Advances in Medicinal Chemistry: Metal-Based Compounds as Innovative Therapeutic Agents

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Abstract

The field of medicinal chemistry owes much of its progress to organometallic compounds since they are known to be important for their therapeutic and bioactive effects. In medicine, they are applied to help cure cancer, different bacteria, and problems linked to swelling and the brain. Many compounds made using organometallic chemistry are effective in treating cancer since they only focus on cancer tissue and not on healthy tissues. The development of drugs using organometallic compounds has the potential to assist in handling drug-resistant bacteria and aid the treatment of Alzheimer's and similar diseases. Since they are able to act on redox reactions, DNA, and the immune system, they are essential for finding new breakthroughs in medicine. This chapter covers how organometallic compounds can play a part in medicine and how they could enable the creation of novel treatments.

Keywords: Metals, Compounds, Medicine, Therapeutics, Health

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Introduction

Since these materials are carbon and other metals, their atoms attaching to one another is made possible by a chemical bond (Gasser et al., 2011). A combination of natural and man-made portions in the molecules ensures that the metal and carbon blend easily in the liquid. Just like ions and covalent molecules, they can strengthen their bonds, which becomes beneficial in many circumstances. The importance of these structures for living things and the world is clear from all kinds of living things (Aziz et al., 2024). Metals have been found to benefit medicine because they ease illnesses and maintain the normal functioning of the body. Iron-based medicines are used by doctors in chemical treatment for various medical concerns, while special metals are applied to find different objects inside the body (Ong et al., 2020). Scientists use them to produce drugs because they interact with body components, exist in several forms, and can be slightly modified. Medical organometallic chemistry focuses on producing some compounds that could benefit medicine and discovering how they are processed in the body (Brown et al., 2015). Ferrocene was the first organometallic chemical to be looked at for its medical use after its anti-cancer properties were discovered. Consequently, more research was done on using organometallic chemicals to treat cancer (Koepf-Maier et al., 1987). The first studies on organometallic compounds resulted in them being used as medicines for several health issues. Iridium, ruthenium, and rhodium from the platinum-group metals can be used to make organometallic compounds that could help treat parasite diseases, for example, malaria. Discovering that ferroquine, a metal-carbon-based medicine, works on malaria shows that such drugs differ in how they interact with enzymes (Mbaba et al., 2020). Using real-world instances, we can show how organometallic compounds are used in medicine. In chemotherapy, cisplatin is used to bind with DNA in testicular, ovarian, and lung cancer patients, preventing the cells from reproducing. It has been found that ferrocene-based drugs may prevent HIV from replicating, which brings new opportunities for developing antiviral medicines (Ong et al., 2020). They point out how organometallic compounds can overcome the resistance to traditional medicines and suggest that they will be significant in future medical breakthroughs.

Medical Uses of Organometallic Compounds

During the last couple of years, organometallic compounds have been valuable in medicine due to the effectiveness they show in treating various illnesses. It connects the research on plant or herbal remedies for the treatment of cancer, various viral diseases, inflammation, and cases of Alzheimer's (Brown et al., 2015). The table that follows discusses the agents used in therapy and explains how they can be helpful, but also points out their limitations. Various benefits are given in the Table 1.

A lot of metal complexes are now used to treat illnesses, as they are able to help the body in their own special ways. As shown in Figure 1 below, several metals like titanium, calcium, sodium, iron, copper, and even a few more are used to address a range of diseases. A good example is titanium, which is used in joint replacement, and strontium is used as a medicine for people affected by bone cancer (Diao et al., 2024). Often, sodium and iron compounds are added to medicines to address conditions such as heartburn and high blood pressure, while copper compounds are used to address Menkes disease (Zhang et al., 2022). It is also important to note that mixing silver and zinc can slow down the growth of harmful bacteria, so these chemicals are often found in treatment for burns and infections. Some other metal complexes, for example, those from vanadium and lithium, are under investigation to see if they can help control blood sugar in diabetes and improve emotional well-being in other patients (Matai et al., 2020). The versatility of metal complexes extends to their roles in cancer therapy, neurodegenerative diseases, and infectious diseases, highlighting their significance as therapeutic agents. Ongoing research continues to expand their applications, emphasizing the importance of organometallic compounds in enhancing efficacy and selectivity for specific medical conditions.

