Platinum based Schiff Base Complexes as anti-cancer agents

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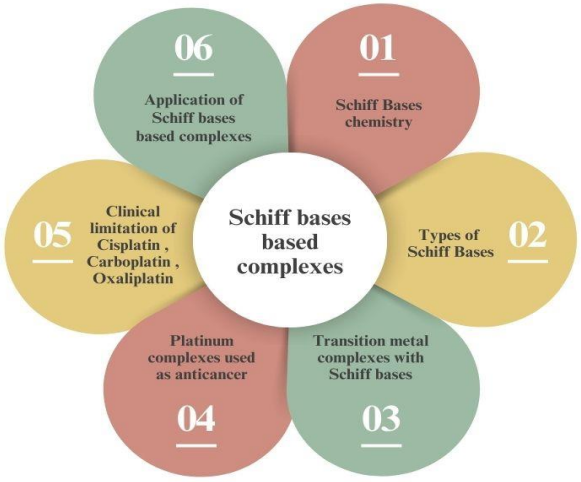
Abstract

This review paper explores the promising realm of metal-based complexes in anticancer therapies, focusing on their diverse applications and efficacy in combating cancer. The investigation delves into the pivotal role of transition metal complexes, particularly the significance of Schiff base complexes, in augmenting anticancer strategies. Notably, platinum metal complexes emerge as a cornerstone in this domain, with a specific spotlight on Cisplatin (Platinol) and Oxaliplatin. The comprehensive analysis encompasses the mechanisms underlying the anticancer properties of metal-based complexes, elucidating their interactions with biological systems and their distinct mode of action against cancerous cells. Specifically, within the platinum metal complexes, the review elucidates the molecular mechanisms underpinning the anticancer activities of Cisplatin and Oxaliplatin. Their distinct structures, modes of action, and clinical applications in various cancer types are outlined, emphasizing their pivotal roles in modern oncology. This review amalgamates current knowledge, recent breakthroughs, and future directions in the utilization of metal-based complexes, particularly platinum-based agents, in anticancer therapies. It serves as a comprehensive resource, shedding light on the promising avenues and challenges in this dynamic field, aiming to advance the development of novel and more effective anticancer treatments.



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Introduction

With the change in time, many of the anticancer drugs have been developed. Anticancer drugs are the medications which are used to treat cancers[1]. These drugs are classified as DNA, hormones, monoclonal antibodies, molecular targeting agents, anti-metabolites, and alkylating agents and many other biological agents. Microbial illnesses have bothered the human advancements or development, causing a significant share of destruction globally. Among them is cancer, which is currently the world's second-leading cause of death[2]. Lung cancer, breast cancer, blood cancer, bladder cancer, colon cancer, and other malignancies are among the many forms of cancer[3]. It has been noted that environment also takes the stand for humans in many fields either in the health treatment or treatment of many diseases. In several parts of the world in the ancient times as well as today's time the plants are used for health treatment. Many of the chemicals are extracted from the different-different parts of plants like leaves, stems, roots etc. Material which are made from the herbs for the purposes of improving health are known to be herbal supplements. In some earlier years many of the deaths have been noticed by the cancer. By seeing this situation the growth of multiple anticancer drugs have been increased which are extracted from different-different parts of plant materials. Even many of the natural products that's are used for cancer treatment were modified to enhance the activity of anticancer[4]. A cancer is a terrible disease that lacks a suitable treatment, exposed the humanity in both developing and developed countries and genetic disorder that affects the body cells is cancer. It is a disorder where one or more cells become unable to regulate their growth, leading to the development of a liquid cancer such as cancer of the blood or bone marrow or a solid mass of cells called a tumor. It ranks among the leading causes of death globally. According to the World Cancer Report 2015, 8.8 million cancer-related deaths and over 14.1 million new cases were reported globally[5].To avoid these diseases the crucial requirement is to design or synthesize the new variety of chemicals. A number of drugs, includingOrita-vancinDaptomycin,GAR-936 and Linezolid have been co-modified in antimicrobial chemotherapy or specifically in the development of antibacterial drugs. The main treatments include surgery, chemotherapy and radiotherapy. The another name of radiotherapy is, radiation therapy which uses the radiation to kill the cancer cells from the body. It also based on the matters like electrons, protons, ions which kills the cells of cancer. Chemotherapy is most commonly used cancer treatment which uses the significant chemicals to stop or kill the fast growing cells in the body. Research on the cytotoxic effects of cisplatin has also significantly boosted studies on the potential applications of novel metal complexes as potent anticancer drugs[6].

Metal based complexes are deigned to work through prohibited enzymes, interacting with intra-cellular bio-molecules, increasing lipophilicity, changing how cell membranes operate and other mechanisms. Because metal complexes have a wide range of coordination spheres and oxidation states, it is hypothesized that these features will alter the complexes' kinetic and thermodynamic behaviour toward biological receptors designs of redox potential ligands [7]. Therefore, chelation alters the biological characteristics of both metal moiety and ligands.

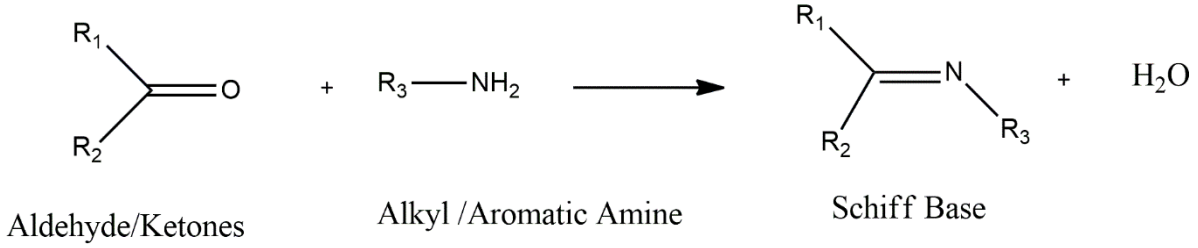
Number of metal complexes of the quinoline group of antibiotics, including norfloxacin, ciprofloxacin and tetracycline were negotiated and found to have more activity than the antibiotic. It was recently found that the combination of bismuth and norfloxacin had more antibacterial activity than norfloxacin alone [8]. Higher bio availability of the complex is assumed to be the cause of the higher activity. As a result, the creation of metal complexes can cooperate in the transfer of organic ligands into bacterial cells. For example: Tetracycline's Pd(II) complex has been shown to be sixteen times more effective than the parent drug against the tetracycline-resistant strain whereas doxycycline's Pd(II) complex is two times more effective than the parent molecule.

