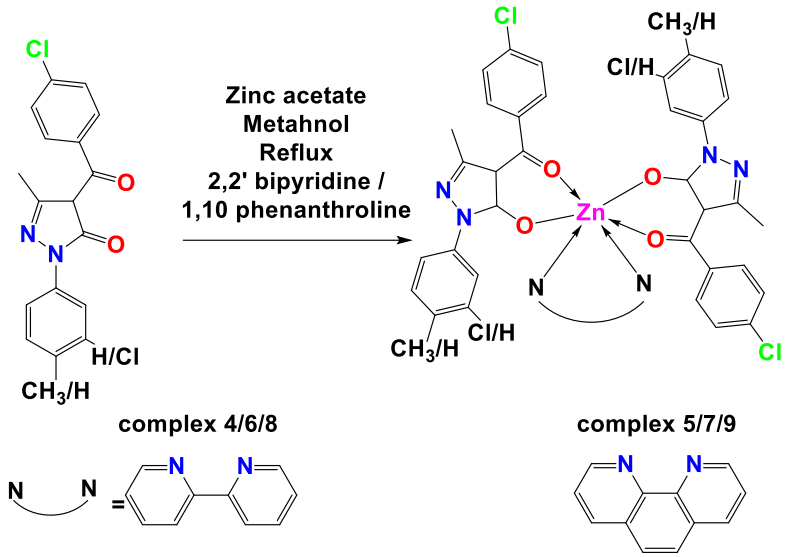
Preparation of complex 4 as follow, The metal salt Zinc-acetate dehydrate ($Zn(CH_3COO)_2.2H_2O$) (0.219 gm, 0.001 mol) was dissolved in methanol and the solution was added to a hot methanolic solution of the ligand (HL^1) (0.625gm, 0.002 mol) and2,2'-bipyridine (0.154 gm, 0.001 mol). After complete addition, little amount of sodium acetate was added and the mixture was refluxed about for 5 hours and cool it for overnight after a night crystalline solid was obtained. The mixture was filtered and washed with hot water and dried in air. M.P. >200ºC, Yield 82.42%, Molecular formula: C42H30Cl2N6O4Zn (cacl.M.W. 819.02 gm/mole);IR (KBr, cm-1): 1622 (m) (C=O p-chloro benzoyl group), 1527 (s) (C=N cyclic), 1469 (C-O, pyrazolone ring), 480 (Zn-O), 422 (Zn-N); ^{1}H NMR ($CDCl_3$, 400MHz) δppm 1.62 (s, 3H, CH_3-Pyrazolone), 7.08-7.90 (H-Ar, phenyl of pyrazolone), 8.01-9.06 (m, 4H, 2, 2'bipyridine).[21]

2.2.1.2. Synthesis of complex 5

The procedure for the preparation of complex **5** is similar to that for complex **5** except for the replacement of 2, 2' bipyridine with 1, 10 phenanthroline.[21] Yield: 86.7%. Anal. Calcd for $C_{48}H_{40}Cl_2N_6O_4Zn$: C, 63.98; H, 4.47; N, 9.33%, Found: C, 64.01, H, 4.55; N, 9.65%. M.w.: 901.17. M.P.: >200°C. Λ_m ($S.cm^2.mol^{-1}$): 9.7. Metal estimation by gravimetrically and volumetrically Zn=7.26%. FTIR (KBr, cm^{-1}): 1562(C=N, cyclic), 1622 (C=O, 4-chloro benzoyl group), 943(s) (N-N), 1436 (s) (Ar-C-C-).^{1}H NMR ($CDCl_3$, 400MHz) δppm:1.6 (s,3H, CH_3-tolyl), 2.2 (s, 3H, Pyz-C-CH_3) ,

6.99-7.02 (d, 2H, aromatic-H, *J*=8Hz), 7.24-7.31(m, 2H, ar-H), 7.60-7.62 (d, 2H, aromatic-H, *J*=8Hz),7.72-7.74(d, 2H, 4-chloro benzoyl-, *J*=8Hz).9.30-9.31 (m, 1H, aromatic), 8.49-8.51(m, 1H, phen). Synthesis route for complexes **4-9** summarized in **Scheme 2.**

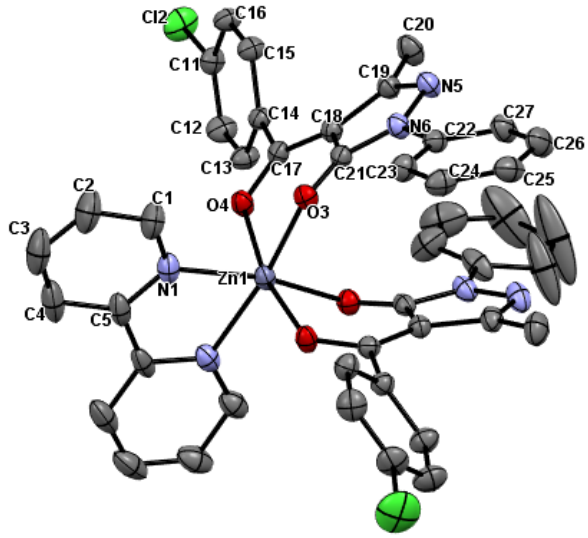
Complex 6, 7, 8 and 9 are prepared by following the method of complex 4 and 5.



