Chapter-I
Chemistry of pyrazolones and their metal complexes

1.1: Introduction:

The coordination chemistry has an old history. It is difficult to predict the discovery of the first metal complex. The earliest one on record is Prussian blue. This was synthesized in the beginning of the eighteenth century.

In 1818, Tassaert,\(^1\) prepared an orange compound with composition \(\text{CoCl}_3 \cdot 6\text{NH}_3\) by the reaction of cobalt chloride and ammonia. Transition elements have strong tendency to form coordination compounds due to small size, high charge density and vacant \(d\) orbitals. In coordination compounds, ligands donate electron pair to the central metal ion. Alfred Werner, Founder of coordination chemistry, put forward a famous theory to explain the bonding in coordination complexes in 1893. He was awarded Nobel Prize (1913). Later on Linus Pauling (1930), Hans Bethe and Van Vleck (1935), L. E. Orgel (1955), Y. Tanabe and S. Sugano (1954) gave significant contribution in the development of coordination chemistry.

The coordination compounds have number of applications in qualitative and quantitative analysis. Coordination compounds are used as catalysts. The Ziegeler-Natta catalyst is used in polymerization of ethylene. The metal carbonyls and their derivatives are used as catalysts in many chemical transformations. The conversion of methanol into acetic acid occurs with \([\text{Rh}_2(\text{CO})_8]\). The \([\text{Co}_2(\text{CO})_8]\) was used as catalyst in hydroformylation.

Recent application of complexes is photolytic decomposition of water producing hydrogen for generating non-polluting fuel.
The coordination compounds are also important in biology and medicine. The presence of about forty naturally occurring elements play a vital role in plants and animals. They are present and transported in the biological systems as coordination complexes.

In animals and plants, various chelating agents like citrate, tartarate, maleate, lactate, amino acids etc, are present to effectively complex with the metal ions. Roots of many plants secrete chelating agents like maleate and citrate. These solubilise the metals in the soil and make available to the plants.

Coordination compounds play an important role in biological process such as nitrogen fixation, synthetic oxygen carriers, oxygen activators etc. Haemoglobin, cytochromes, catalases and many other enzymes are iron-containing complexes, vitamin B\textsuperscript{12} is a cobalt complex and many other examples point toward that metal complexes play an important role in biological systems.

Pyrazolone represent an important class of compound for their number of application in diverse area.\textsuperscript{2\textnormal{-}3} Pyrazolone is five-member heterocyclic compound containing two nitrogen and ketone in the same molecule. Pyrazolone derivatives have pharmacological properties such as analgesic, \textsuperscript{4\textnormal{-}5} antipyretics \textsuperscript{5\textnormal{-}6} and non-steroid anti-inflammatory agents.\textsuperscript{7\textnormal{-}8} The basic ring structure and numbering system of pyrazolone ring are as shown in Fig 1.1

![Pyrazolone Ring](image)

Figure 1.1 Pyrazolone ring
The known pyrazolones are II, III, and IV. (Figure 1.2)

![Chemical structures of pyrazolones](image)

Figure 1.2: Pyrazol-5-one and Pyrazol-3-one

The term pyrazolinone was first introduced by Ruhemann.⁹

Some trivial names are very common for some pyrazolones as follows
A] Antipyrine (2, 3-dimethyl-1-phenylpyrazol-5-one),
B] Aminopyrine (2,3-dimethyl-4-dimethylamino-1-phenylpyrazol-5-one)
C] Amino-antipyrine (2, 3-dimethyl-4-amino-1-phenylpyrazol-5-one)

Theoretically, a large number of tautomers are possible for un-substituted pyrazol-5-one, as shown in Figure 1.3.

![Chemical structures of tautomers](image)

Figure 1.3 Tautomers of unsubstituted pyrazol-5-one
In addition, it also shows ionic tautomeric isomers from (h) to (l) as shown in figure 1.4.

![Diagram of ionic tautomeric isomers of pyrazolone]

Figure: 1.4: ionic tautomeric isomers of pyrazolone

The substitutions at N-1, N-2 and C-4 decide the possible tautomeric and resonance forms. Of which, three forms (a), (b) and (c) supports many physical and chemical evidences.

The substituted acyl pyrazol-5-ones shows tautomerism (figure 1.5).

![Diagram of tautomers of acyl pyrazol-5-one]

Figure: 1.5: Tautomers of acyl pyrazol-5-one

The enol form (1) is predominant in non-polar solvent.

If C-3 or N-1 position is substituted by phenyl ring, it stabilizes NH-amino diketo form (2). An intramolecular hydrogen bonding (OH...O) favor the enol form when C-3 position is substituted by -Ph, -Me, -Et, -CH=CH-Ph.