Multiple studies on Schiff bases transition metal complexes explain their bio activity effectiveness against the variety of bacterial and fungi species. Due to the wide range of properties, they possess, hetero-cyclic Schiff base (HSB) metal complexes which have dominated medicinal chemistry. As broad spectrum antifungal, antibacterial, and antiviral medicines, schiff base complexes coupled with heterocyclic species including 4-aminoantipyrene,1,2,4-triazoles,pyrazole, benzoxazoles and triazines have drawn a lot of attention [9]. The amazing features are that the heterocyclic system bestows on such ligands and their metal complexes are the factor in the huge enthusiasm surrounding the preparation of hetero cyclic schiff base compounds. Pharmaceutical chemists must overcome the obstacles in order to relieve the discomfort brought on cancer, in addition to antimicrobial infections. The metal-based treatments are now at the forefront in the war against cancer Inspite of being highly effective in the treatment of range of malignancies, cisplatin exhibits drug resistance and limits of dose side effects which are partially reversed by the use of additional platinum medicines [10].These problems have spurred a thorough investigation and motivated chemists to develop novel strategies based on diverse ligands and metals with pharmacological characteristics that are targeted at different targets. Schiff base complexes of platinum have garnered attention for their potential anticancer activity. These complexes typically involve platinum(II) or platinum(IV) ions coordinated with Schiff base ligands. The Schiff base ligands can be derived from various primary amines and aldehydes or ketones. These complexes are often designed to exhibit enhanced cytotoxicity towards cancer cells while minimizing toxicity to healthy cells.

1.1 Schiff Bases chemistry:-

Hugo Schiff devised the most well-known and conventional method, which is used to prepare a Schiff Base (SB), which is regarded as a condensation product, by condensing an amine with an aldehyde or ketone (carbonyl compound) under a variety of reaction conditions, including different solvents (**Scheme 1**) [11]. An azomethine (-C=N-) or imine group has taken the role of the carbonyl group (CO) in Schiff bases, which are nitrogen cognates of aldehydes or ketones . Aldehyde’s carbonyl group produces ald-imines, whereas a ketone's carbonyl group produces keto-imines [12].The general formula for Schiff bases is $R_1R_2C=N-R_3$, where R_1, R_2 and R_3 can be any alkyl, aryl, or hetero-aryl group. These azo-methinic or imine compounds have a large range of biological activities. Because of their antibacterial, antifungal, anticancer, antitumor, antiradical, antimalarial, antitubercular and antiviral properties, a number of Schiff bases and their transition metal complexes have drawn the attention of medicinal chemists and biologists towards themselves [13]. Due to these compounds metal chelating properties and

their biological activity has been increased. These compounds are considered versatile ligands (i.e., the ions or molecules that donate the pair of electrons to the central metal atom for the formation of co-ordination complexes) because of their flexibility throughout the synthesis process and structural stability. [14].



Scheme 1 General synthesis of Schiff bases

Many techniques used for the formation of azo-methines or imines. In addition to it Schiff bases are being made through a more effective, safe, and environment friendly strategy that incorporates the use of universal solvent (water) in the manufacture of these compounds [15]. By encouraging a reversible reaction, Schiff base reactions result in the creation of water molecules, which slow down the rate of reaction. Dehydrating substances MgSO4,Na2SO4 or many other molecules can be used to remove water and enhance the activity of synthesis of Schiff bases. When it comes to solvents, ethanol is the ideal option and also a need, for the production of Schiff bases, at room temperature .By conducting the reaction in acidic or basic conditions, a Schiff base reaction often move faster [16].

1.2 There are different types of Schiff Bases and their complexes which plays the vital role in chemistry.

Schiff bases are versatile compounds known for their diverse applications in various fields. They can be produced from a variety of carbonyl compounds and primary amines, giving rise to a multitude of Schiff base types [18].

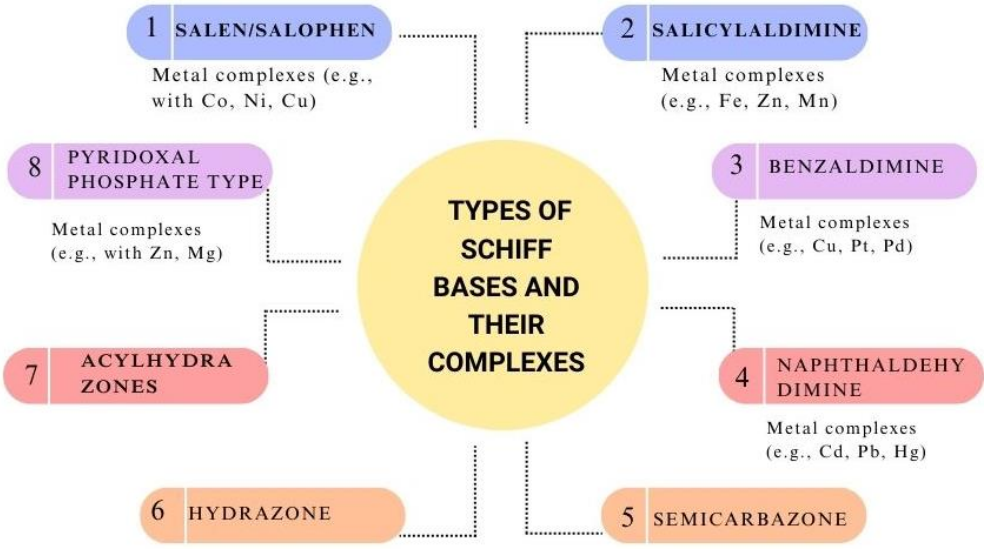
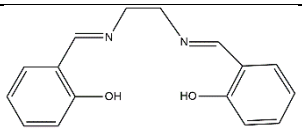
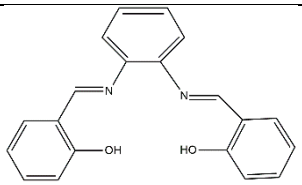
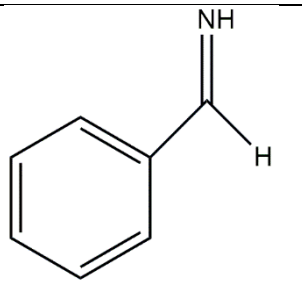
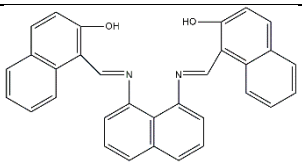
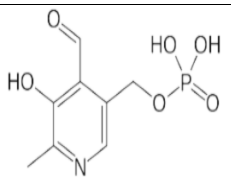


