B.Sc 3rd Year (6th Semester)

Paper-2, Inorganic Chemistry

Topic: Inorganic complexes in cancer treatment and Chelation therapy

By

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Inorganic complexes in cancer treatment:-

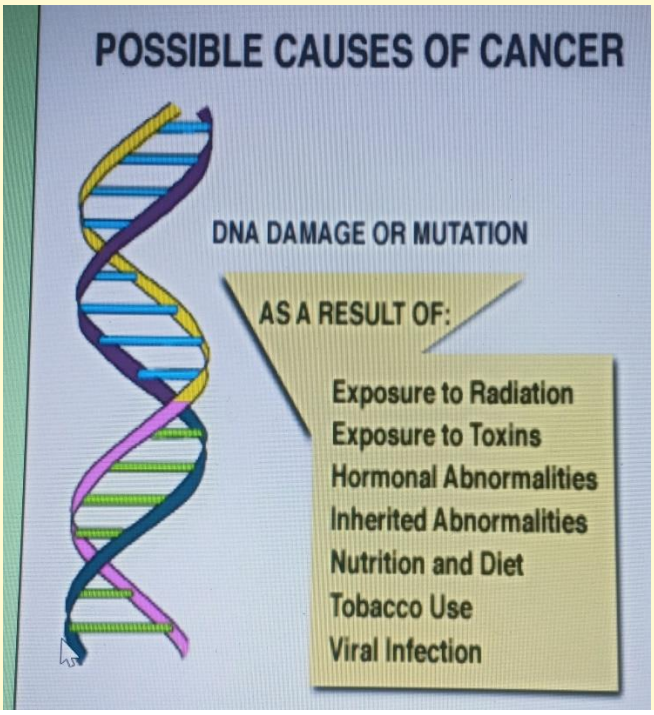
- Metals have unique characteristics such as variable coordination modes, redox activity, and reactivity being indispensable for several biochemical processes in cells. Due to their reactivity, their concentration is tightly regulated inside the cells, and abnormal concentrations are associated with many disorders, such as cancer. As such metal complexes turned out to be very attractive as potential anticancer agents.
- A common characteristic of transition metals is their ability to form reactive oxygen species (ROS), which are a part of cellular redox balance and fundamental in cell metabolism, signal transduction for proliferation, differentiation, and cell death, among others. Redox homeostasis is controlled by compartmentalizing reactions in the cell in subcellular units such as mitochondria and peroxisomes. It is therefore understandable the great impact that metal complexes can have on such redox balance. Disturbing the oxidant-antioxidant balance promotes an oxidizing environment leading to oxidative stress. When ROS are formed inside the cells, they can induce the lipid peroxidation of cell membranes, disrupt the mitochondrial membrane potential promoting membrane depolarization, induce DNA single-strand breaks, and oxidize the cysteine residues resulting in protein structural changes.
- DNA is the main intracellular target for a high number of anticancer metal complexes (e.g., cisplatin, carboplatin, and oxaliplatin); however, several other targets are known. In the following sections, we will summarize the current knowledge on Pt, Au, Ru, Ti, Pd, Ir Cu, V, Co, Ga, and Os complexes, highlighting their uptake mechanisms, biological targets, toxicity, and drug resistance mechanisms and elucidating how far they are from translation to the clinics in cancer therapy.
- **The use of transition metal complexes as therapeutic compounds has** become **more and more pronounced**. These **complexes** offer a great diversity in their action such as; anti- inflammatory, anti-infective and anti-diabetic **compounds**. Considerable efforts are made for the development of transition **metal complexes as drugs**. Beside several limitations and side effects, transition **metal complexes** are still the most widely used **chemotherapeutic agents** and make a large contribution to medicinal therapeutics

What is Cancer?

- A group of diseases
- Characterised by uncontrolled growth of abnormal cells.
- Local destruction/Infiltration.
- Spread to other parts of the body – (metastasis)
- Study of cancer is called Oncology
- • Greek - ONKOS - tumor , LOGY – study

Types of cancer:

- Carcinoma: Cancer of the skin and the tissues that line the body. Includes lung cancer, breast cancer, cervical cancer, head & neck cancer, stomach & bowel cancer etc.
- Sarcoma: Cancer of bone and muscle tissue.
- Lymphoma and Leukaemia ("blood cancer ") : Cancer originating from the lymph and bone marrow tissues.

