

# MACROCYCLIC METAL COMPLEXES: FROM STRUCTURE TO ACTIVITY

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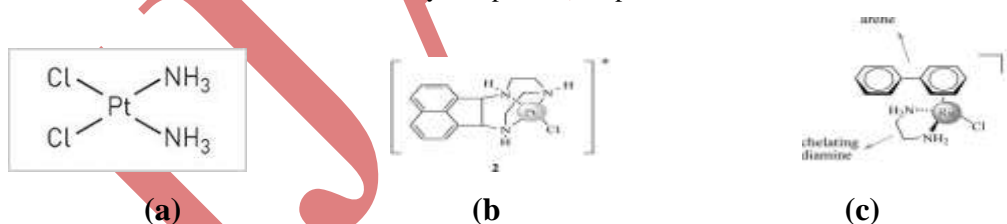
## Abstract:

This article will highlight recent advances in medicinal inorganic chemistry pertaining to the use of multifunctional ligands for enhanced effect. Ligands that adequately bind metal ions and also include specific targeting features are gaining in popularity due to their ability to enhance the efficacy of less complicated metal-based agents. Moving beyond the traditional view of ligands modifying reactivity, stabilizing specific oxidation states, and contributing to substitution inertness, we will discuss recent work involving Macrocyclic metal complexes with multifunctional ligands that target specific tissues, membrane receptors, or endogenous molecules, including enzymes.

**Keywords:** Macro cycle, Multifunctional ligands, Metal complexes

## I. Introduction

Medicinal inorganic chemistry is a discipline of growing significance in both therapeutic and diagnostic medicine. The discovery and development of the antitumour compound cisplatin (cis-[Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>]) played a profound role in establishing the field of medicinal inorganic chemistry (Figure 1). Cisplatin, and the second generation alternative carboplatin, are still the most widely used chemotherapeutic agents for cancer, greatly improving the survival rates of patients worldwide. Pt(II) compounds of cisplatin with additional intercalative moieties have been developed utilizing a p-conjugated macrocyclic ligand. The resulting derivatives were shown to have enhanced in vitro activity compared to cisplatin in all cell lines tested.



**Figure 1.(a) Cisplatin (b) Pt(II)-Intercalative compound (c) Organometallic Ruthenium-arene complex as Anticancer agent**

The history and basic concepts of medicinal inorganic chemistry have been recently reviewed.[1–2] The field now encompasses active metal complexes, metal ions, and even metal binding compounds as potential agents. Metal ions can be introduced into a biological system either for therapeutic effect or as diagnostic aids. Alternatively, metal ions can be removed from a biological system by judicious use of metal binding molecules (termed ligands). In biological systems, metal ions exist as electron-deficient cations and are hence attracted to electron-rich biological molecules such as proteins and DNA. Biological systems themselves provide innumerable examples of ‘designer ligands’