Fig. 1 Types of Schiff bases derivatives

Schiff bases represent a diverse class of compounds (**Fig. 1**) formed by the condensation of primary amines with aldehydes or ketones. Among them, the Salen/Salophen type (**Table 1)** stands out for its wide application in coordination chemistry and catalysis, characterized by the presence of a bis(phenolate) backbone .

Table 1 Salophen based Schiff bases

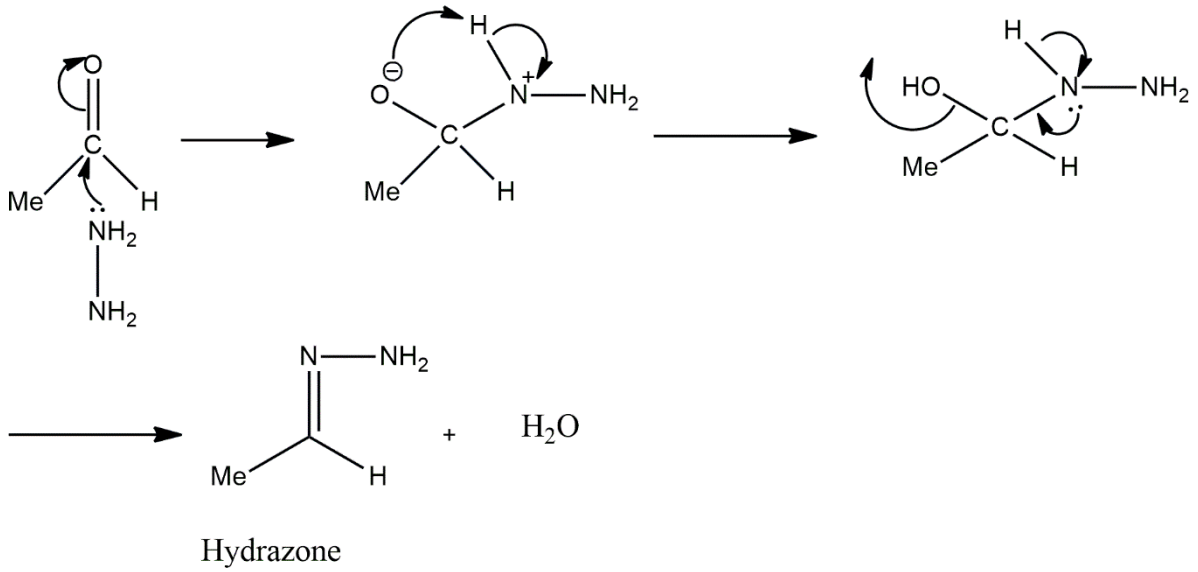
Schiff Base Type	**Derivation**	**Complexes**	**Applications**	**Reference**
Salen/Salophen	Salicylaldehyde or derivatives + primary amines	Metal complexes (e.g., with Co, Ni, Cu)		[19]
Salicylaldimine	Salicylaldehyde + primary amines	Metal complexes (e.g., Fe, Zn, Mn)		[20]
Benzaldimine	Benzaldehyde + primary amines	Metal complexes (e.g., Cu, Pt, Pd)		[21]
Naphthaldehydimine	Naphthaldehyde + primary amines	Metal complexes (e.g., Cd, Pb, Hg)		[22]
Pyridoxal phosphate type	Pyridoxal phosphate + amino acids or other molecules	Metal complexes (e.g., with Zn, Mg)		[23]

1.2.1 **Some other types of Schiff bases :-**

a) Hydrazone-type Schiff-bases:

Hydrazine/hydrazide and their derivatives, are the condensation products of carbonyl compounds to form ligands. These ligands have been found to have a variety of multi-metallic complexes that exhibit various coordination behaviour with various metal atoms[24].Moreover, hydrazones may have acyl-hydrazone or aroyl-hydrazone Schiff base

ligands, which are created when an acyl-hydrazide or an aroyl-hydrazide is condensed with any carbonyl molecule (**Fig. 2**). An extra donor site in the form of a C=O group is added to an acyl or aryl-hydrazone schiff base increasing its adaptability and versatility[25]. Although ligands of the hydrazone type should be uni-dentate because they have only one donating atom (iminic nitrogen) and their subgroups (acyl and aroyl-hydrazones) exhibit bi-dentate (N,O) or tridentate (N,O, X=O,N,S) behaviour [26].



Hydrazone

Fig. 2 Mechanism of Schiff base synthesis from hydrazine

1.2.2 Semicarbazone type Schiff bases:

These types of ligands are good chelating agents which are having the lipophilic(ability to dissolve in the non-polar solvents). The carbonyl compounds' condensation process also yields these ligands [27]. .Due to the presence of different donating sites semicarbazones ligands exhibit in numerous modes of bonding. Such ligands have two donating sites (**Fig. 3)** marked as bidentate but also can act as tridentate [28].