The amino diketo form (2) is stabilized by extensive network of intermolecular N-H...O bonding and it is obtained in polar solvent, it is found in pyrazolone where C-3 position is substituted by Ph, Me, thiazolyl.

The keto and enol forms of 4,4-(3-nitrobenzylidene)-bis-(3-methyl-1-phenylpyrazol-5-one) have been isolated.
3-substituted-; 3,4-substitued and 1,3,4-substituted pyrazol-5-ones favor structure (d), (e) or (g).\textsuperscript{27}

The effect of substitution on the structure of pyrazol-5-one is very important. In substituted pyrazol-5-one, all possible tautomers are not formed.\textsuperscript{29} The substitution at N-1 allows only (a), (b), and (d) as possible tautomers but substitution at N-2 gives only (d) and (h) structures. Pyrazol-5-one predominantly exist as structure (b) when it is either substituted at N-1 and N-2 or at C-4.

Kitamura\textsuperscript{30} suggested the N-2 substituted pyrazol-5-one exist as mixture of (b) and (g). Krohs\textsuperscript{31} has suggested structure (b) based on infrared absorption in the carbonyl region of infrared spectra of some pyrazol-5-ones. Abnormally high dipole moment of 2,3-dimethyl-1-phenyl pyrazol-5-one and its thiono-analog is due to contribution by (h) and (J). Many physical and chemical evidences support that the substitution at N-1 favors form (a) and at N-2 favors form (b). Proton and Carbon-13 nuclear magnetic resonance spectra studies of 3-methyl-1-phenyl pyrazol-5-one shows that it exist in form (a) slowly inter-converting with (b) and (d) in DMSO solution (Figure 1: 6) as well as its temperature dependent $^{15}$N spectrum in deuterated DMSO at 30°C shows all three tautomers are present.\textsuperscript{34}

![Figure: 1.6 Tautomers of 3-methyl-1-phenyl pyrazol-5-one](image-url)
1:2) Synthesis of pyrazolones:

Different methods for the synthesis of pyrazolones are reported in literature. However, one of the most frequently used methods for the synthesis of pyrazolones is by condensing β-ketoester with hydrazine.\(^{35-38}\)

German chemist Ludwig Knorr (1883) was the first to report the synthesis of 3-methyl-1-phenyl pyrazol-5-one by condensing ethylacetoacetate with phenyl hydrazine.\(^{39}\)

![Ludwig Knorr (1859-1921)](image)

Pyrazol-5-one derivatives are synthesized by using non-substituted or mono-substituted β-ketoester with mono-substituted hydrazine.

The yields are better for smaller substituents \(R^1, R^3\) and \(R^4\). When \(R^2\) and \(R^3\) are benzyl and \(R^4\) is phenyl, pyrazol-5-one formation does not occur.\(^{40}\) When \(R^2\) and \(R^3\) are aryl or \(R^3\) is larger than \(CH_3\), the pyrazol-5-one formation is difficult.\(^{41}\) Generally, esters with no substitutions or one α-substitution are used.\(^{42}\) The ester α, α-diethyl acetoacetate with hydrazine fails to form pyrazol-5-one but α, α-dimethyl acetoacetate forms pyrazol-5-one with hydrazine.\(^{43}\)

The pyrazol-5-one formation from β-aldehydoester (\(R^1=H\)) have been reported.\(^{44-45}\)

When \(R^1\) is alkyl\(^{45}\), aryl\(^{47,48}\) or heterocyclic\(^{49}\) also gives good yield.
Mono substituted hydrazines are also used for preparation of pyrazol-5-ones. The alkyl, aryl or heterocyclic hydrazines are used for the synthesis of pyrazolones.

In classical method, hydrazine is condensing with ketoester without addition of catalyst at 100-200 °C.

Firstly, hydrazone is formed which on cyclisation gives pyrazol-5-one.

\[ \text{Acidic and basic conditions promotes cyclisation step. In modified method, acid hydrazides are use in the pyrazol-5-one preparation.} \]

Under mild conditions, the N-1 has acyl substituent. If reaction is carried out at higher temperature, the acyl-group is lost.

In the place of β-ketoester, the corresponding amides and anilides are used.

Mitra have been reported the use of β-thinoacetoacetates and hydrazine for synthesis of pyrazol-5-one. The β-ketoester in which R¹ = -COCH₃ gives 3-methyl-1-phenylpyrazol-5-one with elimination of acyl group.

The unsaturated compounds (RC = CCOR) having triple bond in the β-position with hydrazine gives pyrazol-5-ones. The β-alkoxy-α,β-unsaturated ester and β-alkylthio-α,β-unsaturated ester gives pyrazolone with hydrazine.
Lecher et al. have reported the synthesis of pyrazol-5-one by reacting ketene with phenyl hydrazine. Firstly, hydrazone of the corresponding aceto-hydrazide is formed which on cyclisation at higher temperature to form 3-methyl-1-phenylpyrazol-5-one.