Table 1: Benefits of organometallic compounds and their health risks

Therapeutic Agents	Uses	Limitations	References
Iridium (III) complexes	ROS-mediated apoptosis and mitochondrial malfunction as remedies for cancer.	Potential toxicity to normal cells and the need for further research on their mechanisms and long-term effects.	(Lo et al., 2012)
UiO-66-NH_2 (MOF based on zirconium)	Bone regeneration and the treatment of bone tumors.	Need for further studies on long-term safety and potential side effects in clinical applications	(Yuan et al., 2023)
Complexes based on gold(I) and including SERD and TrxR inhibitors	Treatment of ER-positive breast cancer by producing ROS and degrading estrogen receptors.	While gold complexes exhibit potent activity, their safety profiles and potential side effects require thorough investigation to ensure clinical viability.	(Lu et al., 2023)
Ru (II) half-sandwich complexes	Therapy of melanoma through immune response modulation and ICD induction.	Need for further research on its mechanisms and potential side effects in clinical applications.	(Xu et al., 2023)
Nanoparticles of taxifolin ruthenium-p-cymene (Tax Ru-NPs)	Treatment of lung cancer by preventing metastasis and triggering apoptosis.	The path to clinical use is complicated by stringent regulatory requirements for nanoparticle-based therapies, which may delay their availability.	(Matai et al., 2020)
Gentamicin-loaded MOF, Gm@UiO-66-MA	Overcomes bacterial resistance and increases the effectiveness of antibiotics.	MOFs can be sensitive to environmental conditions, which may affect their stability and drug release profiles.	(Sun et al., 2013)
Zinc phthalocyanine (ZnPc)	Mycobacterial infections can be treated with antimicrobial photodynamic treatment (aPDT).	ZnPc's hydrophobic nature limits its systemic administration, necessitating complex formulations to enhance solubility.	(Keyal et al., 2018)
Heptamethine-based compounds	Staphylococcus epidermidis antibacterial treatment using photoactivation.	Poor water solubility, low singlet oxygen production, and non-targetability, which hinder their effectiveness in photodynamic therapy and clinical applications.	(Zhang et al., 2022)
Organo-osmium (II) half-sandwich complexes	Redox processes are used to treat drug-resistant Mycobacterium TB.	Lack of selectivity between Mtb and human cells, raising concerns about potential toxicity.	(Coverdale et al., 2021)
Copper-based metallo-surfactants	Photodynamic treatment for Staphylococcus aureus that is resistant to many drugs.	Need for innovative approaches to accelerate wound healing.	(Diao et al., 2024)
CO-releasing nanocomposites	MRSA antibacterial therapy and biofilm targeting using ROS production.	Antibiotic resistance leading to challenging infections.	(Tirkey et al., 2022)
Copper-thiosemicarbazone complex	They have potential applications in anti-cancer chemotherapy and as non-tissue selective blood perfusion tracers.	Careful interpretation of percentage uptake measurements is crucial, and active transport mechanisms need further investigation.	(Dearling et al., 2002)