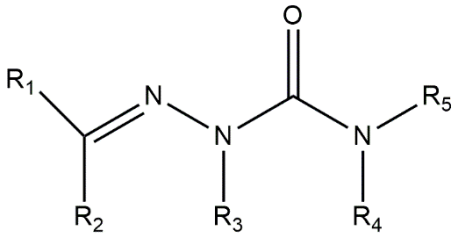


Fig. 3 General structure of semicarbazone

2. Transition metal complexes with Schiff bases:-

These metals are biologically active which makes them important metal complexes. As these transition metals also plays the important role in the medicinal industries [29].These transition metals have different-different oxidation states like +2 to +7 which can interact with multiple of negatively charged molecules. This unique interaction makes the transition metals as pharmacological application [30]. Transition metals are useful in developing anticancer drugs because of their large variety of geometries, coordination numbers, and choices of ligands that will coordinate, all of which have varied redox potentials and stabilities [31].

Varieties of transition metals used as anticancer agents like Platinum(Pt),Gold(Au),Manganese(Mn),Cobalt(Co),Copper(Cu),Ruthenium(Ru),Chromium(Cr), Iron(Fe) and many more (**Table 2**).

Table 2 Transition metal based Schiff base complexes for anticancer activity

Element	**Common Oxidation States**	**Use in Anticancer Activities**	**Example**	**Reference**
Platinum (Pt)	+2, +4	Drugs based on platinum, such as Oxaliplatin, Carboplatin, and Cisplatin, are frequently used in chemotherapy to treat a variety of malignancies.	Cisplatin, Carboplatin, Oxaliplatin	[32]
Gold (Au)	+1, +3	Gold compounds have shown promise in inhibiting tumor growth and potentially overcoming drug resistance.	Auranofin (used in some cancer treatments)	[33]
Manganese (Mn)	+2, +3, +4, +7	Manganese complexes can exhibit cytotoxic effects and have been explored for potential anticancer activity.	Manganese complexes in research studies	[34]
Cobalt (Co)	+2, +3	Cobalt compounds have been investigated for their potential in cancer treatment, but their use is limited compared to other metals.	Cobalt complexes in experimental studies	[35]
Copper (Cu)	+1, +2	Particularly in preventing tumor growth and angiogenesis—the creation of new blood vessels to assist tumor growth—compounds containing copper have demonstrated considerable anticancer efficacy.	Copper compounds in experimental research	[36]
Ruthenium (Ru)	+2, +3, +4	The potential of ruthenium complexes to stop the growth of cancer cells and overcome treatment resistance has been discovered and investigated.	RAPTA compounds (Ruthenium-based drugs in research)	[37]
Chromium (Cr)	+2, +3, +6	Chromium has limited direct use in cancer treatment but is studied for its potential involvement in cancer metabolism and mechanisms.	Chromium in cancer metabolism research	[38]

Iron (Fe)	+2, +3	Iron-based compounds have demonstrated promise in the treatment of cancer, especially when it comes to selectively delivering medications to malignant regions or targeting tumor cells.	Iron oxide nanoparticles in drug delivery systems	[39]

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Transition metal complexes with Schiff bases have emerged as promising candidates for anticancer therapy. These complexes, featuring metals like platinum, copper, nickel, cobalt, and iron, coordinated with Schiff base ligands derived from various primary amines and aldehydes or ketones, exhibit potential cytotoxic effects against cancer cells. Among these, platinum complexes, notably cisplatin derivatives, stand out as established anticancer drugs.

3. Platinum complexes:-

Platinum complexes are also known for the best chemotherapeutic agents for treating the cancers.The evolution of platinum-based anti-cancer drugs has been a significant development in cancer treatment. Platinum complexes have been extensively studied and used as effective anticancer agents, playing a pivotal role in chemotherapy. The most prominent platinum complexes used in cancer treatment include Cisplatin, Carboplatin, and Oxaliplatin.

- Developed in the late 1960s and licensed for use in the treatment of cancer in 1978, cisplatin was the ground-breaking medication. It showed promise as a treatment for a number of tumors, including colorectal, ovarian, and breast cancer [40]. However, its non-specific nature led to systemic toxicity and long-term damage to normal tissues, limiting its use.
- To address these limitations, carboplatin, a second-generation platinum drug, was developed based on cisplatin. It took over a decade to reach clinical use and was designed to have lower hydration rates due to specific chemical modifications. By dramatically lowering systemic toxicity, which includes problems like hepatotoxicity, nephrotoxicity, neurotoxicity, and ototoxicity, carboplatin showed increased safety. Its reduced toxicity allowed for higher doses to be used in aggressive tumors [41].Despite these advancements, the development of resistance to platinum drugs during cancer treatment remained a significant concern. Both cisplatin and carboplatin tended to induce drug resistance, prompting the development of the third-generation platinum drug, oxaliplatin. Oxaliplatin operates similarly to cisplatin but does not generate cross-resistance with either cisplatin or carboplatin [42].
- Oxaliplatin's unique properties enable it to complement the effects of cisplatin in clinical anti-cancer treatments without inducing the same resistance mechanisms. This complementary action has made oxaliplatin and cisplatin valuable in combined therapy approaches and they have been widely used in cancer treatment.

  None of the more recent platinum-based anti-cancer medications have yet found broad clinical use, despite significant attempts to develop them. Researchers continue to explore novel approaches to overcome drug resistance and enhance the efficacy and safety profile of platinum drugs in cancer therapy [43].

Platinum complexes as anticancer agents

The most common used platinum complexes (**Fig. 4**) for anticancer activity are cisplatin, oxaliplatin and carboplatin.

