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The Metallic Edge: Organometallic Compounds As Anticancer Drugs

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ABSTRACT

The study of organometallic compounds as an Anti-Cancer Agents has been focused due to their versatility in various physical and chemical properties. However any attempt to understand how organometallic compounds act as anti-cancer agents i.e. their attacking mechanisms ,site of attack and also the various types of organometallic compounds exhibiting cytotoxicity against cancer cells approaches initially to activation of complexes.

This dissertation discovers the aspects of the chemistry related to many types of organometallic compounds such as Metallocenes (including derivatives of ferrocenes, vanadocenes and zirconocene), Metal-Arenes(ruthenium arenes, gold complexes and osmium arenes).

All these organometallic derivatives are a part of recent researches and their physical and chemical properties along with their cytotoxicity have been detected in detail. Therefore the ideas for enhancing the cytotoxicity of these complexes had also came in idea i.e. by combining a pharmacophore like that in case of osmium complexes according to the latest researches ,as compared to the monodentate ligand, Os(II) arene complexes with specific phenylazopyridine ligands (π-acceptor ligands) were more powerful and unreactive with iodide. They are active in vivo and 49 times more effective on average in a Sanger panel of 809 cancer cell lines than cisplatin.

The evolution of chemical properties of organometallic complexes and their studies over the years progressively developed. Although previous research on the biological effects of cisplatin and the emergence of cisplatin resistance phenotypes provide critical information that can be used to produce platinum and non-platinum metal-based medicines for cancer therapy that are more effective and less harmful. It is to be predicted that non-platinum metal compounds may have toxic side effects and anti-cancer efficacy that are notably different from those of platinum-based medications.

Keywords: *Organometallic compounds, drugs, anticancer drugs, attacking strategy, titanocine*

1. INTRODUCTION

Cancer is dignified as major reason of death and a chief hurdle to expand life hope in every country of world. According to evaluations from the World Health Organization (WHO) in 2019. Cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries(Fig.1) and ranks third or fourth in other 23 countries.[1]

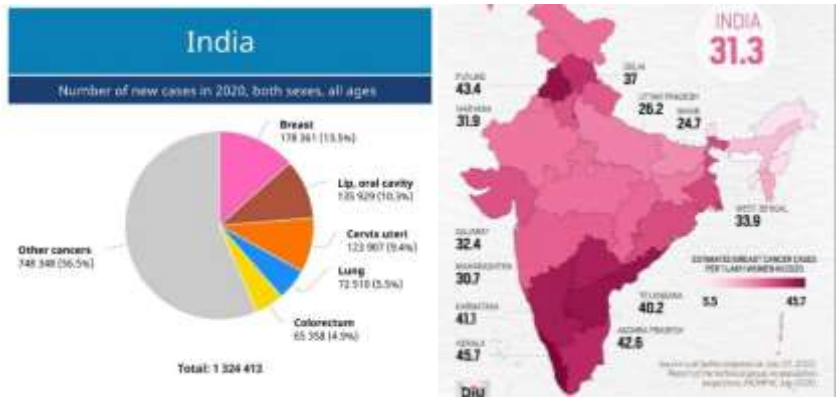


Fig.1: A brief chart of cancerous activity rate in all-over India is given below:

In order to control cancerous activities throughout world, Science has developed wide since ages and especially in field of medicinal chemistry.

1.2 MEDICINAL CHEMISTRY AS A SAVIOR:

Pharmaceuticals which are metal based, provides wide usefulness over medicinal chemistry due to the detailed blocks from which they may be made up of, the kind of to be had interactions (H-bonding, coordination bond, spatial rearrangement or dipole-dipole interactions), the mixture of tension(rigidity) across the steel and the kinetics involved in the ligand substitution when coordinative bonds are formed with molecules, shape and also due to their redox properties.[2]

Wide world of chemistry is possessed of variety of inorganic and organic compounds:

- Organometallic compounds work as intermediate between classical inorganic and organic derivative. Organometallics provide wide control over Rate Kinetic properties (such as hydrolysis of ligand).
- It has diverse stereochemistry[3] for example in case of octahedral complexes 30 isomers exists for different ligands. Because of these properties over normal main group metals and transition metals, the Organometallic Compounds consumed in field of medicinal chemistrty.
- Organometallic Compounds, represent excludes some carbon compounds such as carbides (example CaC2) and cyanides (example NaCN) which are contemplated to be Inorganic Complexes which don't contain metal-carbon bond but are considered as members of Organometallic Compounds example: Wilkinson catalyst [Rh (PPh3)3Cl] which is used for hydrogenation of alkenes and alkynes.[4]

Organometallic compounds have huge variety of applications(Fig.2) due to their immense structural variance.

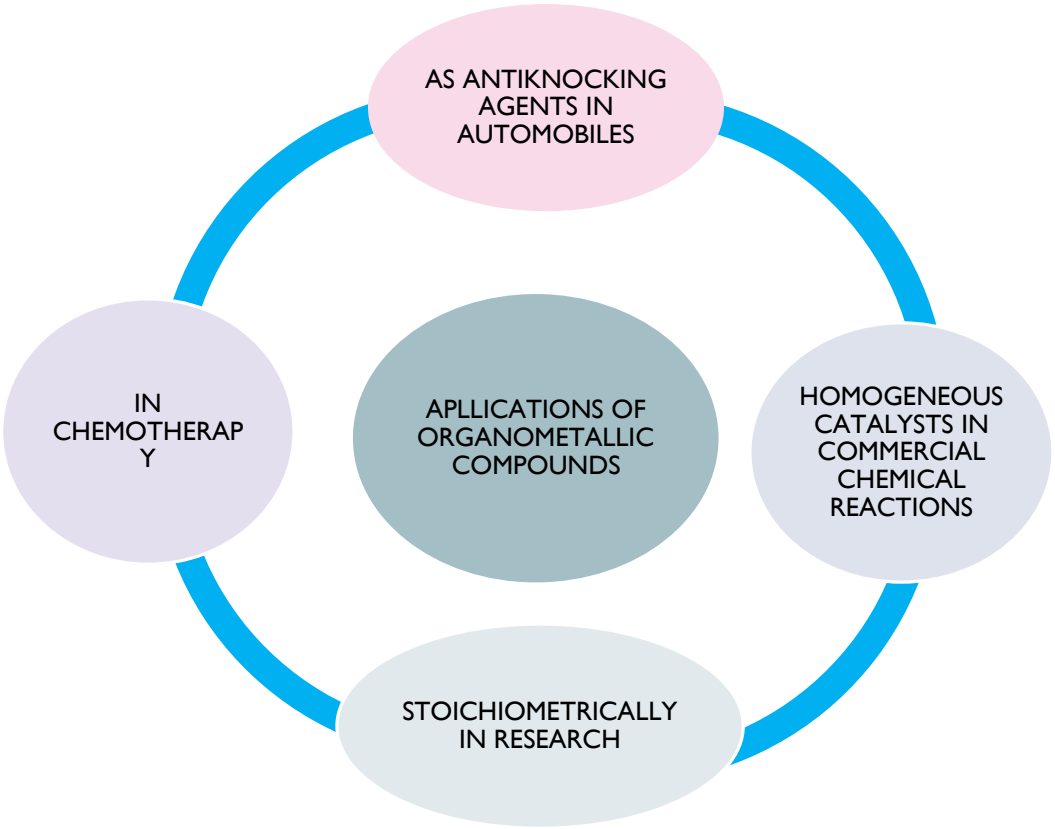


Fig.2: Some important applications of organometallic compounds

Because of these properties such as as organosynthetic reagents in organic synthesis over normal main group metals and transition metals the organometallic compounds considered to be applicable as Anti-cancer, radio pharmaceuticals for diagnosis and therapy and biosensor probes

