Chapter 1

Introduction

1. INTRODUCTION

Chemistry is termed as the science of atoms and molecules and it deals with the composition, structure, properties of matter which can be best described and understood in terms of these basic constituents of matter. Chemistry is the science which has discovered how things are composed, what properties they have and how they will react. The impact of chemistry can be seen in all aspects of our daily life. Chemistry has contributed tremendous growth in the field of medicines, agriculture, industrial technologies etc. Particularly, inorganic chemistry, which is a branch of chemistry, has gathered an enormous interest from the researchers worldwide.[1]

There are many heterocyclic compounds in the chemistry, but nitrogen-containing heterocyclic compounds have gained increasing attention in the field of chemistry due to their efficiency in the biological activities. The nitrogen-containing five-membered heterocyclic compounds have attracted the attention of the researchers due to their potential biological activities.

1.1. Pyrazole

Pyrazole (1*H*-pyrazole; 1,2-diazole) (Fig. 1.1.) and its derivatives have attracted considerable attention due to their broad variety of properties. Five-membered heterocycles containing two adjacent nitrogen atoms can best be discussed according to the number of double bonds present. Pyrazoles contain two double bonds within the nucleus, imparting an aromatic character to these molecules. They are stable compounds and can display the isomeric forms, **(i)** and **(ii)** (Fig. 1.1) when properly substituted. Pyrazoles are scarce when compared to the imidazoles **(iii)**, which are widespread and have a central role in many biological processes.[2]

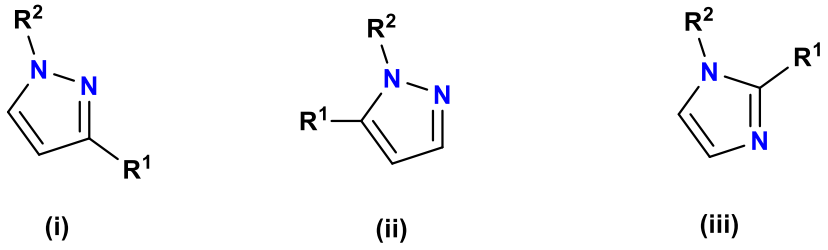


Fig. 1.1. Isomers of pyrazole structure.

Pyrazoles are widely used as core motifs for a large number of compounds for various applications such as catalysis, agrochemicals, and building blocks of other compounds and in medicine. The attractiveness of pyrazole and its derivatives is the versatility that allows for the synthesis of a series of analogues with different moieties in them, thus affecting the electronics and by extension the properties of the resultant compounds. In medicine, pyrazole is found as

a pharmacophore in some of the active biological molecules. While pyrazole derivatives have been extensively studied for many applications including anticancer, antimicrobial, anti-inflammatory, anti glycemic, anti-allergy and antiviral, much less has been reported on their metal counterparts even though metals have been shown to impart activity to ligands. Thus this perspective is intended to demonstrate the potential of pyrazole and pyrazolyl metal complexes in the areas of drug discovery and development. Several examples, that include palladium, platinum, copper, gold, zinc, cobalt, nickel, iron, copper, silver and gallium complexes, are used to bolster the above point.[3]

1.2. Pyrazolone

Pyrazolones, also containing two double bonds, are predominantly in the keto form (Fig 1.2. **(i))**, although they can also exist in the enol form (Fig. 1.2. **(ii))**.[2]

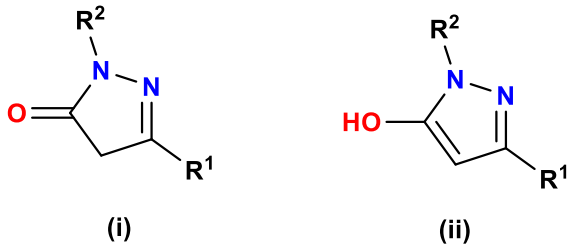


Fig. 1.2. Keto and enol form of pyrazolone.

The oxo derivatives of pyrazolines, known as pyrazolones, are best classified as follows: 5-pyrazolone, also called 2-pyrazoline-5-one (Fig. 1.3**(i))**; 4-pyrazolone, also called 2-pyrazoline-4-one (Fig. 1.3**(ii))**; and 3- pyrazolone, also called 3-pyrazoline-5-one (Fig. 1.3 **(iii))**. Within each class of pyrazolones, many tautomeric forms are possible; for simplicity, only one form is shown.[2]

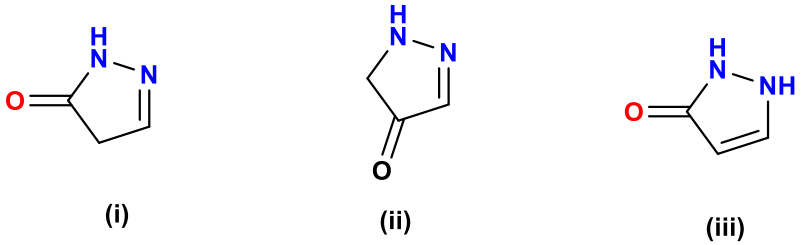
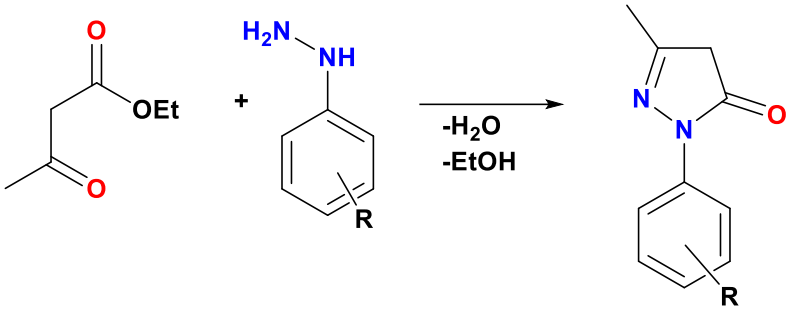


Fig. 1.3. Possible isomers of pyrazolone.

The synthesis of pyrazolone was first reported in 1883 by Ludwig Knorr, by a condensation reaction between ethyl acetoacetate and phenylhydrazine (Scheme 1.1.).[4]



Scheme 1.1. Synthesis route of 3-methyl-1-phenyl-5-pyrazolone.

Pyrazolone-based ligands are rapidly becoming popular for use in catalysis, biological applications, sensors, functional materials and as pigments for dyes. Many metal complexes with pyrazolone based ligands have been reported since the 80s of the last century, and several of them were found to possess interesting features, such as catalytic activity, anticancer, antioxidant, antifungal and anti-microbial activity, and enhanced NLO, photoluminescence and optical properties concerning simple pyrazolone-based ligands.[5] Derivatives of pyrazolone, such as aminopyrine, isopropylantipyrine, sulpyrine and antipyrine are widely used as nonsteroidal anti-inflammatory drugs that exhibit potent antipyretic and analgesic activities (Fig. 1.4).[6–8] Unfortunately, however, the pyrazolones are allergenic, and various side effects, including anaphylaxis, cutaneous reactions, and agranulocytosis, have been reported.[8,9]

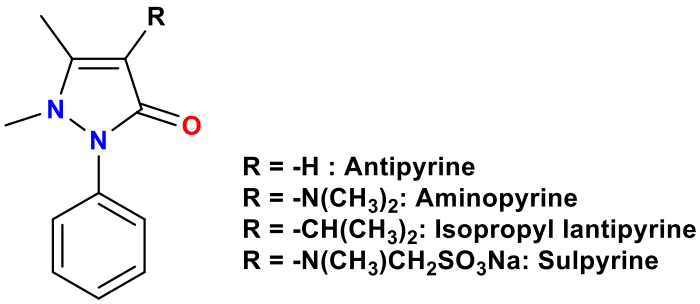
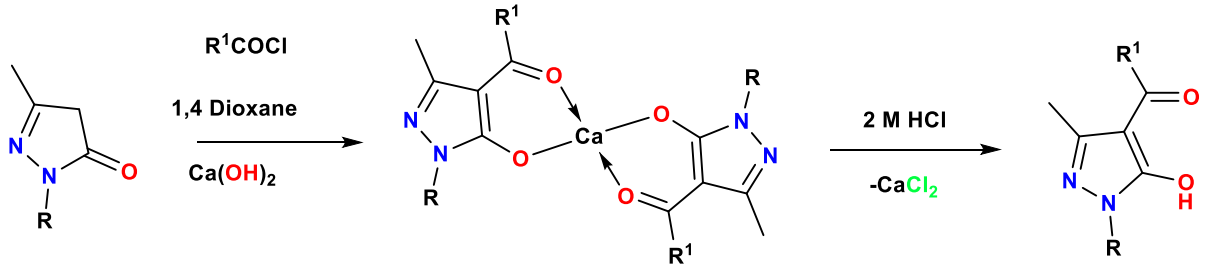


Fig. 1.4. Generic structure of pyrazolone derivatives.