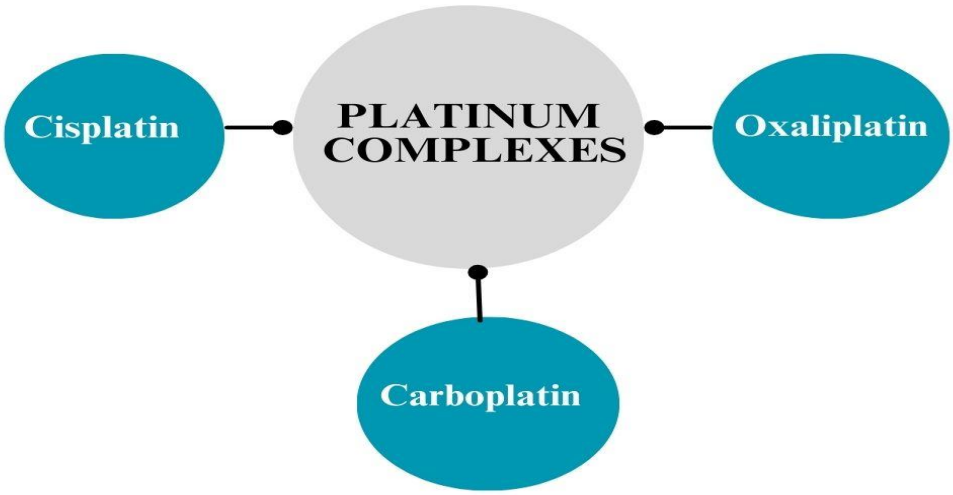

Fig. 4 Classification of platinum based Schiff base complexes

3.1 Cisplatin (Platinol): Cisplatin (**Fig. 5**), also known by its brand name Platinol, is one of the most well-known and widely used platinum complexes in cancer chemotherapy. It has been a cornerstone in the treatment of various types of cancers since its discovery in the 1960s**.**Cisplatin is particularly effective against testicular, ovarian, bladder, and lung cancers, among others. Despite its efficacy, cisplatin can cause significant side effects, including nephrotoxicity, neurotoxicity, and ototoxicity**.**

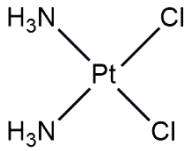

Fig. 5 Structure of Cisplatin

Mechanism of Action: By creating covalent bonds with DNA, cisplatin creates intrastrand and DNA cross-links, which are how it fights cancer. These cross-links prevent transcription and DNA replication, which causes rapidly dividing cancer cells to undergo apoptosis, or cell death [44].

a. **Formation of DNA Cross-Links:**

Cisplatin, a widely used platinum-based chemotherapy drug, exerts its anticancer effects by instigating a sequence of events that profoundly alter the structure and function of DNA within cancer cells. Once administered, cisplatin enters the nucleus of cancerous cells, where it undergoes a chemical transformation known as aquation. This process replaces its chloride ions with water molecules, generating highly reactive species [45]. These activated forms of cisplatin interact with the DNA molecule, specifically binding to the purine bases, primarily guanine. Through coordination chemistry, cisplatin forms covalent bonds with the nitrogen atoms at the N7 positions of guanine bases in the DNA strands. These covalent bonds are important in producing DNA adducts, including intrastrand and inter strand cross-links.

Whereas interstrand cross-links develop between guanine bases on complementary DNA strands, intrastrand cross-links happen between neighbouring guanine bases on the same DNA strand [46]. The formation of these cross-links disrupts the normal helical structure of DNA, causing distortions and preventing the strands from separating properly during replication and transcription processes. This interference impedes the cell's ability to accurately replicate its genetic material and synthesize essential proteins, leading to cellular dysfunction and, ultimately, programmed cell death, known as apoptosis.

a. Interference with DNA Function:

Cisplatin, a potent chemotherapy agent, exerts its influence on cancer cells by profoundly affecting the intricate processes involving DNA replication and transcription. Once cisplatin forms covalent bonds with the DNA molecule, particularly guanine bases, it disrupts the normal structure of the DNA double helix [47]. This structural interference hampers the ability of DNA to unwind and replicate accurately during cell division. DNA serves as the blueprint for cellular functions, and when cisplatin-induced DNA lesions occur, they impede the accurate duplication of genetic material necessary for cell proliferation [48]. Additionally, cisplatin's interference with DNA transcription inhibits the synthesis of vital proteins essential for the survival and growth of cancer cells. The disrupted processes of replication and transcription, crucial for cell proliferation and functionality, contribute to the impairment of cancer cell division and function, ultimately leading to cell death via programmed mechanisms like apoptosis [49].

b. Induction of Apoptosis (Cell Death):

Cisplatin, a key chemotherapeutic agent, triggers a complex cellular response in cancer cells that culminates in programmed cell death, known as apoptosis. When cisplatin causes severe damage to the DNA through the formation of cross-links, it initiates a series of intracellular signaling pathways. These pathways are part of the cell's defense mechanisms against genetic damage [50]. The cell perceives the extensive DNA damage caused by cisplatin as a threat to its integrity and attempts to repair it. However, if the damage surpasses the cell's repair capacity or is irreparable, it activates specific signaling cascades that culminate in apoptosis. These signaling pathways involve various cellular components that orchestrate the activation of specific proteins, such as caspases, which are enzymes responsible for executing the apoptotic process. Activation of caspases triggers a series of events within the cell, leading to DNA fragmentation, cytoskeletal breakdown, membrane blebbing, and ultimately cellular disintegration. Apoptosis serves as a regulated mechanism for eliminating damaged or genetically aberrant cells, preventing their uncontrolled proliferation and spread within the body [51]. In the context of cisplatin treatment, the induction of apoptosis in cancer cells is crucial for limiting tumor growth and facilitating the therapeutic effect of the drug in combating cancer.

B. Clinical Applications:

Cisplatin, a widely utilized platinum-based chemotherapy drug, demonstrates notable efficacy against a diverse array of cancers, making it a cornerstone in oncology. Its effectiveness spans across several malignancies, including testicular, ovarian, bladder, lung, head and neck, and various solid tumors [52]. In testicular cancer, Cisplatin-based regimens have substantially improved survival rates. For ovarian cancer, it is a key component in both initial treatment and recurrent disease management. In bladder cancer, Cisplatin-based chemotherapy remains a mainstay, particularly in advanced stages [53]. Moreover, it plays a pivotal role in treating certain types of lung cancer, head and neck cancers, and other solid tumors. The versatility of Cisplatin in targeting different cancer types underscores its significance in diverse oncological settings, where it continues to be a crucial component in treatment protocols aimed at combating various malignancies [54].

3.2 Carboplatin (Paraplatin): Carboplatin (**Fig. 6)**, marketed under the brand name Paraplatin, is a platinum-based chemotherapy drug used to treat various types of cancer. It is structurally similar to cisplatin but differs in its chemical properties and side effect profile.

