REVIEW ARTICLE

THE SCOPE OF METAL COMPLEXES IN DRUG DESIGN - A REVIEW

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ABSTRACT

A significantly rising interest in the design of metal compounds as drugs and diagnostic agents is currently observed in the area of scientific inquiry, appropriately termed medicinal inorganic chemistry. Investigations in this area focus mostly on the speciation of metal species in biological media based on possible interactions of these metal ions with diverse biomolecules, in an effort to contribute to future development of new therapeutics or diagnostic agents. Metallopharmaceuticals used as anticancer agents, metal-mediated antibiotics, antibacterials, antivirals, antiparasitics, antiarthritics, antidiabetics and radio-sensitizing agents appear in therapeutic medicinal inorganic chemistry. The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance.

INTRODUCTION

Many metallic elements play a crucial role in living systems. A characteristic of metals is that they easily lose electrons to form positively charged ions which tend to be soluble in biological fluids. It is in this cationic form that metals play their role in biology. Metal ions are electron deficient, whereas most biological molecules such as proteins and DNA are electron rich. The attraction of these opposing charges leads to a general tendency for metal ions to bind to and interact with biological molecules. This same principle applies to the affinity of metal ions for many small molecules and ions crucial to life, such as oxygen. Given this wide scope for the interaction of metals in biology, it is not surprising that natural evolution has incorporated many metals into essential biological functions.

Metals perform a wide variety of tasks such as carrying oxygen throughout the body and shuttling electrons. Hemoglobin, an iron-containing protein that binds to oxygen by which it carries this vital molecule to body tissues. Metal ions such as Zn^{+2} provide the structural framework for the regulation of function of genes in the nuclei of cell. Similarly, calcium-containing minerals are the basis of bones, the structural framework of the human body. Zinc is a natural component of insulin, a substance crucial to the regulation of sugar metabolism. Metals such as copper, zinc, iron and manganese are incorporated into catalytic proteins, the metalloenzymes, which facilitate a multitude of chemical reactions needed for life[1]. Metal complexes are already in clinical use, and encourage further studies for new metallodrugs such as metal mediated antibiotics, antibacterials, antivirals, antiparasitics, radio-sensitizing agents and anticancer compounds. However, their mechanisms of action are often still unknown. Recently, more than a thousand potential anticancer metal compounds, from the National Cancer Institute (NCI) tumor-screening database, were analyzed based on putative mechanisms of action and classified into four broad classes, according to their preference for binding to sulphahydryl groups, chelation, generation of reactive oxygen species and production of lipophilic ions. Many potential antitumor agents have been investigated

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based on their anti-angiogenesis or pro-apoptotic behavior. These studies involve both designed and natural products, in association with essential metal ions such as copper, or iron. As the metals ions play such extensive role in biological systems, the following questions arise: Can metal ions be incorporated into drugs? Are coordinate compounds potential medicinal agents? Will metal coordinates be useful?

Metal Complexes - An Emerging Tool in Drug Discovery

Transition metals have an important place in medicinal biochemistry. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases like carcinomas, lymphomas, infection control, diabetes, anti-inflammatory, and neurological disorders. Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. This activity of transition metals has started the development of metal-based drugs with promising pharmacological application and may offer unique therapeutic opportunities. To provide an update on recent advances in the medicinal use of transition metals, a Medline search was undertaken to identify the recent relevant literature. Transition metals represent the'd' block elements, which are included in groups III - XII of the periodic table. Their 'd' shells are under the process of filling. This property of transition metals is the foundation of coordinate complexes. A metal complex or a coordinate compound contains a central metal atom, bonded to a surrounding array of molecules or anions. Sophus Jorgensen in Denmark synthesized metal conjugates for the first time in the mid 1870's. In 1893, the major breakthrough in this field occurred when Alfred Werner investigated a series of compounds, which contained cobalt, chlorine and ammonia. He was awarded the Noble Prize in 1913 for his work[2].