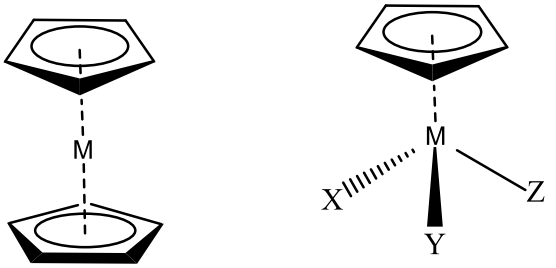
The first Organometallic Compound found for Anti-Cancer activity was (TITANOCENE DICHLORIDE) Cp_2TiCl_2.

Some Organometallic compounds used as anticancer drugs (Fig.3)

*METALLOCENES [5]

*M-ARENES

*M-CARBONYLS



LxM-CO

Fig.3: Some Organometallic compounds used as anticancer drugs .

In this dissertation we are going to study various organometallic compounds with proven anti-cancer aur antiliferative activity.[6]

2. LITERATURE DISSERTATION

2.1 TITANOCENE DICHLORIDE:

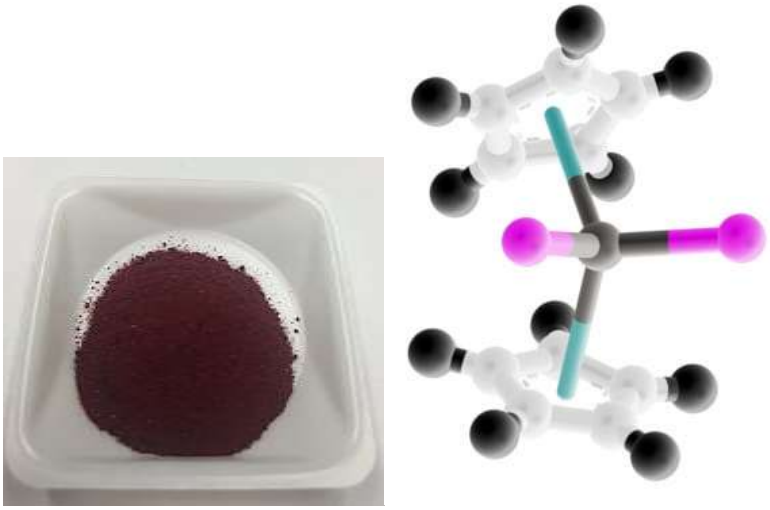


Fig.4: The first organometallic anticancer drug to enter phase II was Titanocene dichloride.

The most important is the well-characterized systematically arranged behaviour towards specific goals. We can classify organometallic complexes with cytotoxic effects according to chemical-physical processes activated against the cells of cancer.

On the basis of discussion before, Classification of biological activity metal complexes based on cytotoxic activity and this activity is closely dependent on metal and few of the ligands as a whole complex. This classification for both organometallics were recently explained completely.

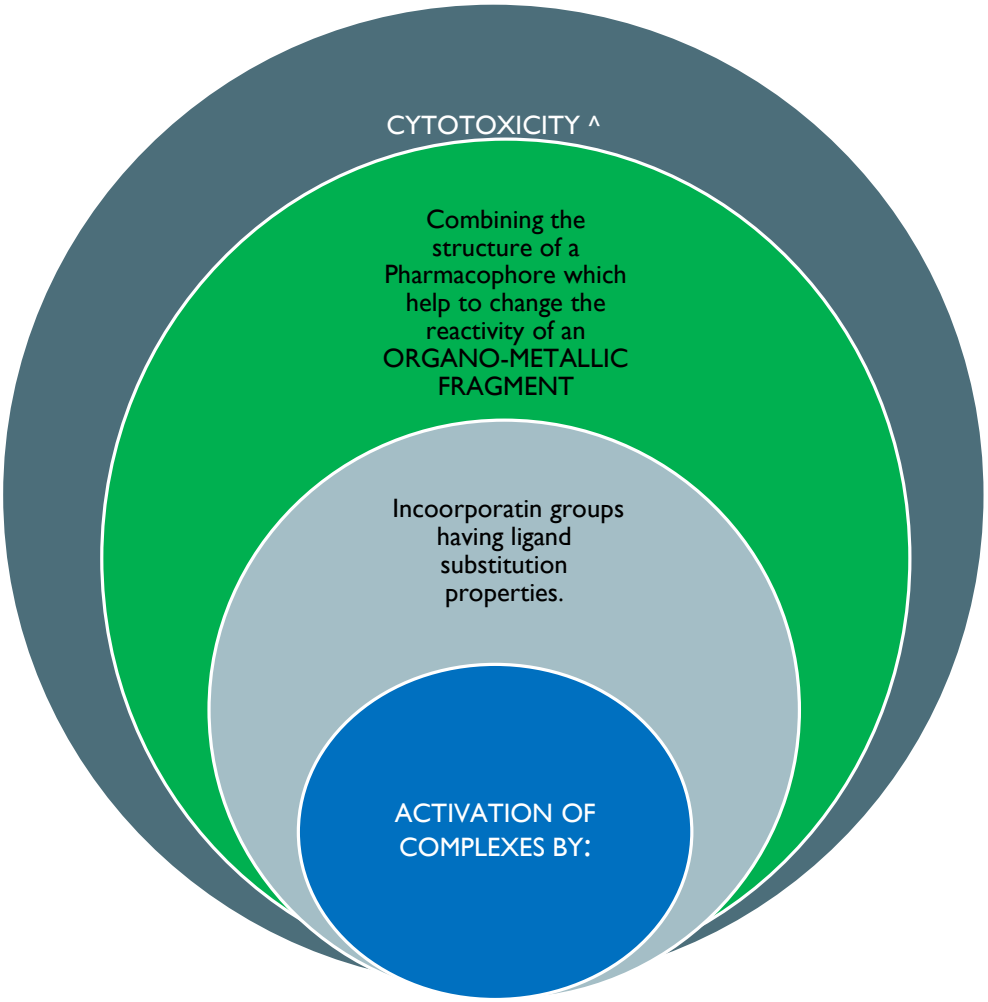


Fig.5: Different strategies organometallic chemistry were used for ACTIVATION OF COMPLEXES in field of Medicinal chemistry.