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{PhNHN} & \quad \text{NPhH}
\end{align*}
\]

Lecher carried out the reaction between ketene and hydrazides in different proportions under different conditions and temperature. It was noted that yield was better in aqueous acid medium at elevated temperature. β-halogenated acids gives pyrazolones with phenyl hydrazine.

\[
\begin{align*}
\text{OH} \\
\text{Br}
\end{align*}
\]

A number of heterocyclic compounds reacts with hydrazine to form pyrazolones.

\[
\begin{align*}
\text{Ref. 64}
\end{align*}
\]

Ref. 65

Ref. 66
The pyrazolone having are -CH₃, -C₆H₄NO₂, -C₅H₄CF₃, -C₅H₄N as substituent at N-1 have been reported.⁶⁷-⁷⁰

Under mild condition, Acid-hydrazides react with β-ketoester to form pyrazolone with N-1 acyl substituent.⁷¹

[Chemical structure]

Where X=O, S, NH

Acyl semicarbazide, carbazide or thio-analogs are used in the synthesis of N-1 acyl substituted pyrazolones.⁷²-⁷⁷

Hydrazides of sulfonic acids are also used in pyrazolone synthesis.⁷⁴

The hydrazone intermediate are isolated and cyclized by heating.⁷⁸,⁷⁹

When R³ is aryl or aryl-alkyl, the reaction carried at low temperature; the 1-acyl pyrazol-5-ones are formed.⁸⁰

In modified method, β-ketoamide is used in the place of β-ketoester.⁸¹

The pyrazolones having no N-1 substitution are acylated at N-1 by using acetic-anhydride or acetyl chloride, benzoyl chloride.⁸²,⁸³

Evans N.A.⁸⁴ have reported the synthesis of 1-acetyl-3-methyl-pyrazol-5-one by adding acetic-anhydride to the solution of 3-methyl-pyrazol-5-one in pyridine.
Another acylating agents arylsulfonyl chloride, alkylchloroformates are used for synthesis of 1-acyl pyrazol-5-one.\(^{85}\)

A series of new pyrazole derivatives has been synthesized by reaction between ethyl acrylate and 5-methoxy-2-nitrodiazoacetophenone.\(^{86}\)

\[
\text{\begin{array}{c}
\text{N} & \text{O} & \text{C} & \text{O} \\
\text{\text{Ph}} & \text{\text{Et}} & \text{\text{COEt}} & \text{\text{C}}
\end{array}} 
\]

Where \(R_1 = \text{OCH}_3, \text{H}, \text{Cl}\) and \(R_2 = \text{Me}, \text{Et}, \text{Pr}, \text{Ph}\)

Bis (1-acyl pyrazol-5-one) linked via N-1 are synthesized by reaction of carbazide with equivalent of \(\beta\)-ketoester.\(^{87}\)

The bis compounds linked at C-4 are synthesis by reaction of \(\beta\)-ketoester and semicarbazide.\(^{61}\)

N-1 substituted pyrazolone gives 4-acyl-5-pyrazolone with acid chloride.\(^{88}\)

Henry Torrey et al.\(^{89}\) synthesized 1-benzoylphenyl-3-methylpyrazol-5-one from hydrochloride of parahydrizinobenzophenone and aceto-acetic ester with a few drops of hydrochloride acid.
Chapter-1: Chemistry of pyrazolones and their metal complexes

N-1 substituted thiocarbamoyl-3,5-diphenyl pyrazol-5-one has anti-amoebic activity and it was synthesized by base catalyzed Claisen-Schmidt condensation of benzaldehyde with acetophenone followed by cyclisation with various thiosemicarbazide.\textsuperscript{90}

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{H} - \text{C} = \text{O} - \text{Ph} \quad \rightarrow \quad \text{Ph} - \text{C} = \text{O} - \text{Ph} \\
\text{R} - \text{N} & \quad \rightarrow \quad \text{Ph} - \text{N} = \text{N} - \text{Ph}
\end{align*}
\]

Vladimir Kepe et al.\textsuperscript{91} described a synthesis of 1-acyl pyrazol-5-one and related derivatives from ethoxymethyleneoxazolone derivatives and reported that these compounds act as good acylating agents.