Scheme 1. Synthesis route for mixed ligand complexes **4-9.**

2.2.2. Crystallography of complexes

2.2.2.1. Crystal features of complex 4



The angels of O(2)–Zn(1)–N(1), O(3)–Zn(1)–N(2)and O(1)–Zn(1)–O(4) are 168.06(12)°, 170.50(12)° and 167.81(9)°, respectively, which are deviated from the theoretical value of 180° of proper geometric structure.

Therefore, the local coordination geometry around the Zn^{+2} centre can be described as a distorted octahedron.

Figure 8. ORTEP diagram of complex 4. H-atoms are omitted.

2.2.2.2. Crystal features of complex 9

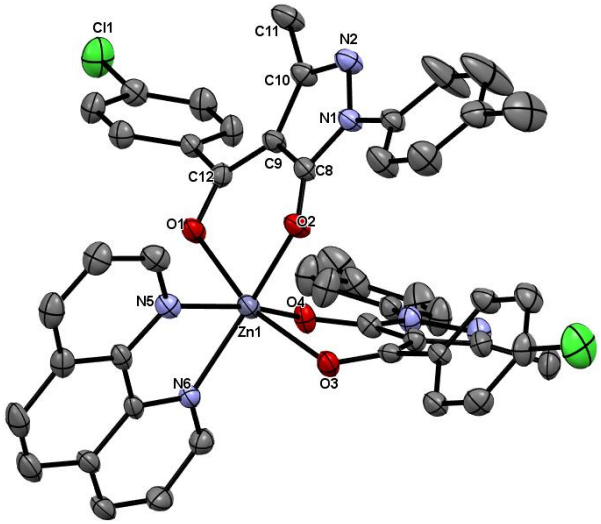


Figure 9. ORTEP view of complex **9**. H-atoms are omitted for clarity.

Angles between O(2)-Zn(1)-N(6), O(4)-Zn(1)-N(5) and O(1)-Zn(1)-O(3) are 166.95(13)°, 164.65(12)°, and 163.50(10)° respectively.

These angles have deviated from the theoretical value of 180° of proper geometric structure. Therefore, the local coordination geometry around the Zn(II) center can be described as a distorted octahedral geometry.

2.2.3. Thermogravimetric analysis

Ternary mixed ligand complexes 4, 6 and 8 show first degradation after 250 °C due to the pyrolysis of coordinated 2, 2' bipyridine in the complexes. Second degradation start after 360 due to pyrolysis of acyl pyrazolone in all complexes.

2.2.4. UV-Vis spectroscopy of compounds.

All complexes were completely soluble in DMSO. In the complexes Uv/Vis spectra, the first intense band is attributed to a ligand-centered (LC) π–π* transition localized on the aromatic rings of the ligand, while the shoulder is due to its metal coordination and LMCT band at around 350-360 nm.[23,24]

2.2.5. Molar conductance of compounds.

The molar conductivity measured for all the complexes in 10^{-3} M DMSO solution is found to be below 14 ohm^{-1} cm^2 mol^{-1}. So the conductance measurements in DMSO suggest that they are non-electrolytes. (Geary *et al*.,

2.2.6. Conclusion

The 4-acyl pyrazolone ligands have been prepared by the acylation of pyrazolone derivatives with 4-chloro benzoyl chloride. They have been characterized by IR, ^{1}H NMR, single crystal X-ray crystallography and ^{13}C NMR. Binary and mixed-ligand Zn(II) complexes of these ligands have been synthesized and fully characterized by metal estimation, molar conductance, Thermogravimetric analysis, UV/Vis, FTIR, ^{1}H NMR, and single crystal X-ray study.

Chapter 3

4-Acylhydrazone-5-pyrazolones and their Zinc(II) metal complexes : Synthesis, Characterization and Crystal study.

Part (a): Synthesis, Characterization and Crystal Study Of Zinc(ii) Complexes Of 4-acylhydrazone-5-pyrazolones.