★ For example, in case of **titanocene**, several titanocene organometallic complexes, which shown to possess cytotoxicity against diverse human tumour cell lines.

ACTIVATION MECHANISM FOR ORGANOMETALLIC-ANTICANCER COMPLEXES:

Tacke et al, in order to improve the stability in aqueous solution , prepared derivatives of titanocene with bridged Cp ring. Complexes containing labile groups that are easily substituted, such as Ru-arenes. Piano stool complex like [Ru (η6 -arene)(XY)(Z)]n+ (where XY = chelating ligand, and Z = labile halide), the activation can arise by the hydrolysis of the Ru-Z bond. Just like in case of cisplatin(Fig.6)

Fig.6: Hydrolysis of Pt-Cl bond in cisplatin inside the cell.

Other methods for activating and displacing organometallic complexes towards substitution reactions are (Fig.7): The labile ligands can be triggered within cells by internal factors such as **cellular oxidation** with the help of less labile ligands, chelate ring opening, or even by external sources (for example, by light of a specific wavelength).

Fig.7: Another strategy used by Jaouen,Meggers and Nils Metzler Nolte :

However, in case of Ferrocifens , the metal atom has been found to be involved in anticancer activity through redox activity.

Finally, there are studies using organometallic cages as transportation drug vehicles.

2.2 METALLOCENES AS ANTICANCER AGENTS:

Metallodrugs consumption in Chemotherapy treatment is based on platinum (cisplatin analogues), also as many side effects are the drawback behind the use of cisplatin-based drugs in chemotherapy, a lot of efforts are done for the search of metal complexes with similar cytotoxity and less side effects as they are used as an alternative of platinum based drugs. Transition-metal complexes have revealed as beneficial properties in cancer treatment , and the most important task to perform in chemotherapy of transition metals which are used are from Group 4, 5, 6, 8, and 11 metals due to their certain chemical properties.A wide variety of metal complexes have been recently studied as a substitute to platinum-based drugs. According to the IUPAC classification, Metallocene consists of a transition metal and two cyclopentadienyl ligands which is present in sandwich form of structure in coordination. These compounds gave rise to a huge concentration or interest in chemistry because of few important properties of metallocenes that can be either chemical or physical property and especially bonding properties (Fig.8).

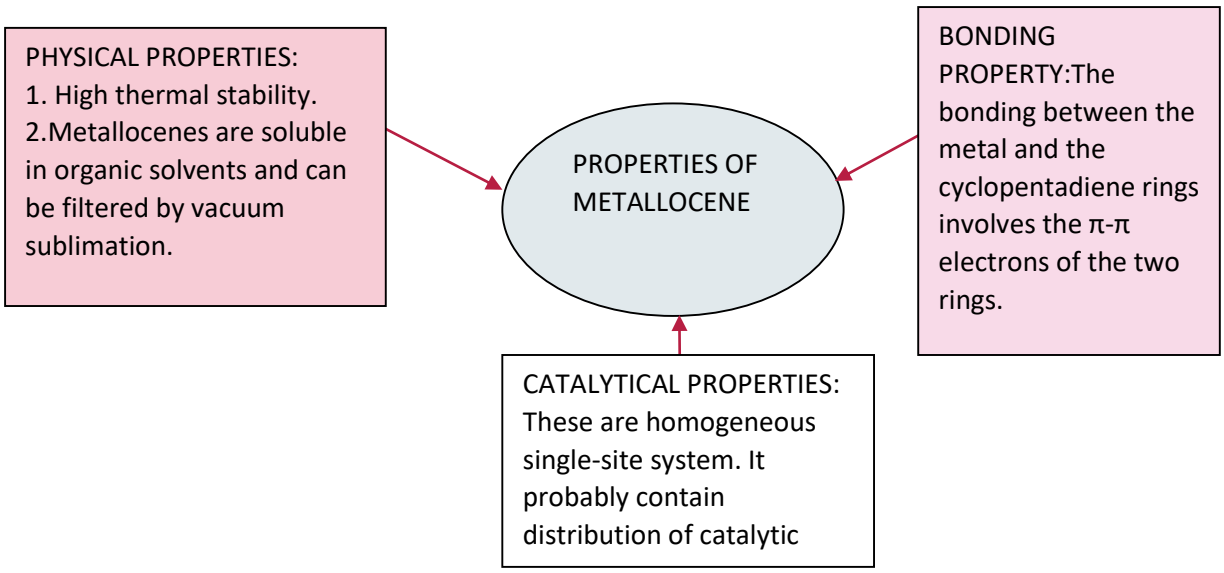


Fig.8: Important properties of Metallocenes

Biological, industrial and laboratory research regarding to metallocene chemistry has open up to the consumption of these derivatives in numerous types of applications (Scheme1).

Olefin polymerization catalysis	Organic synthesis
Irregular catalysis	Magnetic materials (preparation)
As Non-Linear optics	Flame preventors

Scheme1: Industrial use of Metallocene.

Metallocene complexes are generally consumed in form of biosensors or act as antitumor agents. Considering the anticancer applicability of metallocenes such as, Titanocene, Vanadocene, Molybdocene, and Ferrocene have been customly used with wonderful outcomes.

On the other hand, lately also Zirconocene derivatives can be used as anticancer agents due to their high cytotoxicity. Remaining metallocene derivatives have been either not verified or have not shown such remarkable use in the fight against cancer.[7]

Now let's discuss them in detail.

2.2.1 TITANOCENE DERIVATIVES

Titanocene derivatives along with ferrocene complexes are the most studied metallocene as an anticancer drug. The unorthodox work of Köpf and Köpf-Maier in the early 1980's showed the antiproliferative properties of titanocene dichloride [TiCp2Cl2] (Cp = η5-C5H5).

This compound was studied in phase I (Fig.9) clinical trials in 1993 using water soluble formulations developed by Medac GmbH (Germany).

