CHAPTER 1 - INTRODUCTION

1.1 Introduction of Coordination chemistry

Coordination chemistry is the branch of chemistry that deals with the construction of metal complexes. Metal complex consists of a metal ion, often referred to as the central atom (or ion) which binds with a number of ions or molecules called ligands. The story of coordination chemistry is not young and it has been known for more than three centuries but their structures were initially not understood. Prussian blue has been used as a pigment since its accidental discovery by Diesbach in 1704. In 1869, Christian Wilhelm Blomstrand developed the complex ion chain theory of Cobalt(III)hexamine complex and Jorgensen claimed that two possible outcomes: the ions would bind via the ammonia chains or the ions would bind directly to the metal. The modern theory of coordination chemistry was proposed by Alfred Werner. He explained the spatial arrangements of ligands during the formation of the metal complex and distinguished the primary valency and secondary valency in metal complexes [1].

Structure of transition metal complexes is explained by theories like Valence bond theory (VBT), Crystal field theory (CFT) or Ligand field theory (LFT), Molecular orbital theory (MOT), etc. Valence bond theory enumerates the formulation of complexes by the reaction between Lewis acid and Lewis base with the formation of coordinate covalent bond. But, it is unable to explain the interpretation about the spectral and magnetic behavior. So, the crystal field theory is proposed. It assumes that an interaction between metal and ligands is purely ionic. The d-orbital of the central metal ion/atom is degenerate and this degeneracy is destroyed when the ligands are approaching the metal ion. The greater achievement of crystal field theory

is an interpretation of spectra and magnetic behavior exhibited by the complexes. But, the drawback of CFT is ionic bonding feature of ligands. When CFT is modified which allows the effects of covalent character in the bonds, it becomes more useful and it known as Ligand Field Theory. Molecular orbital theory can explain more number of complexes and the interactions between metal and ligands are covalent. It is more complicated but provides more information.

Magnetic properties of the complexes were explained by electronic configuration of metal ions. If mono-metallic complex have unpaired electrons then the complexes are paramagnetic while the complexes does not have unpaired electron then they are diamagnetic. The unpaired electrons in complexes are arising due to odd number of electrons in metal ion. In bi-metallic complexes, the individual centres have unpaired electrons (high-spin), the electrons may couple (antiferromagnetic) which results in the formation of diamagnetic complex. If there is no interaction then individual metal centers are behave as two separate molecules (ferromagnetic). Due to magnetic properties, Metal chelates are involved in ligand exchange, electron transfers and associative reactions. Hence, they are used as catalyst as well as sensor when the ligands are carefully chosen [2].

1.2 Bio-inorganic chemistry

The functions of metal ion in biological systems are more complex and quite interesting in metabolic activities. Developments in biochemistry create interest to inorganic chemists and try to replace some biological enzymes by metallic chelates which are separately studied by “Bioinorganic Chemistry”. One of the principal themes of bioinorganic chemistry is the synthesis of metal complexes that have the ability to mimic the functional properties of natural metalloproteins [3]. Many

enzymes are metal complexes, like carboxypeptidase, carbonic unhydrase, vitamin B_{12}, hemoglobin, cytochromes and chlorophyll (which are dark red or cherry colored, blood red and green in color respectively), etc [4].

1.3 Choice of Ligands

Studies in coordination compounds were initiated with inorganic ligands followed by organic ligands which lead to many interesting features in coordination chemistry. Heterocyclic compounds containing certain functional groups (like amine, thiol, alcoholic, phenolic and carboxylic group) act as superior donors and readily form complexes with metal ion. Among the various ligands, Schiff bases have much interest due to their delocalized π-orbitals, multidonor sites, etc. Due to our interest on the chemistry of Schiff base complexes, a brief review about the Schiff base complexes is discussed below:

Schiff base is the condensation product of carbonyl compound and primary amine (Hugo Schiff - 1864). Formation of Schiff base can be represented as follows (Scheme 1.1)**:**

$$RCHO + R'NH_2 \rightarrow RHC = NR' + H_2O$$

Scheme 1.1 Formation of Schiff base

Where R and R' represents alkyl, cyclo alkyl, aryl, or heterocyclic groups. Schiff bases are considered as 'privileged ligands' because of their capability to stabilize various oxidation states of metal selectivity, sensitivity and flexibility [5-11]. In addition to azomethine nitrogen atom, other donor atoms (O and S) may also present in Schiff base are coordinated to transition metal ions and form stable metal complexes [12]. Schiff base ligands are also notable in catalysis, optical and bioinorganic chemistry points of view [13]. Schiff bases of aliphatic aldehydes are

unstable [14, 15] while aromatic aldehydes are more stable due to extensive conjugation. In general, the reaction centre of aldehyde is sterically less hindered than ketone. Hence, the former reacts faster than ketones in the formation of Schiff bases. In addition, ketone has extra carbon which increases the electron density of azomethine carbon atom and makes it less electrophilic than aldehyde.