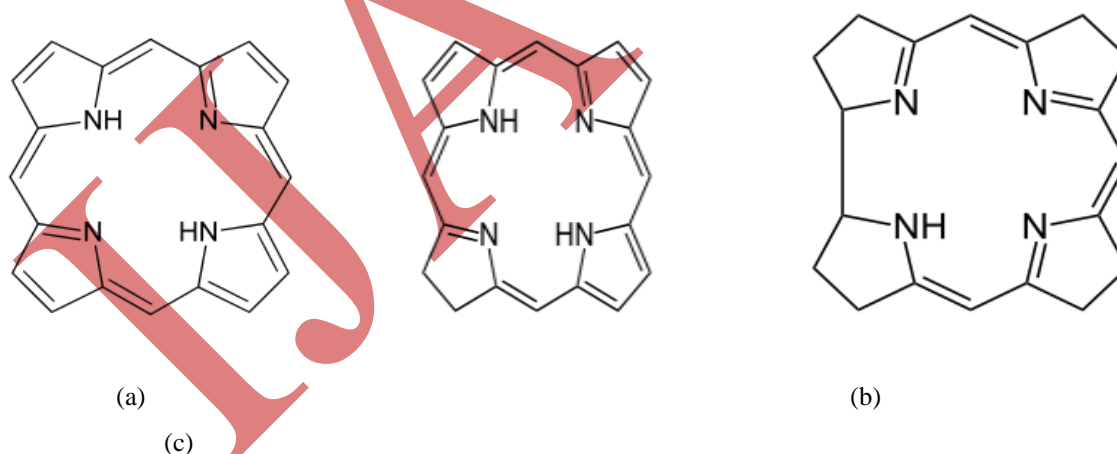
Altering biological processes with small synthetic molecules is a general approach for the design of drugs and molecular probes. Medicinal chemistry and chemical biology are focused predominantly on the design of organic molecules, whereas inorganic compounds find applications mainly for their reactivity (e.g. cisplatin as a DNA-reactive therapeutic) or imaging properties (e.g. gadolinium complexes as MRI diagnostics). In such inorganic pharmaceuticals or probes, coordination chemistry in the biological environment or at the target site lies at the heart of their modes of action. However, past and very recent results suggest that it is also worth exploring a different aspect of metal complexes: their ability to form structures with unique and defined shapes for the design of 'organic-like' small-molecule probes and drugs. In such metal–organic compounds, the metal has the main purpose to organize the organic ligands in three-dimensional space. It is likely that such an approach will complement the molecular diversity of organic chemistry in the quest for the discovery of compounds with superior biological activities.

## II. MACROCYCLIC LIGANDS

The coordination chemistry of macrocyclic ligands and their metal complexes is a fascinating area of intense study for inorganic chemists,[3]. *Macro cyclic ligands are polydentate ligands with their donor atoms either incorporated in or attached to a cyclic backbone.* The aspect of interest in macrocyclic ligands is raised from features such as the nature, number and arrangement of ligand donors, as well as ligand conjugation, substitution and flexibility, which produce different types of macro cyclic molecules suitable for specific uses.

The metal ion directs the reaction preferentially towards cyclic rather than oligomeric or polymeric products. Synthetic macrocyclic complexes may mimic some naturally occurring macrocycles because of their resemblance with metalloproteins, porphyrins and cobalamines[4].

Some important biological macro cycles occurring in nature are as follows:



**Figure2: Naturally occurring macrocycles (a) Porphyrin ring (b) Reduced porphyrin ring(Chlorophyll) (c) Corrin ring**

Heme, an essential part of haemoglobin is a porphyrin ring containing iron. Iron (ferrous) is oxidized to ferric by atmospheric oxygen in lungs. The ferric is again converted into ferrous state in tissues where oxygen oxidizes food to liberate energy. Heme is the prosthetic part of the haemoglobin. Cyanocobalamine is an active form of vitamin B<sub>12</sub> and contains corrin ring and a trivalent cobalt atom. It is essential for the normal maturation of

erythrocytes, for normal growth, neurological function and specially in treating pernicious anaemia and as animal feed supplement. Chlorophyll, a green photosynthetic pigment of plant leaves which is responsible for photosynthesis contains a corrin ring and magnesium atom in its structure.

All the above macrocycles have been extensively studied. The amide macrocyclic complexes have attracted the attention of researchers due to their ability to function as a catalyst in a number of oxidation reactions. Catalytic use for hydroxylation of alkenes has been manifested by iron complexes.

### III. MACROCYCLIC METAL COMPLEXES

Transition metal complexes of synthetic macrocyclic ligands are of significance because porphyrins and cobalamines play vital roles in biological systems, such chelating molecules are important since they are capable of furnishing an environment of controlled geometry and ligand field strength. Macrocyclic ligands have attracted widespread attention due to two unique properties (a) their ability to discriminate among closely related metal ions based on the metal ion radius (ring size effect). (b) The significant enhancement in complex stability constants which is generally exhibited by optimally-fitting macrocyclic ligands relative to their open chain analogues (macrocyclic effect). For a number of systems in which the metal ion fully occupies the macrocyclic cavity, there is tendency for maximum stability to occur in the ligand for which the cavity size best matches the radius of ion.