The 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one (Dehydroacetic acid - DHA) is biological active compound.\textsuperscript{92-94} It shows antibiotic and fungicidal properties and used as preservative and its schiff base metal complexes are antibacterial.\textsuperscript{95}

The most reactive site for nucleophilic attack is carbonyl carbon of the side chain. Dehydroacetic acid, (DHA) undergoes a number of reactions with hydrazines forms various products like pyranopyrazoles, bipyrazoles, pyrazolyl-1, 3-diketones and pyrazolones under different experimental conditions.\textsuperscript{96}

Perkin and Bernhart\textsuperscript{97} have first reported a synthesis of pyrazolone by the reaction between DHA with phenyl hydrazine.

Stolle and Bennary\textsuperscript{98} have isolated two products
(I) 3,6-dimethyl-1-phenylpyrano-[4,3-c]pyrazol-4-one and
(II) 1,1’-diphenyl-3,3’dimethyl-(4,5’-bipyrazole)-5-ol
A. Akherm et al.\textsuperscript{99} also reported the formation of above products (I) and (II) with ketoester as side product.

In modified method, DHA is first treated with phosphorus oxychloride to give 4-chloro-3-(1-chlorovinyl)-6-methyl-2H-pyrane-2-one, which react with hydrazine to form product (I) and its isomer (III).\textsuperscript{100}

The formations of products explain on the basis of initial attack of more nucleophilic nitrogen of the hydrazine on C-4 of pyrone ring.

The reaction of DHA with phenyl hydrazine in methanol followed by refluxing in xylene in the presence of p-toluene sulphonic acid gives the product (I) The structure was assigned by $^{13}$C{$^{1}$H} NOE.\textsuperscript{101}
1.3) Properties of pyrazolones:

All Pyrazolones are almost solids. They are insoluble in non-polar solvents. The N-1 substituted pyrazolones are weaker acids than non-substituted at N-1. Substitution on N-1 and N-2 gives low melting solid but substitution at C-3 or C-4 increases melting point, eg. The melting point of pyrazol-5-one is 163°C and of 3-methyl pyrazol-5-one is 215°C. In pyrazol-5-one, the C-4 position is very reactive due to active methylene group.

Aldehydes reacts with 3-methyl-1-phenyl pyrazol-5-one and gives a mixture of products However, ketones gives mono pyrazolone product. In the presence of piperdine, 3-methyl-1-phenyl pyrazol-5-one undergoes an intermolecular aldol-condensation.

The condensation of amide with hydrazine gives 4-substituted product. Michael addition reaction takes place with β- unsaturated Ketones.

The alkylation of 3-methyl-1-phenyl pyrazol-5-one takes place at N-2 and at the oxygen in addition to C-4. However, at 100 to 130 °C alkylation at N2 is preferred.
Alkylation at N-2 is carried out by methyl-iodide and methanol at 100°C by methyl-sulphate and sodium hydroxide and by Dimethyl-sulphate.

Alkylations of 3-methyl-1-phenylpyrazol-5-one have been extensively studied because the product yields antipyrine (2, 3-dimethyl-1-phenyl pyrazol-5-one). This is commercially important analgesic and antipyretic.

\[
\begin{align*}
\text{N-Ph} & \quad + \quad \text{CH}_3\text{I} \\
\text{N=O} & \quad \rightarrow \\
\text{N-Ph} & \quad + \quad \text{CH}_3\text{I}
\end{align*}
\]

Acylation of N-unsubstituted pyrazol-5-one is carried out by using acetyl chloride or acetic-anhydride. The product is 1-acyl pyrazol-5-one.

Pyrazol-5-one is relative stable to acid hydrolysis. Those having 1-dinitrophenyl substituent are decomposed to form aryl hydrazones. Hydrolysis with sodium hydroxide (33%) destroys the ring.

Majority of reactions such as halogenations, sulfonation, nitration, diazotization takes place at C-4 position. 4-arylazo-pyrazol-5-ones are strongly colored and used in dyeing all types of fabrics and has great importance in dye industry.

The N-1 acyl substituted pyrazol-5-one shows majority reactions at C-4 position due to active methylene group. Usually, N-1 acyl substituted pyrazol-5-one shows similar reaction. N-1 acyl substituted pyrazol-5-one by treatment with aniline or on hydrolysis losses acyl substituent. Rearrangement of N-acetyl group to oxygen atom takes place in acetic acid and pyridine.
I-4: Biological activity and uses of Pyrazolones:

Pyrazolone and their derivatives show diverse types of biological activities. The pyrazolones derivatives have great importance in medicinal chemistry as analgesic, anti-pyretic, and anti-inflammatory agents. Such properties of pyrazolones encourage the search of new pyrazolone derivatives.

Aminoantipyrine, phenylbutazone are used for treatment of rheumatoid arthritics. However, phenylbutazone has side effect and their use is restricted medicine. The synthesis of pyrazolones and research of new pyrazolone derivatives has remained attraction for researcher due to less toxic and more effective biological active compounds.