Amino acids have amino and carboxylic acid group as well as a side chain. The later is used to differentiate among the amino acids. In biochemistry, amino acids are called as α-amino acids and have the general formula $H_2NCHRCOOH$. Where, R is an organic substituent. The uncharged amino group of amino acid at physiological pH values undergoes Schiff base formation. The potential donor (-COOH), group of amino acid readily forms metal chelates which are the scale of thermodynamic and kinetic stability.

Schiff base complexes are great biological importance in the field of model compounds derivatives which represent one of the major classes of biological active agents which have been deeply studied during search on new potential agent [16]. It also have received much attention due to their antimicrobial [17], anti-tuberculosis [18], anti-tumour [19], anticonvulsant [20], anti-inflammatory [21], anti-HIV [22], antihelminthic [23], cardiovascular [24] activities and anti-carcinogenic properties [25].

Metal chelates have high biological activities than free organic compounds. It can be dictated by the hard-soft theory of acids and bases. This theory explains how metal complexes are enhanced activity than the free ligands [26].

The compounds possessing pyrazolone ring showed significant antimicrobial activities, the molecular manipulation of a promising lead compound is still a major

line of approach for the discovery of new drugs. Hence, the synthesis was initiated by the condensation of aromatic aldehyde with pyrazolone compounds containing primary amine. Among the pyrazolone derivatives, 4-aminoantipyrine is well known compound as anti-inflammatory, analgesic, antipyretic and analytical reagent [27, 28]. Aldehydes/ketones readily forms Schiff bases with 4-aminoantipyrine. These aldehydes having additional functional group like –OH, -COOH, -SH, $-NH_2$, etc which enhances donor sites of 4-aminoantipyrine. Because of such different coordination possibilities with transition metal ion and consequently their flexible complexation behavior, it is possible to build up a variety of ligand systems by choosing 4-aminoantipyrine as a basic and fundamental moiety. Due to the presence of two active reactive groups such as amine and carbonyl group present in the 4-aminoantipyrine, it has been used to form a variety of Schiff base derivatives. Literature search reveals that few work has been done on the condensation of cyclic carbonyl group present in the pyrazolone ring in 4-aminoantipyrine with primary amine containing compounds.

Recently, studies on the interaction of DNA with metal complexes are important in designing of new pharmaceutical drugs. Metal complexes interact with DNA *via* covalent and non-covalent interaction which induces breakage of DNA strands. The breakage of DNA strands by metal chelates is the key for generation of newer drugs which may cure some dangerous diseases like cancer, HIV/AIDS, malaria fever, etc. So it is the much more thrust area for young researchers [29-36].

1.4 Biological importance of Transition metal ions

Transition metals exist in biological systems are able to undergo ligand exchange with the component of biological system. Metalloproteins exist in biological

systems like hemoglobin, myoglobin, blue copper proteins, carboxy peptidase, carbonic unhydrase, etc., mainly consists of first row transition metals as active sites. Hence, hereunder we describe the importance of transition metals used in this thesis.

1.4.1 Copper

2.1 to 1.4 mg/kg of copper are present in mammals. In human, copper is found mainly in the liver, muscle and bone. It is also present in cytochrome c oxidase and involved in respiratory process. It is a main constituent of the blood pigment like hemocyanin. Copper also exists in mitochondria, superoxide dismutases, etc. They are involved in oxygen carrier, electron transfer process, oxidation, reduction and hydrolysis reaction. Copper complexes exists in various oxidation states, amongst Cu(II) forms stable complexes with nitrogen/oxygen donor ligands and may involved better electrochemical redox reactions as well as DNA interactions. In addition, copper complexes have somewhat powerful antimicrobial activity. Ceruloplasmin in milk acts as a copper source which undergoes enterohepatic circulation. Copper also involved in body metabolic activities and its deficiency causes genetic abnormalities, nutrient-nutrient interactions and nutrient-drug interactions affects the vascular and immune system [37].

1.4.2 Cobalt

Cobalt complexes are used as synthetic oxygen carrier. It is a micronutrient for bacteria, algae and fungi. Cobalt is essential to the metabolism of all animals and a key constituent of cobalamin (vitamin B_{12}). *Reticulo-rumen* bacteria that live in the guts of ruminant animals and converts cobalt salt into vitamin B_{12}.

A modified corrin ring system is present in Coenzyme B_{12} and has two types of alkyl ligand: methyl and adenosyl. MeB_{12} promotes methyl ($-CH_3$) group transfers.

