CHAPTER 1
Thiosemicarbazones-Biologically active materials, Analytical reagents, Coordinating agents, structure and bonding.

1.1. Introduction:

Coordination chemistry is exactly, the chemistry of metal atoms "coordinated" by molecules or atoms which has always been a challenging task to the inorganic chemist. In the beginning stage of chemistry as a separate branch of study, coordination compounds look unusual (hence the name complexes) to hold the usual rules of valence. But now-a-days, this compromises a large body of current inorganic research. According to survey of various articles in recent issues of journal “Inorganic Chemistry” indicates that perhaps 70% could be interested to deal with coordination compounds. The usual bonding theories can be extended to accommodate these compounds which still provide many challenging problems that are to be resolved. But in synthetic work, this continues to face a challenge in the laboratory. Interdisciplinary research work has become a mark of modern inorganic chemistry. Many chemists today are using the concepts and methods of modern coordination chemistry to solve the problems in research areas such as catalysis, energy conversion, materials chemistry and biochemistry etc. The fast progressing field of bioinorganic chemistry primarily focused on the presence of coordination compounds in many living systems. Chemical reactions were known to man ever since chemistry had been recognized as a specifically isolated branch of study. It was found that substances would change their properties under specific external conditions, and this observation is a characteristic of various chemical reactions involved. For example, the ancient Egyptians discovered that if malachite, a green ore, was burnt with charcoal, a red metal forms which was called as copper. The development of modern medicinal inorganic chemistry has excited by the discovery of cis-dichlorodiamine platinum (II) [cisplatin] and its following usage as a drug in treatment of several human tumors[1-3], has been made easier by the inorganic chemist's intensive knowledge on coordination and redox properties of metal ions. The positively charged metal centers, bind to negatively charged biomolecules and the constituents of proteins and nucleic acids offer as excellent ligands for binding to these metal ions. Hence the metal complexes have excellent potential in pharmaceutical usage.
Thiosemicarbazones (hydrazinecarbothioamides) are a family of compounds having high biological activity. They are very good ligands. The biological activity of these ligands is related to their ability to coordinate to metal centers in enzymes. An interesting feature of pharmaceutically promising thiosemicarbazone derivatives is that, these derivatives possess additional functional group that are not coordinated to their "primary" metal ion, thereby suggesting that the biological activity may also depend on the non-coordinating groups. This class of compounds is in general prepared by condensation of carbonyl group (ketone or aldehyde) with TSC or with N(4) substitution. Based upon the nature of the ketone or aldehyde the resulting thiosemicarbazone may differ. The following strategy may be involved to evaluate the biological activity of TSCs:

a. The sulphur atom of the thiocarbanyl group may be replaced by imine, oxime, selenium or oxygen.

b. The sulphur center may be modified by alkylation.

c. The heterocyclic ring is added to TSC moiety point of attachment.

d. The terminal N(4) position, undergoing various substitutions.

e. By variation in the nature of condensing aldehyde or ketone.

The metal complexes of TSCs have drawn attention as improved drugs because of the following advantages:

1. Since the breakdown of metal complexes results into metal ion, which interacts with the organism, the long term side effects of Therapeutic agents can be avoided.

2. The role of metal complexes to act as a vehicle for the ligand activation, which is the principal cytotoxic agent.

3. Reduction of drug resistance by several magnitudes is due to complexation with metal ion.

4. Biologically essential elements such as Cu, Fe and Zn forms large number of such complexes.

1.2. Thiosemicarbazones in the biological field - a survey:

Nearly 50 years of search out has been done for thiosemicarbazones and their metal complexes, because of their wide range of biological activity, it can be used in various drugs for various diseases [4-6]. Thiosemicarbazones and their metal complexes have been studied in various field such as anticancer [7], antitumour [8], antifungal [9],

The delivery of radioactive isotopes of Copper tumour or leucocytes by hypoxic selectivity of Copper bis (Thiosemicarbazones) in the form of vehicles has drawn much attention recently[15-17]. The substituent’s on the bone of Carbon strongly affects the hypoxic selectivity. Previous studies say that the biological properties of thiosemicarbazones and their metal complexes is due to biologically active thiosemicarbazone molecule in a planar structure and presence of a pyridine ring or NNS tridentate system[18].

