CHAPTER 1

GENERAL INTRODUCTION
Coordination compounds have been a challenge to the inorganic chemist since they were identified in the nineteenth century. In the early days they seemed unusual because they appeared to defy the usual rules of valence. Today they comprise a large body of current inorganic research. Although the usual bonding theories can be extended to accommodate these compounds, they still present stimulating theoretical problems and in the laboratory they continue to provide synthetic challenges. Werner’s coordination theory in 1893 was the first systematic attempt to explain the bonding in coordination complexes [1]. This theory and his painstaking work over the next twenty years won Alfred Werner the Nobel Prize for Chemistry in 1913. There has been much work done in attempting to formulate theories to describe the bonding in coordination compounds and to rationalize and predict their properties.

Metal complexes have played an important role since the early days of coordination chemistry. Indeed, a great deal of work has been carried out on the synthesis and characterization of transition metal compounds, mainly due to their applications in various fields like metal complexes as drugs and chemotherapeutic agents [2-6], catalysis [7-14], specialty dyes and pigments [15-17], non-linear optical materials [18-22], for the conversion and storage of solar energy [23-28], for hydrometallurgy and extraction [29-31], Fluorescent complexes for biomedical applications [32-37], for photodynamic therapy [38-40], as precursors for semiconductor films and nanoparticles [41-43].

The use of metal complexes as diagnostic agents is a relatively new area of medical research, and has flourished during the past few decades. Today, there are a wide variety of radiometals and radiometal complexes used in gamma scintigraphy and positron emission tomography (PET). An even more recent development is the use of paramagnetic metal complexes for enhancing contrast of magnetic resonance imaging (MRI). The use of metal complexes in therapy and diagnostic imaging applications is increasing [44-53].
Throughout history, both ancient and modern, metals and metal compounds have been used in medicine to treat a variety of ailments. In the last century, metal complexes have played an increasingly important role to treat diseases ranging from syphilis (organoarsenic compounds) to cancer (platinum anti-tumor drugs) to arthritis (gold compounds).

Along with major advances in the chemical synthesis and coordination chemistry of new ligands and metal complexes, significant strides have been made in correlating physical characteristics of metal complexes with biological behavior [54-59].

In the twentieth century, this discipline has metamorphized from the province of inorganic chemists to the domain of a broad constituency of researchers, ranging from biochemists to materials scientists. The vigor and ongoing evolution of this subject is richly documented in the literature [60, 61], each of which offers “New Perspectives in Coordination Chemistry”.

The use of metal ions in medicine is not new [62-65]. What is new is the purposeful design of metal-based therapeutics. The designing of the metal-based drugs is to balance the toxicity of these metal ions with substantial positive impact of these increasingly common therapeutic and diagnostic aids. In this perspective, complexation of toxic metals into larger non-toxic molecule is also the key to exploit metal chemistry for therapeutic purpose. Our approach in this regard, is the combination of two processes: designing of bioactive molecules and then combining them with metal ions to end up with non-toxic, more effective molecules. The important feature of such inorganic drug design is to increase the bioavailability and stability of the drug [66, 67].

When designing metal complexes for therapeutic use the following events need to be considered: hydrolysis, protein binding, membrane transport and finally
the molecular target. Hydrolysis of metal complexes is important because of the aqueous milieu of biological systems, but the hydrophobic nature of cell membranes, vesicles and enzyme active sites requires consideration of lipophilic ligands in the design of complexes. Therefore, design of metallo-drugs requires bringing together organometallic chemistry with traditional aqueous coordination chemistry, a merger that is in its infancy [68, 69]. The greatest hurdle, however, is transport of metal complexes through cell membranes, which determines if metals enter cells with their ligands intact.

The ever increasing application of metal complexes in various fields of science is the driving force for the research and development of coordination chemistry. It is in this backdrop that the present study entitled “Transition Metal Complexes of Pharmacologically Important Quinazolinones and Hydrazones” is undertaken.

There are two basic approaches to develop a new drug, a) synthesis of new analogs, modification or derivatives of existing compounds for shortening and improving the treatment; b) searching for a novel structures that the particular organism has never been presented before.