The adenosyl derivatives of vitamin B_{12} act as catalyst in electron transfer reaction between two adjacent atoms. Cobalt proteins (methionine aminopeptidase-2), acts as enzyme that occurs in humans and other mammal. It is also involved in the extraction of energy from proteins and fats [38-40].

The cobalt deficiency causes neurological and muscular lesions which leads to hepatic damage of metabolic consequences.

1.4.3 Nickel

Nickel is an essential nutrient for microbes and plants. It plays an important role in the biology of plants, eubacteria, archaebacteria and fungi. Nickel containing urease enzyme acts as catalyst in the hydrolysis of urea to form ammonia and carbamate in microbes. It is also involved in photosynthetic nitrogen fixation process.

The [NiFe]-hydrogenases can catalyze the oxidation of H_2 to form protons and the reduction of protons to form hydrogen gas. Nickel-tetrapyrrole coenzyme and methyl coenzyme M reductase in methanogenic bacteria catalyze the formation of methane or the reverse reaction. Carbon monoxide dehydrogenase enzymes consist of a Fe-Ni-S cluster. Other nickel-bearing enzymes are superoxide dismutase and glyoxalase I enzymes. They are present in higher organisms including yeast and mammals.

Excess of nickel in human body causes cancer in respiratory tracks [41, 42]. Deficiencies of nickel leads to damage of liver, skin rashes and kidney related problems. It also causes paralysis along the side inflammation of the liver and lungs.

1.4.4 Manganese

It is a required in trace amount for all known living organisms. Human body contains about 12 mg/kg of manganese. It is mainly concentrated in soft tissues like

liver and kidneys. In human brain, manganese is found as manganese metalloproteins. Manganese is essential for photosynthesis of plants in oxygen-evolving system. In photosystem-II, the oxygen-evolving complex (OEC) present in the thylakoid membranes and chloroplasts which is responsible for the terminal photo oxidation of water during the light reactions of photosynthesis and four atoms of manganese are involved in this reaction.

Manganese is also important for detoxification of superoxide free radicals in organisms. The arginase polypeptide chain superoxide dismutase (Mn-SOD) in eukaryotic mitochondria also contain manganese ion. The Mn-SOD enzyme deals with the toxic effect of superoxide (O_2^-). *Lactobacillus plantarum* bacteria and related lactobacilli, Manganese (Mn^{2+}) ions are complexed with polyphosphate [43-47].

Manganese deficiency causes neurotoxin effects in human beings. It leads to neurological damage. Mn is frequently over exposure which creates progressive, permanent, neurodegenerative damage, resulting in syndromes similar to idiopathic Parkinson's disease.

1.4.5 Vanadium

Vanadium is very important nutrient for human being. It controls the secrecation of insulin and maintains the sugar level in blood. 30-150 mg of vanadium is enough to improve the glycemic control in people. It is also involved in body metabolism and increases the strength of bones and teeth. Vanadium is also very important to tunicates and ascidians. It is stored in certain blood cell called vanadocytes. Vanadium binding proteins are vanabins, vanadium bromoperoxidase enzyme and amavadin.

Deficiencies of vanadium lead to decrease the probability of pregnancy of women. It also decreases the formation of blood red cells that leads to anaemia, fragile teeth, bones and poor cartilage formation [48-52].

The excess of vanadium leads to vomiting, nausea, stomach pain, diarrhea, nose bleeding, internal bleeding, anaemia, hyperglycemia, kidney and liver related problems, etc.

1.4.6 Zinc

Zinc is an essential for all living beings. It is found in almost 100 specific enzymes. It is the second most abundant transition metal present in organisms. In proteins, zinc ions act as active site where amino acids such as aspartic acid/cysteine/glutamic acid and histidine side chain are coordinated with metal.

In humans, zinc interacts with organic molecules and involved in the metabolism of RNA and DNA, signal transduction and gene expression. In the brain, zinc is stored in specific synaptic vesicles by glutamatergic neurons and can modulate neuronal excitability. It plays a key role in synaptic plasticity. However, it has been called "the brain's dark horse" because it plays a critical role in the functional regulation of the central nervous system. Dysregulation of zinc homeostasis in the central nervous system that results in excessive synaptic zinc concentrations is believed to induce neurotoxicity through mitochondrial oxidative stress.

Zinc present in various enzymes allows proteins to undergo conformation changes and to perform biological reactions. Examples: Carbonic anhydrase and carboxypeptidase which are involved in the processes of carbon dioxide (CO_2) regulation and digestion of proteins respectively. Zinc fingers help to read the

sequences of DNA. In vertebrate blood, carbonic anhydrase converts CO_2 into bicarbonate and back into CO_2 for exhalation through the lungs [53].