But recent studies say that biological activity majorly due to parent aldehyde or ketone[19-20], while the presence of a bulky group at the terminal Nitrogen remarkably increases the biological activity[21]. Therefore the biological activity can be greatly increases by an additional potential bonding site together with the presence of bulky group at the N(4) position of thiosemicarbazone[22-24].

It is also believed that the biological activity is due to the ability of thiosemicarbazone molecule to chelate with traces of metals in the biological system. Some of the side effects may be reduced by coordination, the lipophilicity which controls the rate of entry into cell, is modified[25-26]. Thiosemicarbazones may block DNA synthesis in mammalian cells by inhibiting the enzyme, ribonucleoside diphosphate reductase either by chelation with an iron ion required by the enzyme or because a preformed metal chelate of the inhibitor interacts with the target enzyme [27-28]. The study also show the ability of thiosemicarbazones to severe the DNA strands [29]. A major clinical challenge in treatment of cancer with anticancer drugs is that fewtumors cells develop a particular phenotype, known as multi drug resistance (MDR), which transform or convert these cells resistant to other classes of anticancer agents to which the tumor cells have not been treated earlier[30].Synthesis and characterization of a palladium complex of phenathrenequinonethiosemicarbazone and evaluation of its antiproliferative properties on breast cancer cells and normal cells have been described [31].

The studies reveal that the complex is a potent antineoplastic agent that has selective activity against tumour cells and is much effective against drug resistant breast cancer cells. In recent years there is much research going on biological and medicinal
properties of transition metal complexes of thiosemicarbazones. Recently a square planar complexes having a general formula \([M(NNS)CI]\) \((M = \text{Pd(II)}, \text{Pt(II)}; \text{NNS} = \text{anionic forms of the 6-methyl-2-tonnylpyridine Schiff bases of S-methyl and S-benzylthiocarbazates})\) have been prepared. Both the Schiff bases exhibit strong cytotoxicity against the human ovarian cancer \((\text{Caov-3})\) cell lines. The S-methyl derivative is two times more active than the S-benzyl derivative\([32]\). Palladium(II) and platinum(II) complexes of 5-chloro-1,3-dihydro-3-[2-(phenyl)ethylidene]-2H-indol-2-one-hydrazone carbothioamide have been synthesized and screened for their antimicrobial activity against the fungi \(\text{Macrophominaphaseolina}\) and \(\text{Fusariumoxysporum}\) by agar plate technique. It has been proved that these compounds showing antimicrobial properties and metal chelates exhibit greater or high inhibitory effects than the parent ligands. The biological potency of these complexes can be increased by increasing the lipophilic character\([33]\).

1.3. Thiosemicarbazones in the analytical field:
Thiosemicarbazones have immense applications in analytical field also. These complexes produce highly colored complexes with metal ions. Thiosemicarbazones have been proposed as analytical reagents that can be used in sensitive and selective determinations of metal ions \([34-35]\). Ferrocene derivatives containing thiosemicarbazone side chain have been investigated by position annihilation lifetime (PAL) and cyclic voltammetry measurements. In molecular solids, positrons can form the positron-electron pair. Positron-electron pair is of great interest because of its formation and also its lifetime depends upon the physical and chemical properties of the solid. It has been proved that the electron capture & redox processes have taken place on the \(\text{Fe}\) atom \([36]\), \(\text{Co(II)}, \text{Cu(II)}\) and \(\text{Fe(II)}\) in pharmaceutical preparations could be determined using solvent extraction and pre-column derivatization with 2-acetylpyridine-4-phenyl-3-thiosemicarbazone as complexing reagent \([37]\).

