Chapter-I
General approach to Coordination Chemistry

Introduction:

The contribution of coordination chemistry in pharmaceutical field is rapidly developing and novel therapeutic and diagnostic metal complexes are currently having an impact in medical field. The modern studies of coordination compounds begins with Alfred Werner. Alfred Werner’s classical idea of coordination bond in 1893 gave a great deal to the development of coordination chemistry[1]. The theory postulated that in coordination compounds the metal exhibits two types of valencies. i.e. primary and secondary. The primary valency is ionisable and non-directional, whereas secondary valency is non-ionisable and directional. The bonds between the ligand and the metal ion are due to secondary valencies of metal ion. The development of electronic theory of valency by Kossel, Sidgewick, Lewis, Langmuir, Fajan and others[2] cleared the ideas regarding primary (oxidation state) and secondary (coordination number) valencies in complexes.

In 1931, Pauling gave valence bond theory (VBT) which is based on electronic structure of central metal ion in its ground state, kind of bonding, geometry (i.e. shape) and magnetic properties of the complexes[3]. According to this theory, the central metal atom or ion makes available a number of empty s, p and d atomic orbitals equal to its coordination number. These vacant orbitals combine together to form hybrid orbitals which are the same in number as the atomic orbitals hybridizing together. These are vacant and have equivalent
energy and definite geometry. The ligands have at least one \( \sigma \)-orbital containing a lone pair of electrons. Vacant hybrid orbitals of the metal atom or ion overlap with the filled (containing lone pair of electrons) \( \sigma \)-orbitals of the ligands to form ligand-metal \( \sigma \)-bond. This theory explains mainly electronic structure of central metal ion, shapes of complexes, magnetic moments and stereochemistry. However, it does not give proper explanation of maximum pairing, the spectra of the complexes and quantitative interpretation of magnetic properties.

Crystal field theory (CFT) advanced by Bethe\(^4\) in 1929 was originally applied mainly to ionic crystals and is, therefore called crystal field theory (CFT). CFT regards a complex as a combination of a central ion surrounded by other ions or molecules with electrical dipoles (i.e. ligands). In its simplest treatment CFT does not consider covalent bonding in complex but the bonding between the metal cation and ligands arises from the electrostatic attraction between the nucleus of the metal cation and the partial negative charge invariably present on the ligands. The interaction between the electrons of cation and those of the ligands is entirely repulsive. It is these repulsive forces that are responsible for causing the splitting of the d-orbitals of the metal cation into two energy sublevels \( t_{2g} \)-triplet and \( e_g \)-doublet. The energies of these sublevels depend upon the type of geometry. The energy difference between \( t_{2g} \) and \( e_g \) level is known as crystal field stabilization energy and is denoted by \( \Delta \) or 10 Dq. The magnitude of 10 Dq depends upon the nature of ligand and charge on central metal ion. CFT interprets the magnetic and spectral properties of transition metal complexes quantitatively.

The molecular orbital theory, developed by Vanvleck\(^5\), although more complicated than VBT and CFT theories explains
more satisfactorily the nature of bonding involved in coordination complexes. The formation of covalent bond with metal ion and donor group occurs with or without replacement of hydrogen atom from an organic functional group.

A complex as defined by Rossotti[6] as a species is formed by the association of two or more simple species each capable of independent existence. When one of the species is a metal ion, the resulting entity is known as metal complex. The term ‘ligand’ is applied to the particular molecule or ion attached to the central metal ion[7]. Some ligands are attached to central metal ion by more than one atom in such a manner to form a ring. This is known as chelation and the resulting complex called metal chelate[8]. The stability of chelate depends upon the size of the ring. Generally, coordinated compounds formed of a saturated five membered ring are more stable than those formed of unsaturated five membered rings. However, a great stability to metal chelate is achieved with the formation of six membered ring[9].