Pyrazolones compounds possess anti-bacterial, anti-fungal, anti-tumor, anti-convulsants, anti-oxidant, neuro-protectives, anti-hyperglycemic, insecticides.

Besides pharmaceutical applications, the pyrazolones are used in photography as colour coupler and sensitizers, in solvent extraction of metal ions, in the synthesis of dyes, in chromatography and in photochemical industries.

Knorr L. (1883) have synthesized 1-phenyl-2,3-dimethyl pyrazol-5-one and reported as anti-pyretic agent.  
The 4, 4-dichloro-1-(2, 4-dichlorophenyl)-3-methyl-5-pyrazolone TELIN is potent inhibitor of human telomerase. It does not combine with DNA and hence is a valuable substance for the treatment of cancer and related diseases. 3-methyl-1-(pyridine-yl)-5-pyrazolone has greater ability to scavenge radical.
Derivatives of pyrazolone have been studied for their importance as antipyretic and analgesic.\textsuperscript{147,148} 2-(4-chlorophenylazo)-5-methyl-2-phenyl-1,2-dihydropyrazolone has anti-microbial activity.\textsuperscript{149}

Mohammed Amir, S M Hasan and A Wadood have reported the synthesis and anti-bacterial activities of 1-isonicotinyl-3-methyl-4-(substituted-phenylhydrazono) pyrazol-5-ones and these pyrazolones derivatives show anti-bacterial activity against staphylococcus auras and Escherichia coli bacteria.\textsuperscript{151} 1-thiocarbamoyl-3-Methyl-4-arylhydrazonopyrazol-5-one behaves as potential anti-neuroplastics.\textsuperscript{152}

Acyl-derivatives of 3-amino-1-phenyl-4, 5-dihydropyrazol-5-one inhibits cyclooxygenase (Cox-1 and-2) and human lipoxygenase.\textsuperscript{153} Novel pyrazolone 4.4-dichloro-1-(2,4-dichlorophenyl)-3-methyl pyrazol-5-one act as potent catalytic inhibitor of human telomerase.\textsuperscript{154} 3-methyl-1-(pyridin-2-yl)-5-pyrazolone acts as hydroxyl radical scavenger.\textsuperscript{155} Bicyclic pyrazolones are inhibitors of tumor necrosis factors.\textsuperscript{156} Occupational asthma caused by pyrazolone derivatives are used in photography.\textsuperscript{157} Pyrimidine-pyrazolone nucleosides show anti-virus activity against vaccinia viruses and cowpox viruses.\textsuperscript{158}

3-methyl-4-(o-methyloximino)-1-phenyl-pyrazolone,(Ek6136) inhibit anti-proliferative activity of MCF-7 (human breast carcinoma) and A-549 (lung carcinoma). It inhibit Cdc-25B which is specific phosphate and plays an important role in the activation of cell-cycle dependent kinase-1.\textsuperscript{159}

The most important commercial use of pyrazolones is as dyes. Zeigler and Locher in 1848 synthesized a pyrazolone dye, Tartrazine. It is used as color for food-stuffs.\textsuperscript{160} Azomethide dyes have been extensively investigated by Vittum.\textsuperscript{161,162} A number of 4.4-arylidene bis(pyrazol-5-one) are used as colour couplers.
Almost all pyrazolone azo dyes have aryl-azo group or groups. These azo dyes are used to dye wool, cotton, silk, leather, rubber. Methylidyne bis-pyrazolones is suitable for dying polyester fabrics. Various orange azo dyes as well as brown, red, green, violet and intermediate shades are reported.

Kazimeirz Blus have synthesized a series of yellow dyes derived from 1-phenyl-3-methylpyrazol-5-one containing one or two aryl-sulphoamide groups. These dyes are suitable for dyeing polyamide fibers and wool.

A number of photochromic pyrazolones such as 1-phenyl-3-methyl-4-(4-bromobenzal) pyrazolone-5-thiosemicarbazone are reported. 1-phenyl-3-methyl-pyrazol-5-one and its derivatives are reported as organic stabilizer for rigid PVC against photo-degradation.

Peng has reported the photochromism in solid state and acidichromism in solution of 1-phenyl-3-methyl-4-(4-methylbenzal)-pyrazolone-5-thiosemicarbzone. Pyrazolones are used as reagents in various qualitative and quantitative analysis. 2-pyrazol-5-one used in gravimetric analysis of number of metal ions. Solvent extraction of from acid media was carried out by 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone. A number of pyrazolones are used in photography as color coupler and sensitizer.
1.5) Complexes of Pyrazolones:

Pyrazolone derivatives attracted the researcher for synthesis of metal complexes due to their biological activity, pharmaceuticals significance, importance in dye industries and also their use in extraction of metal.