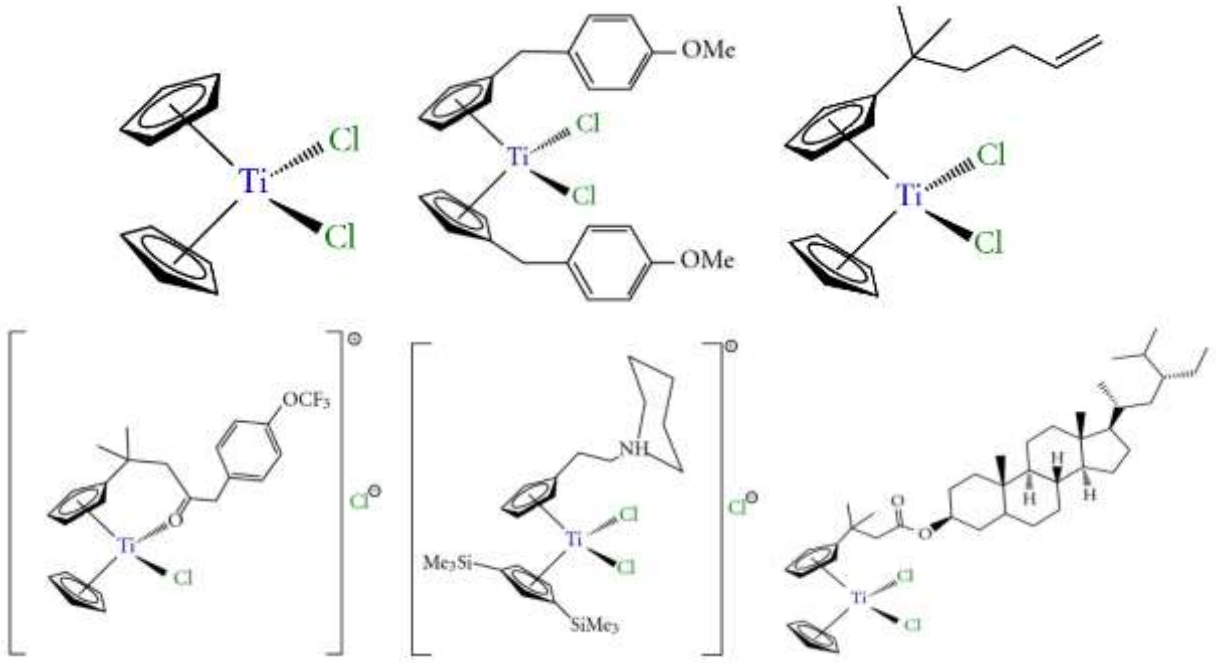


Fig.9: (a) titanocene dichloride; (b) titanocene-Y; (c) alkenyl-substituted titanocene derivative; (d) titanocenyl complex; (e) titanocene derivative with alkylammonium substituents; (f) steroid-functionalized titanocene derivative

Phase I clinical studies resulted that nephrotoxicity (destructive to the kidneys), also low blood sugar, nausea, a taste of metals right after injection, and discomfort through infusion, was a dose-limiting side effect linked with titanocene dichloride.

These side effects appeared to be the weakest aspect of titanocene dichloride. However, one exciting finding that boosted the compound's potential for use in humans was the absence of any influence on bone marrow excess activity.

As the phase I trials did not meet expectations, certain phase II clinical trials with patients who had advanced kidney cancer

and breast cancer were conducted while noticing a very less activity that low further research.

The interest in this area has, however, been revived as a result of the recent work of numerous groups, including Tacke, Melendez, McGowan, Baird, and Valentine. In this context a wide variety of titanocene derivatives are informed with a lot of motivating cytotoxic properties which increases their usage in human.

Titanocene derivatives with amino acids	Benzyl-substituted titanocene	Amide functionalized titanocenyls
Ansa-titanocene derivatives		Titanocene derivatives with alkylammonium substituents on the cyclopentadienyl rings
Steroid-functionalized titanocenes		Alkenyl-substituted titanocene [8]

Scheme2: Titanocene derivatives are informed with a lot of motivating cytotoxic properties

Although the structure of titanocene complexes are being linked to their cytotoxic activity, also many unanswered problems relating to titanocene(IV) complexes' antitumor mechanism. The research that have been reported on the subject, it appears that titanium ions enter cells with the help of the main iron transport protein "transferrin" and the nucleus by an active transport that is likely aided by ATP[30]. In the end, titanium ion attachment to DNA results in cell death .Whereas, new research has revealed interactions between a ligand-bounded to Ti(IV) complex and some other enzymes, revealing alternate cell death processes.

2.2.2 ZIRCONOCENE DERIVATIVES:

- Zirconium(IV) derivatives, which are in the very early stages of preclinical research, may be used as an alternative to titanium complexes. Zirconocene derivatives has a potential of acting as anticancer agents was firstly exhibited by Köpf and Köpf-Maier in the 1980s,[16] and recently, two distinct investigations on the zirconocene anticancer chemistry were reported.[9]
- Only the complexes [Zr5-C5H4(CH2)2N(CH2)52Cl22HCl]and [Zr5-C5H4(CH2C6H4OCH3)2Cl2] (zirconocene Y) have shown promising activity that needs to be improved in order to be used in anticancer chemotherapy.

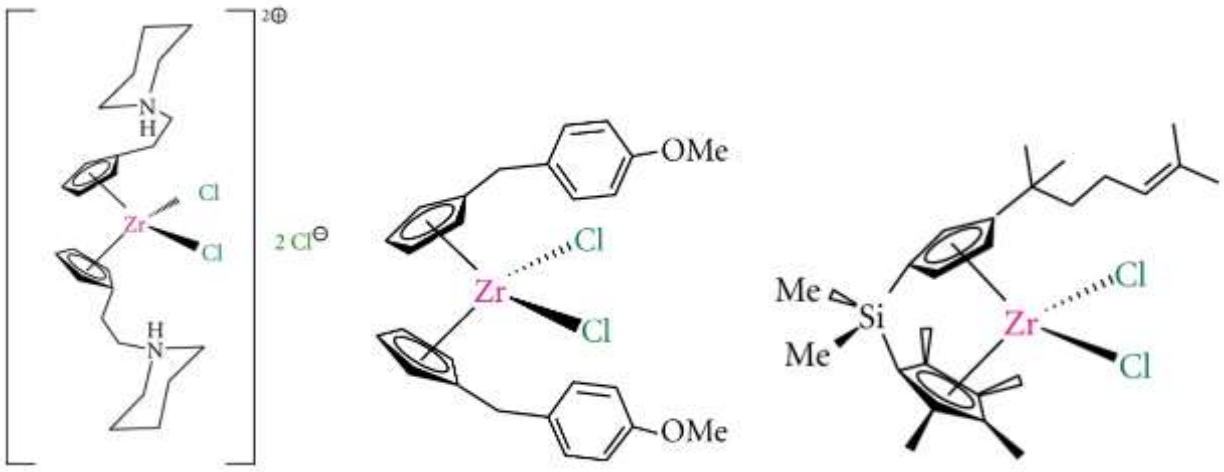


Fig.10: Zirconocene derivatives with anticancer activity: (a) zirconocene derivative with alkylammonium substituents; (b) zirconocene-Y; (c) alkenyl-substituted ansa-zirconocene complex.