The rapid development in the field of bio-inorganic chemistry is centered on the study of coordination compounds present in living systems[10]. Therefore, it is not surprising that the use of coordination compounds such as metal-based drugs has recently become a very active area of research. The application of inorganic chemistry to medicine is a rapidly developing field, and novel therapeutic and diagnostic metal complexes which are of current clinical use[11-14]. The synthesis and study of metal complexes with drugs[15] or biomolecules[16] as ligand, is a research area of considerable interest, particularly with respect to complexes which exhibit synergistic effects between metal and ligand.
The metal ions with biologically active ligands are a subject of considerable interest. Thus, metal ions play an important role in a vast number of biological processes. Some of the biologically active compounds act via chelation. But for most of them, little is known about how metal binding influence their ability\cite{17}. For example, vanadium is a trace but essential element with relevant biological properties and has acquired special status among the biometals, whereas iron present as trace element in food and drink is of critical importance for the normal growth and development of infants. The nutritional status of iron affects the metabolism of other nutrients\cite{18}.

The metal ions play essential roles in about one third of enzymes\cite{19}. These ions can modify electron flow in a substrate or enzyme. Thus effectively controlling enzyme-catalyzed reactions. They can serve to bind and orient substrate with respect to functional groups in the active sites and can provide a site for redox activity if the metal has several valence states. Without the appropriate metal ion, a biochemical reaction catalyzed by a particular metalloenzyme would proceed very slowly, if at all.

**Importance of co-ordination complexes as Drugs:**

**1) Importance of transition metal complexes as potential therapeutic agents:**

Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. This benefit of transition metals has started the development of metal-based drugs with promising pharmacological application and may offer unique therapeutic opportunities. Now a days, transition metals have an important place within medicinal biochemistry. Significant progress
has been done in utilization of transition metal complexes as drug to treat several human diseases like cancer, anti-inflammatory, diabetes and neurological disorders.

2) **Transition metals as anti-diabetic agents:**

   Glucose level in the blood plasma can been controlled by administration of vanadium and zinc in the form of inorganic salts. The complexes of vanadium with organic ligands have proved to be less toxic, with improved lipophilicity. A number of vanadium complexes have been developed, all of which have insulin-mimetic properties. Chromium supplementation significantly improved glycemia among patients with diabetes[20].

3) **Transition metal complexes as anticancer agents:**

   Titanium complexes such as Titanocene dichloride had been recognized as active anticancer drug against breast and gastrointestinal carcinomas. Gold complexes also show anti-cancer activity. Certain gold complexes with aromatic bipyridyl ligands have shown cytotoxicity against cancer cells[21].

   Platinum (II) complexes has been used as anticancer drugs among them cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers[22]. Pt (II) complexes with thiourea have showed anti-cancer activity against leukemia cell lines[23] Pt (II) also forms complexes with estrogen hormone and is used as anticancer agent for the treatment in breast cancer[24].
4) Transition metals as anti-HIV:

Recent studies showed that oxovanadium complexes of thiourea and vanadium substituted polyoxotungstates exhibit potent anti-HIV properties towards infected immortalized T-cells[25].

5) Transition metal complexes as anti-infective agents:

Many magnesium complexes have been screened against a number of pathogenic fungi and bacteria to evaluate growth and potential[26]. Nitrogen containing macrocyclic complexes of Mg (II) have shown antimicrobial activity. An octahedral geometry for these complexes has been confirmed by spectroscopic analysis. Transition metals like silver have been used for years as antimicrobial agents. Silver has low toxicity as compared to other transition metals. One of most commonly used compounds is silver (I) sulfazine. It is used to treat severe burns to prevent them from bacterial infections[27].

6) Transition metal as neurological drugs:

Transition metal complexes are also used in the treatment of neurological disorders[28]. Other transition metals like zinc is involved as a transmitter in the neuronal signaling pathways. Neuronal Zn(II) serves as an important, highly regulated signaling component responsible for the initiation of a neuroprotective pathway[29].

7) Transition metal complexes as anti-inflammatory agents and free radical quenchers:

Tolfenamic acid and its metal complexes has been studied as anti-inflammatory, anti proliferative and radical-scavenging
agents[30]. Magnesium is used for the treatment of asthma in children.

8) Transition metals as delivery probes and diagnostic tools:

Metal complexes may be used as research probes of biological function and as potential diagnostic and therapeutic agents[31]. Ultrasmall particles of iron oxide exhibit super-paramagnetic properties and are used as a negative contrast agent in magnetic resonance imaging (MRI) which significantly improved the sensitivity of detection of inflamed tissues[32]. Unique properties of transition metals like redox activity, lewis acidity, electrophilicity, valency, geometry, magnetic, spectroscopic and radiochemical properties can be used to measure cellular functions[33-34].