1.4. Thiosemicarbazones - the coordinating agents:
Thiosemicarbazones are derivatives of thiourea prepared or synthesized by condensation of \(\text{N(4)-substituted thiosemicarbazide or thiosemicarbazide with a suitable ketone or aldehyde. These thiosemicarbazones are shown by the general formula (I) and when N(4) is substituted with a formula(II). The numbering scheme as shown in the figure is in accordance with IUPAC system. However, it should be noted
that the numbering schemes for crystal structures are in accordance with the atoms present. In formula (II) R₃ and R₄ can be aryl are alkyl groups or a part of a cyclic system. According to IUPAC recommendations for naming organic compounds, derivatives of thiourea can be shown by general formula R₁R₂C=N-NH-CS-NR₃R₄, may be named by adding the class name of condensed ketone or aldehyde [38,39].

![Fig: 1.1 General structures of thiosemicarbazones.](image)

Thiosemicarbazones have a variety of different coordination modes. In such cases, they coordinate as bidentate ligands via azomethine nitrogen and thione/thiolato sulfur. But when additional coordination functionality is present in the proximity of the donating centers, then the ligands will coordinate in a tridentate manner. This can be achieved either by neutral molecules or by the monobasic anion upon loss of hydrogen. In solid state thione form predominates while solutions of thiosemicarbazone molecules show a mixture of both tautomers. Based upon the preparative conditions, the metal complexes may be anionic, cationic or neutral. Hence there have been many cases where the anionic and neutral forms of the ligand are involved in coordination[40]. The various coordination geometries encountered in this study may be discussed in the following chapters.

The ligands are linked or bonded to the central metal ion through their donor atoms. The metallic atom to which the ligands are linked through coordinating bonds is called the central metallic atom. The oxidation state of metallic atom may be zero, negative or positive. Based on the number of donor atoms contained, ligands may be classified as uni, di, tri or quadridentate.

**1.5. Coordination number of central metal atom / ion:**

Coordination number of the central metal atom in a given complex is equal to the total number of donor atoms, which are actually linked with the central metal atom. In case of complex compounds which contain only monodentate ligands, the coordination
number of the central metallic atom is equal to the number of monodentate ligands co-ordinated to the metal atom. But this rule is not applicable for the complexes containing polydentate ligands. Coordination number of metallic atom indicates the geometry of the complex compound. Thus for coordination numbers 2, 3, 4, 5, & 6 the geometry of the complex compounds formed are linear, trigonal, planar, tetrahedral and octahedral respectively. Hence coordination number is that which gives us information about the way in which the ligands are bonded around the central metal atom[41].

1.6. Structure, bonding and stereochemistry:

In general TSCs exist in the thione form in the solid state, but in solution it tends to exist as an equilibrium mixture. Thiol and thione forms as follows

![Thione and Thiol structures](image)

**Fig 1.2 Structures of thione and thiol forms of thiosemicarbazones.**

It is assumed that the TSC generally exist in the *E* form (*trans*). In such cases the compound may act as a unidentate ligand, by bonding through sulfur atom only[42]. If the sulfur center is substituted, the bonding may takes place by hydrazine nitrogen and the amide nitrogen.

Generally, the coordination takes place by the thiovsthione sulfur and the hydrazine nitrogen. But when additional binding sites are present adjacent to the S-N donor system, the ligand will act as a tridentate species. In majority of cases the third coordinating species will be in form of ketonic or aldehydic moiety[45]. The availability of the third coordinating site may lead to the formation of polymeric complexes[46] or could change the oxidation state of metal or may bring changes in the coordination environment of the metal ion. The changes taking place may affect the biological properties of the compound. The alkylation of the thiocarbonyl sulfur induces a complexation through terminal amido group and hence results for mono
acidic character of the ligand[47]. Such ligands may sometimes condense with a second aldehyde or ketone to result quadridentate ligands.

The stereochemistry of the TSC ligands with the transition metal ions essentially depends on the presence of additional coordination sites in the ligand moiety and also on the charge of the ligand. This in turn is effected by the thiol-thione equilibrium in the reaction medium. The equilibrium and the nature of complexation of thiol-thionedepend on the pH of the medium/solvent(s) used. The TSCs Generally act as neutral bidentate ligands which results into formation of octahedral and square planar geometries. TSC derivatives show increased biological activity as antitumour, antimalarial agents[48].

