Abstract

The chemistry of macrocyclic compounds are of profound interest and becoming an indispensable niche of research activity during the past decades. The structural novelties of these compounds lead to the considerable interest in development of bioinorganic chemistry due to their potential applications in the field of host guest chemistry, molecular recognition and supramolecular chemistry. The importance of novel macrocyclic ligands has been raised due to the fact that they serve as models for protein-metal binding sites in biological systems. For example, they act as models for the magnetic exchange phenomena, as therapeutic reagents in chelate therapy for treatment of metal intoxication, etc. The significance of macrocyclic chemistry emerges from their selective chelation towards certain metal ions that depends on some factors such as the number, type and position of their donor atoms, the metal centers ionic radii, the counter ions coordination property etc. The biological importance of synthetic macrocyclic complexes arises from the fact that they mimic naturally occurring biomacrocyclic systems such as iron-porphyrin core in hemoglobin, cobalt-corrin of vitamin B₁₂ and magnesium-hydroporphyrin in chlorophyll. The idea conceived to work for Ph.D. thesis in this area aims to design macrocyclic ligands and its metal complexes bearing nitrogen atoms via organic and template procedures that would display new structural features and biological activities.

The Ph.D thesis entitled “Synthesis, Characterization and Biomedical Application of Macrocyclic Ligands and Their Complexes” has been categorized into 5 chapters.

Chapter-1: Introduction and literature review
A brief introduction to macrocyclic chemistry along with the synthetic routes adopted for the synthesis of macrocyclic ligands and their complexes has been presented. A thorough review of literature has also been given considering the important work done in this area till date and various applications of these macrocyclic compounds.

Chapter 2: Characterization techniques and experimental studies of macrocyclic compounds
The second chapter deals with the characterization techniques opted to investigate several physico-chemical and biological properties of macrocyclic compounds.
Chapter-3: Synthesis and characterization of pharmacologically active 18-membered tetraamide macrocyclic complexes of Mn(II), Co(II), Ni(II), Cu(II), and Zn(II): In-vitro antimicrobial, anticancer screening, DNA interaction and docking studies

The third chapter reports the synthesis of macrocyclic ligand, 2,4:11,13- Dinaphthyl-1,5,10,14 tetraazacyclooctadecane-6,9,15,18-tetraone, (L) obtained from condensation of 1, 8-diaminonaphthalene and succinic acid. The complexes of the type, [MLCl$_2$] [M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II)] were obtained. The ligand and its metal complexes were characterized by elemental analysis, FT-IR, UV-visible, magnetic moments, conductance measurements, EPR, $^1$H NMR, $^{13}$C NMR and mass spectroscopy. The formation of ligand and its complexes has been confirmed on the basis of characteristics FTIR band positions and resonance signals in $^1$H and $^{13}$C NMR spectra. The geometry of the complexes has been inferred from the absorption bands in UV-vis spectra and magnetic moment studies. The EPR spectral studies suggested a distorted octahedral geometry in Cu(II) complex. The comparative in-vitro antimicrobial activities of macrocyclic ligand (L) and its complexes revealed a better activity for Cu(II) complex as compared to other metal complexes. The CT-DNA interaction study with ligand and its metal complexes using fluorescence quenching experiment and circular dichroism studies demonstrated relatively greater binding ability for Cu(II) complex via groove binding mode. The MTT assay revealed that the metal complexes exhibited suitable activity as compared to free ligand. The docking simulation studies were performed to investigate the active sites for probable binding mode. Thus, it can be suggested that Cu(II) complex seems as a superlative candidate offering a probable alternative to traditional chemotherapeutic agents.