Applications in Anticancer Therapies

One of the biggest ailments endangering human health today is cancer. The mortality rate is still high, and its incidence is growing gradually (Kerru et al., 2017). By offering replacements for traditional platinum-based treatments like cisplatin, which are effective but usually hampered by major side effects and drug resistance, organometallic compounds have drastically transformed the way that cancer is treated. More recently, iridium (III) compounds with improved anticancer effects have been discovered. These compounds demonstrate cytotoxicity for tumor cells while preserving the health of the kidneys, liver, and heart. In addition, they prove effective in restraining tumor growth. The mechanisms simultaneously induce DNA damage, disrupt mitochondrial workings, and trigger apoptosis by means of ROS to prevent cancer cell growth. In vivo testing has confirmed that some of these complexes show stronger inhibitory effects against cancerous growth than cisplatin (Du et al., 2019). Bone repair and tumor therapy benefit from metal-organic frameworks and their related materials when treating bone tumors. These materials have been shown to both treat cancer and facilitate new bone growth. Both bone regeneration and faster healing after surgery are promoted by these materials. As a result, these materials can serve as precursors for designing novel medicines that work well in treating bone tumors (Yuan et al., 2023). A range of strategies suggests that organometallic materials are highly promising for the therapy of ER-positive breast cancer. By simultaneously integrating both a SERD and an inhibitor for TrxR, it's possible to both reduce estrogen receptor expression and disrupt the cell's redox balance at once. This ROS production can both stop the growth of cancer and boost the immune system.

The recent advances in multifunctional compound development now allow for more precise treatments of breast cancer (Lu et al., 2023). Derivatives of Cu, Zn, and Co transition metal complexes with a heterocyclic connection to benzene exhibited superior anticancer death properties against a wide range of tumor types, notably esophageal cancer. It is important to mention that the Cu-based compound was the most effective in fighting cancer. It caused DNA damage, changed mitochondria, and increased ROS inside the cells to lead to apoptosis. Such complexes may be useful for further development as anticancer drugs since they can stop cell division and damage the mitochondria. Just as organometallics have been used to attack breast cancer by targeting two areas, using organometallics in cancer therapy is now being considered as they also target both redox balance and cancer cell metabolism (Zhi et al., 2019). Ruthenium-based organometallic compounds could be used to fight cancer since they can induce ICD, which activates the immune system's response. A Ru (II) half-sandwich molecule promotes ICD by activating four important markers, such as calreticulin (CRT), high mobility group box 1 (HMGB1), heat shock protein 70 (Hsp70), and also by releasing more ATP. The complex helps the immune system fight melanoma cells and prevent their spread while enhancing the immune system's attack on tumors. Ru-containing complexes suppress melanoma by damaging mitochondria and causing ER stress to trigger both an attack on the tumor and the activation of an immune response (Xu et al., 2023). TaxRu-NPs may be useful in the treatment of cancer. Taxifolin ruthenium-p-cymene nanoparticle (TaxRu-NPs) are beneficial for chemotherapy since they promote apoptosis, inhibit clumping and prevent the proliferation of cancer cells. It was found that TaxRu-NPs promote wound healing and block cell proliferation. TaxRu-NPs also decrease the levels of important immune cells and control the amount of two proteins involved in the promotion of tumor growth, VEGF and β-catenin. Inhibition of the VEGF/β-catenin pathway via TaxRu-NPs decreases the chances of metastasis and angiogenesis in late-stage lung cancer. we've learned how available data can guide the creation of therapies for advanced cancers of the lung (Das et al., 2024).