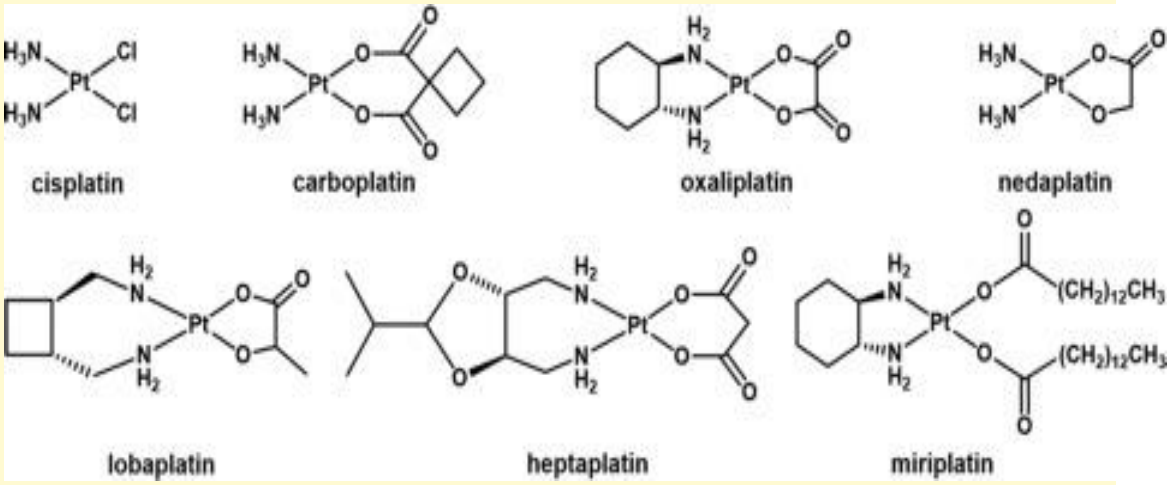


Platinum

- Platinum-containing complexes revolutionized cancer treatment since the introduction of cisplatin. Synthesized in 1844, it was used for the first time, more than 100 years later to treat patients with testicular cancer with survival rates over 90%. Since then, more than 3000 platinum derivatives were synthesized and tested for antiproliferative potential against cancer cells.
- There are six platinum drugs approved in cancer treatment, three of them—cisplatin, carboplatin, and oxaliplatin—by Food and Drug Administration (FDA)

and used worldwide and the other three approved in specific countries—nedaplatin in Japan, lobaplatin in Korea, and heptaplatin in China.

- Chemical structure of cisplatin, carboplatin, oxaliplatin etc, as drugs in clinical use for treatment of tumour diseases.



- Platins are the first-line therapeutics in several cancers either alone, in combination with radiotherapy, or with other antitumor or antiangiogenic drugs.
- Cisplatin metabolism is in part performed by glutathione leading to its decrease, affecting NADPH pools, resulting in dysfunctional mitochondrial redox status, and causing ROS . For all FDA approved platins, the mechanism of action is believed to be very similar, with incremental variations.
- Carboplatin has less toxicity than cisplatin because 1,1-cyclobutanedicarboxylate is a poorer leaving group than chloride lowering its potency being primarily used for ovarian cancer treatment.
- Oxaliplatin was the latest approved platinum drug and is a part of the first-line treatment for colorectal cancer. In contrast to cisplatin and carboplatin, oxaliplatin features a quelating nonleaving group, 1,2-diaminocyclohexane (DACH) in place of the two monodentate amine ligands. It also features a bidentate chelating oxalate leaving group ligand.
- Nedaplatin features *cis* ammine nonleaving group ligand (glycolate), associated with its greater water solubility. It has less toxicity than cisplatin and less nephrotoxic and is mainly used in combination therapy to manage urological tumors.

- Heptaplatin features malonate as a chelating leaving group ligand and a chelating 2-(1-methylethyl)-1,3-dioxolane-4,5-dimethanamine nonleaving group ligand, which forms a seven-membered chelate ring. It is used for gastric cancer, but its advantage over cisplatin has controversial results in clinical trials.
- Lobaplatin, a derivative of heptaplatin, fuses a cyclobutene ring to the seven-membered chelate ring instead of a dioxolane with an S-lactate as a leaving group ligand. It was originally approved to manage patients with chronic myelogenous leukemia, small-cell lung cancer, and metastatic cancer showing noncross-resistance to cisplatin.

Ruthenium

- **Ruthenium anti-cancer drugs** are coordination complexes of ruthenium complexes that have anticancer properties. They promise to provide alternatives to platinum-based drugs for anticancer therapy.
- Ruthenium has numerous properties:-

(i) they can exist in multiple oxidation states (II, III, and IV), all accessible under physiologic conditions, an advantage in the reducing environment of cancer tissues; **(ii)** They have the ability to coordinate ligands that can modulate their activity and have the same kinetics of ligand substitution in aqueous medium as that of Pt(II) complexes.