TSCs can bring about changes in bonding and stereochemistry of the compounds, which may decide the mechanism of the compound in biological systems.

\[
\begin{align*}
\text{N} & \text{N} \\
\text{H}_2\text{H}_2 & \text{N} \\
\text{NH}_2 & \text{NH}_2 \\
\text{R}_1 & \text{R}_2 \\
\text{Z(CIS)FORM} & \text{E(TRANS) FORM}
\end{align*}
\]

**Fig: 1.3 Tautomerism in thiosemicarbazones**

But the recent studies shows that the stereochemistry of the ligand is depends upon the steric effects of the various substituents present in the TSC moiety [51]. While coordinating to the metal ion, the compound is always found to be in Z-form. This phenomenon is due to the "chelate effect" increased stability due to better electron delocalisation in a chelated ring system resulting from the coordination with metal center.

1.7. Important role of metals:

Zinc was discovered centuries ago in the form of metallic which are used for making brass and zinc. Zinc compounds were used for healing wounds and sore eyes. Zinc ores are widespread geologically and geographically. Zinc is found abundantly in the earth's crust which is nearly of about 132 ppm by weight. In general zinc ores are found in combination with copper, lead, silver, gold as well as other metals. The mined ore is rarely good enough to be used directly by the smelters which should be concentrated. Generally Zinc ores contain 3% to 10% zinc and zinc concentrates
usually contain 55% zinc. Zinc is one of the essential trace element, found in high concentration in the human red blood cells as enzymecarbonic anhydrase, which helps to undergo many reactions like carbon dioxide metabolism. Zinc plays an important role in biological functions such as disease, wound healing, resistance, digestion, physical growth, reproduction, diabetes control, taste, smell [1] etc. Every cell in the human body requires zinc to get multiplied and more than 300 enzymes require zinc for proper functioning. According to "World Health Report 2002" estimated that one-third (33%) of the world's population is at risk of inadequate zinc intake. The effects of zinc deficiency may be severe, such as impaired neuropsychological functions, growth retardation and stunting, immune disorders, impaired reproduction, lethargy, dermatitis, loss of hair and loss of appetite [55-56].

Zinc has $d^{10}S^2$ electronic configuration and generally forms M$^{2+}$ ions. Many of their compounds are covalent in nature. Due to stability of the filled $d$ orbital, this element shows characteristic properties of transition metals despite its position in the $d$-block of the periodic table. Zinc also resembles other transition metals information of stable complexes with N, O and S-donor ligands like halide, cyanide etc. This shows the high flexibility in the structure, co-ordination mode and coordination number of the complexes are produced. Among these complexes, some has special attention as model compounds for active sites of zinc-containing enzymes [57], and their functions strongly depend upon the nature of coordination around the zinc ion. For creating functional zinc complexes, it is very important to consider the relationship of the coordination characteristics particular to zinc ion. Biological activity of thiosemicarbazones and semicarbazones increases on complexation with transition metals[58] and higher activity can be obtained with substitution at N4-position[59]. Tetrahedral and octahedral Zn(II) complexes of thiosemicarbazide and TSC of bidentate ligands have been reported[60]. On the other hand, ligands, such as ethylacetoacetatesemicarbazone and TSC acting astridentate in zinc complexes [61], in which the third coordinating center is provided by the carbonyl group. This chapter deals with the preparation and characterization of eight Zn(II) complexes of N4-substituted thiosemicarbazones.