Metal Complexes in Cancer Therapy

As cancer remains a major killer in the developed world, a broad spectrum of novel and exciting approaches are being developed and tested. The importance of metal compounds in medicine is undisputed, as can be judged by the use of many metal-based compounds in the treatment of various diseases. In terms of anti-tumour activity, a wide range of compounds of both transition metal and main group elements have been investigated for efficacy. The existence of a relationship between cancer and metals is widely acknowledged by researchers. Therefore, the aim of the "Metal-Containing Drugs and Novel Coordination Complexes in Therapeutic Anticancer Applications of Anti-Cancer Agents in Medicinal Chemistry" is to present an up-to-date overview of this subject and to cover very recent developments in the field of metal-based anticancer agents. Significant progress in metal-based agents has been achieved. Nevertheless, there is an urgent need for new drugs to treat cancer or to develop drugs with novel mechanisms of action. Metal complexes appear to provide a rich platform for the design of novel anticancer drugs. The metal, its oxidation state, the number and types of coordinated ligands, and the coordination geometry of the complexes can provide a variety of properties. On the other side, the ligands not only control the reactivity of the metal, but also play critical roles in determining the nature of interactions involved in the recognition of biological target sites such as DNA, enzymes and protein receptors. These variables provide enormous potential diversity for the design of metallodrugs. They also introduce many challenges in the synthesis of this kind of derivatives. Changes in composition of heterocycles are likely to be accompanied by changes in the respective biological activity. Hence, it is important to identify the nature of the metal complex, which exists in the biological medium and is undergoing the biological test, and ideally the species which reaches the target site[3].

The compounds mentioned in Fig. 1 are used to treat tumour metastatis and hepato-cellular and nasopharyngeal carcinoma. For thousands of years, metal complexes have played important and diverse roles in medicine. From the antiseptic properties of copper complexes, to the long-standing application of gold complexes in Chinese and Arabic medicine, the unique and useful therapeutic bene□ts of metals have long been recognized and harnessed. The

therapeutic application of metal complexes in modern medicine was arguably initiated by the discovery of the anticancer properties of cisplatin. In addition to the continued clinical use of cisplatin against speci□c types of cancer, this discovery also inspired a new generation of effective, and in some cases selective, metal-based cancer therapeutics, thereby demonstrating the potential of metal complexes as alternatives to classical 'drug-like' small molecule inhibitors of human disease [4-7].

Metal Complexes in Diabetes Therapy

Diabetes mellitus (DM), which develops many secondary complications such as atherosclerosis, microangiopathy, renal dysfunction and failure, cardiac abnormality, diabetes retinopathy and ocular disorders, is classified as either insulin-dependent type 1 or non-insulin-dependent type 2, by the WHO. Although several types of insulin preparations for type 1 DM and those of synthetic drugs for type 2 DM have been developed and clinically used, they have several problems such as physical and mental pain due to daily insulin injections and defects involving side effects, respectively. In the 21st century, a new class of pharmaceuticals should be introduced as a number of drugs are going off patent. For this reason, metallopharmaceuticals containing vanadium and zinc ions are expected to treat both types of DM, by making effective use of unique characteristics of the metals. The current state of development of insulin-mimetic vanadium and zinc complexes with different coordination modes are reviewed, focusing on the preparations and structures of the complexes and *in vitro* and *in vivo* evaluations as well as the possible mechanisms[8]. For this reason, several vanadium compounds are being developed for pharmaceutical use to treat or improve both types of DM. In addition to the therapeutic effect of vanadium ion (Va^{+}) and vanadium complexes, these vanadium compounds have a preventive effect on the onset of streptozocin STZ-induced diabetes in terms of nitric oxide released from the macrophages [9].Thus, vanadium is expected not only to treat DM but to prevent DM. In addition to vanadium complexes, zinc complexes have been proposed to be the new candidates in treating type 2 DM. Designing new vanadium complexes requires stereochemical considerations for binding the complexes with receptors such as glucose transporter and other enzymes, as well as consideration of the redox properties of vanadium. Designing new zinc complexe on the other hand, requires attention to the stability and structural properties under physiological conditions. Zinc and vanadium metal ions were tested for their antidiabetic activity.