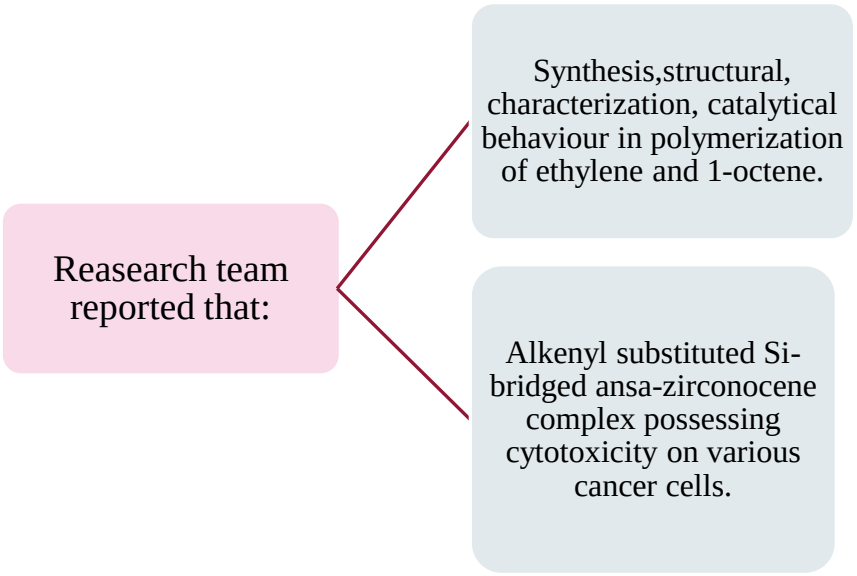


Fig.11: RESEARCH REPORT OF ZIRCONOCENE

2.2.3. DERIVATIVES OF VANADOCENE:

Vanadocene dichloride, [VCp2Cl2] (Cp = 5-C5H5), was found to have a greater in vitro activity when compared directly to titanocene (IV) dichloride.

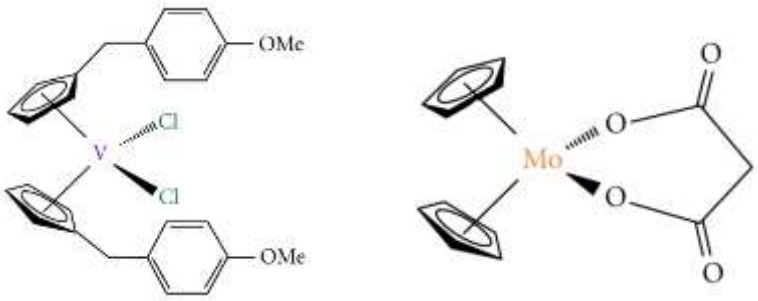


Fig.12: (a) Vanadocene-Y; (b) molybdocene carboxylate derivative

The cytotoxic capabilities of vanadocene Yand related derivatives have lately been the subject of preclinical research. Also recently described is a thorough investigation, T-lymphocytic leukemia cells took up the cytotoxicity by methyl- and methoxy-substituted vanadocene(IV) dichloride .

The majority of the time, Titanocene analogues are less active than the corresponding vanadocene derivatives and due to the paramagnetic nature of the vanadium centre the determination of these compounds and their purely active species is extra challenging, which stops the practice of conventional NMR tools. Their investigation and research are slowed significantly by the requirement of adapting ESR Spectroscopy or X-Ray Crystallography.

2.2.4 DERIVATIVES OF MOLYBDOCENE:

There were some indications of the potential for molybdocene dichloride derivatives to act as anticancer agents[14]. The substantial research conducted in recent years by numerous research teams has confirmed molybdocene's ability to fight cancer. But in addition to their claimed cytotoxic effects, these compounds' hydrolysis chemistry has also received much attention.In the case of molybdocene derivatives the stability of cyclopentadiene ligands has prompted the study of numerous different biological experiments, the findings of which provide new insights into the mechanism underlying the antitumor activity of [MoCp2Cl2] and some related carboxylate derivatives.

2.2.4 FERROCENE DERIVATIVES:

Finding that ferricinium has cytotoxic characteristics an early step in the creation as anticancer drugs was the discovery by Köpf and Köpf-Maier and have the cytotoxic effects of ferricinium salts (Fig.13) on Ehrlich ascites tumours.

Although there are other groups working in this area, Jaouen and colleagues are now doing the most intriguing research

about the anticancer potential of ferrocene derivatives. The active metabolite of ferrocene moieties are linked to create novel functionalized ferrocene derivatives known as "hydoxyferrocifens". This group has published multiple publications on the production of these compounds. The cytotoxic effects of ferrocene and the antioestrogenic features of tamoxifen can be combined in this new family of chemicals.

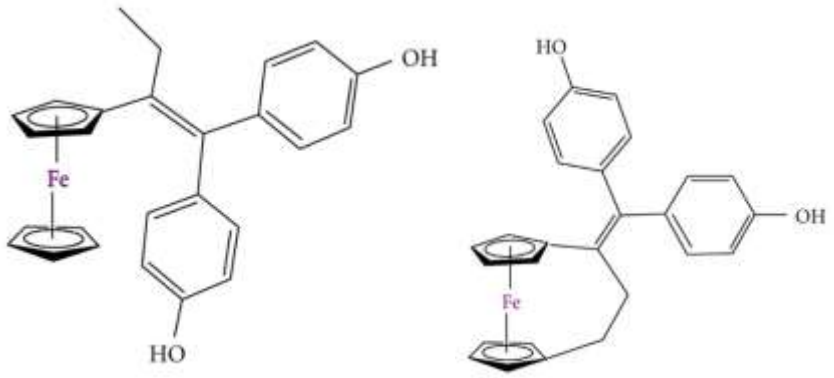


Fig.13: Ferrocene derivatives used in preclinical trials: (a) hydroxyferrocifens; (b) ferrocene complex with a ferrocenophane moiety.

Additionally, it has been noted that complexes which are functionalized over ferrocenes with steroids are particularly effective at concentrating on prostate cancer cells.

In addition to studying ferrocene derivatives with various ligands, design and cytotoxic qualities, several studies on the anticancer medicines' mechanisms for inducing cell death have also been documented. As a result, the generation of ROS species have been suggested as two distinct action mechanisms for ferrocene derivatives.

2.3 M-ARENES AS ANTICANCER AGENTS:

2.3.1. η^6-Arene Ruthenium Complexes

The majority of ruthenium(III) octahedral complexes are unaffected by ligand substitution. In the late 1970s, Clarke and colleagues first suggested:

To reduce ruthenium(III) to ruthenium(II) for activation in DNA binding.

As a result, ruthenium(II) and osmium(II) organometallic arene complexes were come into interest lately as anticancer drugs .The chemical reactivity of π-bonded complexes(Fig.14) of Ru(II) and Os(II) Arenes can drastically changes.