Cadmium is one of the relatively abundant available elements which were invented in 1817 by Fredrich Stromeyer. It is found as an impurity in zinc carbonate. Cadmium
was named after the Latin word for calamine, since the metal was found in zinc compound. Cadmium containing ores are very rarely found and thus to occur in small quantities [62]. Gadreenockite (CdS), the only cadmium mineral is combined with sphalerite (ZnS). As a result cadmium is obtained as a byproduct from mining, smelting and refining sulfide ores of zinc and to a lesser degree for lead and copper. A very small amount of Cd (i.e) about 10% is obtained from secondary sources, mainly from dust generated by recycling iron and steel scrap. It’s Production in United States started in 1907, but it was not used until after World War I. The Only place where metalliccadmium can be observed is the Vilyuy River basin in Siberia [63]. An important commercial use of cadmium is that, it is used as an electrodeposited coating on iron and steel for preventing from corrosion. The second-largest application is Nickelcadmium batteries, which pigment and chemical uses third. A very small amount of cadmium are used in low-melting-point alloys, similar to Wood metal, in automatic fire sprinklers, in brazing alloys, solders, and bearings. Compounds of Cd(II) complexes shows tetrahedral, square pyramidal, trigonalbipyramidal and octahedral geometries. There is substantial interest in the coordination chemistry of cadmium complexes due to toxic environmental effect of cadmium. The mobilization and immobilization of Cd in the environment, in organisms, and in technical processes have been shown to depend significantly on the complexation of the central metal by chelating with nitrogen donor ligands [64]. Cadmium forms complexes with carboxy and acetate ligands as well to result both neutral and charged compounds. The possibility of forming geometries with higher coordination numbers has resulted in the unusual coordination geometries about the metal atom and the formation of polymeric species [65]. The most stable Cd(II) complexes forms with soft donor atoms (S>>N >O). The stability of the complexes increases with the increase in number of coordination groups contributed by the ligand. It has been noticed that some cadmium complexes of TSCs shows quite large SHG efficiency [66].
Copper is one of the important and most abundantly available element in the earth’s crust. It exists in two oxidation states i.e., Cu\(^+\) and Cu \(^{+2}\). Among this the most common oxidation state of Cu is +2 and copper(II) complexes have been widely studied. These complexes show tetrahedral, octahedral, square planar and trigonalbipyramidal geometries [67]. The role of copper in organic reactions depends upon its oxidation states. Copper metal is widely used in electrical industry due to its high conductivity and it is also used for water pipes because of its inert property. Copper catalyses redox reactions are used in biological systems primarily in the reduction of oxygen to water [68]. Due to the presence of unpaired e\(^-\), all the copper(II) complexes are paramagnetic in nature. More interest in Schiff base compounds containing TSCs and their transition metal complexes have improved in the area of chemistry and biology due to biological activity [69-70]. But semicarbazone analogs got much less attention. However, they possess versatile structural features [71]. Metal complexes containing Cu(II) and iron(II) are more active than the uncoordinated TSCs and this increase in biological activity [72]. Cu (II) complexes are more interesting due to their roles in biological and medicinal properties.

Nickel exists in three oxidation states such as Ni(I), Ni(II) or Ni(III) in biological systems as an active sites of certain hydrogenases and dehydrogenases [73]. Hence nickel species are of much interest to inorganic biochemists. Nickel is predominantly divalent and ionic in simple compounds. Nickel shows 4, 5 and 6 coordinate complexes such as square planar, tetrahedral, trigonalbipyramidal, square pyramidal and octahedral geometries. The coordination compounds of nickel are also studied for their magnetic property. In last few years, Ni(II) complexes containing sulfur donors has got most considerable attention due to sulfur rich coordination environment in biological nickel centers such as at the active sites of certain ureases, methyl-S-coenzyme-M-methyl reductase, hydrogenases and can play an active role in mutagenicity of nickel compounds. According to the study, labile four coordinated Ni(II) complexes with tridentate TSC and semicarbazone ligands shows antibacterial activities, where as six coordinated Ni(II) complexes with TSC and semicarbazone ligands exhibit any biological activity against the microorganism test [74].