Examples of Metals Ions useful in Diabetes

Mechanism of insulin-mimetic action of vanadium and zinc

Because a vanadate (VO_4^{-3}) behaves like phosphate, the effect of vanadium in biochemistry has been understood to inhibit protein phosphotyrosine phosphatase, which in turn stimulates protein tyrosine phosphorylation. Thus, a vanadate was reported to activate autophosphorylation of solubilized insulin receptors[10-11]. Similar to insulin action, a vanadate also stimulated the tyrosine kinase activity of the insulin receptor subunit[12-13]. In addition, both a vanadate and a vanadyl (V^{+3}) ion were found to be effective in stimulating glucose metabolism in rat adipocytes. A study has proposed that the vanadyl (V^{+3}) state is a possible active form of vanadium for insulin-mimetic action and for acting on a glucose transporter[14]. Evidence for the proposal comes from the observation that vanadate, which was in turn reduced to vanadyl, restored expression of the insulin-sensitive glucose transporter of skeletal muscles in rats and induced the recruitment of GLUT4 glucose transporter to the plasma membrane of adipocytes[15].

Metal Complex in Antibiotics

Although most antibiotics do not need metal ions for their biological activities, there are a number of antibiotics such as bleomycin (BLM), streptonigrin (SN) and bacitracin that require metal ions to function properly. The coordinated metal ions in these antibiotics play an important role in maintaining proper structure and/or function of these antibiotics. Removal of the metal ions from these antibiotics can cause changes in structure and/or function of these antibiotics. Similar to the case of metalloproteinase,

these antibiotics are dubbed "metalloantibiotics". Metalloantibiotics can interact with several different kinds of biomolecules including DNA, RNA, proteins, receptors and lipids rendering them unique and specific bioactivities. In addition to the microbial-originated metalloantibiotics, many metalloantibiotic derivatives and metal complexes of synthetic ligands also show antibacterial, antiviral and antineoplastic activities, which are also briefly discussed to provide a broad sense of the term "metalloantibiotics"[16].

DNA binding metalloantibiotics

Deoxy ribonucelic acid can bind with many different biomolecules and synthetic compounds, including proteins, antibiotics, polyamines, synthetic metal complexes and organometallic compounds[17]. In case of a very specific protein–DNA interaction, transcription is regulated to turn on or off a specific biological process. Deoxy ribonucelic acid is also a target for therapeutic treatment of disorders and diseases such as cancers, via direct ligand binding to it or binding to DNA-regulating biomolecules, which in turn imparts DNA certain properties[18]. Several clinically used anticancer antibiotics such as bleomycin and actinomycin are DNA-binding (and cleaving) agents. A better understanding of the structure of these antibiotics and their DNA complexes, and a better understanding of the relationship of structure, function, and toxicity of these drugs can provide information for the design of more effective but less toxic drugs for therapeutic treatments[19]. The investigation of the interaction between DNA and synthetic compounds or metal complexes can also further our understanding of DNA–ligand binding specificity, which would provide clues for rational design of DNA-specific drugs in the future[20]. The structure and function of a few natural and synthetic DNA-targeting metalloantibiotics are discussed in this section[21].

Many metals show anti-infective action, e.g. silver and mercury salts have a long history of use as antibacterial agents. The use of mercurochrome as a topical disinfectant is now discouraged. Silver sulfadiazene finds use in the treatment of severe burns; the polymeric materials like HPMC slowly releases the antibacterial Ag^{+1} ion. Silver nitrate is still used in many countries to prevent ophthalmic disease in new born children. The mechanism of action of Ag^{+} and Hg^{2+} is through slow release of the active metal ion inhibition of thiol function in bacterial cell walls gives a rationale for the specificity of bacteriocidal action. Silver and mercury salts have a long history of use as antibacterial agents.