(iii) They have the possibility of occupying a large number of spatial positions due to its octahedral coordination geometry allowing to explore more and different ligands compared to platinum complexes.

(iv) they reduced toxicity compared to platinum compounds and attributed to their ability to mimic iron binding to serum transferrin with higher selectivity for their targets due to selective uptake by the tumour compared with healthy tissues.

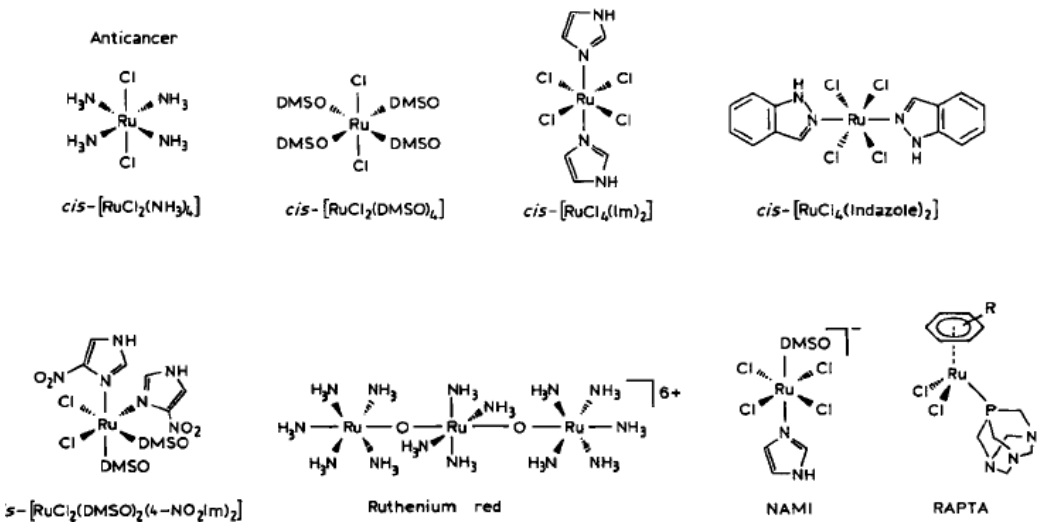
- Ruthenium complexes as anticancer drugs have been traditionally designed to mimic platinum drugs for targeting DNA.

Current ruthenium anti-cancer drugs

- **NAMI** {Na[*trans*-$RuCl_4$](DMSO)(imida)]} and NAMI-A {H_2Im[*trans*-$RuCl_4$(DMSO)HIm[imidH] are the most-stable ruthenium-based anti-cancer drugs.

- **KP1019**, or ***trans*-[tetrachlorobis(1*H*-indazole)ruthenate(III)]**, is a ruthenium anti-cancer drugs.

- RAPTA compounds are ruthenium–arene complexes bearing the 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane ligand.
- **RAED** compounds are ruthenium–arene complexes bearing the 1,2-ethylenediamine ligand.



Copper

- Copper complexes are the most studied transition metal complexes for their antitumor properties because endogenous metal ions may lead to less systemic toxicity.
- The properties of the copper complexes are determined by the nature of their ligands, which themselves may exhibit antiproliferative activity .
- Several Cu(II) complexes with a variety of ligands containing N, S, or O have been developed, demonstrating different mechanisms for their antitumor activity.

Iron

- Iron Several pieces of evidence indicate that iron deprivation could be an excellent therapeutic approach:

(i) Dietary iron restriction markedly decreases tumour growth in rodents.

(ii) Antibodies which block transferrin-binding to cellular receptors inhibit cancer cell growth in vitro and in vivo.

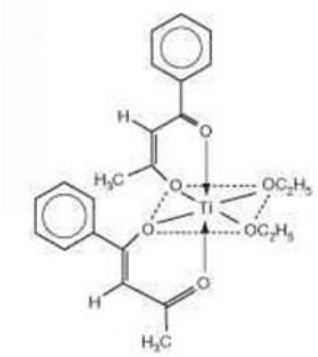
(iii) The anti-tumour effect of bleomycin, an anticancer drug, is mediated by chelation of iron or copper, to form a complex which degrades DNA.

- The thiosemicarbazone Triapine markedly inhibits the growth of several xenograft tumours in mice . Triapine crosses the blood-brain barrier and inhibits the growth of brain graft tumours. The combination of Triapine with etoposide, cisplatin, doxorubicin, or hydroxyurea was synergistic. The mechanism of this

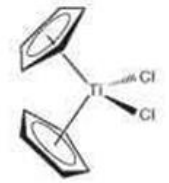
synergistic effect was probably due to triapine preventing the repair of the DNA damage induced by the cytotoxic agents.