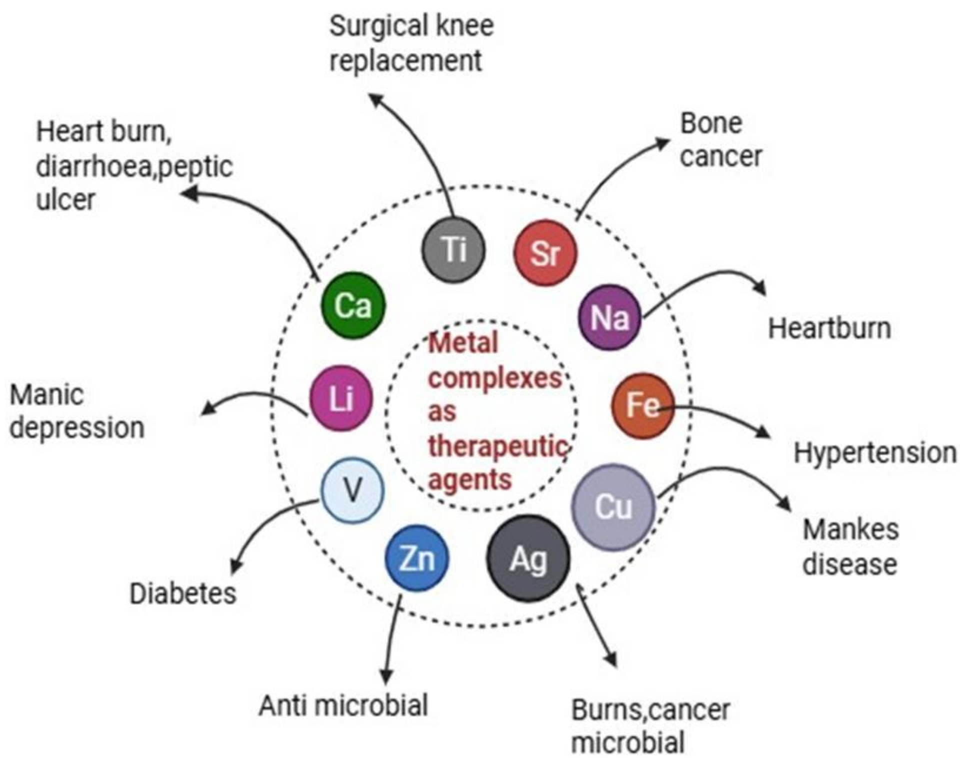

Fig. 1: Therapeutic applications of various metal complexes in the treatment of diverse diseases

Applications in Antibacterial Therapies

Interest in using metal-based medicines to improve outcomes in antibacterial treatment continues to grow (Maqsood et al., 2024). Gm@UiO-66-MA was created by combining gentamicin with a specially prepared material produced through the reaction between UiO-66-NH2 and maleic anhydride. This process has the ability to remove bacterial H2S, which plays a role in developing resistance to some antibiotics. Gm@UiO-66-MA can reduce biofilm strength and improve the potency of gentamicin against antibiotic-resistant *Escherichia coli*. Clinical trials showed that this novel therapy helps prevent infection and promotes faster healing of challenging bacterial wounds (Huo et al., 2023). Resistant to most antibiotics and capable of developing biofilms, *M. chelonae* and *M. fortuitum* cause difficult infections. The photosensitizing qualities of phthalocyanines have proved that the antimicrobial photodynamic treatment works effectively. These compounds do not work well in solutions that contain water. Putting ZnNPs into liposomes elevates the photodynamic effect and the stability and accuracy of the solution used to target *M. fortuitum* (Miretti et al., 2022). Compounds that contain heptamethine and sulfonamide are special for treating infections, especially those caused by *Staphylococcus epidermidis*. After being exposed to certain wavelengths, the compounds show greater antibacterial action and also prevent bacterial carbonic anhydrases (CAs). Antimicrobial resistance is considered a significant problem in health care by organizations across the world. It is necessary to bring new ideas into healthcare to uncover antibiotics that have different ways of working. These half-sandwich organo-osmium (II) complexes have a strong effect against drug-resistant *Mycobacterium tuberculosis* (Mtb) since their minimum inhibitory concentrations (MIC) are very low, ranging between 1.25-2.5 μM. They are able to pass quickly into bacterial cells through thiol-based redox reactions inside the cell. Their ability to fight tuberculosis is increased by their effectiveness and distinctive method of working (Coverdale et al., 2021). Vesicles made from copper-based metallosurfactants and anionic surfactants are very suitable for carrying photosensitizers such as methylene blue (MB) and Rose Bengal (RB). The presence of these vesicles makes it possible for PDT to produce singlet oxygen, which then kills *Staphylococcus aureus*, a bacterium that does not respond to many antibiotics. Besides, they contain dark toxicity and help damage the DNA of bacteria, as confirmed by spectroscopic and comet experiments. Because they can be used in two ways and are easy to produce, they appear to be promising for use as new antibacterial PDT agents (Sharma et al., 2020). OMeTBP@FeCONPs, which make use of photoresponsive CO, are a new approach to treating *S. aureus* and MRSA, as they target biofilms while minimizing the harm to nearby tissues by generating ROS only when exposed to light (Cao et al., 2023). Based on the issue of antimicrobial resistance, a new complex of copper and thiosemicarbazone could be useful against bacteria, as it significantly reduces the growth of two important bacteria. Since it is stable and water-soluble in the body, this complex could make it possible to use safer and better antibacterial drugs (Fabra et al., 2024). The most effective ruthenium-based complex has an antibacterial action against *S. aureus* at a MIC value of 6.25 μg/mL. Only one of the investigated Ruthenium-based complexes displays antimicrobial activity against S. aureus with a MIC of 6.25 μg/mL. The substance produces ROS, which damages the membranes of bacteria and hampers the formation of biofilms while simultaneously enhancing the actions of ordinary antibiotics on the microorganisms. Research in living systems has shown that the compound is effective in battling *S. aureus*. There is a chance that these complexes could help in treating infections caused by drug-resistant bacteria (Wang et al., 2023). The research suggests that incorporating organometallics in therapy could help manage infections and tackle the issue of increased bacterial resistance.