Examples of Metalloantiboitics

1) Bleomycin

Bleomycin (BLM, also known as Blenoxane) was first isolated as a Cu-containing glycooligopeptide antibiotic from the culture medium of *Streptomyces verticullus* and was later found to be also an antiviral agent. It was soon found to be an anticancer agent and has ever since become one of the most widely used anticancer drugs, most commonly used in the treatment of testis cancer, lymphomas, and head and neck cancer, as well as the AIDS-related Kaposi's sarcoma in combination with cisplatin and adriamycin.

2) Antibacterial studies of cephradine metal complexes[22]

Cephradine showed antimicrobial activity against various human pathogens. Although cephradine had a lot of potent activity and bigger zones were formed for *Escherachia coli*, *Corynebacterium hoffmanni*, *Streptococcus faecalis*, *Corynebacterium diptheriae* and *Proteus vulgaris* than *Salmonella typhi*. Just like above complexes, cephradine zinc complex also reduced the activity of the microorganisms. *Corynebacterium diptheriae*, *Streptococcus faecalis*, *Proteus vulgaris* and *Klebsiella pneumoniae* were mildly susceptible. *Salmonella typhi*, *Streptococcus pyogenes*, *Staphylococcus aureus* and *Escherachia coli* were found to be moderately susceptible. *Klebsiella pneumoniae, Escherachia coli*, *Corynebacterium hoffmanni* and *Staphylococcus aureus* showed smaller zone sizes in case of cephradine cadmium complex. *Salmonella typhi*, *Corynebacterium diptheriae*, *Streptococcus pyogenes*, *Proteus vulgaris* and *Streptococcus faecalis* showed moderate susceptibility[22].

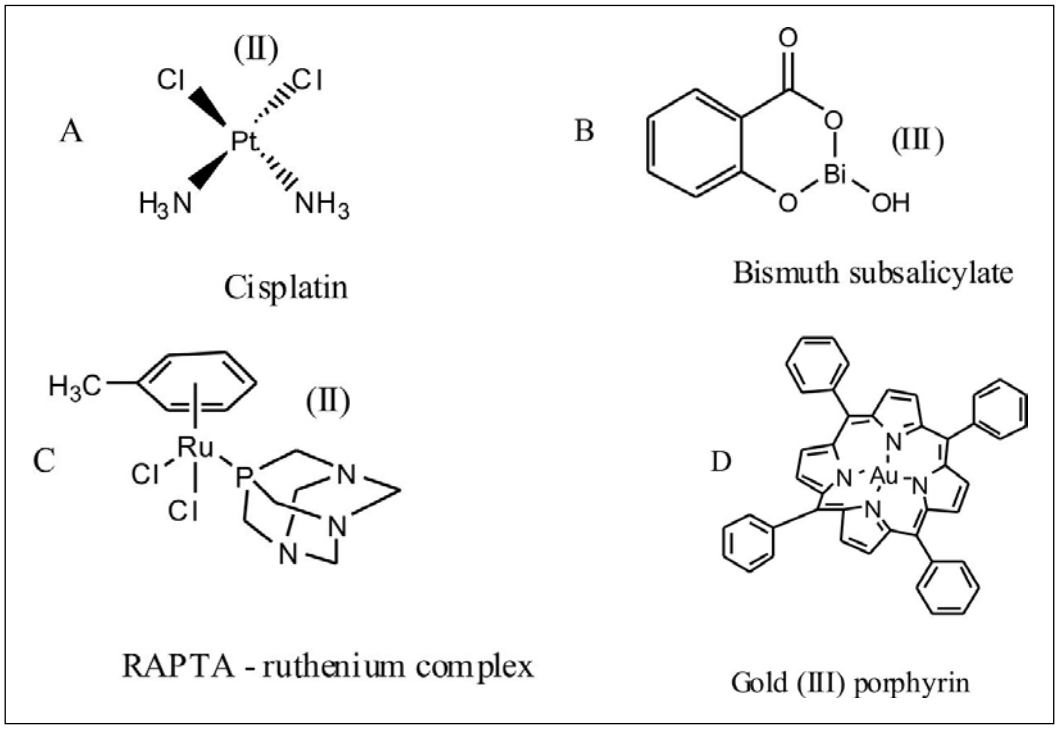

Fig. 1: Chemical structures of (A) Cisplatin; (B) Bismuth subsalicylate; (C) RAPTA ruthenium(II)–arene complex used to treat tumour metastasis; (D) Au(III)–porphyrin used to treat hepato-cellular and nasopharyngeal carcinoma