Titanium

Since the 1970s, when the first titanium complex arises, a series of complexes containing titanium, Ti, as a metal center have been synthesized and characterized, and some of them were shown to possess a wide spectrum of antitumor properties. Indeed, titanium complexes such as titanocene dichloride and octahedral species budotitane are promising anticancer results being translated to (pre)- and clinical trials. Preclinical trials had shown efficacy in a broad of tumors.



I: $Ti(bzac)_2(OEt)_2$
Budotitane



II: Cp_2TiCl_2
Titanocene dichloride

Antimony:

- The most studied antimony(III) compounds are organometallic. A series of antimony(III) compounds with polydentate carboxylic acids have shown anti-tumour activity in mice inoculated with S180 solid tumours.

Bismuth:

Bismuth complexes of 6-mercaptopurine were the first antitumour compounds tested. They yielded promising results, as compared to platinum (II) analogues. Organobismuth compounds were also tested, but no useful activity was observed.

Gold

The use of gold in medicine, to treat a number of diseases, More recently it has been used as a bacteriostatic and subsequently for the treatment of rheumatoid arthritis. Later still, the antitumour activity and anti-HIV activity of gold has been considered.

Chelation therapy

Chelation therapy: Medical procedure that involves administration of chelating agents to remove heavy metals from body.

- When metals like lead, mercury, iron, and arsenic build up in your body, they can be toxic. Chelation therapy is a treatment that uses medicine to remove these metals so they don't make you sick.

How Does It Work?

- Chelation therapy uses special drugs that bind to metals in your blood. You get the chelating medicine through an intravenous (IV) tube in your arm. It's also available in pill form. Once the drug has attached to the metal, your body removes them both through your pee.
- Metals that can be removed with chelation therapy include lead, mercury, and arsenic. Before you get this treatment, your doctor will do a blood test to make sure you have metal poisoning.

Chelating agent: Organic/ inorganic compounds capable of binding metal ions to form complex ring-like structure "chelates".

- There are a variety of common chelating agents with differing affinities for different metals, physical characteristics, and biological mechanism of action. For the most common forms of heavy metal intoxication – lead, arsenic, or mercury – a number of chelating agents are available.
  - Dimercaptosuccinic acid (DMSA) has been recommended for the treatment of lead poisoning in children by poison control centers around the world.
  - 2,3-dimercaptopropanesulfonic acid (DMPS) and alpha lipoic acid (ALA), are used in conventional and alternative medicine.
  - Some common chelating agents are ethylenediaminetetraacetic acid (EDTA), 2,3-dimercaptopropanesulfonic acid (DMPS), and thiamine tetrahydrofurfuryl disulfide (TTFD).
  - Calcium-disodium EDTA and DMSA are only approved for the removal of lead by the Food and Drug Administration while DMPS and TTFD are not approved by the FDA.

➢ These drugs bind to heavy metals in the body and prevent them from binding to other agents. They are then excreted from the body.

Chelator	Used in
Dimercaprol (British anti-Lewisite; BAL)	• acute arsenic poisoning • acute mercury poisoning • lead poisoning (in addition to EDTA) • Lewisite poisoning (for which it was developed as an antidote)
Dimercaptosuccinic acid (DMSA)	• lead poisoning • arsenic poisoning • mercury poisoning
Dimercapto-propane sulfonate (DMPS)	• severe acute arsenic poisoning • severe acute mercury poisoning
Ethylenediamine tetraacetic acid (calcium disodium versenate) ($CaNa_2$-EDTA)	• lead poisoning
Deferoxamine, Deferasirox and Deferiprone	• acute iron poisoning • iron overload

Chelation Therapy for Cancer:-

❖ The most important for cancer patients, is that EDTA binds with and removes from the body the excessive free radicals that many experts attribute to the development and progression of cancer.

Chelation Therapy Side Effects

Some of the common side effects of chelating agents include:

- Burning sensation when injected into a vein
- Fever and chills
- Headache
- Nausea and vomiting
- Diarrhea
- Convulsions or seizures
- Fall in blood pressure
- Breathlessness or tightness in the chest
- Respiratory failure

- Low blood calcium
- Irregular heartbeats or cardiac arrhythmias
- Severe allergic reactions may occur with the use of some chelators and lead to skin rash, eczema, and asthma attacks.
- Severe hypersensitivity reactions may lead to anaphylactic shock and even death.
- Kidney damage and failure leading to end stage renal disease requiring dialysis.
- Liver damage may be seen with some chelating agents and some patients may develop liver failure.