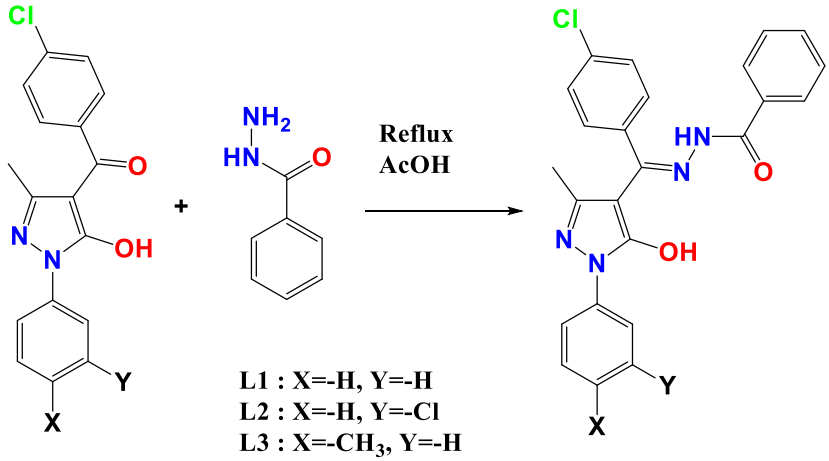
3.1. Synthesis of ligands

3.1.1.(Z)-*N*'-((4-chlorophenyl)(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)methylene)benzohydrazide (L1)

4-(4-chlorobenzoyl)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (L1) was dissolved in the EtOH. Solution of L1 was mixed with a solution of benzohydrazide in EtOH. Acetic acid was used as a catalyst and refluxed for 4 hours. Yellow precipitate was formed and isolated by gravity filtration. Recrystallized in EtOH.

3.1.2.(E)-*N*'-((4-chlorophenyl)(1-(3-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)methylene) benzohydrazide (L2)

3.1.3.(E)-*N*'-((4-chlorophenyl)(5-hydroxy-3-methyl-1-(p-tolyl)-1H-pyrazol-4-yl)methylene)benzohydrazide (L3)



Scheme 2 Synthesis route for ligands L1-L3.

3.2. Synthesis of Simple Zinc (II) complexes of 4-acylhydrazone-5-pyrazolone

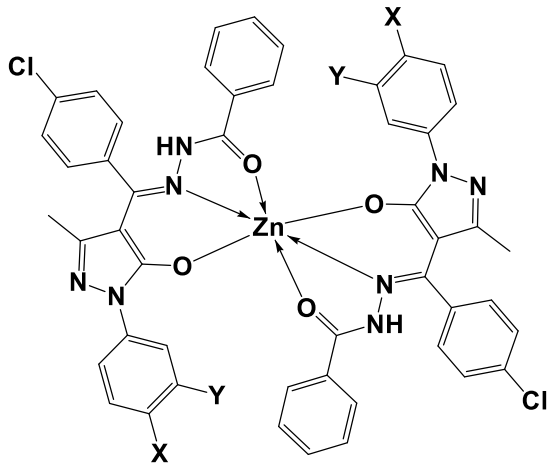


Figure 10. Generic structure for complex **10-12.**

Table 1. Binary Zinc(II) complexes			
Complex Code	**Used 4-Acyl-hydrazone-5-Pyrazolone as a Primary Ligand**	**X**	**Y**
1a	**L4**	**-H**	**-H**
2a	**L2**	**-H**	**-Cl**
3a	**L3**	**-CH_3**	**-H**

3.3. Crystallographic data of ligands and complexes

3.3.1. Crystal study of ligand L2.

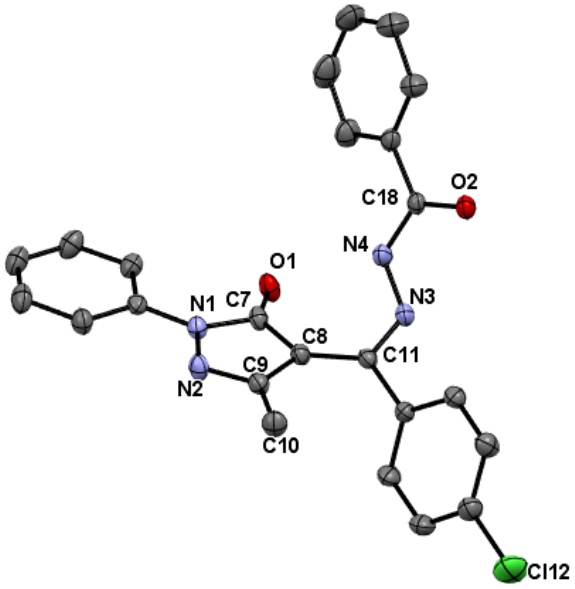


Table 2. Crystal data and structure refinement for L4	
Identification code	**L4**
Empirical formula	$C_{24}H_{20}ClN_4O_2$
Crystal system	triclinic
Space group	P-1
Final R indexes [I>=2σ (I)]	R_1 = *0.0956*, wR_2 = 0.2755

Figure 11. ORTEP view of ligand L4. H-Atoms are omitted for clarity.

