PREFACE

Recent attention in the coordination chemistry of sulphur donor ligands such as dithiocarbamate ligand centered complexes has been extensively studied for their involvement in number of processes which include molecular magnetism, electrical conductivity, optoelectronic properties and biological processes. They have been utilized as single source material for the preparation of metal sulphide nano-particles. In particular, dithiocarbamate have drawn a lot of consideration since its first derivative tetramethylthiuram disulfide, more commonly known as thiram has achieved prominence fungicidal properties. Compounds containing dithiocarbamate group, were proven medicinally significant and utilized as microbicidal, spermicides, anesthetic, anti-HIV, mono glyceride lipase inhibitors, anti-tumour agents. The distinctive redox properties of the sulfur atom in dithiocarbamate make it a key residue for enzyme catalysis, protein folding, and redox signaling and regulation, which are important for metabolism, cellular energy motility and subsistence of cellular systems. The above features of the dithiocarbamate group make it a versatile pharmacophore and hence, it is used in the compounds of biological interest. By proper choice of dithiocarbamate liagnds and transition metal ions, monometallic or polymetallic dithiocarbamate complexes can be prepared.

The work presented in this thesis is based on the synthesis, characterization, computational investigation and *in-vitro* cytotoxic activity of some bimetallic bis-dithiocarbamate macrocyclic complexes derived through metal directed self-assembly of suitable diamine precursors bearing diverse linkers, CS_2 and metal ions or diphenyltin^{IV} fragment. The effective and forthright methodologies have been employed in the synthesis of these complexes. The thesis is mainly divided into six chapters.

PREFACE

Chapter 1 contains a literature review on self-assemblies, dithiocarbamate ligand system and its versatile coordination chemistry with transition metals as well as organometallic fragments that display a wide range of applications. The emphasis has been made on the biological applications, especially anti-cancer properties. The main objectives of the present investigation are also described in this chapter.

Chapter 2 is devoted to the synthesis of novel diamine ligand precusors **L^1-L^3** based on 4,4'-diamino diphenyl sulfone and their bimetallic macrocyclic dithiocarbamate complexes of the type [M_2-μ^2-bis-{(κ^2S,S-$S_2CN(R)CH_2CONHC_6H_4)_2SO_2$}] {R = *Cy*, M = Ni^{II} **1a**, Cu^{II} **1b,** Zn^{II} **1c**; R = ^{i}Pr, M = Ni^{II} **2a**, Cu^{II} **2b,** Zn^{II} **2c**; R = ^{n}Bu, M = Ni^{II} **3a**, Cu^{II} **3b,** Zn^{II} **3c**}. Sodium salt of dtc of ligands **L^1-L^3** has been prepared *in situ* by the reaction of **L^1-L^3** with CS_2 in the presence of base. All the newly synthesized compounds were characterized by ESI-MS, IR, NMR (^{1}H, ^{13}C and DOSY), UV-visible absorption, fluorescence spectral studies. The DOSY NMR study confirms the phase purity of these diamagnetic complexes. The thermal stability of these compounds has been investigated by thermogravimetric analysis. The DFT calculation studies were carried out on representative compounds to determine the optimized geometries of the complex around the metal centers. All the compounds such as ligand precursors and their complexes were screened for their potential cytotoxic activity against malignant human cell line HEP G2 and C6 by MTT assay. The results on normal cell line WRL-68 confirmed the specificity of these compounds for cancer cells. The enhanced cytotoxicity of the ligands and most of the complexes against human cancer cell line HEP G2 as compared to the lead compound as well as standard drug "cisplatin" makes these compounds biologically significant.

Chapter 3 deals with the derivatization of 4,4'-diamino diphenyl methane into suitable secondary diamine precursors and their bimetallic macrocyclic dithiocarbamate complexes with Ni(II), Cu(II) and Zn(II) metal ions. The secondary diamine ligand precursors **L^1-L^3**. reacted with CS_2 under basic condition to form corresponding dithiocarbamate ligangs *in situ* which on interaction with metal acetates affords access to

a new series of complexes **1a-1c,2a-2c,3a-3c**. All the compounds such as diamine precursors and their dithiocarbamate complexes **1a-1c, 2a-2c, 3a-3c** have been characterized by relevant spectroscopic techniques such as mass, IR, ^{1}H and ^{13}C NMR, DOSY NMR, UV-visible absorption, fluorescence studies. Density Functional Theory studies were carried out to determine the optimized structure of the representative compounds *viz.* **L^1** and **1a-1c.** The *in vitro* cytotoxic studies were carried out to study the bioactivity on cancer cell line HEP G2. The results on normal cell line WRL-68 confirmed the specificity of these compounds for cancer cells.