Transition metal macrocyclic complexes have received great attention because of their biological activities, including antiviral, anti carcinogenic [5], anti fertile, antibacterial and antifungal properties. The possibility of using synthetic macro cyclic ligand complexes as models for the biological systems has provided an impetus much of this research. The 1987 Nobel laureate Charles, J.Pederson, Donald J. Cram and Jean-Marie Lehn, paved the way for the development of macrocyclic and supra molecular molecules.

The most important property of macrocyclic molecules is the macrocyclic effect. The decrease of entropy in the binding energy of molecule due to the fixed position of the donor atoms provides more stability to the complexes than the polydentate ligands of the identical donors containing moieties are of great interest because of their great versatility as ligands, due to presence of several potential donor atoms, their flexibility and ability to coordinate in either neutral or deprotonated form. They can yield mono or polynuclear complexes some of which are biologically relevant. Particularly first row of transition metal complexes with such ligands have a wide range of biologically properties.

The interest of researchers lie in the area to design and prepare new macrocyclic ligands with increased capacity to coordinate the given metal ion selectively gained momentum. It has been reported that the transition metal complexes are being used as specific DNA modification and cleavage agents. Complexes of Mn(II) ions have been found to possess antibacterial, antifertility, antifungal activity and in some cases anti-inflammatory character[6].

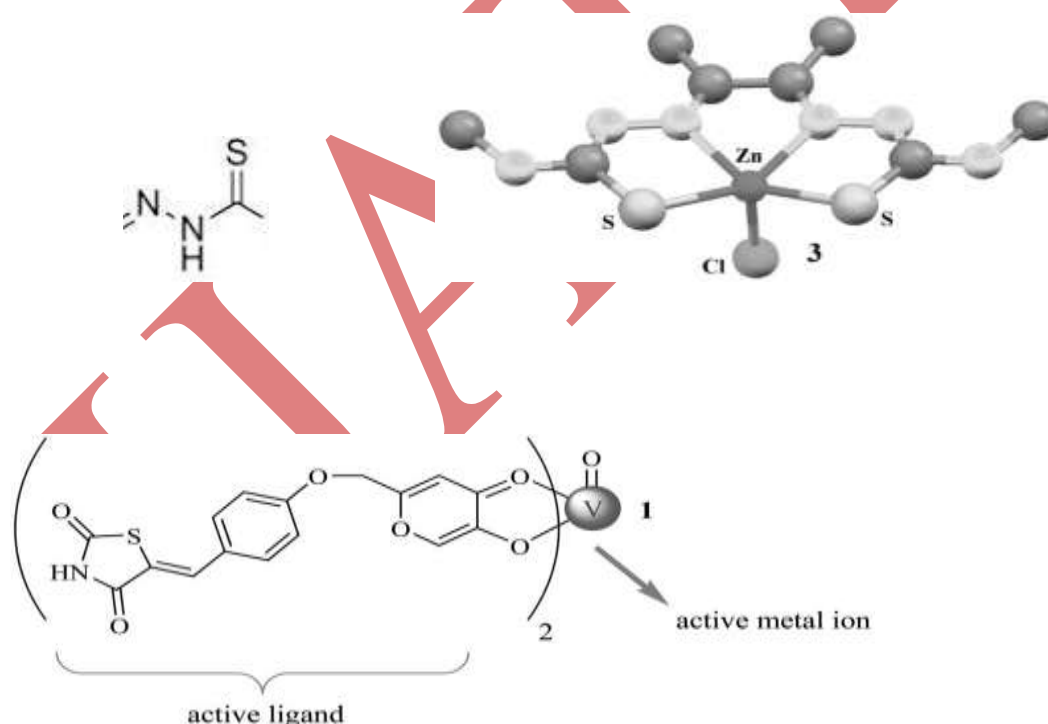
### IV. THIOSEMICARBAZONE AS AN IMPORTANT THERAPEUTIC AGENT