1.3. 4-Acyl-5-pyrazolone

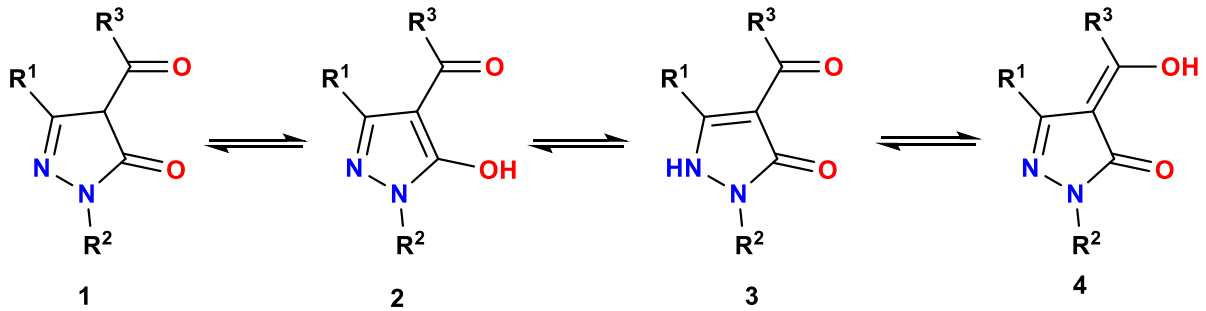
In many countries the pyrazolone derivatives, which include dipyrone, antipyrine, aminopyrine and propyphenazone are widely used analgesics. Dipyrone the most widely used pyrazolone has been most studied. The pyrazolidine derivatives phenylbutazone and oxyphenbutazone, which are not generally used for analgesia, since they differ from the pyrazolones in terms of efficacy and tolerance are not discussed in this chapter.[7] Jensen *et al.*, (1959) reported that a direct one-step synthesis was effected by treating a solution of 1-phenyl-3-methyl-pyrazol-5-one in dioxane containing suspended calcium hydroxide as a catalyst with an acid chloride or

anhydride.[10] A rapid reaction led directly to the calcium complex of the 4-acylpyrazolone which is stable under the alkaline condition and which is expected to protect the wanted derivative from further reactions. This method was successfully used to prepare the acetyl-, propionyl-, butyryl-, valeryl-, choroacetyl-, benzoyl-, *p*-bromobezoyl-, *p*-nitrobenzoyl- and ethoxycarbonyl derivatives of 1-phenyl-3-methyl pyrazole-5-one and to prepare the benzoyl derivative of 1-*p*-nitrophenyl-3-methyl pyrazole-5-one.[10] Acylation easily occurs at the C-4 position of the pyrazole ring in basic (calcium hydroxide) dioxane at reflux. Subsequent treatment with an acid aqueous solution affords the acylpyrazolone (AP) in high yield as a solid powder insoluble in water (Scheme 1.2).



Scheme 1.2. Synthesis route of 4-acylpyrazolone. (**R** = Substituted phenyl, **R^1**= Substituted phenyl or alkyl group)

The neutral acylpyrazolones (AP) can exist both in solution and in the solid-state in several possible tautomeric forms presented in scheme 1.3.[11,12] The acylpyrazolones ligands have shown to possess structural and electronic features for versatile coordination chemistry, which has rapidly grown in the last decade and expanded to metallic elements previously underestimated. The versatility of these molecules as ligands derives mainly from the easy functionalization on the C4 carbon of pyrazolone ring with different acyl moieties (R^1 in Scheme 1.3) that can vary in complexity.[13]



Scheme 1.3. Tautomerism of acylpyrazolone (AP).

The spectroscopic characterization of many acylpyrazolones (Aps) ligands through IR, Raman, UV–vis, ^{1}H and ^{13}C NMR, mass spectra and *ab initio* calculations have been reported, factors influencing the equilibrium between the tautomeric forms being mainly explored.[11,14] The -OH enol form **2** is generally preferred in non-polar solvents, however, a phenyl ring in R^3 position stabilizes the -NH amino-diketo form **3** (Scheme 1.3).[14,15] Crystal structure X-ray analyses of some acylpyrazolone (AP) ligand have been performed, crystallized from chloroform, in the enol form **2**, and an intramolecular O–H· · · O system. Whereas, the amino diketonic form **3**, stabilized by an extensive network of intermolecular N–H· · ·O bonding, can be obtained from re-crystallization in polar solvents like methanol.[14,16]

1.4. 4-Acylhydrazone-5-pyrazolone

In recent years, 4-acylhydrazone-6-pyrazolones have much investigated due to their structure analogies and many applications.[17] 4-acylhydrazones are prepared by reaction of 4- acyl-5-pyrazolones and acylhydrazides.[5] 4-acylhydrazone-5-pyrazolones have been much less investigated than 4-acylpyrazolone, till 2019 only three papers dealing on the molecular structure of such ligands being found in the free neutral keto form.[5]

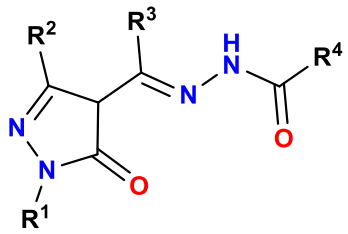
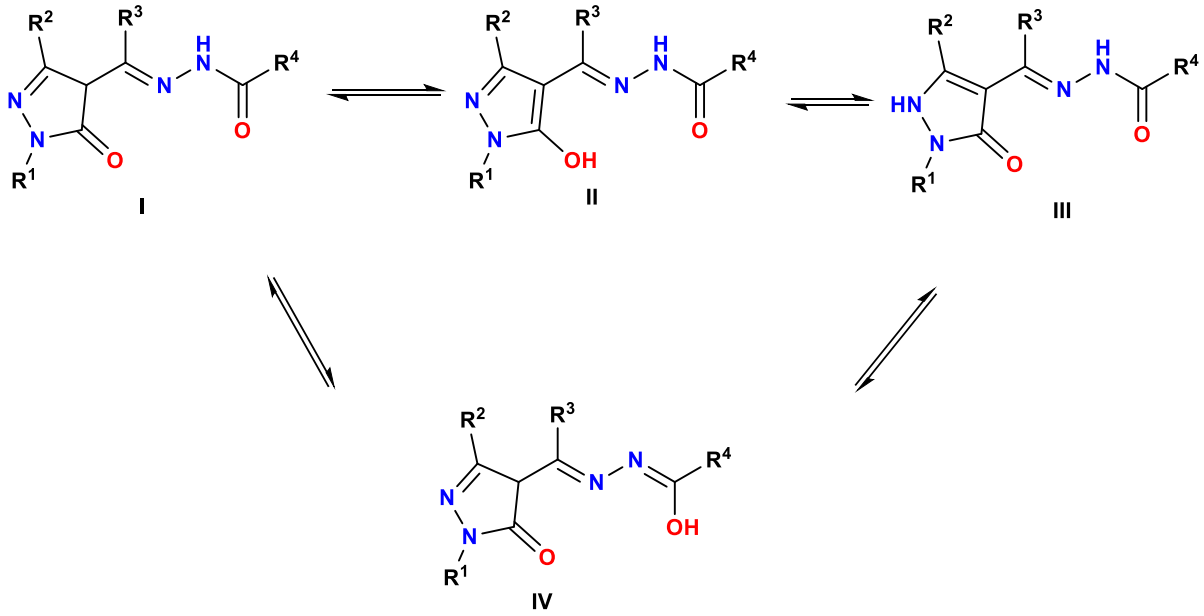


Fig. 1.5. Generic structure of 4-acylhydrazone-5-pyrazolone.

4-acylhydrazone-5-pyrazolones have reacted as bidentate or ONO-tridentate ligand (Fig. 1.5) in metal complexation.[5] 4-Acylhydrazone-5-pyrazolones can exist in several tautomeric forms, which correspond to acylpyrazolones and hydrazone moieties. This keto-enol form favoured in coordination chemistry and biological activity. As shown in scheme 1.4, these molecules may exist in four tautomeric forms corresponding to H at the C (imine-one (I)), O (imine-ol (II)), C (imine-one (IV)) and atoms of the pyrazolone ring or at the azomethine N (amine-one (III)) and possible tautomer imine-ol (IV) form correspond to a 4-acylhydrazone moiety.[18]



Scheme 1.4. Tautomeric form in 4-acylhydrazone-5-pyrazolone.