3.3.2. Crystal study of complex 12.

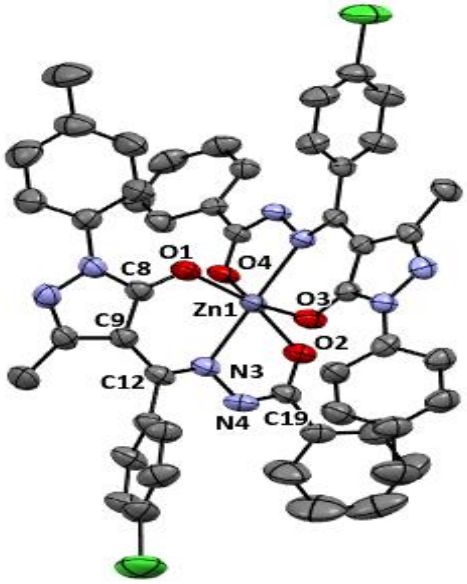


Table 3. Crystal data and structure refinement for 12.	
Identification code	**$[Zn(L^3)_2]$**
Empirical formula	$C_{52}H_{43}Cl_2N_8O_5Zn$
Space group	P-1
Final R indexes [I>=2σ (I)]	***R_1 = 0.0828***, wR_2 = 0.2107

Figure 12. ORTEP view of complex **12.**

3.3. Electronic spectra of complexes 10-12

All complexes were completely soluble in DMSO and UV/Visible spectra were recorded in the range 250–500 nm. In the complexes Uv/Vis spectra, the first intense band is attributed to a ligand-centered (LC) π–π* transition localized on the aromatic rings of the ligand, while the shoulder is due to its metal coordination. There is no d-d transition in all complexes due to d^{10} metal.

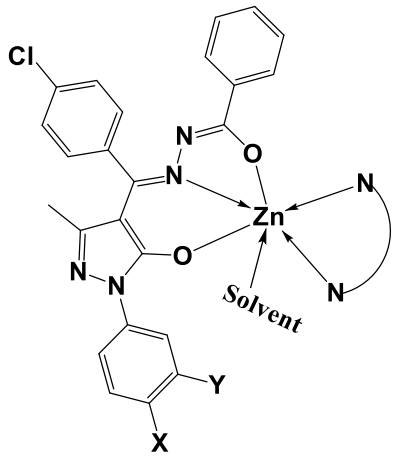
3.4. Conclusion

In summary, three new Schiff bases of 4-acylpyrazolone were synthesized and **characterized by various spectroscopic and analytical techniques.** The structures of the synthesized Schiff bases were determined by **single-crystal X-ray diffraction and found to be exists in amine-one form in the solid state**. These Schiff bases were **used to synthesize nine new Zinc complexes**, which were characterized by spectroscopic and analytical techniques.

Chapter 3

Part (b): Mixed ligand Zinc(II) complexes of 4-acylhydrazone-5-pyrazolone; Synthesis, characterization, and crystal study

3.2.1. Synthesis of mixed ligand Zinc(II) complexes



4a: X=-H, Y=-H, N N =bpy

5a: X=-H, Y=-H,, N N =phen

6a: X=-H, Y=-Cl, N N =bpy

7a: X=-H, Y=-Cl, N N =phen

8a: X=-CH_3, Y=-H, N N =bpy

9a: X=-CH_3, Y=-H,, N N =phen

Figure 13. Generic structure of complex of Acylhydrazone-5-pyrazolone.

3.2.3. Crystallographic study

3.2.3.1. Crystal study of complex [Zn(L5)(phen)(DMF)]

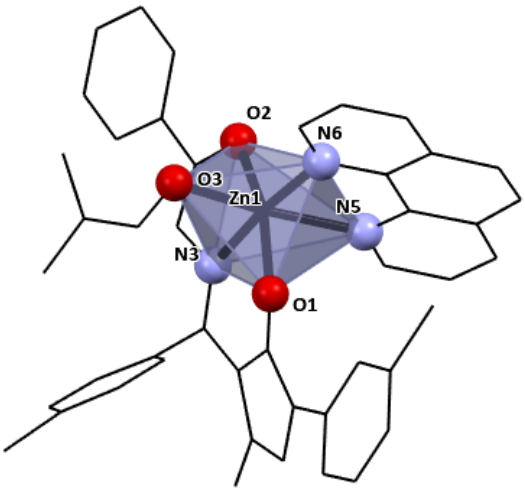


Table 5. Bond Angles for [Zn(L5)(Phen)(DMF)].			
Atom	**Atom**	**Atom**	**Angle/°**
O2	**Zn1**	**O1**	**165.93(9)**
N5	**Zn1**	**O3**	**165.28(11)**
N3	**Zn1**	**N6**	**174.34(11)**
O2	**Zn1**	**O3**	**88.87(10)**
O2	**Zn1**	**N3**	**77.24(10)**
O2	**Zn1**	**N6**	**107.01(10)**
O2	**Zn1**	**N5**	**99.57(11)**

Figure 14 Geometry showing scheme of complex 15.