The zinc deficiency symptoms include: Poor neurological function, weak immunity, Diarrhea, Allergies, etc. Zinc deficiency leads to hypothyroidism which causes thinning of hair, skin disorders, allergies, auto-immune disease and other thyroid problems.

General roles of metal ions in biological processes and their toxicity are summarised in Table 1.1.

Table 1.1 Function and toxicity of the elements in biological systems.

Element	Biological function	Toxicity
Copper	Essential to all organisms; constituents of redox enzymes and oxygen transport pigments.	Very toxic to most plants; highly toxic to invertebrates, moderately so to mammals.
Nickel	Essential trace element. Chicks and rats raised on deficient diet show impaired liver function and morphology.	Very toxic to most plants; moderately so to mammals.
Cobalt	Essential for many organisms including mammals; activates a number of enzymes	Very toxic to most plants and moderately so injected intravenously in mammals
Manganese	Essential for all organisms; activates a number of enzymes; deficiencies in soils lead to infertility in mammals, bone malformation in growing chicks.	Moderately toxic
Zinc	Essential for all organisms; used in enzymes.	Moderately to slightly toxic.
Vanadium	Essential to chicks and rats. Deficiencies cause reduced growth, impaired reproduction and survival of young, impaired tooth and bone metabolism. Thought to inhibit cholesterol biosynthesis in mammals; has a beneficial effect against tooth decay.	Highly toxic to mammals if injected intravenously.

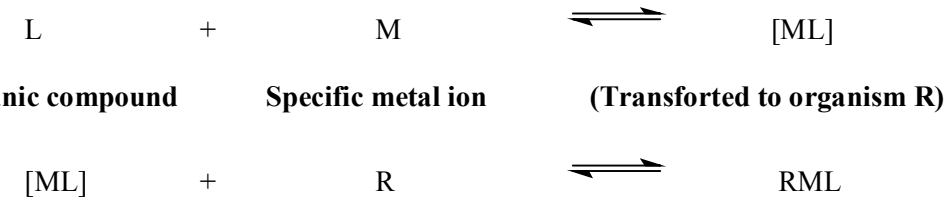
1.5 Antimicrobial activity of metal complexes

Complexes of transition metal ions with various ligands exhibit antimicrobial activity against a spectrum of microbes and possess toxicity against a number of cell lines of human and rodents in cell culture. A variety of compounds are reported as strong antibacterial, fungicidal, herbicidal and insecticidal reagents.

Schiff base transition metal complexes are one of such reagent and control a number of infectious diseases. Thus, a number of antibacterial agents are extensively used in everyday life for the preclusion of public health issues caused by the ubiquity of micro-organisms and their ability. Though an antibacterial agents are mostly used in the fresh packaging materials for health care and food applications, the most vital parameters to be taken care of high efficiency in controlling bacteria and low toxicity to human beings. The increasing use of inorganic antibacterial agents is great interest since of their effectiveness towards highest safety and stability when compared with organic antibacterial agents. Schiff base metal complexes can develop the antimicrobial [54] efficacy and preventing microbial growth. In this study is an investigation of the antibacterial activity of Schiff base metal complexes are against pathogenic bacterial and fungal species.

A search through the literature reported that the activity of biometals is often altered through the formation of complexes with biologically important compounds [88-108]. Metal chelates play an important role in biological systems in which enzymes are known to be activated by metal ions. The metal ion present in enzyme acts as a cofactor for enzyme activity. Metals have been used to do two functions; one is to provide proper stereochemical orientation and another one is to bring the reacting molecules closer to the active sites of the enzyme so that the reaction may occur.

The activity of the metal chelates depends upon the steric, electronic and pharmokinetic factors. The mechanism of organic compound action depends upon the interactive forces that bind the compound with organisms. These forces may vary from the rigid covalent bonding to the weak Vander walls forces. There are several possible mechanisms, the most well known are the interaction, the electrostatic binding and groove binding mechanisms. According to chelate hypothesis, the compound-organism interaction visualised in the equilibria is given below:



Metal-bridged organic compound-organism (mixed ligand chelate)

The pure organic compound (L) reacts with the specific metal ion (M) to form chelate (ML) which binds with the organism forming the hypothetical metal-bridged organic compound-organism complex (RML). The chelating properties of organic compound are used to transport across membranes or to attach the organic compound to a specific site as they can hinder the growth of bacteria.

The heterocyclic compounds exhibit antibacterial activities due to the presence of multifunctional groups. Most of them have N, O and S containing groups which form strain-free five or six-membered ring and give 1:1 or 1:2 (metal-organic compound) chelate with the biologically important metal ions such as copper(II), cobalt(II), zinc(II), manganese(II), magnesium(II)/iron(II) and vanadium(II). They are mostly in octahedral or square planar geometry.