The present investigation involves the designing, synthesis, characterization and biological screening of new analogs of biologically active ligands belonging to important class of organic compounds such as Quinazolinones and Hydrazones and their transition metal complexes. This study focuses on the coordination behavior of Quinazolinones and Hydrazones of biological interest derived from o-amiobenzoylhydrazide (o-ABH) for specific activity and in order to contribute to the field of Bioinorganic and Medicinal Chemistry. The transition metal ions used for the preparation of the complexes in this study are Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) chlorides.
4(3H)-Quinazolinones are the fused heterocycles that are of considerable interest because of the diverse range of their biological properties, for example, anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities [70-78]. Many of the reported synthetic methods for elaboration of this simple ring structure are, however, time consuming, tedious and often low yielding [79-83]. Advances in synthetic methodology and technology in recent years and the continued interest in the quinazoline skeleton in medicinal chemistry and drug development, an efficient and reliable method for the construction of these molecules ensures that this is an active and important area of research in heterocyclic chemistry [84]. A good deal of research has been carried out on the coordinating behavior of 2,3-disubstituted quinazolin-4(3H)-ones which offer various potential donor sites. This prompted us to take up the study of ligational behavior of some 1,2-dihydroquinazolinones.

In the present study quinazolinone ligands are designed for the possible anticonvulsant, anti-inflammatory and analgesic activities. Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. The potent mediators of inflammation are derivatives of arachidonic acid (AA), a 20-carbon unsaturated fatty acid produced from membrane phospholipids during inflammation. The arachidonic acid metabolises by cyclooxygenase (COX) pathway to produce various inflammatory mediators such as prostaglandins, histamines etc. and these mediators are responsible for inflammatory responses. Various non-steroidal anti-inflammatory drugs (NSADIs) such as Indomethacine, Ibuprofen, Aspirin, Diclofenac sodium, Meloxicam etc are available in market. These NSAIDs achieve their effects by blocking the activity of cyclooxygenase. It is well known fact that metal chelation is one of the excellent ways to increase the lipophilic character of the organic moiety. In fact, on coordination, ligands might improve their bioactivity profiles, while
some inactive ligands may acquire pharmacological properties. Activity of various anti-inflammatory drugs mentioned above has enhanced on complexation with transition metal ions. In the present investigation the various quinazolinones prepared were chelated with transition metal ions and evaluated for their anticonvulsant, anti-inflammatory and analgesic activity.

Hydrazones derived from organic acid hydazides are attractive owing to their wide spectrum of pharmacological activity profile especially as antimicrobial and anti-tubercular agents [85-89]. Aroyl and heteroaroyl hydrazones are known to be a class of versatile ligands capable of generating varied molecular architecture and coordination polyhedral [90-92]. In view of this, six new aroyl hydrazones and their transition metal complexes were synthesized from o-ABH and some biologically important aldehydes and ketones. These are designed in order to investigate their effectiveness towards antibacterial, antifungal and antitubercular activities.

Tuberculosis (TB) is a contagious chronic bacterial infection. The lengthy therapy involved in the treatment of tuberculosis makes Mycobacterium tuberculosis to develop multi-drug resistant power. Up to 50 million people are infected with drug-resistant TB. The resistance is often a corollary to HIV infection. Drug-resistant TB is more difficult and expensive to treat, and more likely to be fatal. Among anti-tubercular agents, isonicotinic acid hydrazide (INH) is a frontline antituberculosis agent. Once taken up by Mycobacterium tuberculosis, INH requires activation by the catalase-peroxidase KatG, converting INH from its prodrug form into a range of bactericidal reactive species. Nitric oxide free radical is generated from oxidation at the hydrazide nitrogens during the activation of INH by KatG and it is involved in the anti-mycobacterial action [93]. The multi drug resistance has forced the search for new anti-tubercular agents, in spite of the availability of effective drugs such as isoniazid (INH) and rifampicin (RMP). Derivatives
of INH like fluorinated isonicotinoyl hydrazones, monosubstituted isonicotinoylhydrazide and their cyanoborane adducts were proved to be highly potential anti-tubercular agents. Isonicotinoylhydrazone derivatives containing heterocyclic moiety have found to exhibit better anti-tubercular activity. It is well known that hydroxy substituted Schiff bases [94] and o-aminobezoic acid hydrazides have shown good anti-tubercular activities [95]. The cell wall of *Mycobacterium tuberculosis* has high lipid content and allows the bacteria to survive within macrophages. It also provides the organism with a resistant barrier to many common drugs. Cu(II) and Ni(II) chelates of isonicotinoylhydrazones have displayed significant *in vitro* anti-mycobacterial activity and low cytotoxicity. Metal coordination is one of the most efficient strategies to increase the lipophilic character which in turn will result in enhancing the activity of drug molecules. In view of these facts, new hydrazone ligands and their transition metal complexes were evaluated for their antimicrobial and anti-tubercular activity.