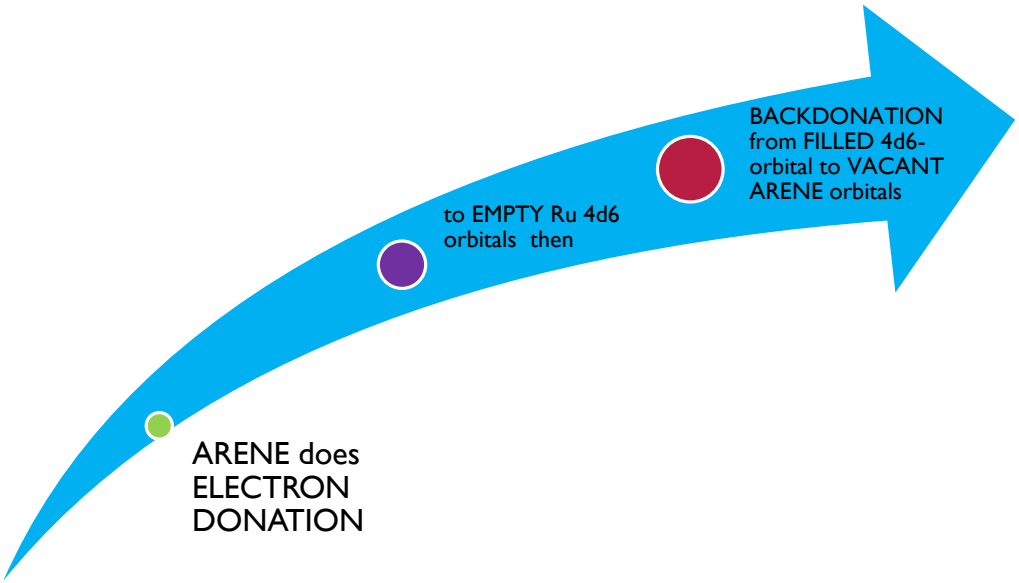


Fig.14: Delicate electron flow in π-bonded complexes

Instead of biphenyl, a potent donor such as hexamethylbenzene, which might influence the the presence of strong π-acceptor chelating ligands like bipyridine and azopyridine or the strength of the monodentate ligands' donors (for example, iodide vs. chloride) , thus Ru 4d6 electrons availability increases . It has been investigated whether RuII and OsII η6 complexes in the form [MII(η6–arene)(X)(Y)(Z)] could be used as antitumor medications.

The 'piano-stool' structures of these complexes are recognizable (where XY is a neutral chelating ligand and Z is a monoanionic ligand) [11]. The metals are already in their reduced oxidation state in these complexes, which may be crucial for the drug's in vivo cytotoxicity . The arene ligand stabilizes the +2oxidation state by binding as a π-acceptor and a η6-electron donor.[12]

The chelating ligand XY contributes to the further stability of the entire structure and the capacity to adjust the metal center's electrical characteristics. If labile, like a halide, the monodentate ligand Z can offer a free coordination site for biomolecules, activating the molecule. Small adjustments to the arene and the "legs of the stool" give the molecule diversity and the opportunity to customize its pharmacological properties.

RuII and OsII arene complexes(Fig.15),in general, have encouraging cytotoxic action against human ovarian cancer cell lines, with some of them being as effective as cisplatin and carboplatin.

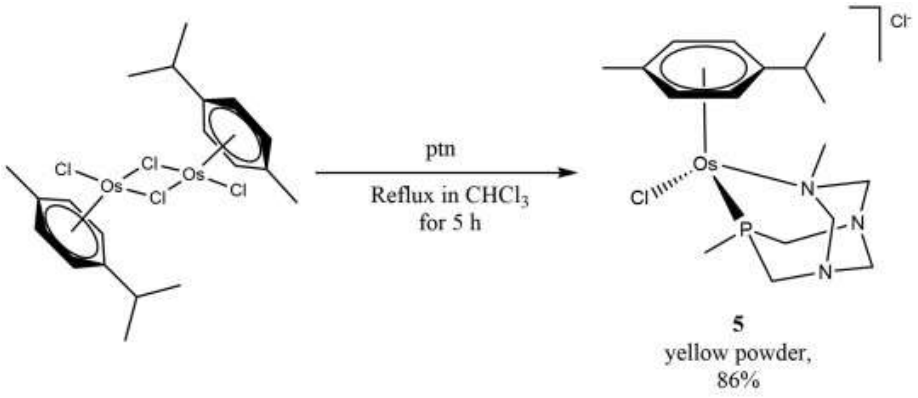


Fig.15: Anticancer Osmium complex

On increasing the size of coordinated arenes, the cytotoxicity against ovarian cells increases when ethylenediamine is the chelating ligand and chloride is the leaving group.

However, the cytotoxicity of ethylenediamine compounds is only slightly reduced by replacing chloride with bromide or iodide. Additionally, less cytotoxic complexes result from replacing the chelating ligand with relatively labile monodentate ligands.[13]

When chelating complexes are compared with that of non-chelating complexes.[14] Ruthenium Arene complexes possessing monodentate ligands exhibit poor activity whereas the complexes containing chelating ligands has high activity.

Due to their big responsiveness, they can be inactivated before reaching their target, which could amount for this lack of activity.

Ru III complexes are now being tested in laboratories (ImH)[trans-RuCl(4)(dmso)(Im)] (NAMI-A; dmso is dimethyl sulfoxide, Im is imidazole) and [ImH][trans-RuCl(4)Im2][15], and several [16] demonstration of Ru complexes to exhibit anti-cancer action. There has been an increase in interest in pseudo-octahedral organometallic Ru II arene complexes where the arene stabilizes ruthenium in the +2 Oxidation State as a result of the theory that these compounds' [17] mechanism of action involves in Vivo reduction to more reactive Ru II species.

There is a possibility of altering the Arene by changing its:

i)Substituents(R) ii) monodentate leaving group(X) iii) chelating ligand (YZ) and iv) the complex's total charge(n+) are all the features of these half-sandwich "piano stool "type constructions [18]. These characteristics offer handles for the control of the system's general structural architecture as well as its kinetics and thermodynamics.

Complexes of Ruthenium arene which contain [19] chelating ligand ethylenediamine, for example $[(\eta6\text{-arene})Ru(en)Cl]^+$, show promising activity both in vitro(studies performed with microorganisms) and vivo(studies performed with humans) and are thought to have a mode of action that is analogous to that of cisplatin.

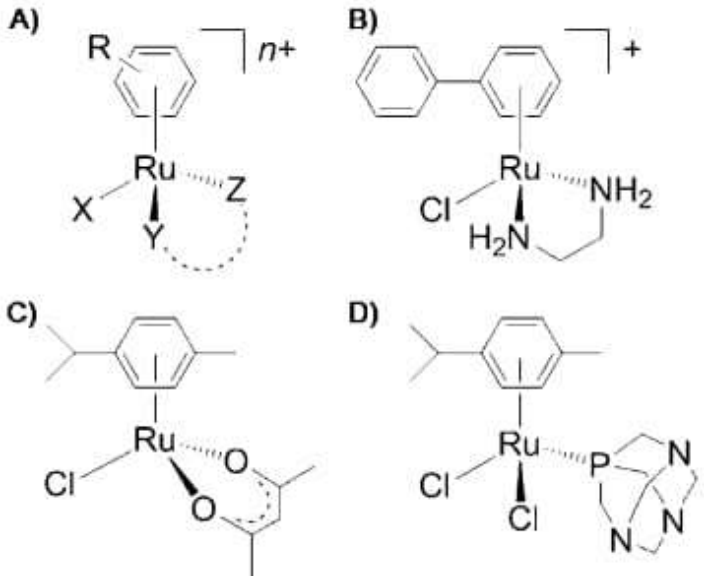


Fig.16: Half-sandwich metal arene complexes which exhibit cytotoxicity towards cancer cells. A) General chemical structure of RuII arene "piano stool" complexes,A) [(6 -arene)Ru(X)(Y)(Z)]n+. B) [(η6 -bip)Ru(en)Cl]+; bip=biphenyl, en=ethylenediamine. C) [(η6 -p-cym)Ru(acac)Cl]; pcym=p-cymene, acac=acetylacetonate. D) [(h6 -p-cym)RuCl2(pta)]; pta= 1,3,5-triaza-7-phosphatricyclo [3,3,1,1]decane. [16]