Applications in Anti-Inflammatory Therapies

Delivering small interfering RNA using zinc-based polyplexes improves the treatment of lung tissue harmed by acute lung injury. The use of polyplexes improves the delivery of siRNA to macrophages when compared to other methods. Integrating zinc dipicolylamine and carboxylated mannan into gene delivery leads to better results in managing persistent inflammation within the lungs. It offers an alternative approach for delivering siRNA to treat varied inflammatory disorders (Zhang et al., 2024). It has been established that, since zinc pyrithione (ZPT) has a metal component, it plays a part in colitis treatment by managing TRP and $Ca2+$ pathways in the intestinal wall cells. Because ZPT can reduce inflammation and help mend the inner lining of the digestive system, it could be useful for treating diseases of the GI tract, as other metals are being explored for their anti-inflammatory activities in different parts of the body (Zhang et al., 2024). The study shows that systems containing organometallics could be applied to treat inflammatory conditions. Using UiO-66-NH2 MOF, scientists coated the surface of macrophages to develop a new system for emodin, which can treat inflammation. By using this technology, doctors achieve better results when treating patients with AP due to the long-term medication they can supply. Some scientists believe these treatments can play a key role in addressing inflammatory illnesses (Yang et al., 2024). Doctors are testing polaprezinc (Pol) because it is made from zinc and is believed to reduce inflammation in the brain, improving treatment for diseases such as Alzheimer's. It manages to reduce the production of waste in microglial cells by blocking the NF-κB pathway, mainly stopping the creation of NO, ROS, and cytokines. Therefore, zinc helps reduce neuroinflammation, suggesting that it can contribute to the treatment of neurodegenerative illnesses. Together with Asp G, there is evidence that Pol works better for treating neuroinflammatory diseases (Ban et al., 2024).

Table 2: Applications of metal-based compounds in treating various infectious diseases

Therapies	Applications	References
Anticancer Therapies	The integration of nonsteroidal anti-inflammatory drugs (NSAIDs) with organometallic complexes has shown enhanced anticancer properties, demonstrating the potential for hybrid therapeutic strategies.	(Paunescu et al., 2016)
	Treatment for rheumatoid arthritis with gold-based compounds.	(Casini et al., 2018)
	Enhancing efficacy and improving safety in cancer therapies.	(Chen et al., 2017)
Antibacterial Therapies	Compounds made from metals usually disrupt the cell membrane or the metabolism of bacteria, while existing antibiotics are not likely to do the same.	(Evans et al., 2021)
	Acting as catalytically active sites and photosensitizers and killing bacteria by releasing metal ions and micro-molecules.	(Han et al., 2022)
	Act as photocatalytic agents for indoor air pollutant control.	(Biegański et al., 2021)
Anti-inflammatory Therapies	Treatment of inflammatory bowel diseases (IBD) and diagnosis and treatment of colorectal cancer (CRC).	(Szczepaniak et al., 2019)
	Immobilized metal-organic compounds have shown promise in treating purulent-inflammatory diseases of the skin, improving healing processes.	(Кадомцева et al., 2021)
	Metal complexes of nonsteroidal anti-inflammatory drugs (NSAIDs) like tenoxicam have demonstrated superior anti-inflammatory effects compared to their parent compounds.	(Muslu et al., 2021)
Anti-neurodegenerative Therapies	The efficacy of bis(thiosemicarbazone) metal complexes in treating animal models of Alzheimer's and Parkinson's diseases.	(Mckenzie-Nickson et al., 2016)
	Metal chelation to slow neurodegenerative disease progression and redistributing metal ions to alleviate cellular deficiencies.	(C Badrick et al., 2011)
	Protection of neuronal cells from inflammation and from oxidative stress in neurodegenerative diseases.	(Rapposelli et al., 2021)