The synthesis and reactivity of cobalt complexes of Schiff base ligands have played a very important role in coordination chemistry [75-76]. Coshows +2 and +3 oxidation
states and salts of Co(II) are more stable since they are difficult to oxidized to Co(III) state. However, in basic solutions, oxidation of Co(II) to Co(III) takes place easily. The overall formation constant is greater for higher oxidation state and thus the complexation makes it difficult to reduce. However, in spite of stabilization of Co(III) by complexation, high spin 6 coordinate, high/low 5 spin coordinate and 4 coordinate complexes of Co(II) are mostly reported. It has been noticed that Co(II) forms tetrahedral complexes than any other transition metal ion except Zn(II) because of its d^7 configuration. The cobalt complexes having tetradeinate Schiff base ligands are widely used to mimic cobalamin (B12) coenzymes [77-80], oxygen activators[81-84], dioxygen carriers and also in enantioselective reduction[85]. Radioactive isotope of cobalt is used in radiotherapy. Co compounds are in general used in the production of varnishes, inks and pigments. Co acts as ferromagnetic and the Curie temperature observed is 1388 K with 1.6~1.7 Bohr Magneton/atom. Cobalt oxides, CoO and Co_3O_4 are antiferromagnetic in nature at low temperatures.

Manganese is a naturally occurred metal, found in many rocks. Mn is widely used in steel production to improve its strength, stiffness and hardness. It is also used as an additive in gasoline to improve octane rating. Manganese is naturally present in the environment. Mn is required for normal physiologic functioning in humans and animals. Chronic exposure by inhalation affects central nervous system (CNS). Visual reaction time, eye-hand coordination and hand steadiness were affected in chronically-exposed workers. A syndrome called manganism would result from chronic exposure. This is characterized by feelings of weakness and laziness, tremors, a mask-like face and psychological disturbances. Impotence and loss of libido has been noticed in male workers afflicted with manganism.

Manganese is also an essential trace element, forming a number of active sites for metalloprotiens. In metalloprotiens, Mn can exist in any of the five oxidation states or in mixed valence states [86]. In photosystem II (PSII) it is found as tetranuclear manganese complex[86]. Manganese coordination compounds have improving as homogeneous catalysts in oxidation reactions. Manganese has an important role in many enzymatic systems such as peroxidase, peroxide dimutase, dioxygenase in which mononuclear manganese active sites are seen[87]. Manganese metal complexes play an important role starting from bioinorganic chemistry to solid state physics [88-
Manganese complexes are also studied for their magnetic property. The chemistry of manganese in various oxidation states in various combination of nitrogen and oxygen donor environment is currently witnessing intense activity [90-91]. The common oxidation states of Mn are +2, +3, +4, +6 and +7. The most common and stable oxidation state exhibited by manganese is +2 and most of these complexes are high spin paramagnetic $d^5$ systems and shows colored.

1.8. Objectives and Scope of the present work

As discussed previously, transition metal complexes of thiosemicarbazones possess a large spectrum of properties. The significance of thiosemicarbazones and their metal complexes, as part of their diverse chemical and structural characteristics, stems from not only their potential but also their proved application as biologically active molecules have encouraged as to explore their coordination chemistry further. The work embodied in this thesis mainly aims at weaving a network about their interesting spectroscopic, antimicrobial properties. Several new complexes have been synthesized and characterized using elemental analysis, molar conductance, magnetic measurements, IR and electronic spectral studies. The present study mainly aims at:

1. To synthesize and physico-chemically characterize the following thiosemicarbazone ligands without substitution at the N(4)-position.

a) Acetylcyclohexanethiosemicarbazone (HL$^1$=ACTSC)

\[
\text{N} \quad \text{N} \quad \overset{\text{S}}{\text{H}} \quad \overset{\text{NH}}{\text{H}} \quad \overset{\text{NH}}{\text{2}}
\]

b) 3-Methylbutanalthiosemicarbazone (HL$^2$=MBTSC)

\[
\text{H}_2\text{N} \quad \overset{\text{H}}{\text{N}} \quad \overset{\text{N}}{\text{N}} \quad \overset{\text{S}}{\text{H}}
\]
c) 4-Bromo-2-thiophenecarboxaldehyde thiosemicarbazone (HL3=BTSC)

2. To synthesize some metal complexes of above ligands.
3. To investigate the spectral characteristics of these complexes.
4. To study the biological activities of the ligands and the complexes