Unsubstituted pyrazol-5-one has two donor atoms (N and O). It coordinate with metal ion either by N of pyrazole ring or by O atom of CO group. Substituted pyrazol-5-ones displays different coordination modes due to phenomenon of tautomerism. The substituted pyrazolones without additional donor atoms are coordinate with metal ion only by oxygen of carbonyl group.

Antipyrine, in which both the ring nitrogen (N-1 and N-2) are blocked by substituent, it form complexes with metal ion through oxygen of antipyrine and are mononuclear.

Antipyrine (Figure: 1.7) is neutral ligand hence for neutrality the presence of anion inside or out of coordination sphere is necessary. Metal complexes with anti-pyrine (Apy) were known before 1900.174-176

\[
\text{Fe(Apy)}_6
\]

Figure1.7: Metal complexes with anti-pyrine

The donor properties of antipyrine and its complexes with cobalt halide, copper halide and copper nitrate have been reported.177-179
The octahedral complexes [Fe(Apy)$_6$], square planar [Fe(Apy)$_4$Br$_2$] and [Fe(Apy)$_4$I$_2$] has been prepared and characterized by Prabhakaran C.P. and Patel C.C.$^{180}$

The pyrazolones, without donor atoms at C-3 shows different coordination modes with metal ion, as shown in figure 1.8.

![Coordination modes with metal ion](image1)

Figure: 1. 8: Coordination modes with metal ion

In neutral form, they behave as monodentate ligand but in deprotonated form, they coordinate with two, three or four metal ions. 3-methylpyrazol-5-one (MPy) with Co(II) chloride forms [CoCl$_2$(MPy)$_4$] complex.$^{181}$

![Octahedral Co(MPy)$_4$Cl$_2$ complex](image2)

Figure: 1. 9: Octahedral [Co(MPy)$_4$Cl$_2$] complex

A large number of complexes of pyrazolones having additional donor atoms in C-4 substitution are known.

Nitrogen contacting substituent at C-4 of pyrazolone (If Nitrogen is present in substituent in appropriate position) act as ligand to co-ordinate with metal ion along with oxygen of carbonyl moiety and nitrogen of C-4 substituent.
The bidentate 4-dimethylaminoantipyrine-1-phenyl-2,3-dimethyl pyrazol-5-one forms complex with Co(II) in which O and N acts as donor atoms.\textsuperscript{182}

Complexes of Co(II) Ni(II) and Zn(II) with 4-aminoantipyrine and 4-dimethylaminopyrine (dmapy) have been prepared and characterized.\textsuperscript{183}

![Octahedral $[\text{Co(dmapy)}_2 (\text{NCS})_2]$ complex](image)

The complexes of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) with 3-methyl and 3-phenyl-4-nitroso-5-pyrazolones have been reported, of which the former acts as monobasic bidentate ligand, bonded to metal ion through the oxygen atoms of the carbonyl group of pyrazole ring and oxygen atom of nitroso group. The latter acts as neutral bidentate ligand and form octahedral complexes.\textsuperscript{184}

Samir Kandil have prepared the Co(II), Ni(II) and Cu(II) complexes with 4-(4-azidosulfopyenylazo)-5-phenyl-3,4-dihydro-pyrazolone, 4-(4-azidosulfophenylazo). In this complexes coordination with metal ion is observed by enolic O of pyrazole ring and N of C-4 substituent.\textsuperscript{185}

When C-4 substitution has donor atom with bulky group, the modes of coordination with metal ion are different.4-diazo pyrazolones coordinate with metal ion with carbonyl oxygen as well as N of C-4 diazo substituent. The complexes of 1-phenyl-2, 3-dimethyl-4-(2-hydroxynaphthalylazo) pyrazol-5-one have been reported. In which carbonyl O of pyrazole ring and N of C-4 substituent acts as donor atoms.\textsuperscript{186}
Emeleus L. C. et al. has proposed Cu(II) complex with 1-Phenyl-3-methyl-4-(phenylazo)pyrazol-5-one, in which ligand coordinate with central metal ion by O and N.\textsuperscript{187}

M. R. Gopalkrishnan and C. P. Prabhakaran have synthesized the complexes of Cu(II) and Ni(II) with 1-phenyl-2,3-dimethyl-4-(2-hydroxynaphthylazo)pyrazol-5-one and characterized by element analysis, magnetic moments and electronic spectra.\textsuperscript{188}

S. A. Abdel-Latif et al., have reported the complexes of Mn(II), Co(II), Ni(II) and Cu(II) with 3-phenyl-4-(p-methoxyphenylazo)pyrazol-5-one and proposed stereochemical structure for octahedral geometry for Co(II) complex, tetrahedral for Ni(II) and square planar for Cu(II) complexes on the basis of spectral and thermal analysis.\textsuperscript{189}