3.2.4. Electronic spectra of 4-acylhydrazone-5-pyrazones and its Zinc(II) complexes

All complexes were completely soluble in DMSO and UV/Visible spectra were recorded in the range 250–500 nm. In the complexes Uv/Vis spectra, the first intense band is attributed to a ligand-centered (LC) π–π* transition localized on the aromatic rings of the ligand, while the shoulder is due to its metal coordination. There is no d-d transition in all complexes due to d^{10} metal.[7–10,23,26,27]

3.2.5. Conclusion

In summary, three new Schiff bases of 4-acylpyrazolone were synthesized and characterized by various spectroscopic and analytical techniques. The structures of the synthesized Schiff bases were determined by single-crystal X-ray diffraction and found to be exists in amine-one form in the solid state. These Schiff bases were used to synthesize six mixed ligand Zinc complexes with 2,2' bipyridine and 1,10' phenanthroline, which were characterized by spectroscopic and analytical techniques.

Chapter 4

Synthesis and Characterization and Biological Evolution of Zinc(II) metal complexes of 4-semicarbazone-5-pyrazolone and 4-thiosemicarbazone-5-pyrazolone.

4.1. Synthesis of 4-Semicarbazone-5-pyrazolone.

Semicarbazide hydrochloric acid was dissolved in ethanol in round bottom flask. Same equivalent of sodium acetate was dissolved and added for neutralization of semicarbazide. Added ethanolic solution of 4-acyl pyrazolone in it. Acetic acid used as a catalyst. Filtered obtained ppts and placed for recrystallization.[2]

4.1.1. (E)-2-((4-chlorophenyl)(1-(3-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)methylene)hydrazine-1-carboxamide [L7]

And

4.1.2. (E)-2-((4-chlorophenyl)(5-hydroxy-3-methyl-1-(p-tolyl)-1H-pyrazol-4-yl)methylene)hydrazine-1-carboxamide [L8]

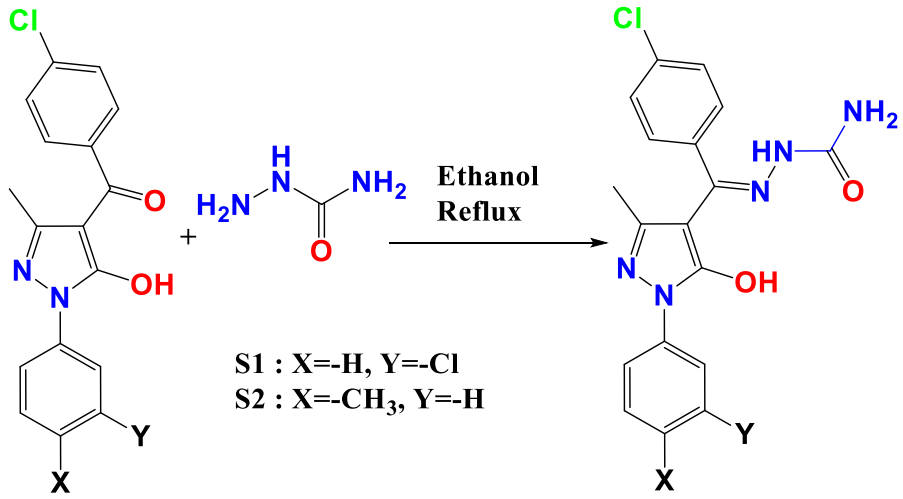


Figure 15. Synthesis route for semicarbazone of pyrazolone based ligands.

4.2. Synthesis of 4-thiosemicarbazone-5-pyrazolone.

Dissolved the thiosemicarbazide in ethanol with heating in the RB flask. Dissolved 4-acyl pyrazolone in ethanol in a separate beaker and added drop wise in the RB (solution of thiosemicarbazide). Used acetic acid as a catalyst. Refluxed the reaction mixture for the 4 hour. Obtained the ppts and filtered.

4.2.1. (Z)-2-((4-chlorophenyl)(1-(3-chlorophenyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide [T1]

And

4.2.2. (Z)-2-((4-chlorophenyl)(3-methyl-5-oxo-1-(p-tolyl)-4,5-dihydro-1H-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide [T2]

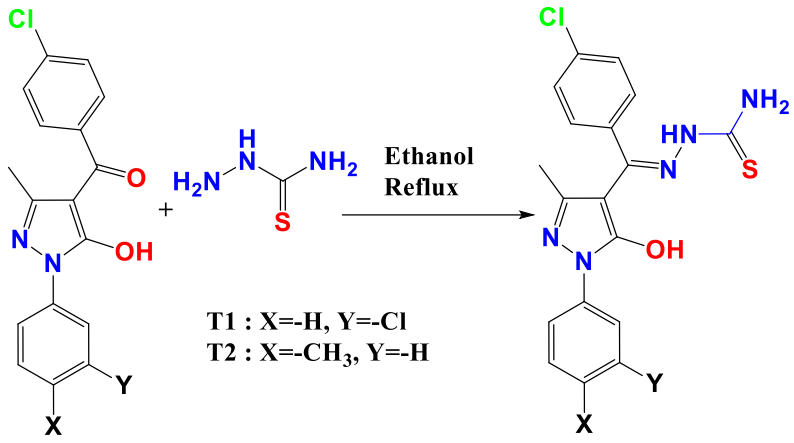


Figure 16. Synthesis route of Thiosemicarbazone.