A "pro-drug" called the intact chloro-adduct is activated in vivo by hydrolysing the RuCl link (replacing Cl with a water molecule). The complex is substantially hydrolysed in the nucleus (4 mm Cl) to produce the reactive species, [(h6 -arene)Ru(en)(OH2)]2+ [20], although it is highly suppressed in the blood, where high chloride concentrations are present (about 100 mm).

The N7 location of guanine (G) nucleotides is thought to have a high affinity for the aqua species' binding to nuclear DNA. This strong[21] affinity for G has even been seen in the presence of a glutathione concentration that is 250 times too high. Although the hypothesized route of action is similar to cisplatin, there are still distinct distinctions. As the ruthenium arene binds to DNA, a distinct way of binding is seen.

2.3.2 ORGANOGOLD COMPLEXES:

Gold has been used as a therapeutic substance to treat many disorders for ages.

However, after the clinical introduction of auranofin, a triethyl phosphine gold(I) glucose-thiolate used to treat rheumatoid arthritis, its chemotherapeutic potential as an anticancer agent was expedited. This antiarthritic's oral availability led to a significant advancement in the treatment of cancer. Auranofin was later discovered to have strong in vitro anticancer effects and encouraging in vivo effects in a P388 leukaemia mice model. Due to their distinct methods of action from the traditional medication cisplatin, which works only on DNA, several gold chemotherapeutics are also very successful against cisplatin-resistant cell lines.

According to the literature, thioredoxin reductase (TrRx) and other thiol-containing proteins/enzymes interact with the endoplasmic reticulum (ER), mitochondria, and other targets to exert their cytotoxic effects on cancer cells because tumour cells create a lot of ROS and this enzyme aids in sustaining the oxidative stress brought on by ROS, the enzyme thioredoxin reductase (TrRx) is abundantly expressed inside tumour cells.

As a result, cancer cells will die through apoptosis (cell suicide) if the TrRx enzyme's activity is somehow suppressed.87,90 Similar to this, because of the electron movement in the respiratory chain, mitochondria are one of the primary producers of intracellular ROS(reactive oxygen species)[. Antitumor medications that target the mitochondria cause an internal drug buildup.

The mitochondria, increasing mitochondrial permeability and ROS generation, which leads to malfunction in the numerous metabolic processes. This ultimately results in apoptosis, or cell death, without having any negative impacts or toxicity problems. In addition, a number of medications affect the endoplasmic reticulum and stress the ER in tumour cells, which triggers the unfolded protein response (UPR). The UPR either stimulates cell death or apoptosis or restores equilibrium and encourages cell survival. As a result, all of these approaches are crucial in the creation of anticancer medications.

In the field of organometallic chemotherapeutics, organometallic gold(I) N-heterocyclic carbene (NHC) complexes have recently received substantial research.

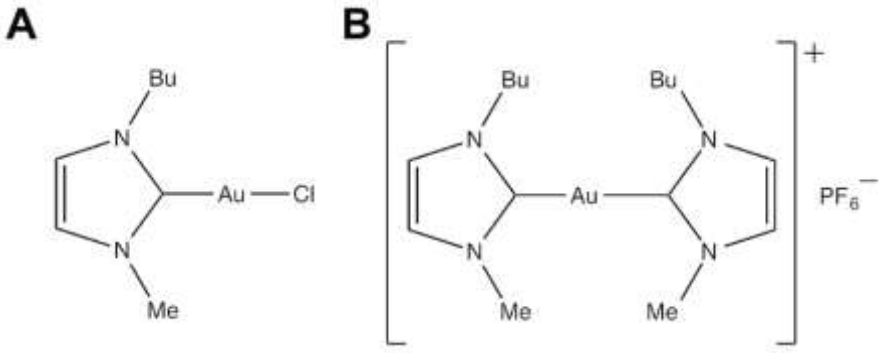


Fig.17: Au(NHC) and Au(NHC)2, i.e. a monocarbene gold(I) complex and the corresponding bis(carbene) complex

These are two structurally related composites, endowed with cytotoxic parcels against several cancer cell lines. Herein, we explore the molecular and cellular mechanisms at the base of their cytotoxicity in A2780 mortal ovarian cancer cells

Low nanomolar attention of this kind of emulsion were shown to block the action of thioredoxin reductase(TrRx), which is most likely as a result of the bioactive essence being delivered to the target position and the NHC ligand stabilizing the essence ion there under physiological circumstances. As a result of their distinct mechanisms of action from traditional specifics, organometallic gold complexes serve as implicit remedial campaigners with important anticancer goods on treatment- resistant nasty tumours. Other experimenters felt that the crucial intracellular targets for organometallic gold chemotherapeutics were mitochondria and the oxidative phosphorylation pathways. However, exploration on multitudinous organometallic gold(I) and gold(III) complexes showed that their primary murderous medium was the inhibition of thioredoxin reductase(TrRx), which eventually caused apoptosis via the mitochondrial route and endoplasmic reticulum stress. thus, compared to cisplatin,[22] anticancer gold complexes have different modes of action. Cisplatin resistance is a problem that can be answered by developing gold chemotherapeutics, as the maturity of cytotoxic gold complexes are also effective against cisplatin- resistant cancer cells. also, it has been shown [23] that some Au(I) and Au (III) complexes parade considerable. tinct mechanisms of action from traditional medications, organometallic gold complexes serve as potential therapeutic candidates with powerful anticancer effects on treatment-resistant malignant tumours. Other researchers felt that the key intracellular targets for organometallic gold chemotherapeutics were mitochondria and the oxidative phosphorylation pathways. However, research on numerous organometallic Au (I) and Au (III) complexes showed that their primary lethal mechanism was the inhibition of thioredoxin reductase (TrRx), which ultimately caused apoptosis via the mitochondrial route and endoplasmic reticulum stress.[24] Therefore, compared to cisplatin, anticancer gold complexes have different modes of action. Cisplatin resistance is a problem that can be solved by developing gold chemotherapeutics, as the majority of cytotoxic gold complexes are also effective against cisplatin-resistant cancer cells[25]. Additionally, it has been shown that [26] some Au(I) and Au(III) complexes exhibit considerable.