When C-4 substituent has two or more donor atoms, can coordinate with metal ion. 1-phenyl-3-methyl-4-(2-hydroxyphenylazo) pyrazol-5-one behave as tridentate ligand with N, O, O, donor atoms.\textsuperscript{191} The ligand 1-phenyl-3-methyl-4-[1-naphtylaminoethylidene] pyrazol-5-one coordinate through O and N donor atoms to form complex [NiL\textsubscript{2}(EtOH)\textsubscript{2}]\textsuperscript{19}

Synthesis and characterization of Cu(II) complexes of azo dyes derived from 1,2-dihydro-1,5-dimethyl-2-phenyl-4-amino pyrazol-5-one have been reported.\textsuperscript{192}

The octahedral complex 1,2 dihydro-1-phenyl-2,3-dimethyl-4 (2,4-pentadieone-3-hydrazone) pyrazol-5-one with Fe(III) in the presence of chloride ion have been synthesized and characterized.\textsuperscript{193}
Dinuclear complex of ligand 1-phenyl-3-methyl-4-[1-(2-hydroxyphenyl)aminoethylidene] pyrazol-5-one have been reported.\textsuperscript{194}

Acyl pyrazolones display different coordination modes due to phenomenon of tautomerism.\textsuperscript{195}

In neutral form, it coordinates to metal ion through
(a) Ring-OH and chain carbonyl oxygen,
(b) Carbonyl oxygen of ring and carbonyl oxygen of chain
(c) Ring nitrogen of the pyrazole ring.

![Coordination modes of acyl pyrazolone in neutral form.](image1)

In the presence of base, such as \textit{NR}_3, NaOMe, Acyl pyrazolone ligands can be deprotonated and form ionic form, it coordinates with metal ion by
d) Ring oxygen and carbonyl oxygen of chain,
e) Either carbonyl oxygen of pyrazole ring or ring N-2
f) Carbonyl oxygen of pyrazole ring and carbonyl oxygen of chain,
g) Both carbonyls oxygen as well as nitrogen of pyrazole ring.

![Coordination modes of acyl pyrazolone in deprotonated form.](image2)
The octahedral complexes of Co(II), Ni(II), with 1, and 3 diphenyl-2-pyrazol-5-ones were reported.\(^{196}\)

Fe(III) forms a high spin octahedral complex with 1-phenyl-3-methyl-4-acetyl-pyrazolone (PMAP) in the metal ligand ratio 1:3. PMPA acts as bidentate ligand and coordinates with Fe(III) ion through carbonyl O of pyrazole ring and carbonyl O of C-4 acyl group.\(^{197}\)

\[
\text{Figure 1.13: Octahedral } [\text{Fe(PMAP)}_3] \text{ complex}
\]

Cu(II) coordinate with 1-phenyl-3-methyl-4-benzoyl-2-pyrazol-5-one(PMBP) forms distorted square-planar [Cu(PMBP)\(_2\)] and distorted octahedral [Cu(PMBP)\(_2\)(MeOH)\(_2\)] complexes (Figure: 1.14) in which donor atoms are O, O, of both carbonyl groups.\(^{198,199}\)

\[
\text{Figure: 1.14: Complexes of Cu(II) with PMBP}
\]
Casas J.S et al. reported a series of different N-1 carbothioamide pyrazol-5-one (Figure 1.15) and their complexes with Zn(II), Cd(II) and Rh(IV) ions.\textsuperscript{200-201}

Distorted tetrahedral [ZnL\textsubscript{2}] complex is formed by ligand L-3. Zn(II) is bonded to ligand by N-2 and S atoms of pyrazolone. Zn(II) forms distorted trigonal bipyramidal complexes [ZnL\textsubscript{2}(MeOH)] with L-5.\textsuperscript{202}

Cd(II) also forms trigonal-bipyramidal complexes [CdL\textsubscript{2}(Solv)] by coordinating with N-2 and S atoms of above pyrazolones ligands.\textsuperscript{203}

1-(pyridine-2-yl)-4-(trifluoroacetyl)-3-methyl-3-pyrazol-5-one form mononuclear complex with Ag(I) which coordinate by N-2 of pyrazole ring and N of pyridine substituent.\textsuperscript{204}
1:6) Scope of the Present Work:

Literature survey reveals that, in general many organic compounds and particularly heterocyclic aromatic compounds are physiologically active.