The present study entitled “**Transition Metal Complexes of Pharmacologically Important Quinazolinones and Hydrazones**” deals with the designing, synthesis and characterization of pharmacologically important Quinazolinone and Hydrazone molecules. The molecules are tailored in order to offer various potential coordinating sites such as N, O, >C=N, and OH for tridentate chelation with metal ions. The ligands presented in the present work are designed with various potential ligating sites by suitably orienting the groups in a way to produce interesting core structures. Structural modifications have been done by using different biologically important aldehydes and ketones having functional group which is made available as another coordination site within the suitable environment in order to scrutinize biological activity profiles of the molecules. The Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes of these ligands have been prepared, thoroughly characterized and screened for their biological activity.
The content of the thesis is organized as following.

**Chapter 1** covers a brief survey of coordination chemistry and important applications of coordination compounds in various fields with a special emphasis on the field of Medicinal Inorganic Chemistry. Followed by this, the introduction about the work undertaken during the tenure of doctoral programme is also discussed in brief.

**Chapter 2** outlines the details of materials, methods and various analytical and physico-chemical measurements employed in the synthesis, characterization and biological evaluation of the ligands and their metal complexes.

**Chapter 3** deals with the transition metal complexes of 2,3-disubstituted quinazolinones and hydrazones derived from the condensation of o-ABH with aromatic aldehydes.

This chapter is sub-divided into two sections. **Section A** describes the synthesis and characterization of transition metal complexes of 1,2-dihydroquinazolinones derived from the one step condensation of o-ABH with aromatic aldehydes namely salicylaldehyde and imidazole-2-carboxaldehyde. **Section B** describes the synthesis of hydrazones isolated by the condensation of o-ABH and aromatic aldehydes namely salicylaldehyde and imidazole-2-carboxaldehyde in 1:1 ratio at low temperature.

**Chapter 4** deals with a new approach to get 1,2-dihydroquinazolinones in two steps, in which o-ABH is converted to hydrazone by treating with ketones in the first step. The reaction of these hydrazones with salicylaldehyde in the second step results in the formation of biologically active 1,2-dihydroquinazolinones, with different substituent at C-2 and N-3 positions. This chapter is sub-divided into two sections **Section A** and **Section B** depending on the ketone used in the first step to form hydrazones.
Section A describes the synthesis and characterization of transition metal complexes of 1,2-dihydroquinazolinone derived from the condensation of 3-acetylcoumarin-o-aminobenzoylehydrazone with salicylaldehyde. Section B describes the synthesis and characterization of transition metal complexes of 1,2-dihydroquinazolinone derived from the condensation of 3-acetyl-2(1H)-quinolinone-o-aminobenzoylehydrazone with salicylaldehyde.

Chapter 5 describes the synthesis and characterization of transition metal complexes of 3-amino-2-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylic acid derived from o-ABH and pyruvic acid.

Chapter 6 summarizes the transition metal complexes of aroyl and heteroaroyl hydrazones isolated by the condensation of o-ABH with aldehydes at low temperature. The transition metal complexes of hydrazones synthesized by reacting o-ABH with 2-oxo-1,2-dihydroquinoline-3-carbaldehyde and 4-oxo-4H-chromene-3-carbaldehyde are compiled in Section A, while that of hydrazones derived from 3-methoxysalicylaldehyde and pyridine-2-aldehyde are outlined in Section B.

Chapter 7 summarizes the details of biological activities studied during this work. This chapter is divided into two sections based on the biological activity studied.

Section A deals with the in-vivo anticonvulsant, analgesic and anti-inflammatory activities of quinazolinones along with their transition metal complexes.

Section B presents the in-vitro antimicrobial activities along with their metal complexes. The anti-tubercular activities of selected hydrazones along with their complexes were assessed against \textit{M. tuberculosis H}_{3}R_{V} at different concentrations.
Chapter 1

The modified strategy for the synthesis of 2,3-disubstitued quinazolinones presented in this thesis has clear technical advantages over previously reported methods in terms of yields and versatility involving the use of non-drastic reaction conditions and employing easily available and cheap starting materials. The isolation of hydrazones instead of quinazolinones by reacting o-ABH and aromatic aldehydes under temperature-controlled conditions was another accomplishment in the present study. The synthesis of some of the quinazolinones and hydrazones were proved with single crystal X-ray diffraction studies. The preliminary results on anticonvulsant, anti-inflammatory, analgesic and anti-microbial activities of our newly synthesized compounds are impressive and further studies are needed to develop them as future drugs.
References