Importance of β-diketones:

β-diketones and relative derivatives are considered as a class of very important ligands in the growth of coordination chemistry. In recent years, number of β-diketones in which carbonyl function(s) gained considerable importance mainly because of the fact that such compounds structurally related to active chemical constituents of several traditional medicinal plants. Eg. The rhizomes of turmeric play an important role as coloring agent in food, cosmetics and textiles[35]. The main bioactive substance in the rhizome are due to curcumin and related dimethoxy compounds[36]. Due to presence of two oxygen donor atoms and facile keto-enol tautomerism[37], they easily coordinate with metal ions after deprotonating the enolic hydrogen atom and provides stable metal complexes with six membered chelate rings and hence can exist in solution as well as in
solid. The β-diketones are versatile metal coordinating agents and have played a significant role in coordination chemistry.

In the last decades, β-diketones and their metal complexes have been used as model compounds in Physical Chemistry studies. These are the most widely used ligands in coordination chemistry. Literature survey revealed that β-diketones and their metal complexes are associated with various pharmacological and biological properties and thus find importance in medicine. A wide variety of β-diketones with different substituents and their complexes have been synthesized and their properties such as volatility, lewis acidity or aggregation state, standard molar enthalpies of formation, standard molar enthalpies of sublimation, vapour pressures and enantioselective catalytic property have been studied. β-diketones have a wide range of uses in metal extraction by chelation. Europium (III) β-diketonates show excellent luminescent properties. It is used as chelating agents in some process based on supercritical CO₂ as extractants for lanthanide ions. Curcumin (diferuloylmethane) is a β-diketone constituent of the spice turmeric that is prepared from the powdered rhizome of Curcuma longa Linn. The rhizomes of turmeric (Curcuma longa L., Zingiberaceae) play an important role as a coloring agent in food, cosmetics and textiles.

1,3-diketones exhibit biological activities such as antioxidants, antitumor and antibacterial activities and are also key intermediates to various heterocyclic compounds. β-diketones and their metal complexes are associated with various pharmacological and biological properties such as anti-inflammatory, heptoprotective, antiviral, antiviral, anticancer activity. These are also used in treatment of gastrointestinal and respiratory disorders. The presence of β-
Diketone moiety also has been reported to be important for the antioxidative action of tetrahydrocurcumin[52], conjugated linoleic acid[53] and for transport of calcium ions across organic barriers by drugs[54]. β-diketone in its keto-enol form is an important pharmacophores of HIV-1 integrase inhibitors[55]. β-diketones like (4-tert-butyl-4’-methoxydibenzoyl methane) and 1-(4-t-butylphenyl)propane-1,3-dione and 1-p-cumenyl-3-phenyl-propane-1,3-dione are used in UV sunscreen cosmetics that can filter ultraviolet rays to protect skin[56]. β-diketonate complexes are also well known for their wide applications as laser chelates[57], extraction agents[58], chemical and photochemical catalysts[59] as well as for their biological activities as evidenced from their anticancer [60], anti-viral[61] and immunomodulatory activities[62].

Dibenzoylmethane, a reported antimutagen[63], possess a β-diketone moiety linking two phenyl groups. Metal complexes of dibenzoylmethane and other β-diketonates have been studied for use as radiopharmaceuticals because of their considerable lipophilic properties[64]. Several isoprenoid-substituted dibenzoylmethanes have been isolated from Glycyrrhiza species (licorice) as well[65-67]. Dibenzoylmethane and other structurally related β-diketones warrant further examination as breast cancer chemopreventative agents[68].