1.5. 4-Semicarbazone-5-pyrazolone

Recent studies seem to indicate an increasing interest toward 4-hydrazone-5-pyrazolones, 4-acylhydrazone-5-pyrazolones and 4-thiosemicarbazone-5-pyrazolones, due to their superior coordinating ability arising from additional donor atoms in their molecular structure, adding complexity and difficulty in their structural investigation from one side, but also greater possibilities to selective functionalization on the other side (Fig. 1.6).[5]

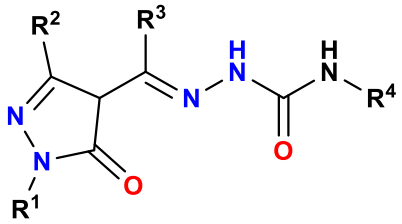
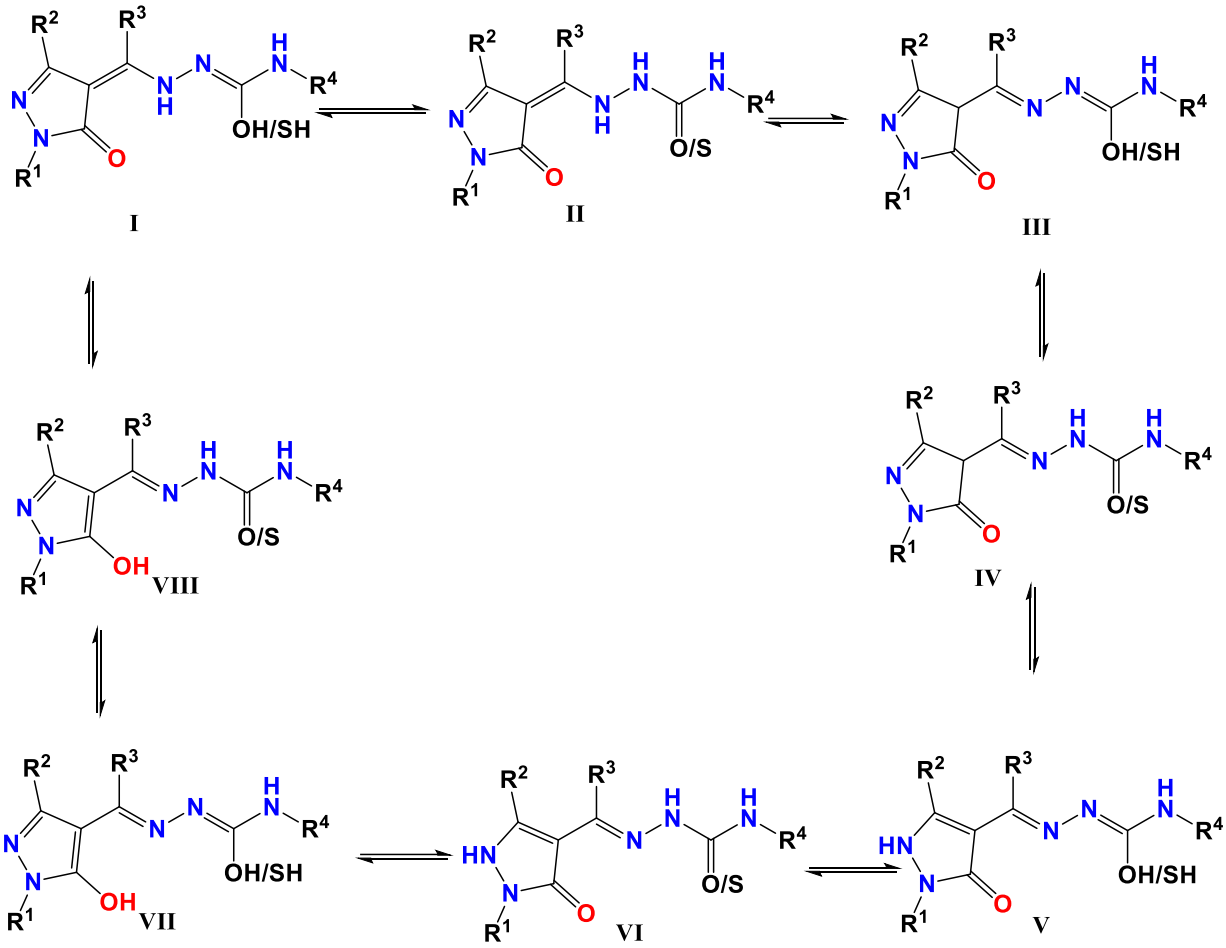


Fig. 1.6. Generic structure of 4-semicarbazone-5-pyrazolone.

It is noteworthy to remind that pyrazolone-based ligands possess themselves excellent biological activities and often their coordination to metal fragments leads to an increase in such activity. The presence of the heterocycle conjugated to other aromatic scaffolds often leads to interesting optical properties that can be finely tuned. In conclusion, the number of researchers involved in this field is constantly increasing, as well as scientific publications centered not only on the synthesis and characterization of metal complexes but also on their possible

applications in different technological fields. We are confident that many results with interesting technological effects can come from this field in the near future.[5]



Scheme 1.5. Tautomerism in 4-semicarbazone-5-pyrazolone or 4-thiosemicarbazone-5-pyrazolone.[5]

Recent studies on pyrazolone derivatives especially those which bearing semicarbazone and thiosemicarbazone moieties show compounds have potential biological activities.[5] 4-semicarbazone-5-pyrazolone can be derived from corresponding 4-acyl pyrazolone and the desired alkyl(aryl) Semicarbazide.[5]

In the generic structure of 4-semicarbazone-5-pyrazolone, R^1= phenyl or substituted phenyl, R^2 = methyl group, R^3 = alkyl or aryl group and R^4 = -H or alkyl or substituted phenyl group (Fig. 1.6). 4-semicarbazone-5-pyrazolone has tautomerism presented in scheme1.5.[5] Jixi *et. al* (2011), reported 4-semicarbazone-5-pyrazolone undergo reversible photo colouration and

thermal leaching reactions in pure solid-state. Upon irradiation with light of 365 nm, the Enol-form (VIII) converted to Keto-form (IV).[19]

1.6. 4-Thiosemicarbazone-5-pyrazolone

4-thiosemicarbazone-5-pyrazolones have reported behaving as effective chelating and extracting reagents for many metal ions. They are also the focus of research as potential biological activity and widely used in coordination chemistry**.** Tautomeric forms of 4-thiosemicarbazone-5-pyrazolone are presented in scheme 1.5. The ligand with ONS-tridentate 4-thiosemicarbazone-5-pyrazolones have derived from 4-acylpyrazolone and thiosemicarbazide (Fig. 1.7). Several transition metal complexes with pyrazolone-based *N*(4)-substituted 4-thiosemicarbazone-5-pyrazolone have been reported, where the ligands behave as N,S-bidentate donors through the thiosemicarbazone moiety, either in the thione (VI) or thiolato Form (VII) (scheme 1.5).[20]

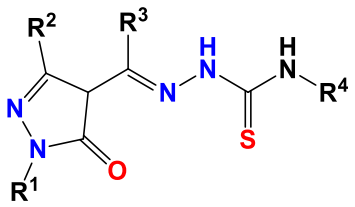


Fig. 1.7. Generic structure of 4-thiosemicarbazone-5-pyrazolone.

4-thiosemicarbazone-5-pyrazolone can be a mixture of keto-imine/enol-imine tautomer (scheme 1.5) in solution. On crystallisation, as a result of delocalisation of electrons due to extended conjugation, the compound undergoes rearrangement and tends to exist in a stable conformer (VII). However, during complexation, in the presence of metal ions in solution, the ligand can exist in enol-imine tautomer (VI) and coordinates through enolic oxygen after deprotonation.[20]

1.7. Zinc in coordination Chemistry

Alloys and salts of zinc have been known from many centuries; commercial production of the metal dates from early in the eighteenth century. Of the several million tons now produced annually, by electrolytic and smelting processes, much is used in alloys, in batteries, in corrosion prevention, and the manufacture of a range of compounds with various uses. In particular, zinc oxide and zinc chloride have a large number of uses. Zinc sulphide is both one of the main zinc ores and the archetype for the two main structural forms of 4:4-coordinated structures (zinc blende and wurtzite). Many zinc compounds and complexes have interesting

structural, spectroscopic, optical, magnetic, and conductivity properties, some of which are of actual or potential value in technical and industrial applications. Zinc-containing species have also proved valuable in synthesis and self-assembly of a range of supramolecular structures. Both in the solid-state and solution zinc exhibits a range of coordination numbers, though tetrahedral and, especially in solution, octahedral stereo chemistries dominate. Zinc forms a variety of complexes, especially with nitrogen, oxygen, sulphur, and halide donor ligands. Many of these complexes show high stability, but they are generally labile in solution. Zinc plays an essential role in biology, being a key constituent of at least 200 metalloproteinase. It is an essential element in human nutrition, but toxic in large quantities. Many zinc complexes have been synthesized as biochemical models; a few zinc salts are used in dietary supplements.[21]

1.8. Biological status of zinc(II) compounds

A metal element, atomic number 30, atomic weight 65.37, symbol Zn. It is a trace element in the diet, a component of several enzymes, including DNA and RNA polymerases and carbonic anhydrase. It is abundant in red meat, shellfish, liver, peas, lentils, beans and rice. A well-balanced diet assures adequate intake of zinc. Those who may suffer from zinc deficiency include persons on a strictly vegetarian diet and those who are on a high fiber diet. In the latter case, the zinc is bound to the fiber and is eliminated in the faeces without having been absorbed through the intestinal wall. Poor absorbance of zinc also can occur in persons with chronic and severe bowel disease.[22] The recommended daily intake is 12-15 mg for an adult. A severe deficiency of zinc can retard growth in children, cause a low sperm count in adult males, and retard wound healing. Signs of a deficiency include anorexia and a diminished sense of taste. An excessive intake of zinc (usually in those who work with the metal or breathe its fumes) can either cause pneumoconiosis or interfere with the body's use of copper and other trace elements, producing diarrhoea, nausea, vomiting, and other signs of intestinal irritation.[23,24]