4.3. Synthesis of complex 1z-4z

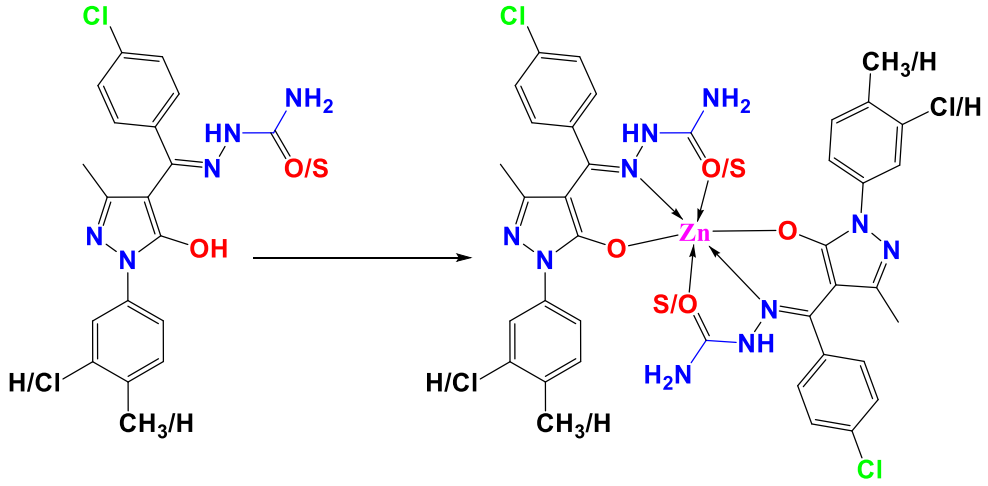


Figure 17. Synthesis of **complex 1z-4z**.(**19=**[$Zn(L7)_2$], **20**=[$Zn(L8)_2$], **21**=[$Zn(L9)_2$] and **22**=[$Zn(L10)_2$].

4.4. FTIR spectral data of ligands and complexes.

	Table 1. FTIR spectral data of ligands and complexes. $\nu\,(cm^{-1})$										
Compound code	***OH***	***-NH***	***C=O***	***C=O***	***C=S***	***C-O***	***C=N***	***N-N***	***M-N***	***M-O***	***M-S***
L7	3470	3190	1670	1600	-	-	1565	821	-	-	-
L8	3470	3190	1679	1601	-	-	1565	820	-	-	-
$[Zn(L7)_2]$	-	-	1622	1602	-	1128	1549	824	443	510	-
$[Zn(L8)_2]$	-	-	1669	-	-	1128	1556	824	449	514	-
L9	-	3168	1662	-	865	-	1602	958	-	-	-
L10	-	3151	1670	-	859	-	1599	936	-	-	-
$[Zn(L9)_2]$	-	-	-	-	862	1160	1612	959	587	511	480
$[Zn(L10)_2]$	-	-	-	-	855	1159	1597	948	596	511	477

4.5. Crystallographic data of ligand and complex

4.5.1. Crystal study of ligand L8.

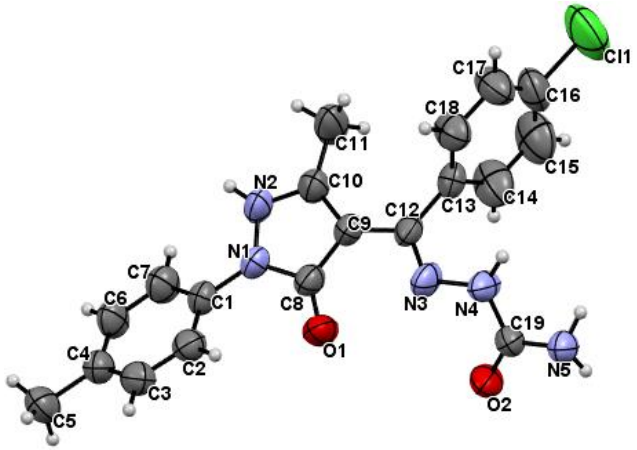


Figure 18. ORTEP view of ligand L8. Small white balls are indicating H-Atoms.