Turmeric powder, Curcumin and its derivatives and many other extracts from rhizomes were found to be bioactive. Turmeric has been reported to possess anti-inflammatory, hepatoprotective, antitumor, antiviral[69], anticancer activity[70] and used in gastrointestinal and respiratory disorders[71]. This phytochemical has been reported to possess anticarcinogenic properties in several experimental models[72]. Because of lack of toxicity, its efficiency in inhibiting
tumorigenesis in several models and its multiple mechanisms of action, curcumin has been selected for further evaluation as a candidate chemopreventative agent[73]. However, it has been reported recently that dietary curcumin at levels of up to 1.0% was ineffective in inhibiting DMBA-induced rat mammary tumorigenesis[74]. It has been observed that both curcumin and demethoxycurcumin were effective as inhibitors of chemically induced skin tumor promotion[75]. Curcumin is also reported to have antibacterial[76], antiamoebic[77] and its manganese complexes offer protective action against vascular dementia by exerting antioxidant activity[78-80]. Safety evaluation studies indicate that both turmeric and curcumin are well tolerated at a very high dose without any toxic effects. Thus both turmeric and curcumin have the potential for the development of modern medicine for the treatment of various diseases[81].

![Fig. 1.1 Structure of natural curcuminoids](image-url)
**Theory of Literature:**

Design and synthesis of new ligands and complexes with special structures and properties are attracting more and more interest in recent years. The chemistry of 1,3-diketones has attracted the attention of scientists for almost century[82]. Metal diketonate complexes were among the best-known classes of coordination compounds, and nearly all of the transition metal elements displayed stable complexes. As a result of this, chemical diversity in these compounds offers many opportunities for the formation of new transition metal-based materials. β-diketones are important class of organic compounds frequently encountered in synthetic chemistry[83-85]. They have been used as ligands for coordination of transition metals and have been investigated for use as potential antiviral agents[86]. β-diketones were also encountered in nature as both metabolic intermediates in the microbial metabolism of aromatic and terpenes and also as anthropogenic environmental contaminants. As a result of their usability, the biological transformation of these compounds have recently arised interest[87-88]. Extensive literature is available on synthesis, structural characterization and applications of metal complexes of β-diketones. Literature survey revealed that β-diketones and their metal complexes are associated with various pharmacological and biological properties and thus find importance in medicine. In recent years, number of β-diketones with carbonyl functional groups have gained considerable importance mainly because of the fact that such compounds structurally related to active chemical constituents. β-diketonato transition metal complexes have been the subject of many different investigations ranging from synthetic, kinetic and structural topics, to catalysis and electronic transfer processes.
Mbabazi[89] studied biologically active derivatives of 1,3-diketones by coupling aromatic aldehydes with 5,5-dimethylcyclohexane-1,3-dione (dimedone). Vettaikaranpudur[90] investigated catalytic activity of mixed ligand complexes of Fe(III), Co(II), Ni(II), Cu(II) containing β-diketones and triphenyl phosphine. Verma[91] synthesized β-diketone and its metal complexes of type ML₂ where M=Co(II) Ni(II), Mn(II), Cu(II) and Zn (II) and L=1-(2,4-dihydroxyphenyl)-3-phenyl-propane-1,3-dione. Chauhan[92] synthesized isoxazole derivatives from diaryl-1,3-diketones under microwave irradiation.

The synthesis and use of complicated multinucleating ligands has been a common strategy for the preparation of polynuclear coordination complexes with new and sophisticated structures[93-94]. The synthesis and use of complicated ligands has been a common strategy in the preparation of polynuclear coordination complexes with new and sophisticated structures[95]. One of these ligands contain two β-diketone groups separated by one phenol functionality, so as to display an array of five oxygen donors disposed in a linear manner, thus enabling four adjacent coordinating pockets to chelate simultaneously an equal number of metals in close proximity[96]. Unmathur[97] reported some unsaturated polycarbonyl compounds and their Ni (II), Cu (II), and Zn (II) complexes and their nature of bonding was discussed on the basis of analytical, IR, ¹H-NMR and mass spectral data. The unsaturated polycarbonyl compounds in which the keto group attached to aryl/ alkyl functions (olefinic linkage) has been synthesized by the reaction of acetoacetanilide and aromatic aldehydes under specified conditions. The existence of these compounds predominantly in the
intramolecular hydrogen bonded enol form has been well demonstrated from their IR, $^1$H-NMR and mass spectral data. Biological studies of unsaturated β-carbonyl compounds and their metal complexes were tested for antifungal activities in vitro for their species, *Aspergillus niger*, *Aspergillus parasiticus* and *Rhizopus oryzae* species. The results revealed that the compounds possessed significant activity against all the tested organisms.