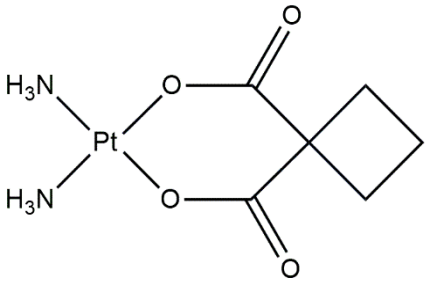

Fig 6. Molecular structure of Carboplatin

A. **Mechanism of Action:**

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a) **DNA Cross-Linking:**

- Carboplatin enters the cell and undergoes a hydrolysis process, forming reactive species similar to Cisplatin.
- Once activated, carboplatin interacts with DNA by covalently binding to the purine bases within the DNA strands, notably guanine, just like Cisplatin [55].
- DNA adducts, such as intrastrand and interstrand cross-links, are created as a result of this interaction, upsetting the structure of the DNA and preventing it from working normally [56].

b) **Disruption of DNA Function:**

- Similar to Cisplatin, the formation of DNA cross-links by carboplatin distorts the DNA double helix, impairing its ability to unwind during replication and transcription processes [57].
- This interference with DNA replication and transcription impedes cancer cells' ability to accurately duplicate genetic material and synthesize crucial proteins, thereby inhibiting their proliferation and survival [58].

c) **Induction of Cell Death:**

- The disruption caused by carboplatin-induced DNA lesions initiates a cellular response, activating repair mechanisms within the cell to counteract the damage.

- When the degree of damage exceeds the ability of the cell to heal itself, the cellular machinery triggers programmed cell death, known as apoptosis, leading to the elimination of the damaged cancer cells [59].

B. Differences from Cisplatin:-

Carboplatin, an analog of the well-established chemotherapy drug Cisplatin, exhibits distinctive characteristics in its mechanism of action and clinical profile, stemming from subtle structural differences. While both compounds operate by forming DNA adducts, Carboplatin's altered structure results in differences in reactivity and kinetics of DNA binding compared to Cisplatin. Notably, Carboplatin forms DNA cross-links at a slower rate than Cisplatin, influencing the spectrum and efficiency of DNA lesions it induces within cancer cells [60]. This variance in reactivity impacts the potency and cytotoxic effects observed. Furthermore, Carboplatin is considered to possess a relatively lower reactivity, contributing to a modified toxicity profile, potentially mitigating severe side effects associated with Cisplatin, such as nephrotoxicity and neurotoxicity [61]. These differences in reactivity, kinetics, and toxicity profiles between Carboplatin and Cisplatin underscore their distinct clinical applications and highlight Carboplatin's relevance as an alternative with potentially reduced adverse effects while retaining anticancer efficacy.

C. Clinical Applications of Carboplatin:

Carboplatin's clinical significance lies in its role as a valuable alternative to Cisplatin in cancer treatment, especially in cases where reduced toxicity or certain tolerability profiles are preferable [62]. Its application spans across various malignancies, positioning Carboplatin as an essential component in chemotherapy regimens aimed at combating different cancers while striving to minimize adverse effects on patients.

i. **Ovarian Cancer:**

- Often used in conjunction with other chemotherapeutic drugs such as paclitaxel, carboplatin is a cornerstone in the treatment of ovarian cancer. It is employed both in the initial treatment (first-line therapy) and for recurrent ovarian cancer [63].

ii. **Lung Cancer:**

- In the treatment of lung cancer that is not small cell (NSCLC), Carboplatin is frequently utilized in combination regimens, especially for patients who cannot tolerate Cisplatin due to its higher toxicity potential [64].

iii. **Other Cancers:**

- Carboplatin finds application in various other solid tumors, including head and neck cancers, bladder cancer, testicular cancer, and some types of brain tumors [65].

3.3Oxaliplatin:-

Oxaliplatin (**Fig. 7)**, marketed under the brand name Eloxatin, is a platinum-based chemotherapy drug that distinguishes itself from Cisplatin and Carboplatin due to its unique structural features and mechanism of action [66].

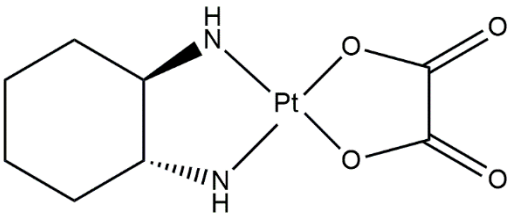

Fig. 7 Molecular structure of Oxaliplatin

A. Mechanism of Action of Oxaliplatin:

1) Structural Differences:

Oxaliplatin, a platinum-based chemotherapeutic agent, displays structural disparities from its counterparts, Cisplatin and Carboplatin, which significantly impact its mode of action [67]. Unlike Cisplatin and Carboplatin, Oxaliplatin features a unique chemical composition characterized by an additional oxalate ligand and a bidentate 1,2-diaminocyclohexane (DACH) ligand instead of the diaminocyclobutane (DACH) ligand found in Carboplatin. This structural dissimilarity endows Oxaliplatin with distinctive interactions within cancer cells. The presence of the DACH ligand influences the geometry and reactivity of the compound, contributing to its specific mode of binding to DNA. This distinct structural arrangement influences Oxaliplatin's ability to generate intrastrand DNA cross-links, a different type of DNA lesion compared to the interstrand cross-links induced by Cisplatin and Carboplatin [68]. Consequently, these unique structural features underlie Oxaliplatin's altered mechanism of action, contributing to its clinical efficacy and distinct biological effects in cancer treatment protocols.

2) Formation of DNA Adducts:-

Oxaliplatin, a platinum-based chemotherapy drug, exerts its anticancer effects by initiating the formation of DNA adducts within cancer cells. Once administered, Oxaliplatin undergoes activation, leading to the generation of reactive species that interact with DNA [69]. Specifically, it forms covalent bonds predominantly with guanine bases in the DNA strands. Unlike Cisplatin and Carboplatin, Oxaliplatin's binding pattern primarily induces intrastrand DNA cross-links [70]. This unique interaction involves the formation of covalent bonds between adjacent guanine bases on the same DNA strand, leading to the creation of intrastrand cross-links within the DNA double helix. These intrastrand cross-links distort the DNA structure, impeding the normal processes of DNA replication and transcription. Consequently, the impaired DNA function hampers cancer cell division and triggers cellular responses that may culminate in programmed cell death, contributing to Oxaliplatin's efficacy as an anticancer agent against various malignancies [71].