Thiosemicarbazones and their metal complexes have stimulated widespread interest, due to their coordination chemistry and biological properties, notable for antiparasital, antibacterial and antitumor activities [7-9]. The biological activities of thiosemicarbazones often depend on the parent aldehyde or ketone. Moreover, the biological activities of thiosemicarbazones often showed a high dependence on their substituent. Earlier reports

on N(4)substituted thiosemicarbazones have concluded that the presence of bulky groups at the N(4) position of the thiosemicarbazone moiety greatly enhances biological activity [10-12]. On the other hand, the biological properties of metal thiosemicarbazones often differ from those of either ligands or the metal ions which are considered to be related to metal ion coordination [13-15]. In some cases, the highest biological activity is associated with a metal complex rather than the parent ligand and some side effects may decrease upon complexation.[16-18]. Thiosemicarbazones are compounds that have been studied for a considerable period of time for their biological properties. Traces of interest date back to the beginning of the 20th century but the first reports on their medical applications began to appear in the Fifties as drugs against tuberculosis and leprosy [19-22].

Thiosemicarbazones and their metal complexes exhibit numerous therapeutic properties, including anti-tumour activity. While the  $Zn^{2+}$  complexes have been shown to be active as anti-tumour agents, only recently has the intrinsic fluorescence(in built optical probe ) , interpreted in terms of intraligand excitation, been utilized to display uptake and distribution of thiosemicarbazone complexes in a variety of cancer cell lines. (Fig.3)

Vanadium as vanadyl ( $VO^{2+}$ ) or vanadate ( $VO_4^{3-}$ ) is known to enhance the effects of insulin, whereas the thiazolidinediones act by indirectly improving peripheral insulin sensitivity. The combination of these two agents therefore potentially modulates multiple targets, offering a new treatment option for diabetes therapy. These vanadium–thiazolidinedione complexes showed promising characteristics in an in vivo study.(Fig. 3)



**Figure 3; (a)Functional unit of Thiosemicarbazone (b)  $Zn^{2+}$  complex of Thiosemicarbazone (c) Vanadium–thiazolidinedione complex**

In the Sixties their antiviral properties were discovered and a huge amount of research was carried out that eventually led to the commercialization of methisazone, Marboran®, to treat smallpox [23]. In this period one of the first antitumor activity results was published. Recently Triapine® (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) has been developed as an anticancer drug and has reached clinical phase I on several cancer types [24-25]. Presently, the areas in which thiosemicarbazones are receiving more attention can be broadly classified according to their antitumor, antiaptozoal, antibacterial or antiviral activities and in all cases their action has been shown to involve interaction with metal ions [26-27].

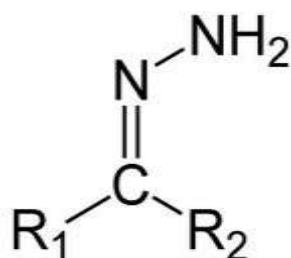
It is important to note that recently papers have appeared using theoretical methods to predict the specific activity of a series of thiosemicarbazones. However, to date there are no such investigations on metal complex derivatives.

One of the most promising areas in which thiosemicarbazone compounds are being developed is their use against cancer. Their antitumor activity is extremely differentiated and it is very much dependent on the typology of tumour cells. This characteristic renders the whole class of compounds very interesting because it implies selectivity. At the same time it makes difficult to extract from the literature general information valid for the whole class of compounds since their activity is certainly due to more than one target in the cell machinery. Nevertheless, the presence of a metal ion almost systematically increases the activity or contributes to mitigate the side effects of the organic parent compounds [28]. In some cases, the highest biological activity is associated with a metal complex rather than the parent ligand and some side effects may decrease upon complexation.

The main known effects related to their anticancer activity are, in order of discovery, ribonucleotide reductase (RR) inhibition, reactive oxygen species (ROS) production, topoisomerase II inhibition, mitochondria disruption, and more recently, a multidrug resistance protein (MDR1) inhibition.

Azomethine complexes of transition metals possess remarkable growth inhibition characteristics for a number of pathogenic micro-organisms [29] and found applications in pharmacology. Macrocyclic complexes of Gd(III) have achieved a useful place as magnetic resonance imaging (MRI) contrast agent as they greatly enhance the relaxation rate of water protons of tissues in which they distribute. Complexes obtained from tetra-aza-macrocyclic ligands such as cyclen, cyclam and bicyclam have been found to possess antitumour activities. Macrocyclic complexes are also used as NMR shift reagent [30].