Metal-1,3-diketones have found applications in the production of laser devices,[98] as NMR shift reagents[99] and in analytical chemistry[100]. Neodymium-1,3-diketonates have found applications as shielding agents for plastics[101] and europium complexes have been used as UV-sensitive luminescent compounds for ink and resins[102]. It is well known that β-diketonates and their thio and seleno-analogue give rise to metal chelates of type on interaction with metal salts[103] and under condition of gas phase synthesis or electrosynthesis[104]. Shishkina[105] also reported molecular and crystal study of Eu and Cu complexes of 4,4,4-trifluoro-3,3-dihydroxy-1-thiophene-2-yl-butane-1-one by X-ray diffraction analysis and quantum calculations. From all the β-diketones obtained, 2-thenoyl trifluoroacetone (TTA) was one of the most widely used for extraction and purification of metals.

The enzyme was also shown to cleave a variety of related alkyl diketones and 1-phenylpentane-2,4-dione but not cyclic β-diketonates such as cyclohexane-1,5-dione. Few biochemical studies were performed with this system but an analog enzyme, PDH was reported by Kawagoshi and Fujita[106]. Cyclohexane 1,3-dione was reported to be hydrolysed to 5-oxohexanoic by cell extracts on pseudomonas
strain growth under anaerobic conditions on cyclohexanol as sole carbon source[107].

Prasad[108] synthesized mixed ligand complexes of β-diketone with 5-chlorosalicylaldehyde of the type ML₂ where M= Mg(II), Ca(II), Sr(II) and Ba(II). As β-diketones are chelating agents, kinetic study of co-polymerization of various unsaturated β-diketones with styrene were reported by Voloshanovskii[109].

Yubiao Liu et al.[110] synthesized a columnar-like Cu-complexes of β-diketones with oligo (ethylene oxide) groups in order to combine one dimensional columnar phase assembled by the discotic metal complex cores with the ordered ionic channel organized by the oligo side groups. Aromi et al[111] devoted efforts to designing and synthesizing a class of ligands displaying linear arrays of oxygen donors, based on the adjacent disposition of phenol and 1,3-diketone group with the aim of favouring the formation of chains of closely spaced transition metals. Novel linear transition metal clusters of heptadentate bis-β-diketone(H₅L) ligands were synthesized and dinuclear complexes or linear zigzag tetranuclear clusters of Mn have been synthesized and characterized crystallographically.

A series of new binuclear Ru(II) complexes of bis-β-diketone synthesized by R. Karvembu[112]. An octahedral geometry was assigned for those complexes. β-diketonato transition metal complexes have been the subject of many different investigations ranging from synthetic, kinetic and structural topics, catalysis and electronic transfer processes. G. Vettaikaranpudur[113] investigated catalytic activity of mixed ligand complexes of Fe (III), Co (II), Ni
(II), Cu (II) containing β-diketones and triphenyl phosphine. Sheikh[114] studied antibacterial activity of functionalized 1-(2,4-dihydroxy-5-substituted phenyl)-3-Thienyl-propane-1,3-diones bearing potential O, O, S-pharmacophores.

A systematic study of the mesomorphic properties of two homologous series of copper (II) and palladium (II) complexes derived from unsymmetrical β-diketonate derivatives containing a variety of functional substituents (X= H, CH₃, C₂H₅, OCH₃, Cl, Br, I, CN) on the phenyl ring is reported. These disc-like molecules contain eight n-octyloxy chains, required for the formation of columnar phases appended to the central β-diketonate core. All complexes exhibited columnar phases studied by differential scanning calorimetry, polarized optical microscopy and powder-X-ray diffraction[115].

Dubey[116] studied mixed ligand (phenoxo-alkoxo- and acetylacetonato) complexes of cobalt (II) derived from Schiff bases. The mixed ligand complexes were also reported by R. N. Prasad[117]. Synthesis and spectroscopy studies of mixed ligand complexes of cobalt (II) with salicylaldehyde, hydroxyaryl ketone and β-diketonate is shown in figure 1.2.