3) Induction of DNA Lesions:-

The induction of DNA lesions by Oxaliplatin, a platinum-based chemotherapy agent, involves a distinctive mechanism compared to its counterparts, Cisplatin and Carboplatin. Oxaliplatin primarily creates intrastrand DNA cross-links within the DNA double helix. This unique process involves the formation of covalent bonds between adjacent guanine bases on the same

DNA strand. The intrastrand cross-links disrupt the DNA structure by preventing the DNA from unwinding properly during replication and transcription processes [72]. These alterations hinder the accurate duplication of genetic material and the synthesis of essential proteins required for cancer cell proliferation and survival. The specific induction of intrastrand cross-links by Oxaliplatin results in distinct DNA lesions, differentiating its mechanism of action from Cisplatin and Carboplatin and contributing to its efficacy in impeding cancer cell growth and inducing cellular responses that may lead to programmed cell death.

B. Clinical Applications of Oxaliplatin:

1. **Colorectal Cancer Treatment:**

- Oxaliplatin is prominently utilized in combination therapies for both early and advanced stages of colorectal cancer.
- It is often part of chemotherapy regimens used after surgical removal of the tumor (adjuvant therapy) or in advanced cases where the cancer has spread (metastatic colorectal cancer) [73].

2. **Combination Regimens:**

- Other chemotherapy drugs including folinic acid (leucovorin) and 5-fluorouracil (5-FU) are frequently given in addition to oxaliplatin.
- This combination, known as FOLFOX (folinic acid, fluorouracil, and oxaliplatin), has become a standard treatment approach for colorectal cancer [74].

3. **Effectiveness Against Resistance:**

- Oxaliplatin has demonstrated efficacy in cases where tumors may have developed resistance to other platinum-based drugs, offering a valuable alternative treatment option for patients resistant to certain therapies.

C. Significance in Colorectal Cancer:

- **Improved Survival Rates:** Incorporating Oxaliplatin into combination therapies has significantly improved survival rates and outcomes for patients with colorectal cancer.

- **Adjuvant and Palliative Settings:** Its application spans both adjuvant settings (post-surgery) and palliative care (advanced or metastatic disease), showcasing its versatility in different stages of the disease [75]

4. Clinical limitation of Cisplatin, Carboplatin, Oxaliplatin

Table 3 Clinical limitations of platinum complexes

5. Application of Schiff bases based complexes for anticancer activity:

Because of their many biological properties, including possible uses in anticancer therapy, schiff bases and their metal complexes have attracted a lot of attention in medicinal chemistry [81]. Here's an overview of the application of Schiff base-based complexes in anticancer activity:

5.1 Metal Complexes with Schiff Bases:

Schiff bases are versatile ligands that can coordinate with various metal ions, forming metal complexes. These complexes often exhibit enhanced biological activities compared to the free

Clinical Limitations	Cisplatin (Platinol)	Carboplatin (Paraplatin)	Oxaliplatin (Eloxatin)	Reference
Nephrotoxicity	Significant risk of nephrotoxicity, affecting kidneys.	Less nephrotoxic compared to Cisplatin.	Moderate risk of kidney-related issues.	[76]
Neurotoxicity	Known for causing neurotoxic effects, including nerve damage.	Lower incidence of neurotoxicity compared to Cisplatin.	Peripheral neuropathy is a common side effect.	[77]
Gastrointestinal Issues	Can cause severe nausea, vomiting, and gastrointestinal disturbances.	Generally better tolerated in terms of GI side effects.	May lead to gastrointestinal discomfort.	[78]
Resistance Development	Prolonged use can lead to cancer cells developing resistance.	Resistance development may occur but less frequent.	Can be effective in cases resistant to other platinum drugs.	[79]
Ototoxicity	May lead to hearing loss or auditory impairment.	Lower risk of causing ototoxicity.	Not typically associated with significant ototoxic effects.	[80]

ligands.Transition metal ions like copper, cobalt, nickel, and others, when coordinated with Schiff bases, create complexes with distinct structural and chemical properties that influence their biological functions.

- Metal complexes with Schiff bases exhibit diverse chemical, structural, and biological properties influenced by the choice of metal ion and the ligand's structure [82].
- They often possess unique geometries and coordination modes that impact their stability, reactivity, and electronic properties.

a. Catalysts

Schiff base metal complexes stand as pivotal catalysts in organic synthesis, pivotal due to their exceptional ability to activate specific substrates selectively. These complexes serve as catalysts by providing a platform for intricate chemical transformations, facilitating numerous organic reactions that might otherwise proceed sluggishly or not at all under normal conditions [83].

Their catalytic prowess lies in their capability to selectively activate functional groups within molecules, thereby initiating and guiding specific chemical reactions towards desired products. Schiff base metal complexes act as efficient catalysts by coordinating with substrates, allowing for controlled activation of chemical bonds and facilitating the formation of new bonds critical in organic synthesis [84]. The selectivity and specificity of these complexes in activating particular functional groups contribute significantly to their utilization in various synthetic methodologies, ultimately aiding in the synthesis of complex organic molecules essential in pharmaceuticals, materials science, and diverse branches of chemical research [85].

b. Biological and Medicinal Applications:-

Schiff base metal complexes have demonstrated notable potential in biological and medicinal applications, showcasing their significance in these domains. These complexes offer a promising avenue in medicinal chemistry and various biological systems due to their diverse properties and interactions.