1.9. Zinc(II) complexes of 4-acyl-5-pyrazolone and biological evolution

4-Acyl pyrazolones consist of keto-enol tautomerism where the enolic form (–OH) reacted as a weakly acidic and very suitable as a bidentate ligand. The 4-acyl-5-pyrazolones and their

metal complexes show decent catalytic activity, biological activity, and photochromic properties.[13]

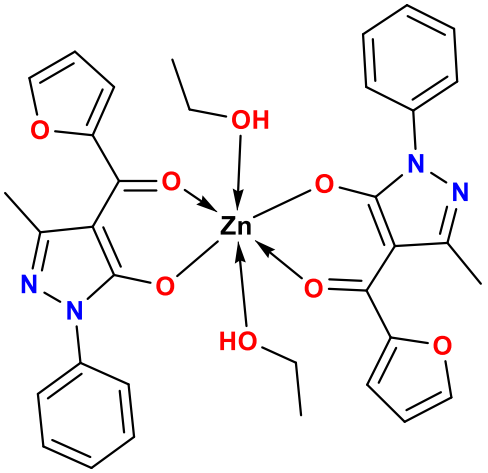
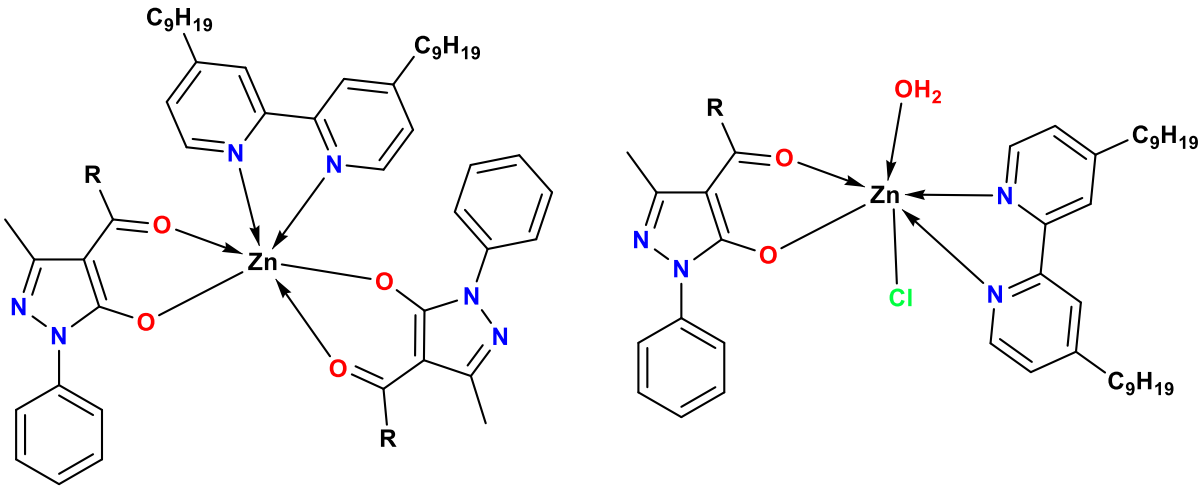


Fig. 1.8. Structure of $[Zn(PMPO)_2(EtOH)_2]$.



R = $C_6H_4C(CH_3)_3$ for **1**
R = $CH_2ClC(CH_3)_3$ for **2**

R = $C_6H_4C(CH_3)_3$ for **3**
R = $CH_2ClC(CH_3)_3$ for **4**

Fig. 1.9. Structures of zinc (II) complexes.

An acylpyrazolone complex $[Zn(PMPO)_2(EtOH)_2]$ (PMPO = 1-phenyl-3-methyl-4-(α-furoyl)-5-pyrazolone) shows a slightly distorted octahedral structure, Zn^{2+} is located at an inversion

center from four oxygens, two of acylpyrazolone ligands in the equatorial plane two ethanol molecules at the apical site (Fig.1.8).[25]

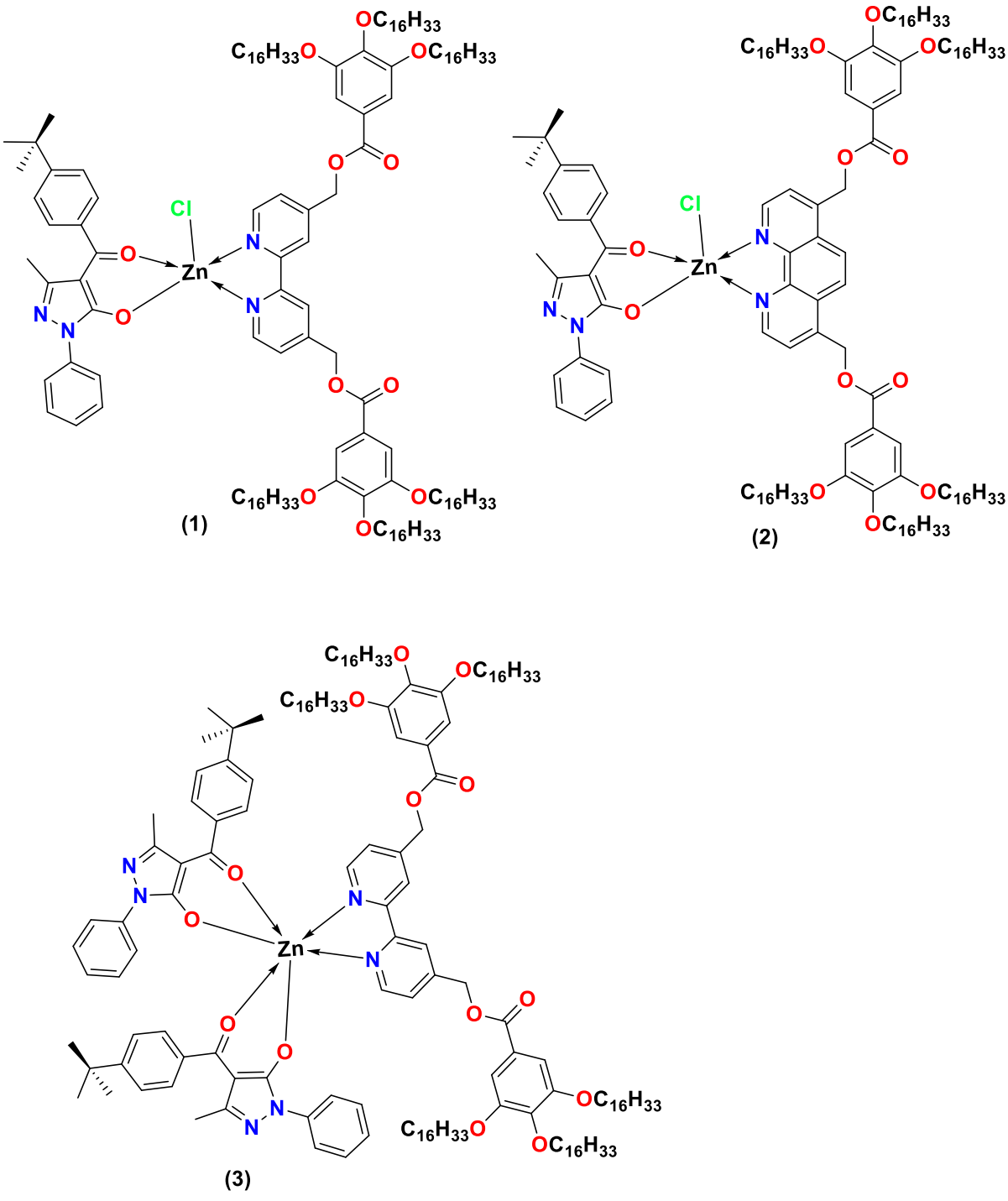


Fig. 1.10. Structures of zinc(II) complexes **1-3**.