Table 2. Crystal data and structure refinement for S2	
Identification code	**L8**
Empirical formula	$C_{19}H_{16}ClN_5O_2$
Formula weight	**390**
Temperature/K	**293(2)**
Crystal system	**monoclinic**
Final R indexes [I>=2σ (I)]	R_1 = *0.0625*, wR_2 = **0.1367**
Final R indexes [all data]	R_1 = **0.1536**, wR_2 = **0.1889**

4.5.2. Crystal study of complex 21.

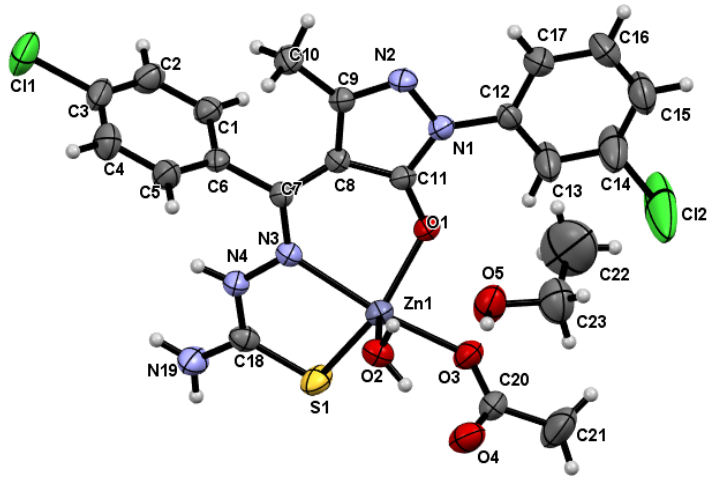
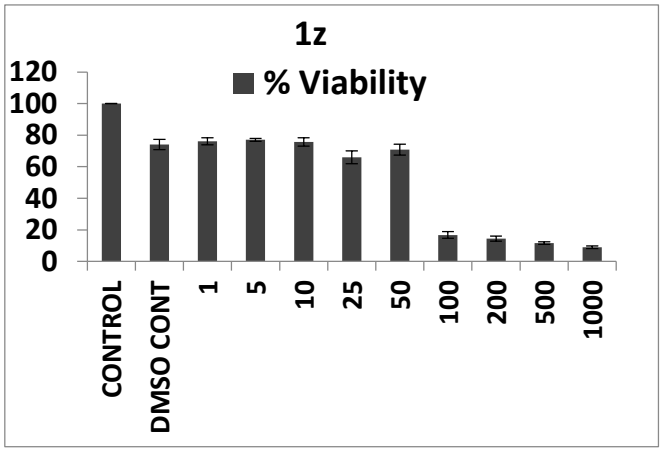


Figure 19. ORTEP view of complex 21.

4.6. Cytotoxicity of Zinc(II) complexes 19-22.[8,14,22,27–30]



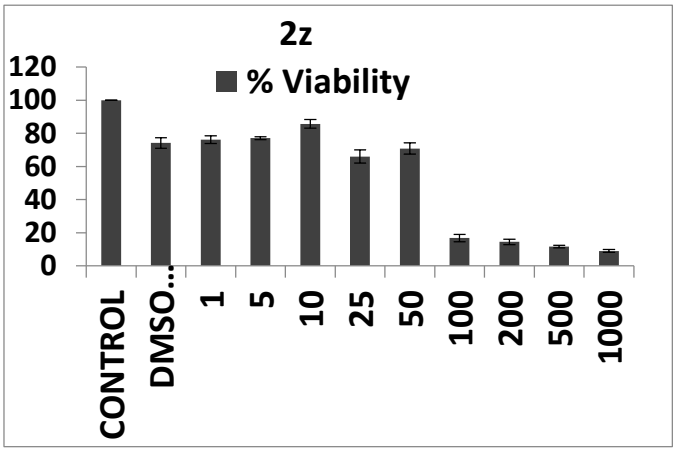


Figure 16. Cytotoxicity of compound by MTT assay.

4.7. Conclusion

Synthesized and well characterized 4-semicarbazone -5-pyrazolones and 4-thiosemicarbazone-5-pyrazolones and their Zn(II) complexes. Ligands and Zinc(II) complexes are characterized with ^{1}H NMR , FTIR, UV/Vis spectroscopy and Molar conductance. 4-semicarbazone-5-pyrazolone and 4-thiosemicarbazone-5-pyrazolone based Zn(II) complexes showed the promising cytotoxicity results.

Chapter 5

Molecular Docking and Antimalarial Activity of Synthesized Ligands and Zinc(II) Complexes.