Effective chemotherapy medications can be those that cause both apoptosis and autophagic death.In the current study, we created two organometallic gold (III) complexes called Cyc-Au-1 (AuL1Cl2, L1 = 3,4-dimethoxyphenethylamine) and Cyc-Au-2 (AuL2Cl2, L2 = methylenedioxyphenethylamine) that include [27]C-N ligands that structurally mimic tetrahydroisoquinoline (THIQ). We discovered that both gold complexes had greater antitumor efficacy when compared to cisplatin and showed lesser toxicity and resistance characteristics. The organometallic Au (III) complexes build up in mitochondria and, through dysfunctional mitochondria, cause increased ROS and an ER stress response [28]. Apoptosis and autophagy ultimately occur simultaneously as a result of these actions. Importantly, Cyc-Au-2 displays superior anticancer effectiveness and less toxicity in a mouse tumor model when compared to cisplatin. Cyc-Au-2 is the first organometallic Au (III) molecule that we are aware of that triggers apoptosis. We consider Cyc-Au-2 to be a promising anticancer agent or lead chemical for additional anticancer medication development based on our findings [29].

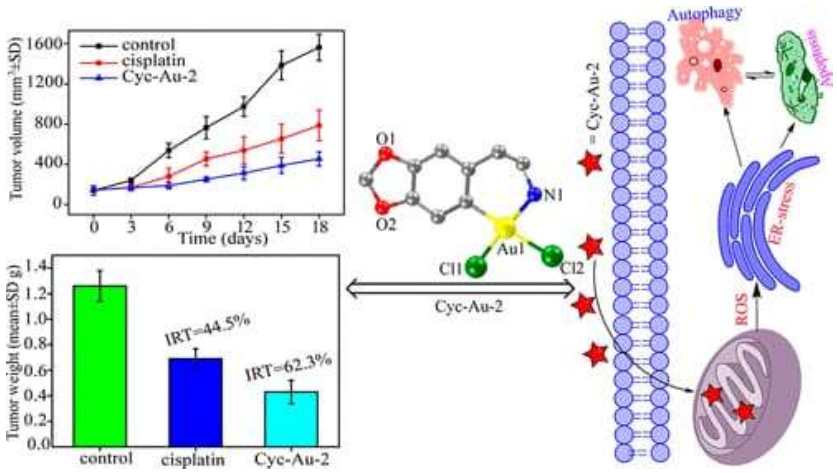


Fig.18: Apoptosis and Autophagy in Mitochondria.

2.3.3 OSMIUM ARENES AS ANTICANCER AGENTS:

Even though there had been very few statements on the aqueous chemistry of 5d6 Os(II) complexes, this suggested that almost all osmium complexes are reasonably inert, so we did not expect much success when we began work on the design of Os(II) arene anticancer complexes.

For instance, the rates of hydrolysis are almost 100 times slower, while the acidity is 1.5 pka units higher in case of coordinated water [28]. By switching from O, O to O, N to N, N chelates, and specially towards π-acceptors like phenylazopyridines, coordinated water pka decreased. We found good activity, for example, in some chelated complexes like N, O-Chelated picolinated complex reactive and capable of attacking DNA.[29]

As compared to the monodentate ligand, Os(II) arene complexes with specific phenylazopyridine ligands (π-acceptor ligands) were more powerful and unreactive with iodide. They are active in vivo and 49 times more effective on average in a Sanger panel of 809 cancer cell lines than cisplatin. Redox methods of action are main reason to cause fast bursts of reactive oxygen species (ROS), especially superoxide, in cancer cells. Recent discoveries of the osmium distribution in cancer cells treated with physiologically appropriate dosages of the complex is almost shown using nano focused x-ray fluorescence shows localisation in specific areas of cells resembling mitochondria.

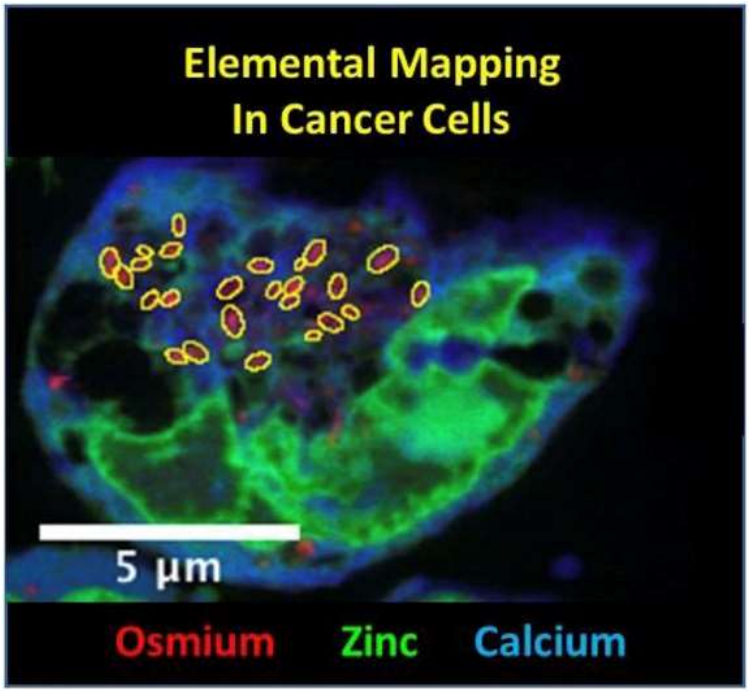


Fig.19: Elemental mapping in cancer cells.

These complexes are candidates for preclinical development.

3. FUTURE TRENDS IN THE USE OF METALLOCENES IN CANCER CHEMOTHERAPY

The bioavailability of almost all metallocene derivatives tested in preclinical or clinical studies is constrained by their severe hydrophobicity when delivered intravenously.

Macromolecular formulations of Metallocenes such as cyclodextrins , which likely have a higher application in humans. [30] Additionally, several metallocene-functionalized from various titanocene dichloride compounds use a different strategy but still aim to overcome the solubility issues of metallocene in medium.

4. CONCLUSION

As one of the few antitumoral medications with a healing effect, cisplatin is one of the most effective and requires special attention. Nuclear DNA contact and the inability of the cell to respond to DNA strains having covalently linked moiety of dichloridoplatinum(II) play a significant role in the action of cisplatin.

In addition to DNA, cisplatin may interact with other biomolecules (thioproteins, RNA), which could deactivate or even modify various signaling pathways involved in mediating cell death, depending on the cell type.

Specifically, cisplatin has significant impacts on MAP-mediated signaling pathways (such as ERK, JNK, and p38). Only recently, the information of cisplatin on the cellular processing become available. Studies on the biological effects and the arrival of cisplatin resistance phenotypes provide critical information that can be used to produce platinum and non-platinum metal-based medicines for cancer therapy that are more effective and less harmful. It is to be predicted that non-platinum metal compounds may have toxic side effects and anticancer efficacy that are notably different from those of platinum-based medications.

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