Chapter 10

SUMMARY AND CONCLUSION

Coordination chemistry is dominated by the utilization of Schiff bases as ligands due to its chelating ability and complexing ability towards transition metal ions. Heterocyclic Schiff base complexes incorporating phenolic group as chelating moieties in the ligand are considered as models for executing important biological reactions and mimic the catalytic activities of metallo enzymes. Schiff-bases are every important material for inorganic chemists as these are widely used in medicinal inorganic chemistry due to their diverse biological, pharmacological, antitumor activities. Recently, there has been tremendous interest in studies related to the interaction of transition metal ions with nucleic acid because of their relevance in the development of new reagents for biotechnology and medicine.

The thesis is divided into ten chapters. Contents of various chapters are briefly described as follows:

Chapter 1

This chapter involves a general introduction to Schiff bases and their transition metal complexes. Brief discussion about the applications of Schiff bases and their metal complexes in various field, importance of heterocyclic Schiff base transition metal complexes, antioxidants and its relevance, enzyme and its kinetics are included in this chapter. A brief discussion about the structure of DNA and its interactions with small molecule are also discussed in this chapter. The scope of the present work is highlighted at the end of this chapter.
Chapter 2

Chapter 2 is broadly divided into two sections. Part A provides details of the reagents used and various analytical and physico-chemical techniques employed in the characterization and biological studies of ligands and its complexes. Part B gives the details of the preparation and spectral characterization of six new heterocyclic Schiff bases. Schiff bases have been synthesized by the condensation of 2-aminophenol, 2-amino-4-nitrophenol and 2-amino-4-methylphenol with thiophene-2-carboxaldehyde and pyrrole-2-carboxaldehyde. Single crystal X-ray studies of the Schiff bases also included in this part.

Chapter 3

Chapter 3 describes the synthesis and characterization of Ni(II), Cu(II) and Zn(II) complexes of synthesized Schiff bases. All metal complexes were synthesized by refluxing methanolic solution of metal salt with corresponding Schiff bases. Synthesized metal complexes were characterized by elemental analysis, FT-IR, UV-Visible, TG-DTG, EPR, AAS, conductance and magnetic susceptibility measurements. The analytical data suggest that all Ni(II), Cu(II) and Zn(II) complexes are mononuclear. Low molar conductance values indicates that all Ni(II), Cu(II) and Zn(II) complexes are non electrolytic in nature. All the complexes are found to be thermally stable. Ni(II) complexes with magnetic moment values ranging from 2.91-2.96 B.M shows octahedral structure and that from 3.5-3.7 B.M shows tetrahedral structure. Copper complexes exhibited square pyramidal and square planar geometry. All Zn(II) complexes are tetrahedral in nature.
Chapter 4

Chapter 4 deals with antioxidant activity of phenolic Schiff bases - solvent effect, structure activity relationship and mechanism of action. Radical scavenging activity of Schiff bases (TA, TNA, TMA, PA, PNA and PMA) have been investigated using DPPH and ABTS methods. The fixed reaction time and steady state measurement methods were used to find out antioxidant activity of these compounds in five different solvents (methanol, acetonitrile, acetone, ethyl acetate and chloroform) of varying polarity. BHA was used as standard. All Schiff bases exhibited higher antioxidant activity. Schiff bases with electron donating substituent at para position of the phenol ring showed higher activity than Schiff base without any substituent. On the other hand Schiff bases, which having electron withdrawing substituent at para position of the phenol ring showed lower activity. Influence of solvent in the activity are in the order methanol > chloroform > acetonitrile > acetone > ethyl acetate. The potent activity of the synthesized compounds was due to the presence OH groups in its structure. Polarity and protic nature of solvent play vital roles in the radical scavenging ability.

Chapter 5

This chapter describes DNA binding studies of Schiff bases and their metal complexes. The binding behavior of the ligands and metal complexes toward HS-DNA were investigated by electronic absorption spectroscopy, CD spectral studies and voltammetric techniques. Intrinsic binding constants were calculated. DNA binding studies with HS-DNA indicate that ligands and metal complexes bind to DNA by intercalation modes. Results also showed that metal complexes have stronger binding affinity than ligands.
Chapter 6

This chapter deals with the HIV-1 RT inhibitory activity of heterocyclic Schiff bases and their transition metal complexes. HIV-1 RT kit assay was used for testing the reverse transcriptase inhibition activity of the ligands and their metal complexes. Reference drug used was Nevirapine. Results showed that the new copper complexes effectively inhibited HIV-1 replication. Among them heterocyclic Schiff base complex with thiophene moiety showed higher anti-HIV activity than pyrrole moiety. Synthesized ligands and their complexes with nickel or zinc have not shown any reverse transcriptase inhibition activity.