5.1. Molecular docking study

During the intra-erythrocytic stage of *P. falciparum*, degradation of haemoglobin into hemozoin inside the acidic food vacuole is essential for the survival of parasite into the host cell (Krugliak et al., 2002). *P. falciparum*; Plasmepsin I, Plasmepsin II, Plasmepsin IV, and histo-aspartic protease (HAP). Previously, Plasmepsin II has attracted attention as a novel anti malaria drug target within last few years.[31]

5.2. Malaria

5.2.1. Cause

Malaria is caused by the protozoan parasite Plasmodium. Human malaria is caused by four different species of Plasmodium: *P. falciparum, P. malariae, P. ovale and P. vivax.*

Humans occasionally become infected with Plasmodium species that normally infect animals, such as P. knowlesi. As yet, there are no reports of human-mosquitohuman transmission of such "zoonotic" forms of malaria.[32–34]

5.2.2. Transmission

The malaria parasite is transmitted by female Anopheles mosquitoes, which bite mainly between dusk and dawn.

5.2.3. Nature of the disease

Malaria is an acute febrile illness with an incubation period of 7 days or longer. Thus, a febrile illness developing less than 1 week after the first possible exposure is not malaria.

The most severe form is caused by P. falciparum; variable clinical features include fever, chills, headache, muscular aching and weakness, vomiting, cough, diarrhoea and abdominal pain.

5.2.4. Geographical distribution

The current distribution of malaria in the world is shown on the map; affected countries and territories are listed both at the end of this chapter and in the Country list.

5.3. Molecular docking with protein of synthesized ligands and their Zinc(II) complexes.

5.3.1. Falcipain-2 (PDB code: 3BPF)

All the test compound had lower binding energy than control ligand for Falcipain-2 (PDB code: 3BPF).

The lowest binding energy -13.1 observed for $[Zn(L3)_2(H_2O)_2]$ as complex **3** by -12.8 and -10.7 respectively for [Zn(L4)2(byp)] as Complex **4** , and $[Zn(L4)_2(CH_3OH)_2]$ as Complex **1**.[21]

5.3.2. Plasmepsin 2 (PDB code: 2R9B)

Plasmepsin 2 (PDB code: 2R9B) docking demonstrated better docking score for all compound in comparison to control ligand. C04 was lead compound with -16.2 docking score followed by -15.3 and -13.4 for respectively C03 and C01.

5.3.3. Plasmepsin-1 (PDB code: 3QS1)

For Plasmepsin-1 (PDB code: 3QS1) best binding energy -16 reported for 3. complex 1 had similar bonding pattern to control at asn7 and Ser77 .

5.3.4. plasmapsin-2 for M1 aminopeptidase (PDB code: 4ZW3)

Similar to plasmapsin-2 for M1 aminopeptidase (PDB code: 4ZW3) also all the test compound docking score was better than control ligand. C03 had lowest binding energy -16.3 followed by C04 and C01 respectively -14.8 and -13.8.

5.4. Antimalarial Activity.

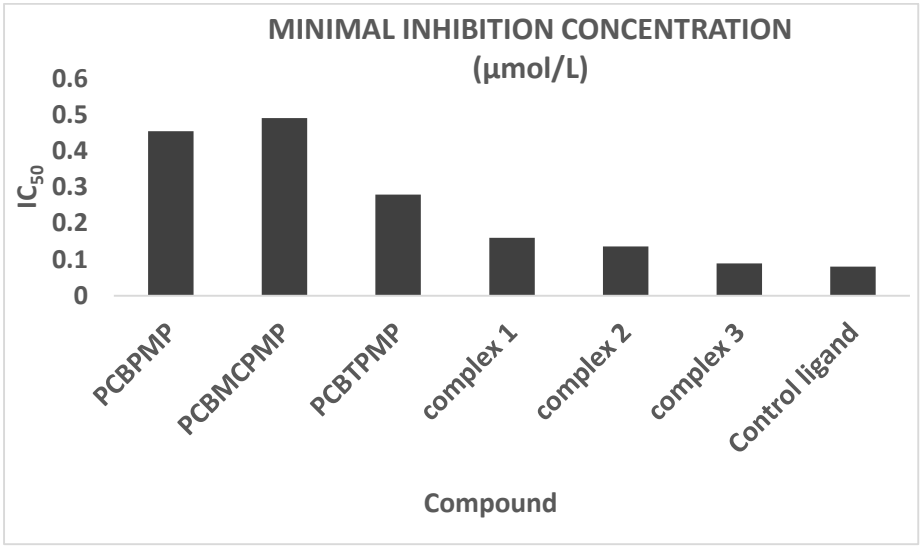


Figure 17. ***Plasmodium falciparum in vitro*** **growth inhibition assay**

Antimalarial activity of binary and ternary mixed ligand complexes of acyl pyrazolone showed promising results.

5.5. Conclusion

From the Binary and mixed Zinc(II) complexes of acyl pyrazolone, The Complex **3, 5** and complex **6** are best compound were reported for *P. Falciparum in vitro* growth inhibition assay. Complex 3 had also the first leading compound in molecular docking study for Falcipain 2, Plasmepsin 1 and M1 aminopeptidase and second lead compound for Plasmepsin 2.

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