When such hetereocyclic ligands are complexed with the metal ions, the resulting complexes show enhanced activity. Chelation with metal ions gives some important properties to the organic compounds that also play important role in their biological activity such as low dissociation constant, special redox potential, electron distribution, etc. These properties play markedly effect on the solubilities of the complex in the lipid and their pharmacological transport mechanism.

According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid soluble materials due to which liposolubility has been considered as one of the important factors which controls the antimicrobial activity. Complexation of antimicrobial active organic part with metal ion reduces the polarity of metal ion considerably because of partial sharing of its positive charge with donors groups and delocalisation of π-electrons over the whole chelate ring resulting in high lipid solubility. The increasing lipid solubility character of the metal chelate favours its permeation through lipid layer of the microorganism which probably leads to break-down of permeability barrier of cell process.

Variety of substituents introduced on the organic part by using heterocycles and with ether -O- atom, etc., increase antimicrobial activity because this increases the basic strength and furnishes delocalisation of π-electrons over the whole chelate rings. Such molecules possess higher activity in consistent with the greater stability of the chelates. The influence of the presence of -C=C- bond in amide, acid or phenolic hydroxyl groups in adjacent positions on the modes of metal ion coordination of the ligand show increased activity due to the formation of stable chelate rings.

The above literature clearly indicates that the importance of biological screening studies using metal ion, heterocyclic compounds etc. depend greatly upon

the nature of the microorganisms. The nature of the microorganisms and the diseases caused by them are briefly reviewed below:

***Escherichia coli*:** It is Gram-negative anaerobic bacteria. *E-coli* are rod-shaped and 2.0 μm long and 0.25-1.0 μm in diameter. During staining process, it takes up the color of counter stain safranin and tarnishes pink. *E. coli* constitutes nearly 0.1% of gut flora and fecal-oral transmission. *E. coli* causes urinary tract infections, neonatal meningitis and gastroenteritis. It is also responsible for peritonitis, hemolytic-uremic syndrome, mastitis, pneumonia and septicemia.

***Proteus vulgaris*:** It is Gram-negative and heterotroph bacteria. It is rod-shape with 0.4 - 0.6 to 1.2 - 2.5 μm size. *P.vulgaris* possesses peritrichous flagella. It inhabits the soil, polluted water, raw meat and gastrointestinal tracts of cattles. It is isolated from urine samples using phenol red indicator, ammonia produced by *P. vulgaris* raise the pH and changes yellow to red colour. In humans, *Proteus* species most frequently cause urinary tract infections and severe abscesses. *P. vulgaris* is associated with nosocomial infection.

***Klebsiella pneumoniae*:** It is Gram-negative, encapsulated, non-motile, facultative, anaerobic, lactose fermenting, white translucent colour and rod shaped bacteria. It enters into the respiratory tract which causes pneumonia, leading to blood stream infection and liver abscess (end-organ damages). It also causes lungs abscesses (respiratory system damages). *Klebsiella pneumoniae* bacteria spread through person to person contact or by contamination of the environment. *K. pneumoniae* can produce extensive hemorrhagic necrotizing consolidation of the lung. It occasionally produces urinary tract infection in debilitated patients.

Streptococcus aureus: It is a facultative anaerobic Gram-positive and coccal bacterium. It is also known as golden staph. It appears as grape-like clusters, large golden-yellow colonies, round and hemolytic when grown on blood agar plate. *S. aureus* causes a wide range of mild illnesses like skin infections such as pimples, impetigo, boils (furuncles), cellulities folliculate, carbuncles, scalded skin syndrome and abscesses. It also causes life-threatening diseases such as pneumonia, meningitis, osteomylitis, endocarditis, toxic shock syndrome, bacterimia and sepsis.

Pseudomonas aeruginosa: It is Gram-negative and rod-shaped bacteria. It has bluish green color of culture. The genome of *P. aeruginosa* is relatively large (5.5-6.8 Mb) and encodes between 5,500 and 6,000 open reading frames. It affects plants and animals. It is a multidrug resistant pathogen and its association with serious illnesses hospital-acquired infections are found in the lungs of people with cystic fibrosis and primary ciliary dyskinesia and can prove fatal. It induces an immunologic response in immuno competent patients.

Salmonella typhi: It is a rod-shaped, bluish green with black center gram negative bacteria. It is about 0.7-1.5 by 2.0-5.0 μm in size. It has a complex regulatory system and survives in the intestinal organs of its hosts. Salmonella has adapted to grow under both an aerobic and anaerobic conditions. It contains two types which are typhoid and paratyphoid. It is growing readily on simple media over a range of pH 6-8 and the optimum temperature is 37 ºC. It causes enteric fever, gastroenteritis and septcemia.