![Fig. 1.2](image-url)
A new β-diketone ligands derived from 2-hydroxyacetophenone and 3,4,4-triethoxy benzoic acid by Vaidya[118]. The study of monothio-β-diketones and their metal complexes was done by Chaston[119]. It was indicated that the replacement of one oxygen atom of an 8-diketone markedly alters the metal-bonding properties of the ketone. Tris(β-diketonato) Europium (III) with a series of variably fluorinated ligands derived from 3,5-heptanedione were synthesized with the aim of determining their hydration state under β-diketonates were also described and the synthesis of the fluorinated β-diketones were re-investigated and discussed in detail[120]. Oloshin[121] studied mono-thio-β-diketone ligands suitable for sensitization of lanthanide luminescence specially infrared luminescence of an intensely coloured neodymium and ytterbium mono-thio-β-diketonate chelates. Hegazy and Al-Motawaa[122] synthesized lanthanide complexes of substituted β-diketones hydrazone derivatives through condensation of β-diketone with aromatic aldehyde followed by reaction with phenylhydrazine

Sheikh[123] synthesized novel antibacterial agent 1-(2,4-dihydroxy-5-chlorophenyl)-3-arylpropane-1,3-diones by employing Baker-Venkatraman transformation on 2-aroyloxy-4-hydroxy-chloroacetophenones with NaOH in DMSO regardless of pyridine. Yang[124] synthesized copper complexes of β-diketone and β-imino-ketone containing ligands. New [2+2] type open cyclic multidentate ligands are also obtained from the reaction between 1,3-propanediamine and 2-hydroxyl-1,3-propanediamine respectively. They each contain five C=O, three C=N and one NH$_2$ groups. The complexes were characterized by Elemental analyses, Conductivity, FT-IR, FAB-MS, ESR, electronic spectra and extended X-ray
absorption fine structure. Copper ions are basically 4 coordinate with tetragonal geometry.

β-diketo acid containing compounds were a promising class of human immunodeficiency virus type 1 (HIV-1) integrase (1N) inhibitors. Starting from hypothesis that these inhibitors were able to coordinate ion in solution before interacting on the active site, a series of potentiometric measurements have been performed to understand the coordination ability of the diketo acid pharmacophore toward the biologically relevant Mg$^{2+}$. By using β-diketo acid/ester as model ligands with a set of divalent metal ions (Mg, Mn, Ni, Co, and Zn) a series of complexes were prepared and tested for anti-HIV-1 1N activity[125].

Synthesis of β-diketones from diazonium salt of 3-amino-1,2,4-triazole and its derivatives were carried out by Singh[126]. The electronic spectra of α-substituted β-diketone complexes of Cu (II) are presented and assignments of the various bands are discussed in literature[127]. In a series of platinum (II)-acetylacetone derivatives, it has been established that the platinum was bonded to 3-carbon atoms. Criteria for the determination of the presence of metal-carbon bonding in these and related complexes from the infrared and NMR spectra have been investigated[128].

Some of scientists prepared the complexes of K [Pt(diketone)$_2$X] (diketone = trifluoro-acetylacetone and benzoyl acetone X= Cl or Br). The NMR spectra of trifluoroacetylacetone complexes and IR spectra of all the complexes indicated the presence of both oxygen and carbon-bonded β-diketone group[129]. A similar bonding pattern was also observed in the complex Cd[Pt(acac)$_2$Cl$_2$].

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The versatility of acetylacetone as ligands was first demonstrated by Werner and more recently by several investigators[130-131]. It provides a system in which the variety of metal-ligand bonding was shown and studied using spectroscopic methods. The purpose of this series of investigation was to analyze the IR spectra of acetylacetonato Pt (II) complexes involving these three types of coordination and to characterize their IR spectra and chemical bonding[132].

New β-diketonate with oligo ether side chain and their complexes with Ba and Cu were synthesized. Crystal and molecular structure of (bis 9,1-phenyl-1-7,10-dioxa-undane-1,3-dionato)Cu(II) at 150 K were also reported [133]. A systematic study of the mesomorphic properties of two homologous series of Cu(II) and palladium (II) complexes derived from unsymmetrical β-diketonate derivatives containing a variety of functional substituents (X= H, CH₃, C₂H₅, OCH₃, Cl, Br, I, CN) on the phenyl ring has been reported. These disc-like molecules all contain eight n-octyloxy chains, required for the formation of columnar phases studied by differential scanning colorimetry, polarized optical microscopy and powder x-ray diffraction[134].