Two binary zinc(II) complexes of acylpyrazolone display ICAM-1 inhibitory activity.[26] As shown in Fig. 1.9, two mixed ligand zinc complexes of acylpyrazolone (AP) and 4,4′-dinonyl-

2,2′-bipyridine were synthesized by Paola *et al*. These zinc complexes (**1-4** (*see* Fig. 1.9)) showed well *in vitro* activity against three different human cancer cells, DU145, LNCaP, and PC-3.[27]

[Zn(Q)(L^1)(Cl)] **1**, [Zn(Q)(L^2)Cl] **2** and hexacoordinated [Zn(Q)$_2$(L^2)] **3** zinc(II) complexes of 1-phenyl-3-methyl-4-(1-tert-butylphenyl)-pyrazol-5-one (HQ), two hexacatenar N,N chelating ligands, the 4,4′-bis-[(3,4,5-(tri-hexadecyloxy)benzoyloxy-methyl)]-2,2′-bipyridine (L^1) and the 4,7-bis[3,4,5-(tri-hexadecyloxy)benzoyloxy-methyl]-1,10-phenanthroline (L^2) (Fig. 1.10) and these complexes display green luminescence which is retained also in the mesophase and even in the isotropic state, with a general and reversible red-shift related to the increase of temperature.[28]

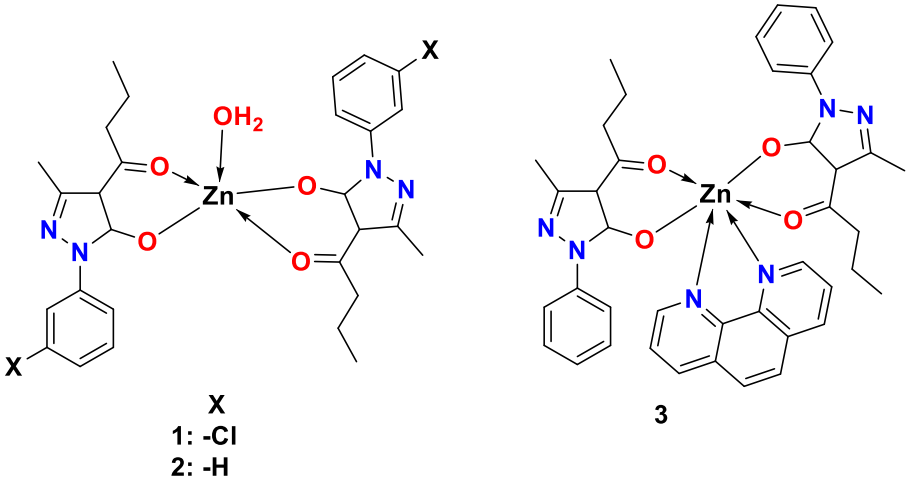


Fig. 1.11. Structures of zinc(II) complexes of the article Jadeja et. al.

Three Zn(II) coordination complexes [Zn(L^1)$_2$H$_2$O] **1**, [Zn(L^2)$_2$H$_2$O] **2** and [Zn(L^2)$_2$(phen)] **3** (L^1 = 4-propionyl-3-methyl-1-(3-chlorophenyl) pyrazolone-5-one, L^2 = 4-propionyl-3-methyl-1-phenyl pyrazolone-5-one) have synthesized by Jadeja et al. The coordination geometry described as slightly distorted trigonal bipyramidal for both complexes **1** and **2**. Ternary mixed ligand complex **3** is octahedral with acylpyrazolone (L^2) and phen. These complexes have been tested for DNA binding properties (Fig.1.11).[29] Among d^{10} metal, we have synthesized zinc(II) complexes of 4-acyl pyrazolones and tested for *in silico* and *in vitro* antimalarial activity.[30]

The Zn(II) complexes of 4-acyl-5-pyrazolones along with other novel complexes of 4-acyl-5-pyrazolones with the coligand 1,10-phenanthroline were prepared and screened for their antibacterial and antifungal activity. Zinc complexes showed powerful antifungal activity.[31]

More recently, a number of homo- and heteroleptic Zn(II) acylpyrazolonates have been reported by F. Marchetti et al., fully investigated in solid state and solution (where the heteroleptic ones exist as a mixture of geometrical isomers) and shown to display antitumor activity against human breast cancer.[32]

However, other scientific publications deal on new Zn(II) complexes with acylpyrazolones and although not expressly dedicated to biological studies, they can be of interest from a strictly chemical and structure point of view.[33–35] Heteroleptic Zn(II) complexes containing 8-hydroxy quinoline and various pyrazolone-based derivatives showed good photoluminescence properties in the solid state and in solution.[36]

1.10. Zinc(II) complexes of 4-acylhydrazone-5-pyrazolone and biological evolution

The carbonyls on the 5-position of the pyrazolone and the salicylhydrazide moiety lose protons, and the ligand coordinates with Cu(II) in the form of a negative divalent anion, suggesting that the ligand switches from keto-form to enol-form during the coordination process.[37]

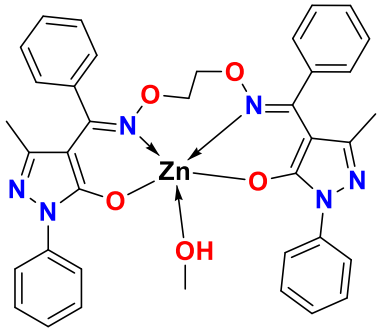


Fig. 1. 12. Structure of [Zn(L)(CH_3OH)] synthesized by salen type tetradentate N_2O_2 bisoxime chelate ligand.

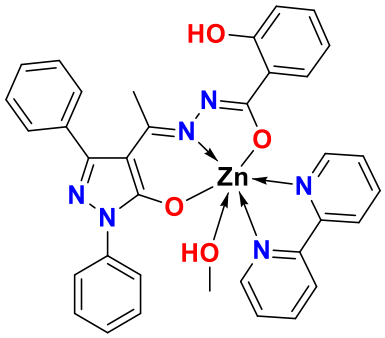


Fig. 1.13. Mixed ligand zinc(II) complex of 4-acylhydrazone-5-pyrazolone with 2,2′-bipyridine.

4-Acylhydrazone-5-pyrazolones (AHPs) and their Cd(II) complexes showed interesting biological activity and strong fluorescent behaviour in the solid-state.[38]

The square pyramidal Zn(II) complex was synthesized by salen type tetradentate N_2O_2 bisoxime chelate ligand (H_2L) derived from 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone and 1,2-bis(aminooxy)ethane (Fig. 1.12). Octahedral mixed ligand zinc(II) complex [Zn(DSAP)(bpy)(CH_3OH)] (Fig. 1.13) synthesized by an ONO trident 1,3-diphenyl-4-(salicylidene hydrazide)-acetyl-pyrazolone-5 (DSAP) ligand with bpy and additional coordinated methanol molecule.[39]

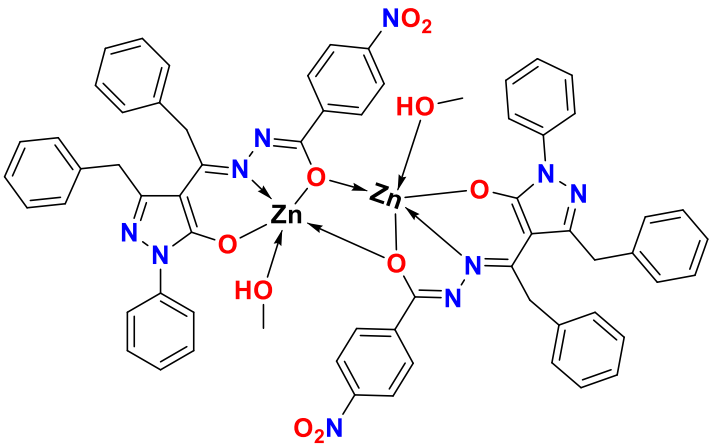


Fig. 1.14. Structure of $[Zn(L)(CH_3OH)]_2$, where H_2L = N-(1-phenyl-3-phenylethyl-4-phenylethylene-5-pyrazolone) *p*-nitrobenzoylhydrazide.

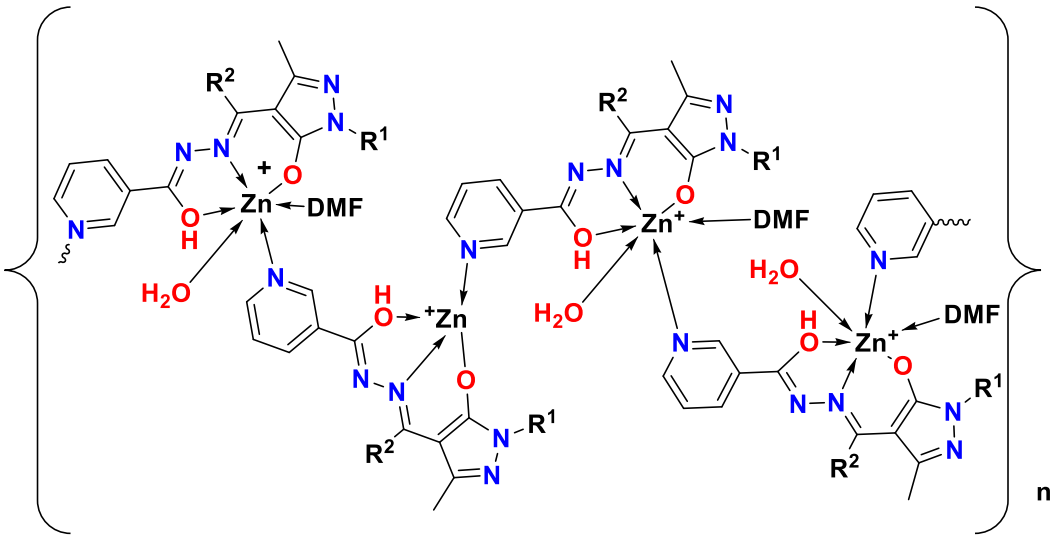


Fig. 1.15. Polymeric zinc complex structure of 4-acylhydrazone-5-pyrazolone, where R^1=R^2=phenyl ring.