Bacillus subtilis: Gram-positive, dull white colour and catalase-positive bacteria. It is found in soil and the gastrointestinal tract of ruminants and humans. It grows on both aerobic and anaerobic condition. *B. subtilis* is rod-shaped bacteria. It can form a

tough, protective endospore allowing it to tolerate extreme environmental conditions and survive long period of time. It is found in soil, gastrotestinal tract of ruminants and humans. It contaminates food which results in food poisoning.

Candida albicans: It is a type of pathogenic fungi. It is a common member of the human gut flora. It is detected in the gastrointestinal tract and mouth in 40-60% of healthy adults. *C. albicans* is easily cultured in the lab and can be studied both *in-vivo* as *in-vitro* condition. It causes candidemia. This disease is prevented by maintaining a good oral hygiene, keeping a healthy lifestyle, careful/safe antibiotic use and treatment of infected area.

Aspergillus flavus: It is a saprotrophic and pathogenic fungi with cosmopolitan distribution. It is present in cereal grains, legumes and tree nuts. It is a rough surface and colourless bacteria. It causes pre-harvest and post-harvest infections like aspergillosis in immuno compromised individuals. In grains and legumes, post harvest disease results in the production of mycotoxins. The largest economic lost caused by this pathogen is due to production of aflatoxin.

Aspergillus niger: It is a fungus. It causes disease called black mould on certain vegetables, fruits, onions, peanuts, apricots, grapes, etc. It is common contaminants of food. It is also present in both indoor and outdoor environments. It is utilizing minerals such as silver, gold, iron, copper and zinc, etc from soil. It produces mycotoxin and isoflavone orobol. These two chemicals are responsible for disease caused by this organism.

Rhizopus stolonifer: It is a thread-like mucoralean mould and a heterotrophic fungus. It is mainly present on bread surfaces. It takes food and nutrients from the bread and damage bread surface. It is dependent on carbohydrate. It is generally used the foods

like breads and soft fruits (like strawberries or grapes) for their growth and reproduction. It is involved in carbon cycle and acts as decomposer in soil, dung and many foods. They grow inside food, take the nutrients and dissolve the substrate with extracellular enzymes. *R. stolonifer* is an agent of plant disease and decompose the organic matter. In this process, the black bread mould causes rotting of fruits and affects the humans [55-58].

1.6 Structure, function and binding mode of nucleic acids

In 1869, Friedrich Miescher isolates deoxyribonucleic Acid (DNA). Avery and his co-workers published the historical report that "the genetic informations were carried only by DNA" [59]. Later, Chargaff developed the complementary base pair rule [60] and the double helix structure of DNA was determined by James Watson, Francis Crick, Rosalind Franklin and Maurice Wilkins [61]. DNA contains a long chain of paired molecules which are called as "nucleotides". Each nucleotide contains a phosphate base, pentose sugar and nitrogenous base [62-76].

To understand the drug-nucleic acid interactions, we must have the knowledge on kinetics, mechanism and energy involved in the interactions [77]. Hence, understanding the mechanisms of drug interaction nucleic acids and their correlation with biological effects has been the object of great attention. Outcome of these researches are designing of structure-based drugs and its subsequent production [78].

Drug-nucleic acid interactions induce changes in the nucleic acid structure which results in conformational alterations as well as loss, addition or substitution of the bases and modifying the DNA sequence leads to affecting the genetic message. These changes inhibit the synthesis of proteins (inhibition of the gene expression), modified the structure and enzymes activity through mutation of DNA [79-83].

The covalent binding of metal complexes with DNA is kinetically controlled one. As DNA is a polyanion, the pre-association step is particularly significant if the metal complex is cationic in nature. The covalent binding in DNA is irreversible and invariably leads to complete inhibition of DNA processes and subsequent cell death or gives way to adduct species that prevents cell replication which also results in cytotoxicity. Cis-platin is a famous covalent binder used as an anticancer drug and makes an intra/interstrand cross-link *via* the chloro groups with nitrogens on the DNA bases.

Groove binding and intercalation are the main modes of non-covalent interaction. These reversible interactions are the main mechanism followed by anticancer and antiviral pharmaceutical drugs [84, 85]. For this reason, it is important to study whether their effect is external or internal. Many researches insist that the function as intercalators or groove binders under the pH, temperature and ionic strength solvent conditions [86, 87].

Recently, studies on the interaction of DNA with metal complexes are important in designing of new pharmaceutical drugs. Metal complexes interact with DNA *via* covalent and non-covalent interaction which induces breakage of DNA strands.