Table I: Medical and prospective medical uses of inorganic compounds[23]

Element	Compound	Uses	Trade Names/comments
Li	Li_2CO_3	Manic depression	Camcolit;Cibalith-S; Lithane (of many)
Fe	$[Fe(NO)(CN)_5]_2$	Vasodilation	Nipride. For acute shock. NO release
Ga	$Ga(NO_3)_3$	Hypercalcemia of malignancy	Ganite. Possible anticancer agent. In clinical trials for use in lymphomas
Ag	$AgNO_3$ Ag(Sulfadiazine)1% cream	Disinfectant Neonatel Conjunctivitis Treatment of burns	Flamazine; Silvadene
Pt	Cis-[Pt (amine)$_2$X$_2$]	Anticancer agents	Platinol; Paraplatin; Eloxatine Testicular, ovarian, colon cancers
Au	Acetylthioglucose derivative	Rheumatoid arthritis	Ridaura. Orally active
Bi	Bi(sugar) polymers	Antiulcer; antacid	Pepto-Bismol;Ranitidine Bismutrex; De-Nol
Hg	Hg-organic compounds	Antibacterial, Antifungal	Thiomersal; mercurochrome (amongst many Slow release of Hg

Antiviral Activity of Cobalt (III) Complexes

The simple Co^{3+} ion is unstable in water, but can be stabilized against reduction to Co^{2+} by coordination to ligands or chelators. By far, the most common ligand type used to stabilize the cobalt ion in aqueous solution is the chelating N, O donor

ligand. Surprisingly, cobalt complexes derived from this ligand donor set, have found application as antibacterial or antiviral agents. 2-Methylimidazole is a promising class of cobalt complexes of CTC series. In 1998, Epstein and coworkers reported that the cobalt complex CTC-96 was effective in the treatment of epithelial herpetic keratitis, one of the major causes of blindness in industry. Studies using the CTC class of drugs were performed using a rabbit eye model, infected with Herpes Simplex Virus Type 1 (HSV-1). All complexes inhibited HSV-1 replication *in vitro* with as little as 5 mcg/mL required for strong antiviral activity[24].

Anti-HIV Vanadium Complexes

Vanadium complexes are well documented to have therapeutic applications[25]. Recent studies showed that oxovanadium (V_2O_3) complexes of thiourea and vanadium substituted polyoxotungstates exhibit potent anti-HIV properties towards infected immortalized T-cells.[26]

Gallium nitrate - a versatile Metal complex

The principal approved use of Ga $(NO_3)_3$ (Ganite, gallium nitrate) is in treating hypercalcemia of malignancy, by reducing the elevated Ca^{2+} in blood. This disorder is often associated with bone cancers and is an acute-care condition in which the rapid bone loss leads to the life-threatening levels of blood calcium. Gallium () reduces the rate of bone loss by inhibition of the action of osteoclasts, which produce acid onto the bone surface, dissolving mineral and protein components. Inhibition of this "proton" pump is thus a well-defined mechanism of action for gallium[27]. Relatively low levels (200 mg/day) are effective. At therapeutic doses, it has few side effects and is well tolerated. Most recent attention has focused on the activity of gallium nitrate against malignancies, especially non-Hodgkin's lymphoma, non-squamous cell carcinoma of the cervix, and bladder cancer. Clinical trials under the auspices of Genta will evaluate its efficacy on patients with low- or intermediate-grade non-Hodgkin's lymphoma. The results of phase II trials in non-small-cell lung cancer and prostate cancer have also been reported[28].