This [Zn(L)(CH_3OH)] exhibits unique luminescence mechanochromism tuned by coordinated methanol.[40] The binuclear zinc(II) complex which general formula is [Zn(L)(CH_3OH)]$_2$ (Fig. 1.14) was synthesized by (Yang et al) the mixing of methanolic solution of 1-phenyl-3-phenylethyl-4-phenylethylene-5-pyrazolone, *p*-nitro benzoyl hydrazide and zinc acetate dihydrate. This complex showed hydrogen bonding linked 2D rhombus grid network.[41]

The Zn(II) complex (*see* Fig. 1.15) has been found polynuclear in the solid state though the Zn-N interaction of nicotinic moiety in the Schiff base pyrazolone, with water and DMF molecules completing the octahedral surroundings of zinc centers.[5,42]

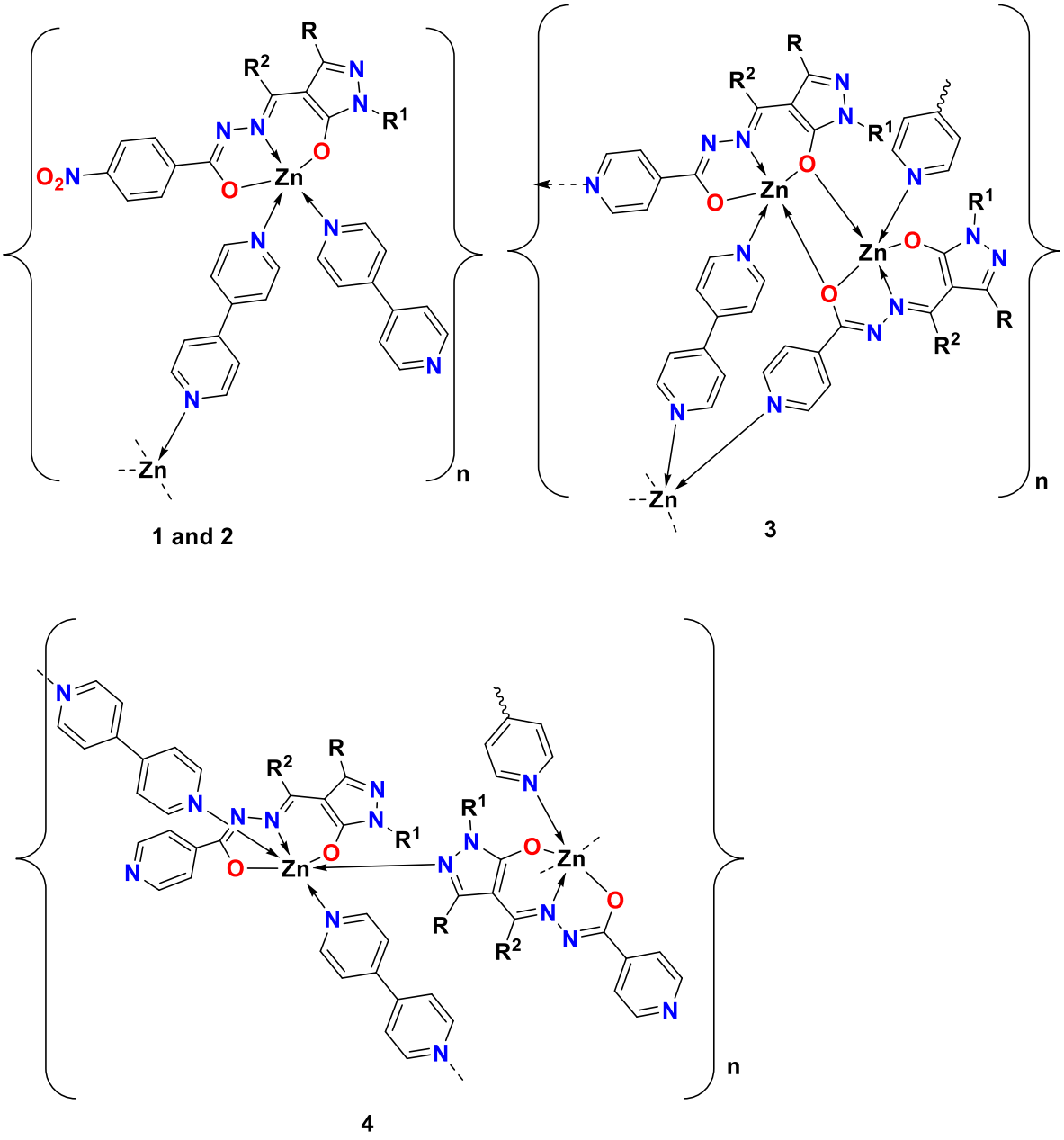
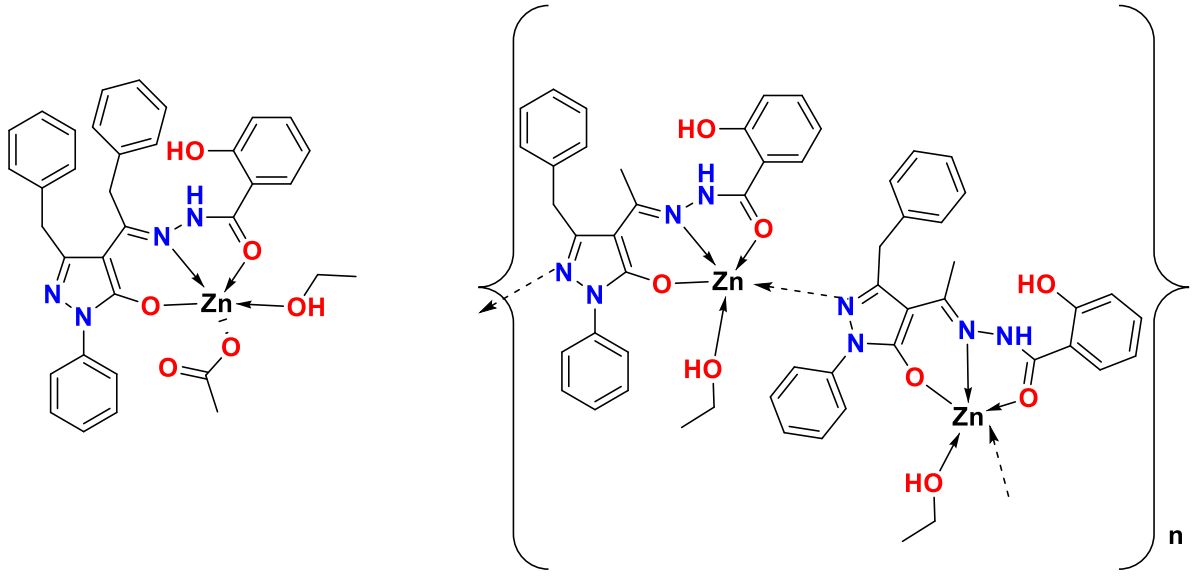


Fig. 1.16. Polymeric zinc(II) complexes of 4-acylhydrazone-5-pyrazolone, where general formula for **1**= {[Zn(L1)(4,4'-bipy)]0.52CH_3OH}$_n$, **2**= {[Zn(L2)(4,4'-bipy)]CH_3OH}$_n$, **3**=

{[$Zn_3(L3)_3(4,4'\text{-bipy})_{0.5}$] $3CH_3OH\}_n$, **4**= {[Zn(L4)(4,4'-bipy)]$2CH_3OH$}n,. (ligands H_2L1 = N-(1,3-diphenyl-4- propylene-5-pyrazolone) *p*-nitro benzoyl hydrazide, H_2L2 = N-(1-phenyl-3-benzyl-4-propylene-5-pyrazolone) *p*-nitro benzoyl hydrazide, H_2L3 = N-(1,3-diphenyl-4-propylene-5-pyrazolone) isoniazid, H_2L4 = N-(1-phenyl3-benzyl-4-propylene-5-pyrazolone) isoniazid, 4,4'-bipy = 4,4'-bipyridine).[5,43]

Four Zn(II) coordination polymers **1-4** (*see* Fig. 1.16) of 4-acylhydrazone-5-pyrazolones with 4,4′-bipyridine were synthesized in which 3 and 4 showed intense fluorescence properties in the solid-state, which may have potential application in fluorescence chemistry.[43] Mononuclear zinc complex with tetragonal pyramidal geometry **(1)** [Zn(HL1)(OAc)(EtOH)] and polynuclear **(2)** $\{[Zn(L2)(MeOH)]\cdot(MeOH)\}_n$ were synthesized by the reaction of ethanolic 4-acyhydrazone-5-pyrazolone (H_2L1=N-(1-phenyl-3-phenylmethyl-4-phenylethylene-pyrazolone-5)-salicylidene hydrazide and H_2L2=N-(1-phenyl-3-phenylmethyl-4-ethylene-pyrazolone-5)- salicylidene hydrazine) and zinc acetate dihydrate (*see* Fig. 1.17). The complex **1** contains a mono-deprotonated tridentate 4-acylhydrazone-5-pyrazolone ligand, an acetate group and an ethanol molecule coordinated to Zn, while in complex **2** the tridentate 4-acylhydrazone-5-pyrazolone ligand has lost two protons and the Zn environment is completed by an ethanol molecule and an N atom by a pyrazolone ring of a neighbour unit, affording a 1D network. Both complexes were showed strong fluorescence in the solid state.[5,38]



1 **2**

Fig. 1.17. Structure mononuclear zinc(II) complex **1** =[Zn(HL)(EtOH)(OAc)] and polynuclear complex **2** = {[Zn(L2)(MeOH)]·(MeOH)}.