A new series of β-ketoanilides in which keto group attached to olefinic linkage have been synthesized by the reaction of acetanilide and aromatic aldehyde under specified conditions. The existence of these β-ketoanilides predominantly in the intramolecularly hydrogen bonded enol form has been well demonstrated from their IR, ¹H-NMR and mass spectral data. Details on the formation of [ML₂] complexes of these unsaturated β-diketoanilides with Ni (II), Cu (II), Zn (II) and their nature of bonding are discussed[135].
Spectroscopic, thermal and powder diffraction studies of bis-(benzoylacetonato)cobalt (II) and nickel (II) complexes were studied by Bhubon Singh\cite{136}. Ando\cite{137} directly synthesized 1,3-diketones by Rh-catalyzed reductive $\alpha$-acylation of enones by treatment with acid chlorides and Et$_2$Zn in the presence of RhCl(PPh$_3$)$_3$. Some synthetic curcuminoids and their antitumor studies were reported by Krishnakutty\cite{138}. 1,7-diaryl-1,6-heptane-3,5-dione were synthetic curcuminoid analogs. Their VO(IV), Co(II), Ni(II) and Cu(II) complexes has been prepared and characterized. The complexes showed best antitumor activity. Copper chelates showed more toxicity than the other metal complexes.

![Fig.1.3 Structures of metal complexes of 1,7 diaryl-1,6-heptane-3,5-dione](image)

**Fig.1.3 Structures of metal complexes of 1,7 diaryl-1,6-heptane-3,5-dione**

Some $\beta$-diketones and $\beta$-ketoesters of 4-methyl sulphonyl benzoyl methylene bromides were synthesized by Joshi\cite{139}. Tharmaraj\cite{140} studied spectral, NLO, fluorescence and biological activity of Knoevenagel condensation of $\beta$-diketone ligands and their metal(II) complexes of the type ML where $M=$Cu(II), Ni(II), Co(II) and $L=3$-(aryl)-pentane-2,4-dione. Verma\cite{141} synthesized $\beta$-diketone and its metal complexe of the type ML$_2$ where $M=$Co(II),
Ni(II), Mn(II), Cu(II) and Zn(II) and L=1-(2,4-dihydroxyphenyl)-3-phenyl-propane-1,3-dione.

![Diagram of ligand synthesis and metal complexes](image)

**Fig. 1.4 Synthesis of ligand and its metal complexes**

Some of the Cu (II), Ni (II), Co (II) and VO (IV) complexes of β-diketones or 1-(3-hydroxy-2-naphthyl)-5-(p-x-phenyl)pent-4-ene-1,3-diones were reported and characterized by elemental analysis, IR, electronic, $^1$H-NMR, and ESR spectroscopic and by magnetic susceptibility measurements. It was reported that metal ions coordinated through both carbonyl oxygen atoms and the effect of conjugation of the ligand structure ($d\pi-\pi^*$ interaction) was strong enough to stabilize the metal ligand bond[142]. A brief mention has been made by Mehrotra[143] on a new class of metallo-derivatives of β-diketones. Different types of metal β-diketonato complexes were prepared. Out of these, the reaction of various β-diketones and ketoesters with simple and bimetallic alkoxides in different stoichiometric ratios in benzene medium have discussed for synthesizing novel derivatives and their structural properties. Tris (β-diketonato) Europium (III) with a series of variably fluorinated
ligands derived from 3,5 heptanedione were synthesized with the aim of determining their hydration state under β-diketonates were also described and the synthesis of the fluorinated β-diketones were reinvestigated and discussed in details[144]. Guthrie[145] has clearly shown by $^1$H-NMR that three major aqueous solution forms of acetopyruvate exist at pH value of 1.5 to 6.5. He confirmed this with $^1$H-NMR spectra and obtained a pKa of about 7.5 for α-ketoenol tautomerism of carboxulate anion.