Chapter 4 is devoted to the use of lead compound **"**m- phenylene diamine" to derive three novel diamine precursors **L^1-L^3** and these were successfully utilized in a single-pot reaction with CS_2 and transition metal ions leading to corresponding bimetallic macrocyclic dithiocarbamate compouds. The ligand precursors **L^1-L^3** derived from m-phenylene diamine were well characterized, prior to their further use. The dithiocarbamate ligands have been prepared *in situ* by the reaction of precursors **L^1-L^3** with CS_2 in the presence of base which on further reaction with transition metals like Ni(II), Cu(II) and Zn(II) yielded bimetallic macrocyclic dithiocarbamate complexes. All the complexes **1a-1c, 2a-2c, 3a-3c** have been characterized by thermogravimetric analysis and relevant spectroscopic techniques such as ESI-MS, IR, ^{1}H, ^{13}C, DOSY NMR, UV-visible, fluorescence spectroscopies. Spectral data reveals the structural features of the newly synthesized compounds. DFT calculations were carried out which also supported the experimental outcomes. Excellent bioactivity was measured for these compounds against HEP G2 carcinoma cell line by MTT assay. The results on normal cell line WRL-68 confirmed the specificity of these compounds for cancer cells.

Chapter 5 deals with the synthesis of three novel ligand precursors 4,4'-bis(alkylaminoacetamido) diphenyl ethers (**L^1-L^3**) and a series of bimetallic Ni(II), Cu(II) or Zn(II) dithiocarbamate macrocyclic complexes bearing polar subunits in the organic linker. The ligand precursors **L^1-L^3** have been derived from 4,4'-

diaminodiphenyl ether and well characterized, prior to use. The required polydentate dithiocarbamate ligands have been prepared *in situ* by the reaction of precursors $\mathbf{L^1}$-$\mathbf{L^3}$ with CS_2 in the presence of base which on further reaction with various transition metal ions yielded bimetallic macrocyclic dithiocarbamate complexes. All the complexes **1a-1c, 2a-2c, 3a-3c** have been characterized by thermogravimetric analysis and relevant spectroscopic techniques such as IR, ^1H, ^{13}C, DOSY NMR, UV-visible, fluorescence, spectroscopy. The structures of these macrocyclic complexes have been optimized by DFT calculations performed at B3LYP/lan2dz and the theoretical data are consistent with the experimental results. The *in vitro* cytotoxic studies revealed enhanced activity of these compounds against human cancer cell line HEP G2 as comparaed to cisplatin. The results on normal cell line WRL-68 confirmed the specificity of these compounds for cancer cells.

Chapter 6 is dedicated to the six novel ligand precursors 4,4'-bis(alkylaminoacetamido) diphenyl sulfone and m-phenylene linkers $\mathbf{L^1}$-$\mathbf{L^5}$ studied earlier in chapter 2 and chapter 4, have been utilized to derive a new series of bimetallic diphenyltin(IV) dithiocarbamate macrocyclic complexes bearing amide subunits in the organic linker. Dithiocarbamate ligands have been prepared *in situ* by the reaction of precursors $\mathbf{L^1}$-$\mathbf{L^5}$ with CS_2 in the presence of base which on further reaction with diphenyltin dichloride yielded bimetallic diphenyltin(IV) dithiocarbamate macrocyclic complexes. All the complexes **1-5** have been characterized by thermogravimetric analysis and relevant spectroscopic techniques such as IR, ^1H, ^{13}C, DOSY NMR. Spectral data reveals the structural features of the newly synthesized compounds. Single phase purity of the compounds has been confirmed by the presence of single sharp peak in ^{119}Sn NMR and by DOSY NMR study. Excellent results corresponding to the cytotoxic behaviour of these compounds were obtained against carcinoma cell line HEP G2 by MTT assay. The results on normal cell line WRL-68 confirmed the specificity of these compounds for cancer cells.