1.11. Coordination behavior of 4-Semicarbazone-5-pyrazolone and 4-Thiosemicarbazone-5-pyrazolone

Many studies recently appeared on pyrazolones, mainly those bearing hydrazone, semicarbazone and thiosemicarbazone moieties, as potential photochromic materials, which exhibit a reversible colour change in the solid state in response to light, with potential application in several fields, such as high-density information storage systems, optical switches, and also as selective fluorescent probe for metal ions such as aluminium and iron.[5,44–46]

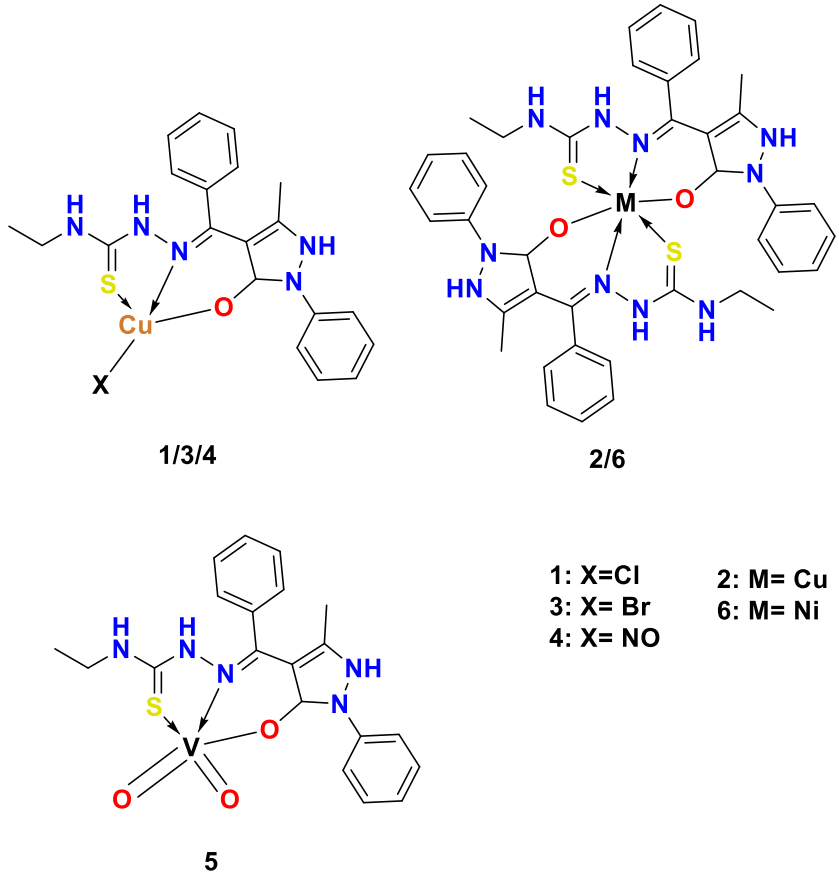


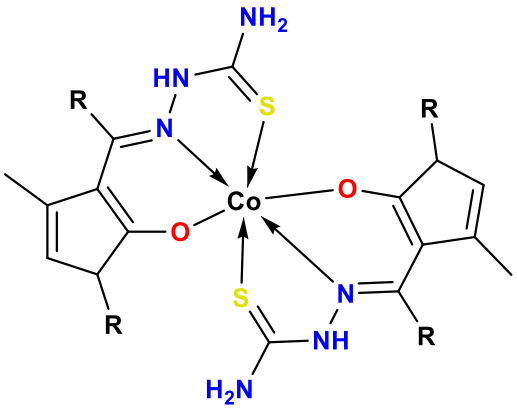
Fig. 1.18. Structures of 4-thiosemicarbazone-5-pyrazolone based Cu(II), Ni(II), and V(V) complexes.

The photochromic mechanism of enol–keto tautomerism was investigated for 1,3-diphenyl-4-(4-fluoro)benzal-5-pyrazolone *N*(4)-phenyl semicarbazone. The isomers may be involved in the reaction path have been studied both in the gas phase and in ethanol solution. SCXRD revealed H-bonds existing in the crystal structure. The transition states between keto and enol form have been located to investigate the photochromic mechanism.[47] Previous studies show

the 4-acyl pyrazolone based derivatives, especially the 4-semicarbazone-5- pyrazolone usually exhibit various coordination pattern. However, studies on the coordination behavior of 4-semicarbazone-5-pyrazolones toward d^{10} metal coordination are still comparatively rare.

The 4-thiosemicarbazone-5- pyrazolones have been intensively studied for many years, largely because they have the potential to form ONS tridentate coordination compounds. The binding ability of 4-thiosemicarbazone-5-pyrazolones is potentially flexible as bidentate or tridentate ligands and can be used as efficient organic connectors. Elena *et al.*, (2019) reported the coordination ability of 1-phenyl-3-methyl-4- benzoyl-5-pyrazolone-4-R thiosemicarbazone, HL^{1-3} (R = CH_3, C_6H_5, C_5H_5N) has been proved in complexation reaction with Cu(II), Ni(II) and Co(II) ions.[48]

1-phenyl-3-methyl-4-benzoyl-5-pyrazolone, 4-ethyl-thiosemicarbazone (HL) and its copper(II), vanadium(V) and nickel(II) complexes: $[Cu(L)(Cl)]\cdot C_2H_5OH\cdot$(**1**), $[Cu(L)_2]\cdot H_2O$ (**2**), $[Cu(L)(Br)]\cdot H_2O\cdot CH_3OH$ (**3**), $[Cu(L)(NO_3)]\cdot 2C_2H_5OH$ (**4**), $[VO_2(L)]\cdot 2H_2O$ (**5**), $[Ni(L)_2]\cdot H_2O$ (**6**), (*see* Fig. 1.18) were synthesized by mixing of ligand and respective metal salt in the solvent. The *in vitro* antibacterial activity of the complexes against *Escherichia coli*, *Salmonella abony*, *Staphylococcus aureus*, *Bacillus cereus* and the antifungal activity against *Candida albicans* strains was higher for the metal complexes than for free ligand. The effect of the free ligand and its metal complexes on the proliferation of HL-60 cells was tested.[49]



1

Fig. 1.19. Structures of cobalt complexes of thiosemicarbazone $[Co(L_2)]$, where R= Ph.

The octahedral cobalt complex [Co $(L)_2$] (*see* Fig. 1.19) was synthesized by the reaction of ONS tridentate ligand (HL) (HL = l-phenyl-3-methyl-4-benzoylpyrazol-5-one-thiosemicarbazone) and cobalt salt [$Co(OAc)_2$ $4H_2O$] in the ethanol-water mixture.[50]