Chapter-4: Pharmacologically significant tetraaza macrocyclic metal complexes derived from isatin and 3,4-diaminobenzophenone: Synthesis, spectral studies and comparative in-vitro biological assessment

This chapter describes the synthesis of 12 membered Schiff base macrocyclic complexes, [Dichloro (5,6;11,12-dibenzo-1,4,7,10-tetraazacyclododeca-1,3,7,9-tetraene-2,3,8,9 diindole) metal(II)] [M= Co(II), 1; Ni(II), 2; Cu(II), 3 and Zn(II), 4] via template condensation of isatin and 3,4-diaminobenzophenone. These macrocyclic complexes were characterized employing FT-IR, NMR ($^1$H and $^{13}$C), Mass, UV-vis, EPR, TGA/DTA and SEM. The FT-IR and NMR spectra confirmed
the formation of metal complexes. The absorption bands in UV-vis spectra and magnetic moment analysis signify the geometry of the complexes. The distorted octahedral geometry in case of Cu(II) complex was inferred by EPR. The comparative in-vitro antibacterial study and XTT reduction assay of the metal complexes revealed the enhanced activity for Cu(II) complex and its efficacy to resist biofilm formation, respectively. The antioxidative properties using DPPH method showed substantial radical scavenging potency of the Cu(II) complex. The binding profile of the metal complexes with CT-DNA was monitored by fluorescence and circular dichroism (CD) spectroscopy coupled with molecular docking studies. The hypothesis of preferential binding in the minor groove of double stranded DNA is supported by CD and docking results.

**Chapter-5: Pharmacological approach for bio-relevant N-functionalized homobinuclear macrocyclic complexes based on 16-membered tetraaza units: Synthesis, spectral studies, biological screening, HSA binding and molecular docking**

This chapter of the thesis explores the synthesis of bio-efficient homobinuclear macrocyclic complexes, \([\text{Co}_2\text{LCl}_4].2\text{H}_2\text{O} \ (1), [\text{Ni}_2\text{LCl}_4].2\text{H}_2\text{O} \ (2), [\text{Cu}_2\text{LCl}_4] \ (3)\) and \([\text{Zn}_2\text{LCl}_4].\text{H}_2\text{O} \ (4)\); Tetrachloro[1,1' biphenyl bis(1,6,9,14-tetrahydro-3,4;11,12-diphenyl-1,6,9,14-tetraazacyclohexadecane)] di metal(II).nH2O, via metal ion controlled reaction using 3,3'-diaminobenzidine, 1,2-bis(bromomethyl)benzene and ethane-1,2-diamine. The stoichiometry, geometry, thermal stability and morphology of the synthesized compounds were determined by the results of FT-IR, \(^1\text{H}\) NMR, \(^{13}\text{C}\) NMR, Mass, TGA/DTA and SEM studies. The DPPH assay revealed substantial radical scavenging potency in case of Cu(II) complex. The metal complexes were also screened for the comparative in-vitro antibacterial analysis and revealed the enhanced activity for Cu(II) complex which was further confirmed by XTT assay. In addition, various biophysical measurements were performed for the assessment of HSA binding affinity for all the complexes. The fluorescence quenching mechanism revealed static quenching of the complexes that inferred them as potent HSA binder.
LIST OF PUBLICATIONS:

1. Synthesis and characterization of pharmacologically active 18-membered tetraamide macrocyclic complexes of Mn(II), Co(II), Ni(II), Cu(II), and Zn(II): In-vitro antimicrobial, anticancer screening, DNA interaction and docking studies.

Mohammad Shakir, Nausheen Bano, Ahmar Rauf, Shadab Kazmi, Mahboob Alam

2. Pharmacologically significant tetraaza macrocyclic metal complexes derived from isatin and 3,4-diaminobenzophenone: Synthesis, spectral studies and comparative in-vitro biological assessment.

Mohammad Shakir, Nausheen Bano, Mohammad Ahmar Rauf, Mohammad Owais


Mohammad. Shakir, Nausheen Bano, Mohammad Ahmar Rauf, Mohammad Owais
[Communicated]

4. Synthesis and characterization of novel 18-membered, tetradeinate (N_2O_2 donor) Schiff base macrocyclic complexes of Co(II), Ni(II), Cu(II) and Zn(II): Biophysical and molecular docking insight into interaction mechanism of human serum albumin.

Mohammad. Shakir, Nausheen Bano, Mohammad Ahmar Rauf, Mohammad Owais
[Communicated]