Chapter 7

Chapter 7 deals with antibacterial studies of heterocyclic Schiff bases and their Ni(II), Cu(II), Zn(II) complexes. The antibacterial activity of synthesized Schiff bases as well as their metal complexes was tested against gram positive and gram negative bacteria using disc diffusion method. The bacteria used in the present investigations included -Bacillus coagulans, Bacillus pumilis, Bacillus circulans, Clostridium, Staphylococcus aureus, Entrococcus faecalis, Salmonella typhi, Escherichia coli, Pseudomonas, proteus vulgaris and Klebsilla pneumonia. Minimum inhibitory concentration (MIC) was evaluated for compounds which showed higher antibacterial activity. Ampicillin was used as standard antibiotics. Compared to Schiff bases, metal complexes exhibited higher degrees of inhibitory effects on the growth of the tested bacterial species.

Chapter 8

This chapter describes α-amylase activity studies of heterocyclic Schiff bases and their Ni(II), Cu(II) and Zn(II) Complexes. α-amylase activity of the synthesized compounds were measured by DNS method.
Kinetic studies were carried out to identify the mode of inhibition using Michaelis-Menten and Lineweaver-Burk plot. Ligands TA, TNA, PA, PNA and their Ni(II), Cu(II) and Zn(II) complexes has enhanced \( \alpha \)-amylase activity. Ligands TMA, PMA and their Ni(II), Cu(II) complexes exhibited \( \alpha \)-amylase inhibition. IC\(_{50}\) values of these compounds were also calculated. Results indicates that ligands TMA, PMA and their Ni(II), Cu(II) complexes inhibit \( \alpha \)-amylase non competitively.

Chapter 9

Chapter 9 describes cytotoxicity studies of heterocyclic Schiff bases and their Ni(II), Cu(II) and Zn(II) Complexes. The cytotoxicity of Schiff bases and their metal complexes have been evaluated by MTT assay against normal 3T3L1 cells. All ligands exhibited 100% cell viability against normal 3T3L1 cells. \([\text{Ni(PA)}_2\cdot\text{H}_2\text{O}], [\text{Ni(PNA)}_2\cdot2\text{H}_2\text{O}], [\text{Ni(PMA)}_2], [\text{Cu(TNA)}_2\cdot2\text{H}_2\text{O}], [\text{Cu(PNA)}_2\cdot3\text{H}_2\text{O}], [\text{Cu(PMA)}_2\cdot\text{H}_2\text{O}], [\text{Zn(TA)}_2], [\text{Zn(TNA)}_2], [\text{Zn(PA)}_2]\) and \([\text{Zn(PNA)}_2]\) also showed 100% cell viability. \([\text{Cu(TA)}_2\cdot\text{H}_2\text{O}\cdot\text{H}_2\text{O}]\) showed high toxicity in all concentration against 3T3L1 cells. Mild toxicity was observed for other complexes in concentration dependent manner.
Future outlook

- Docking studies- Docking Studies have become nearly indispensable for study of macromolecular structures and interactions. Docking studies are computational techniques for the exploration of the possible binding modes of a substrate to a given receptor, enzyme or other binding site. Which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. Docking studies provides most detailed possible view of small molecules drug-receptor interaction and has created a new rational approach to drug design where the structure of drug is designed based on its fit to three dimensional structures of receptor site, rather than by analogy to other active structures or random leads. This may help to increase ligand specificity and if the drug produces undesirable side effect by binding to another macromolecule, it may be possible diminish affinity for that competing site and thus may achieve a better therapeutic index.

- In vivo studies – Testing effects of synthesized biological entities on whole, living organisms or cells.

- Synthesis of new heterocyclic ligands and metal complexes with different substituent groups for enhancing the biological activity.

- Development of the pharmacophore in to commercially viable cells.