- In medicinal chemistry, Schiff base metal complexes serve as essential building blocks for the design and development of potential pharmaceutical agents. Their ability to bind selectively to specific biological targets, such as enzymes or receptors, opens avenues for designing drugs with enhanced efficacy and reduced side effects. These complexes exhibit varied pharmacological activities, including enzyme inhibition, antioxidative properties, and interactions with biomolecules, contributing to their relevance in drug discovery and development [86].
- Furthermore, in biological systems, Schiff base metal complexes have displayed interactions with biological molecules, modulating cellular processes, and exhibiting potential therapeutic effects. They have demonstrated promising results in preclinical studies as candidates for treating various diseases due to their ability to influence biochemical pathways, target specific cellular components, and exert cytotoxic effects on cancer cells or microbial pathogens [87].
- Their versatility and tunable properties contribute to their potential applications as diagnostic agents, imaging probes, and tools for understanding biological processes. Continual exploration and research into the biological and medicinal aspects of Schiff base metal complexes hold promise for future advancements in medicine, facilitating the development of novel therapeutic agents, diagnostic tools, and insights into biological mechanisms [88].

c. Anticancer and Antimicrobial Activities:-

Schiff base metal complexes have emerged as promising candidates in the fields of oncology and antimicrobial research, showcasing their potential as agents with notable anticancer and antimicrobial activities. Schiff base metal complexes, owing to their structural diversity and ability to interact selectively with biological targets, demonstrate substantial potential in combating cancer and microbial infections [89]. Their specific mechanisms of action, cytotoxicity towards cancer cells, and antimicrobial activities underscore their significance as potential candidates for future therapeutic interventions in oncology and infectious diseases [90].

Anticancer Activities:

1. Cytotoxic Effects: Some Schiff base metal complexes exhibit significant cytotoxicity against cancer cells. They interfere with crucial cellular processes, inducing cell cycle arrest or promoting programmed cell death (apoptosis) in cancerous cells while sparing healthy cells to some extent [91].
2. Targeted Actions: These complexes often demonstrate selective interactions with specific molecular targets within cancer cells, disrupting signaling pathways or DNA replication mechanisms, thereby impeding tumor growth [92].
3. Potential for Chemotherapy: Due to their cytotoxic effects, selectivity towards cancer cells, and potential to overcome resistance mechanisms, some Schiff base metal complexes hold promise as potential chemotherapeutic agents [93].

Antimicrobial Activities:

1. Antibacterial and Antifungal Properties: Certain Schiff base metal complexes exhibit notable antimicrobial activities against bacterial and fungal pathogens. They interfere with microbial cell structures or enzymatic functions, inhibiting their growth or causing cell death [94].
2. Antiviral Effects: While research in this area is ongoing, some studies suggest that certain complexes might possess antiviral properties, showing inhibitory effects against viral replication or attachment to host cells [95].

5.2 Anticancer Potential:

Schiff base metal complexes' anticancer properties offer a possible path for the creation of cutting-edge anticancer treatments. These complexes exhibit notable properties and mechanisms that contribute to their efficacy in impeding tumor growth and influencing cancer cells' fate [96].

A. Mechanisms of Anticancer Action:

1. **Selective Cytotoxicity:** Schiff base metal complexes demonstrate selective cytotoxicity towards cancer cells while having less impact on normal, healthy cells. This selectivity is crucial in minimizing side effects during treatment[97].
2. **Interference with Cellular Processes:** These complexes often interfere with vital cellular processes within cancer cells, such as DNA replication, transcription, and repair mechanisms [98]. They induce DNA damage, leading to cell cycle arrest or triggering apoptotic pathways, ultimately causing cell death in cancerous cells.
3. **Targeting Specific Pathways:** Some complexes exhibit specificity in targeting particular signaling pathways or molecular targets within cancer cells, disrupting their growth-promoting mechanisms or inducing their apoptosis [99].
4. **Overcoming Drug Resistance:** In certain cases, Schiff base metal complexes have shown potential in overcoming drug resistance mechanisms in cancer cells, making them attractive candidates for addressing resistance issues often encountered in chemotherapy [100].

6. Future direction:

The future prospects in the field of metal-based complexes for anticancer activities are incredibly promising. Ongoing research aims to harness the potential of these complexes by focusing on several key aspects. Firstly, scientists are diligently working to design and synthesize novel metal-based compounds with enhanced selectivity towards cancer cells, minimizing adverse effects on healthy tissues. Furthermore, the exploration of combination therapies involving metal complexes alongside other anticancer agents or treatment modalities

holds immense potential in overcoming drug resistance mechanisms and improving overall efficacy.

- The development of targeted drug delivery systems utilizing these complexes, such as nanoparticles or nanocarriers, presents an exciting avenue to precisely deliver therapeutic payloads to tumor sites while reducing systemic toxicity. Additionally, the integration of advanced computational methods and structural biology techniques continues to provide deeper insights into the molecular interactions and mechanisms of action of these complexes, facilitating the rational design of more potent and specific anticancer agents.
- Collaborative efforts between interdisciplinary fields, including chemistry, biology, and medicine, are pivotal in driving innovation and translating discoveries into clinically viable treatments. As research progresses, the future of metal-based complexes in cancer therapy appears promising, offering the potential for more effective, targeted, and personalized approaches to combat various forms of cancer.

Conclusion:

In conclusion, the realm of metal-based complexes for anticancer therapies represents a captivating frontier in modern oncology. The remarkable progress and extensive research conducted thus far underscore their significance as potential game-changers in cancer treatment. Through this review, it becomes evident that the versatility and efficacy of these complexes, particularly platinum-based agents like Cisplatin and Oxaliplatin, have revolutionized the landscape of chemotherapy. Their distinct mechanisms of action, including DNA damage induction and interference with crucial cellular processes, have demonstrated substantial success in combating various cancers. However, challenges such as drug resistance and adverse side effects necessitate continued exploration and innovation in this field. Looking ahead, future endeavors focus on refining these complexes to improve their selectivity, potency, and specificity towards cancer cells while mitigating toxicity to healthy tissues. The amalgamation of interdisciplinary approaches, including advanced drug delivery systems, novel compound design, and deeper molecular insights, is pivotal in unlocking the full therapeutic potential of these complexes. Moreover, the emergence of combination therapies and personalized medicine, coupled with a deeper understanding of the molecular intricacies of cancer, offers exciting prospects in tailoring treatments to individual patients, potentially enhancing outcomes and reducing adverse effects.

In essence, while challenges persist, the prospects for metal-based complexes in anticancer therapies remain immensely promising. Continued research endeavors and collaborative efforts hold the key to realizing more effective, targeted, and safer treatments, ultimately reshaping the landscape of cancer therapy and offering hope for improved patient outcomes in the future.

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