Therapies for Neurodegenerative Diseases

While Alzheimer's disease (AD) cannot be cured, it is one of the leading neurodegenerative diseases that may cause a person to die. Dementia due to Alzheimer's disease is the leading cause of mental decline, memory issues, and issues with language use (Wan et al., 2020; Dubois et al., 2021). Practically, zinc-based amide carboxylates are used to manage Alzheimer's disease in a way that is not done with other compounds. They are expected to be helpful in treating Alzheimer's, as they bring down phosphodiesterase IV, which in turn improves learning and memory in animals. They may help alleviate oxidative stress by turning on enzymes that help reduce it, and by regulating the work of acetylcholinesterase. Using zinc scaffolds might help to alter important biochemical factors like neurotransmitters, tau proteins, and amyloid-β, which hints at their potential as a therapy for AD (Waseem et al., 2022). Triphenylphosphoranylidene derivatives are part of a group of chemicals called organometallic compounds, and they can stop two important things related to Alzheimer's disease: the breakdown of acetylcholine and the grouping together of sticky protein fragments called beta amyloid. This means they might be useful for treating Alzheimer's disease. The compounds were found to be safe to use with cells, and they worked well when tested in real living things, also passing easily through the barrier that separates blood from the brain. This shows that these oils can help solve some of the reasons why Alzheimer's happens in the first place (El-Hussieny et al., 2023). Substances made from zinc and amide carboxylates have been found to help animals learn and remember better, and there's hope they might also work the same way in people with Alzheimer's. They help to lower the effect of damaging molecules in the brain and affect important brain chemicals such as acetylcholinesterase and amyloid-β, which makes some people think that these drugs could be useful in treating Alzheimer's disease. Different doses of zinc scaffolds suggest that they might help with treating diseases where the brain and nerves break down, like dementia or Parkinson's (Waseem et al., 2022). Cationic methylated Zinc phthalocyanines (called cZnPc for short) work well in blocking amyloid beta peptide from clumping together, which can help slow down or prevent Alzheimer's disease. Because (cZnPc) helps to stop the damage caused by sticky Alzheimer's proteins and keeps nerve cells healthy, this discovery could lead people to look into using zinc-based compounds to treat the disease.. This ability to go through the blood-brain barrier increases the significance of drugs for treating neurodegenerative diseases (Sheikh et al., 2024). Various applications of metal-based compounds are shown in Table 2.

Conclusion

The chapter talks about how organometallic compounds are becoming more important in medicine and highlights their possible application as drugs. For example, organometallics, with metal-carbon bonds, have proved helpful in the treatment of cancer, infections, and diseases of the brain. Platinum drugs, such as cisplatin, have been applied for a long time in cancer treatment, and the use of ruthenium, iridium, and similar metals in new medications is being tested for resistance to antibiotics and Alzheimer's. Ways in which these chemicals do their work, including their effects on DNA, redox reactions, and the immune system, are also discussed. The chapter notes that organometallics are constantly being studied since they introduce new methods to tackle illnesses that do not respond to typical therapy.

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