Hydrazones are a versatile class of ligands having great physiological and biological activities and have found use as insecticides, anticoagulants, antitumor agent, antioxidants and plant growth regulators. Hydrazone derivatives and their complexes have been studied for their antifungal and antibacterial activities and as antiviral drugs.



#### Figure 4: Functional unit of Hydrazone

It is found that metal complexes of dithiocarbazate often display enhanced biological activities compared to corresponding ligands[31].

Schiff bases are a kind of versatile ligands in coordination chemistry. In recent years metal complexes of Schiff bases have attracted considerable attention due to their remarkable biological activities, such as antifungal, antibacterial and antitumor[32]. Schiff base complexes derived from salicylaldehyde and its derivatives with primary amines bearing the  $N_2O$ ,  $N_2S$ ,  $NO_2$  or  $NSO$  donor sets have interesting biological activities. Schiff bases derived from S-alkyl/aryl esters of dithiocarbazic acid are among the most widely studied sulphur-nitrogen chelating agent. The metal complexes of these ligands differ from those of either the ligand or the metal ion itself and increased/decreased biological activities are reported for several transition metal complexes such as copper(II) and cobalt(II).

Triazoles and their derivatives are found to be associated with various biological activities such as anticonvulsant, antifungal, anticancer, and antibacterial properties. Several complexes of various transition metals with Schiff bases derived from 3-substituted phenyl-4-amino-4-hydrazino-1,2,4-triazole have been reported. Dithiocarbamate ligands are known to form stable and biologically active complexes with many transition metals. Benzimidazoles are remarkably effective compounds both with respect to their bacteria inhibitory activity and their favourable selectivity ratio. Extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms.

Transition complexes containing an imidazole and pyrimidine ligand are commonly found in biological studies and plays an important role in processes such as catalysis of drug interaction with biomolecules[33]. Thiazoles represent a class of heterocyclic compounds of great importance in biological chemistry. They exist in many condensed fused system that were found to possess a wide range of activity [34].

Synthetic superoxide dismutase mimetics have emerged as a potential novel class of drugs for the treatment of oxidative stress related diseases. Among these agents, metal complexes with macrocyclic ligands constitute an important group. Reactive oxygen species (ROS) are implicated in several human pathological processes including tissue injury, inflammation, ageing, cancer, cardiovascular, pulmonary and neurodegenerative diseases [59]. Superoxide anion ( $O_2^{\cdot-}$ ) may cause several harmful effects, leading to tissue injury and inflammation [35]. By catalyzing the conversion of  $O_2^{\cdot-}$  to  $H_2O_2$  and  $O_2$ , superoxide dismutases (SOD) represent the first line of defence against  $O_2^{\cdot-}$ . Preclinical studies have revealed that SOD enzymes play a protective effect in animal models of several diseases. Mn SOD has shown to suppress cancer phenotypes in a large number of cancer models. However, the therapeutic use of the native SOD has several limitations related with low cell permeability and short half-life. In addition, bovine Cu Zn- SOD was tested in clinical trials but immunological problems lead to its withdrawal from the market. To overcome this problem, synthetic SOD mimetic compounds have emerged as a potential novel class of drugs. Transition metal complexes [e.g. complexes of Mn(II), Mn(III), Cu(II) and Fe(III)] have notably shown important antioxidant properties, namely SOD mimetic activity. The metal containing SOD mimetic agents more extensively studied are manganese (III) metalloporphyrins, manganese (III) salen complexes and manganese (II) macrocyclic complexes.[36]

#### V. CONCLUSION



The field of medicinal inorganic chemistry has benefited greatly from advances in ligand design, leading to the development of improved diagnostic and therapeutic agents.

As we move beyond our traditional view of ligands as just metal binders, ligands are increasingly being used to enhance the applicability of metal-based agents. Numerous opportunities exist to design ligands that better target disease tissue or specific endogenous molecules. Indeed, in this review we have highlighted numerous cases where tailored ligands have made a positive impact on the field of medicinal inorganic chemistry.

As our understanding of biological processes and disease physiology improves, opportunities for the design of new metal-based and metal-binding agents will arise.

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