1.7 Literature Review of pyrazolone derivatives

A search through the literature reveals that the considerable number of pyrazolone derivatives is already used as drugs for some diseases and its applications are extended to many other medicinal problems. Hence, it is essential to discuss the survey of pyrazolone derivatives which are furnished below:

Transition metal complexes of pyrozolone derivatives is reported which are great interest due to their excellent biological activity. Among various pyrozolone compounds, 4-aminoantipyrine readily forms a variety of Schiff bases with aldehydes/ketones and are reported to be very good reagents in biological, pharmacological, clinical and analytical applications. The biological activities of such Schiff bases are further improved by complexation with transition metal ions. 4-aminoantipyrine has an added advantage that it has two potential donor sites and is likely to form three types of compounds with metal ions i) Chelates utilizing both donor atoms, ii) using only the amino nitrogen atom and iii) using only from the carbonyl oxygen atom.

Because of such different coordination possibilities with transition metal ion and consequently their flexible complexion behavior, it is possible to build up a variety of ligand systems by choosing 4-aminoantipyrine as a basic and fundamental moiety.

In 1996, Agarwal *et al.* have synthesized some new Schiff bases by condensing with 4[N-(benzalidene) amino]-antipyrine and semicarbazide. The semicarbazide forms azomethine group with the cyclic carbonyl group present in the 4-aminoantipyrine. Due to the presence of two active reactive groups such as amine and carbonyl group present in the 4-aminoantiprine, it has been used to form a variety of Schiff base derivatives. Literature search reveals that few work has been done on the condensation of cyclic carbonyl group present in the pyrazolone ring in 4-aminoantipyrine with primary amine containing compounds. Such primary amines contain additional functional groups such as -OH, -SH, -COOH etc., which create one more donor site in 4-aminoantipyrine derivatives. Due to the presence of

thiol/hydroxyl groups, such Schiff bases have been considered as very good potential donor ligands towards transition metal ions.

Aminothiazoles as well as histidine have the ability to act as primary amine and condensing it with 4-aminoantipyrine derivative and enhance the three donor sites to four donor sites.

Till now, β-diketonato complexes continue to attract considerable attention from both theoretical standpoints concerning the mode of bonding and their general reactivity as coordinated ligands. The coordinating ability of β-diketones has been well established. A large number of β-diketones are also prepared continually by organic chemists. β-diketone exists in keto-enol equilibrium as revealed by thermodynamic and spectroscopic examination. The hydrogen atom of $-CH_2-$ group is activated by the adjacent C=O groups and a conjugate system arised by a prototropic shift. Due to the importance of the chelating behaviour of β-diketones, Schiff bases of 4-aminoantipyrine with β-diketones are used as the precursor to investigate large number of organic compounds. Knoevenagel condensation of β-diketones and aldehydes which can act as dicarbonyls and they have fruitful sources of macrocyclic polyaza ligand systems. Among the various β-diketones, curcumin is a versatile compound because of their traditional importance in biological, pharmacological and clinical applications. Recently, studies on the interaction of DNA with metal complexes are important in designing of new pharmaceutical drugs. Metal complexes interact with DNA *via* covalent and non-covalent interaction which induces breakage of DNA strands.

Literature search reveals that no work has been done on the condensation of cyclic carbonyl group present in the pyrozolone ring in 4-aminoantipyrine with

2-aminothiazole/histidine/2,6-diaminopyridine [88-108]. Hence, we are interested in examining the synthesis, structural characterization and biological activities of Schiff bases and their transition metal complexes derived from (i) Salicylidene-4-iminoantipyrine and 2-aminothiazole, (ii) Benzalidene-4-iminoantipyrine and 2-aminothiazole, (iii) Benzylidene-curcuminyl-4-iminoantipyrine and 2,6-diaminopyridine, (iv) Salicylidene-4-imino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and Histidine, (v) Benzil, *p*-nitroaniline and 2, 2'-bipyridyl. In addition, we report DNA interactions of copper complexes using electronic absorption spectroscopy and cyclic voltammetry.

The above reviews clearly make out the significance of the coordination chemistry of transition metal complexes. Here, we list out some major objectives of our work.

1.8 Scope of the present work

- To synthesizes new Schiff bases and their transition metal complexes.
- To characterize the synthesized compounds by adopting CHNS (O) analyzer, X-ray diffraction studies, SEM, FESEM, Spectral studies (IR, UV-Vis., Mass, NMR and ESR spectroscopy), cyclic voltammetry and photoluminescence spectrophotometer.
- To study the interaction of Calf-Thymus DNA with copper complexes using absorption spectra and cyclic voltammetry studies.
- To investigate the antimicrobial studies of the synthesized compounds by *in vitro* method (Antibacterial, antifungal and anticancer activities).
- To carried out the statistical analysis by the comparison of antimicrobial activities for some prepared Schiff base metal complexes.