Number of heterocyclic compounds particularly pyrazolones are reported to possess a variety of physiological activity such as anti-pyretic, anti-bacterial, anti-fungal, anti-tumor and anti-oxidant. Pyrazolones and their derivatives has great importance in medicinal chemistry. Pyrazolone are also important in photography as colour coupler, sensitizer and in dyeing industries. Pyrazolones are also important in analytical chemistry for qualitative and quantitative analysis of metal ions.

A lot of work has been reported on the pyrazolones derivatives having additional donor atoms in C-4 Substitution. However, less attention is given on the complexes of pyrazol-5-ones having additional donor atom in N-1 substitution.

Hence, in the pyrazolone and pyrano-pyrazolone derivatives having additional donor atom at N-1 have been selected for present investigation. These are acts as ligands with transition metal ions.

The following pyrazolones derivatives are synthesized and characterized on the basis of spectral analysis.

1) 1-(2-hydroxybenzoyl)-3-methyl-pyrazol-5-one (HBMP)
2) 1-(2-aminobenzoyl)-3-methyl-pyrazol-5-one (ABMP)
3) 1-benzoyl-3-methyl-pyrazol-5-one (BMP)
4) 1-(2-hydroxybenzoyl)-3,6-dimethylpyrano[4,3-c]pyrazol-4(1H)-one (HBDPP)
5) 1-(2-aminobenzoyl)-3,6-dimethyl-pyrano[4,3-c]pyrazol-4(1H)-one (ABDPP)
6) 1-benzoyl-3,6-dimethyl-pyrano[4,3-c]pyrazol-4(1H)-one (BDPP)
The pyrazolone derivatives were synthesized by condensation of substituted acid hydrazide and ethylacetoacetate and pyrano-pyrazolone from 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one DHA and substituted acid hydrazide. These ligands were characterized by Infrared, $^{1}$H NMR, $^{13}$C NMR and mass spectra. The pyrazolone derivatives HBMP act as tridentate ligand and have O, O and O center. The ABMP also act as tridentate ligand with donor atoms O, O and N. The pyrano-pyrazolone ligands HBDPP and ABDPP acts as tridentate ligand having O, O and N donor atoms.

The transition metal ions used in the present investigation are Cu(II), Ni(II), Mn(II), Fe(II), and Co(II).

The HBMP, ABMP, HBDPP and ABDPP act as monobasic tridentate ligands while BMP and BDPP act as bidentate ligands.

The complexes of above metal ions with synthesized pyrazolone and pyrano-pyrazolone ligands are prepared and study their by using different techniques such as electronic spectra, infrared spectra, conductivity, magnetic-moment measurements, ESR and XRD spectral study.
1.7) References:
20) Van Rothenburg, *Ber*, 27 (1884) 785.
30) Kitamura N, *J Pharm Soc Japan* 60 (1940) 45
38) Brian S, Furniss, Antony J Hannaford, Peter W G Smith
39) Knorr L, *Ber*, 16 (1883) 2597.
43) Baeker and Meyer, *Rec Trav Chim* 45 (1926) 82.
54) Thomas and Ritsert, Chem Abstracts 15 (1921) 2852.
56) Decombe, Chem Abstracts 27 (1933), 2135.
60) Mitra, J Indian Chem Soc, 10 (1933) 491.
62) Zoss and Hennion, J Am Chem Soc, 63 (1941) 1181.
64) Fichter, J Prakt Chem, 74 (1906) 297.
67) A Cingolani, F Marchetti, C Pettinari, R Pettinari, B W Skelton, 
69) B Bovio, A Cingolani, F Marchetti, C Pettinari, J Organomet Chem, 
70) C Pettinari, F Marchetti, A Cingolani, A Gindulyte, L Massa, et al., 
71) De and Dutt, J Indian Chem Soc, 7 (1930) 473.
72) Cangnon, Biovin and Craig, Canadian J Chem, 30 (52) 1952.
74) Jensen B S and Hensen, Acta Chem Scad, 6 (1952) 195.
76) Oddo, *Gazz Chim Ital.*, 50 (1920) 258.
79) Bulow and Schauf, *Ber.*, 41 (1908) 2355.
99) A A Akherm, A M Moiseenkov, F A Lakhvich and S P Smulskii

109) Knorr L, *Ber*, 17 (1884) 546.
119) Knorr L, *Ber*, 17 (1883) 2032.
144) Knorr L, *Ber*, 17(1883) 2032.
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References

160) Ziegler and Locher Ber. 20 (1887) 834.
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References

191) Jose S Casas, Maria S Garcia-Tasende, Agustin Sanchez, Jose Sordo, Angeles, Coordination Chemistry Reviews 251 (2007) 1571.
194) Jose S Casas, Maria S Garcia-Tasende, Agustin Sanchez, Jose Sordo, Angeles Coordination Chemistry Reviews 251 (2007) 1574.