**Aim of Present Investigation:**

A careful review of literature on structural and biological properties of β-diketones and their metal complexes indicates that extensive work has been carried on β-diketones. It was surprising that very little work has been reported on thermal (TGA, DTA and DSC) and X-ray diffraction studies. The β-diketonates complexes thus formed have been the topic of many papers and reviews[146-150]. The research being stimulated by the versatility of β-diketonate complexes as NMR shift reagents[151-152], laser chelates[153-154], extraction agents[155], heat stabilizers for polymers[156], chemical and photochemical catalysts[157], as well as their use in manufacture of super conductors[158-159] and in gas chromatography[160]. Few papers have shown that β-diketones act as neutral ligands by establishing a coordinative interaction with the metal cation[161-165].

The coordination chemistry and reactivity of higher valence metal ions have continued to play a significant role not only because of their complexing tendency but also their importance in various fields like, their biological role as trace elements, as catalysts, in
enzyme activities, in metabolism and in various industrial processes. All the metals selected for present study possess one or more of these properties.

β-diketone and their copper metal complexes are precursors for chemical vapour deposition. Thermal transfer printing materials containing Cu-β-diketonates exhibits good whiteness and image stability and it has been found that toners containing Cu-complexes of β-diketonates are stable, controllable and capable of producing clear colour images even at high temperature and high humidity without producing copier stain. It is well established that Co-ferrocyanides acts as adsorbent, ion-exchangers and photosensitizers. Iron is important for growth and development of infants. The nutritional status of iron affects the metabolism of other nutrients. It also plays an important role in oxygen binding in haemoglobin electron transport via cytochromes. Iron is also used as a catalyst in the manufacture of NH$_3$ by Haber’s process. Finely divided nickel or active nickel is used in hydrogenation reaction for a) conversion of oils into fats b) conversion of CO and steam into CO$_2$ and H$_2$.

In biological front, many of the β-diketones were reported to be physiologically active and find applications in the treatment of many diseases. The biological activities of these compounds have often been attributed to their ability to form complexes with the metals present in the biosystem. In many cases, the metal ion association exerts synergistic effect on the activity of free ligand.

In view of the above applicational importance of transition metals of higher oxidation states, the scientists are engaged to explore the metal complexes as antibacterial, antifungal,
anticarcinogenic, antiviral, antitumor agents and considerable results have brought through the discovery of these metal based complexes.

Despite of the fact that β-diketone metal complexes have been endowed with different types of biological activities, the detailed chemistry of their action remains obscure. In an effort to get more insight into these mechanistic aspects, coordination chemists have evinced greater interest in the synthesis and structural characterization of metal complexes of these ligands. These studies would throw light on the properties of ligands and their metal complexes are known for partaking the interest in this regard, we have synthesized β-diketones from simple and substituted o-hydroxy acetophenone with substituted aromatic benzoic acid by Baker Venkatraman Transformation[166].

Therefore our aim was to prepare new β-diketones containing phenol group in their structure as additional potential donor in order to exploit their coordination properties and to test their bioactivity since the same group plays an important role in biological activity.

The following series of β-diketones have been synthesized:

1. 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione.
2. 1-(2-hydroxyphenyl)-3-p-tolylpropane-1,3-dione.
3. 1-(2,4-dichlorophenyl)-3-(2-hydroxyphenyl)propane-1,3-dione.
4. 1-(5-chloro-2-hydroxyphenyl)-3-phenylpropane-1,3-dione.
5. 1-(5-chloro-2-hydroxyphenyl)-3-p-tolylpropane-1,3-dione.
6. 1-(5-chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)propane-1,3-dione.
Since the β-diketones and metals of higher oxidation states, both show antimicrobial activities, it was thought worthwhile to see their combined effect in the form of metal complexes.

Hence from these β-diketones different metal complexes were prepared by reacting with metal ions having higher oxidation states. We have selected Fe(III), Co(II), Ni(II), Cu(II) and Cr(III) metals for the synthesis of metal complexes as they are having large applicational areas.

\[
\text{Where } R = H, \text{ Cl}; \quad R_1 = H, \text{ Cl}; \quad R_2 = \text{CH}_3,\text{Cl}
\]

The present β-diketones are containing three donor sites. But in view of the stereochemistry of the ligands, β-diketones can act as only bidentate rather than tridentate ligands.
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