The detailed scope of the work has been discussed below:

Chapter - I described the Introduction, importance of coordination complexes, choice of ligands, biological studies, literature review and scope of present work is briefly furnished.

In Chapter - II, General experimental methods, materials employed, purification of solvents, instruments used, procedure for antimicrobial activity and DNA interaction studies are fully discussed.

In Chapter - III, Synthesize and characterization of new tetradenate N_2OS type Schiff base and its [CuL]Cl, [CoL]Cl, [NiL]Cl, [VOL]Cl and [ZnL]Cl complexes are to be dealt. Complete prominent structural features of the synthesized compounds to be done by elemental analysis, molar conductance, magnetic susceptibility, FAB-Mass, Powder XRD, FESEM, ^{1}H-NMR, ^{13}C-NMR, FTIR, UV-Vis. and ESR spectral techniques. Interaction studies of copper complex with CT-DNA are to be done by electronic spectral and cyclic voltammetric measurements. The *in-vitro* antibacterial activities of the investigated compounds are to be tested against the two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and three Gram-negative (*Escherichia coli, Klebsiella pneumoniae* and *Salmonella typhi*) bacterial strains by using nutrient agar as medium. The *in-vitro* antifungal activity of chelates is to be tested against *Candida albicans, Rhizoctonia bataicola, Aspergillus flavus, Aspergillus niger* and *Rhizopus stolonifer* by well diffusion method using potato dextrose agar as medium. Statistical analysis is to be compared for antimicrobial activities.

In chapter - IV, Synthesis, spectral, DNA interaction and antimicrobial studies of Schiff base derived from Benzalidene-4-iminoantipyrine and 2-aminothiazole are

to be reported. The structural features of the chelates to be confirmed by micro-analytical data, FAB-Mass spectra, Powder XRD, SEM, FTIR, UV-Vis, ^{1}H-NMR, EPR, CV and thermal analysis techniques. DNA interaction studies of [CuL_2] complex are to be done by optical and cyclic voltammetric measurements with CT-DNA. The synthesized Schiff base (HL) and its complexes are to be tested for their *in vitro* antimicrobial activity against two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and three Gram-negative (*Escherichia coli, Klebsiella pneumoniae* and *Salmonella typhi*) bacterial strains and for *in-vitro* antifungal activity against *Candida albicans, Rhizoctonia bataicola, Aspergillus flavus, Aspergillus niger* and *Rhizopus stolonifer* by well diffusion method using nutrients agar as medium for bacteria and potato dextrose agar as medium for fungi respectively. Tetracycline and Nystatin were used as standard control drugs for bacteria and fungi respectively.

In chapter - V, Synthesis and characterization of new cationic 14-membered fully conjugated macrocyclic Schiff base metal complexes by condensation of Benzylidene-curcuminyl-4-iminoantipyrine and 2,6-diaminopyridine are to be discussed. Structural characterization of the compounds to be done using Elemental analysis, Molar conductivity, Magnetic susceptibility, Mass, SEM, XRD, ^{1}H-NMR, UV-Vis., IR and EPR spectra. The *in-vitro* biocidal activities of the compounds are to be done against some bacterial and fungal strains by well diffusion method. Anticancer activity of Schiff base and copper complex are to be carried out by MTT method and discussed.

In chapter - VI, Synthesis and characterization of novel tetradentate Schiff base transition metal complexes derived from histidine and salicylidene-4-imino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one are to be discussed and characterized by

elemental analysis, molar conductance, magnetic susceptibility measurements, IR, FAB-MS, ^{1}H-NMR, UV-Vis., EPR, CV, Fluorescence emission, Powder XRD and SEM techniques. DNA interaction studies of [CuL] complex are to be reported. Electronic absorption spectra and cyclic voltammetry studies of copper complex with CT-DNA is to be analyzed. The *in-vitro* antimicrobial activity of compounds is to be tested against the growth of some bacterial and fungal species.

In chapter - VII, Synthesis of new biologically active transition metal complexes of Cu(II), Ni(II), Co(II), Zn(II) and VO(II) ion derived from the benzil, 4-nitroaniline and 2,2'-bipyridyl is to be described. The structural features of the synthesized complexes are to be arrived by their elemental analyses, FAB-mass, IR, UV-Vis., ^{1}H-NMR and ESR spectral studies. The binding mode of copper complex with CT-DNA is to be analyzed by electronic absorption spectra and cyclic voltammetry. The *in vitro* biological screening effects of the investigated compounds are to be tested against bacteria: *Escherichia coli, Staphylococcus aureus, Salmonella typhi, Bacillus subtilis* and *Klebsiella pneumoniae*.

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