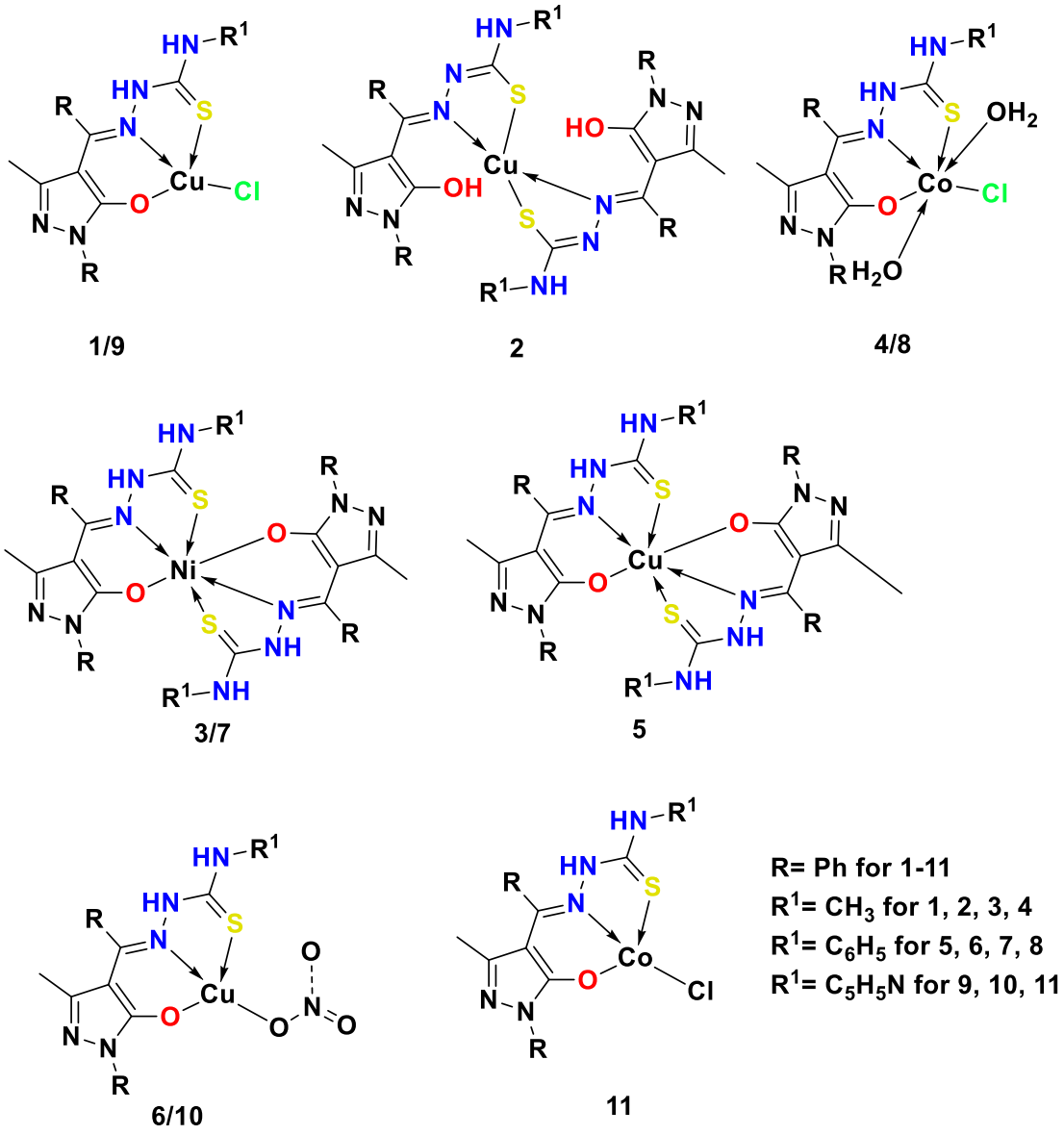
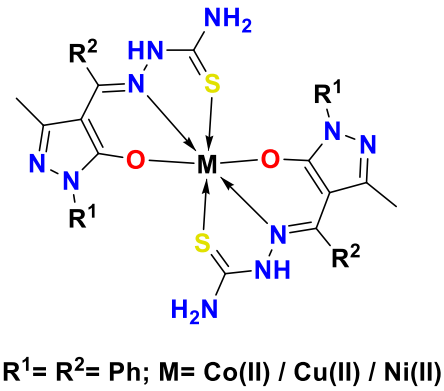


Fig. 1.20. Cu(II), Co(II) and Ni(II) complexes of 4-thiosemicarbazone.

The eleven complexes of Cu(II), Ni(II) and Co(II) were synthesized by the complexation reaction of 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone-4-R thiosemicarbazone with a respective metal salt. As shown in Fig. 1.20, complex 1 exhibits a square planar environment provided by one molecule of deprotonated tridentate ligand and one chloride anion while in the complex 6, the cooper atom exhibits a distorted square-pyramidal environment. For complexes

3 and 7, the nickel atom exhibits a slightly distorted octahedral coordination environment provided by the two molecules the ligand. The copper complexes manifest an important antiproliferative activity for HL-60 leukaemia cells compared to those containing nickel and cobalt ions. The modification of functional groups in the ligand attached to the Cu atom could regulate geometry and their antiproliferative activity.[48]

Cu(II), Co(II) and Ni(II) complexes which occupy octahedral geometry for all the complexes (*see* Fig. 1.21). The metal complexes showed better antimicrobial activity when compared with the ligands.[51]



R^1= R^2= Ph; M= Co(II) / Cu(II) / Ni(II)

Fig. 1.21. The general structure of Co(II), Cu(II) and Ni(II) complexes reported by Asegbeloyin *et al.*

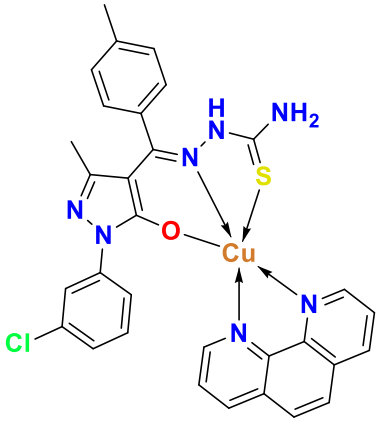


Fig. 1.22. The structure of the copper complex reported by Komal *et al* (2013).

The copper (II) complex displays a geometry of the metal centre between square pyramidal and trigonal bipyramidal (Fig. 1.22). It is able to interact with both DNA and BSA (bovine

serum albumin) and shows cytotoxicity against A549 cells and mitochondrial damage via an oxidative mechanism and ability to induce cell cycle arrest in the sub G0/G1 phase.[52] The distorted octahedral complex of d^{10} metal (Cd(II) complex) (*see* Fig.1.23) with two O,N,S tridentate 4-thiosemicarbazone-5-pyrazolone ligands was synthesized by Sangeetha *et al*.[20]

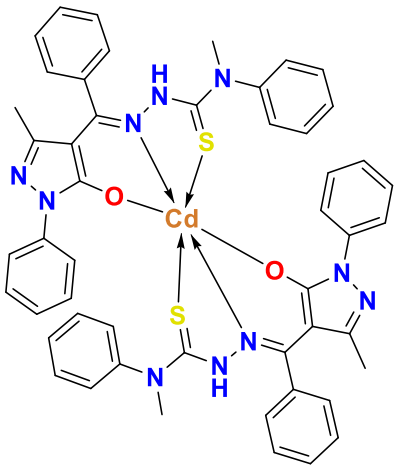


Fig. 1.23. The binary d^{10} metal complex of 4-thiosemicarbazone-5-pyrazolone.

1.12. Biological aspect and purpose of this work

The acyl pyrazolones and their derivatives are very interesting due to their structural analogues, coordination and biological potential. Pyrazolone scaffolds are present in several bioactive natural alkaloids and several pharmaceuticals with antipyretic, analgesic, neuroprotective, antitumor, antioxidant, antibacterial and anti-infective properties, and also in inhibitor agents of some biological enzymes.[5,53–57] the ruthenium metal complexes of acyl pyrazolone derivatives were tested against ovarian carcinoma, breast carcinoma, cervical carcinoma and hepatocarcinoma, some showing interesting selectivity and efficiency.[58–60] Many of copper complexes of pyrazolone synthon were investigated for their anticancer potentials against lung carcinoma[61], ovarian carcinoma[62], epidermoid carcinoma[63], esophageal carcinoma[64], cervical carcinoma[64], liver carcinoma[65], promyelocytic leukemia[66] and acute lymphocytic leukemia[66], some complexes being very promising and efficient.[5] 1-phenyl-3-methyl-5-hydroxypyrazole-4-methylene-8′-quinolineimine, and its Cu^{II}, Zn^{II}, and Ni^{II} complexes were subjected to cytotoxic tests, and experimental results indicated that the metal complexes show significant cytotoxic activity against lung cancer A 549 cells.[67] The cadmium complexes of 4-acylhydrazone-5-pyrazolone have higher cytotoxic activities against HeLa and Eca-109 tumor

cells than that of the ligand and cisplatin.[17] The cytotoxicity of acylpyrazolone based zinc(II) complexes has been evaluated *in vitro* against MCF-7 human breast cancer cell line in a biohybrid membrane system. Results revealed that zinc complexes possess antiproliferative activity inducing apoptosis by activation of caspase-3 and p-JNK.[32]

Antimicrobial activity of tridentate Schiff base ligands containing pyrazolone moiety and their transition metal complexes of VO(II), Cu(II), Fe(III), and Co(II) showed that the complexes have enhanced antibacterial activity against S. aureus, E. coli, and S. Typhi and antifungal activity against C. Albicans, Rhizopus sp., and A. Niger compared to the ligands.[68] Acylpyrazolone based vanadium, chromium, ion, cobalt, manganese, nickel, palladium, platinum, and copper complexes have been screened for antibacterial activity.[49,51,65,69–71]

4-Thiosemicarbazone-5-pyrazolones and their Cu(II) complexes show either modest or no growth inhibitory activity against Aspergillus niger and Paecilomyces variotii.[72] Antifungal and antibacterial activity have been studied for pyrazolone based Ni(II), Pt(II) and Pd(II) complexes and result was revealed that compounds were moderate to highly active against selected bacterial strains but inactive as antifungal except for Pd(II) which showed a moderate antifungal activity.[73]

Relatively fewer studies were undertaken on antioxidant and scavenging activity of metal complexes with pyrazolone-based ligands, mainly focused on manganese, iron, cobalt, nickel and copper, where it's evident that some complexes with manganese and nickel are very efficient.[5,67,70,74]

Based on the fact, we have synthesized zinc (II) complexes of 4-acylpyrazolone and its derivatives. All ligands and their complexes have been screened for the *in vitro* and *in silico* anti-malarial activity. Semicarbazone and thiosemicarbazone of pyrazolone based ligands and their four zinc(II) complexes have been screened for anticancer activity.[30,75,76]

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