Metal complex fused with NSAIDS

Synthesis and investigation of metal complexes with active pharmaceuticals, in which the drug molecules play a role of ligand, have been regarded as a research domain of increasing interest for inorganic, pharmaceutical, and medicinal chemistry. These studies have attracted much attention as an approach to new drug development. It has been revealed that metal complexes of anti-inflammatory drugs have lower toxicity and higher pharmaceutical effect compared to the free drug owing to the inhibition of metal complexation with other important biological compounds[29]. Carboxylates are among the most ubiquitous compounds and the increasing interest in their complexes can be attributed to significantly important biological properties. The chemical structure of mefenamic acid, which possesses a carboxylate group, is promising for chelation with metal ions. The active binding site of mefenamic acid with metal ions is the oxygen atom of the carboxylic group. Moreover, the high molecular weight of this compound provides supporting evidence of its suitability for spectrophotometric methods. Complexation of mefenamic acid with alkaline metals has been reported, while there has been no report of complexation between mefenamic acid and transition metals. The importance of cobalt as a transition element can be attributed to its various applications, particularly in the pharmaceutical domain. Various cobalt complexes have been developed that are able to inhibit the protein tyrosine kinases selectivity. These complexes are useful in the treatment of various diseases.

Metal complexes in gene therapy

One experiment has been carried out on the 'Biodegradable Polymer-Metal Complexes for Gene and Drug Delivery' it has introduced some of the recent developments in enhancement of non-viral gene expression. It is anticipated that this field will continue to advance and expand to address issues pertinent to non-viral methods of gene delivery. While improvements to transfection efficiency have been made and research towards understanding

the underlying mechanism underlying several gene delivery vehicles has been carried out, the issues of toxicity, transfection efficiency, and host response, still remain problems for some gene delivery applications. There are many issues that still need to be resolved regarding the application of non-viral gene delivery vehicles to human treatment. However, the polymer-metal complex efficacy in enhancing the *in vitro* and *in vivo* level of gene expression suggests that this is a promising method. Further research on gene expression, using polymeric materials bound with metal, would certainly appear to be worthwhile[30].

Transition metal complexes as anti-inflammatory agents and free radical quenchers

Transition metals have also been used as anti-inflammatory and anti-arthritic agents. Several injectable transition gold complexes like sodium aurothiomalate, aurothioglucose and sodium aurothiopropanol are used clinically in the treatment of severe cases of rheumatoid arthritis. Gold and silver nanoparticles conjugated with heparin derivative possess antiangiogenesis properties. Silver nanoparticles are used in the development of an antimicrobial gel formulation for topical use. Gold has been used in the treatment of peripheral psoriatic arthropathy. As a product of oxygen metabolism, superoxide anion can trigger oxidative injury to tissues. This activity has been suggested to be associated with riper fusion and inflammatory diseases as well as neurological disorders such as Parkinson's disease and Alzheimer's disease.

Future Scope

Therapeutic application of transition metal complexes is an under-developed area of research and is full of opportunities for further progress. Basic principles to guide the synthesis and development of transition metal based pharmaceuticals are lacking. Development of new methodologies such as combinatorial chemistry will be helpful in the synthesis of inorganic compounds as therapeutic agents. Similarly, the action of metal complexes in the whole living organisms are expected to differ, in general, from the action of non-metal containing agents, and may offer unique research, diagnostic or therapeutic opportunities.

CONCLUSION

With the advancement in the field of medicinal chemistry, the role of transition metal complexes as therapeutic compounds is becoming increasingly important. Recent advances in medicinal chemistry have made possible formation of number of transition metal complexes with organic ligand of interest, which can be used as therapeutic agent. Significant progress in the synthesis of platinum based anti-cancer drugs like cisplatin has been made. These drugs have proven to be highly effective chemotherapeutic agents for treating various types of cancers. The use of transition metal complexes as therapeutic compounds has become more and more pronounced. These complexes offer a great diversity in their action; they do not only have anti-cancer properties but have also been used as anti-inflammatory, anti-infective and anti diabetic compounds. Development of transition metal complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Besides all these limitations and side effects, transition metal complexes are still the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics in a way that was unimaginable few decades back.

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