Medicinal Applications of Coordination Complexes

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Abstract

Coordination compounds and organometallics have very special place in chemistry due to their different structural arrangements and application in various fields. They also play vital role in biological system particularly in human and plant life. The blood oxygen carrier haemoglobin is a coordination compound of iron which is essential for human life, also the chlorophyll is a coordination compound of magnesium essential for plant the life and the continuation of the life on this planet. These compounds are not only biologically important but also comprise a group of drug like molecules and medicines. Coordination compounds such as platinum, palladium and ruthenium complexes are anti-cancer drugs. Also, many of the coordination compounds are anti-bacterial. The coordination compounds have been showed effective behaviour against many diseases like Alzheimer's and malaria. Recently coordination compounds used as antiviruses such as coronavirus. In present review, we highlighted the most important coordination complexes that show a significant role in the field of medicine.

Keywords: Coordination compounds, complexes, cis platinum, antimalarial, anticancer, photosensitizer

Introduction

Coordination compounds and Organometallics are not very new in field of medicine and drug discovery but this area still does not get much attention by medicinal chemists. This area is at the interface between medicine and inorganic chemistry, it embraces metal-based therapeutically important compounds, metal sequestering or mobilizing agents, metal-containing diagnostic aids, and the medicinal recruitment of endogenous metal ions. Nevertheless, our body and biological system contains hundreds of inorganic complexes and metals in form of different enzymes and protein cofactors, which are essential for a normal biological process. It is the biological importance and their essential role in maintaining the vital biological processes which attracts chemists always to work in field of synthesis and application of coordination compounds and organometallics. Inspiring from these observations and the role of Coordination compounds in the area of medicine here we decided to compile a mini review with the discussion on the medicinal application of coordination compounds and organometallics.

Many coordination compounds exhibited biological activities against bacteria and fungi\(^{1-4}\). The mix ligands of piperacrine, acetaminophen and piperacrine, acetylsalicylic of copper II, cobalt II, zinc II, and iron II ions (Figure 1) exhibited biological activity against Escherichia coli and Staphylococcus aureus\(^5\).
Pyrazolinethiocarbamoyl palladium (Figure 2) exhibited high effect on *Entamoebahistolytica* more than the free ligand\(^6\).

On the other hand, nickel and copper ions with thiocarbamoyl dihydropyrazole (Figure 3) exhibited high inhibitory activity towards *Candida strains*\(^6\).

Many azo dyes and coordination compound of azo dye showed high evaluated contrary to the growth of bacteria and fungi\(^7\). The chelate ligand of 1\{[5mercapto1-H1,2,4triazole3yl]diazenyl]-naphthalen2-ol with metals of Mn\(^{2+}\), Co\(^{2+}\), Ni\(^{2+}\) and Cu\(^{2+}\) (Figure 4) exhibited high evaluated against the growth of (*Escherichia coli, Staphylococcus aureus, Aspergillus flavus*and *Candida albicans*)\(^8\).
Anticancer: The difference between the cis isomer and trans of [PtCl₂(NH₃)₂] is a geometry whereas cis isomer is biological activity and it uses as anticancer drug because the Cl ligand in cis isomer is active and it replaces by water molecule then the new product platinum complex with water reacts with DNA of the cancer cell by replacing water molecule which leads to inhibition growth the cells of cancer.

In the mice, the complex of Ti(IV) oxalate shown attractive effects such as improve the weight and reduction the growth the tumour. Titanium(IV) complexes such as badotitane (Figure 5) which is β-diketonato complexes of titanium and titanocene dichloride shown antitumor activity in human clinical trials like platinum complexes with low toxicity in many different cell lines but unfortunately these complexes are not stable.

There are many drug coordination compounds based on Schiff bases. The complexes of copper (II) with Schiff bases of (6-methyl-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde semicarbazones) and (8-methyl-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde semicarbazones) (Figure 6) exhibited satisfactory cytotoxic activity against A431 cancer cell line.
Complex \([\text{CuCl}_2(\text{Bipy})(L)]\) (Figure 7) is considered a drug for anti-Candida therapy and it exhibited fungicidal activity against planktonic and sessile cells.\(^{13}\)

The complex \([\text{CuLCl}_2]\) (Figure 8) exhibited activity against B16F10 mouse melanoma cells.\(^{14}\)

**Antimalaria:** The many metal complexes such as iron, gold, ruthenium, cobalt, rhodium, copper, cobalt, zinc, osmium, and palladium, etc., have shown effective anti-malarial.\(^{15,16}\) The complex of zinc (II) with amodiaquine (Figure 9) exhibited efficacy towards *Plasmodium berghei* with safety evaluation.\(^{17}\)
The malaria becomes more resistance to large antimalarial drugs. The ligands of o-vanillin-(4-methyl thiosemicarbazone) with Ga(III), Fe(III) and (III) (Figure 10) were shown activity against malaria\(^\text{18}\). The M(II) complexes of Mn, Co, Ni, Cu and Zn with cross bridge dtetrazamcrocyclic ligands were shown potential activity \textit{in vitro} against strains of chloroquine-resistant (W2) and chloroquine-sensitive (D6)\(^\text{19}\).

Ferrocene having Ferroquine (FQ or SSR97193) (Figure 11) was shown a unique organ active against the chloroquine-susceptible, chloroquine-resistant Plasmodium falciparum and P. vivax strains. Thus, it prefers that both ferrocene compounds took in one dose\(^\text{20-23}\).

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**Figure 9** Structure of zinc(II) with amodiaquine ligand

**Figure 10** [Cu(L)(OAC)(PF\(_6\))]

**Figure 11** Chemical structure of ferroquine (7-chloro-[(2'-N,N-dimethyl-aminomethyl) ferrocenylmethylamino]quinolone
Other compound of ferrocenyl carbohydrate (Figure 12) shown potential as an anti-malarial compound\textsuperscript{24-26}.

![Figure 12 Ferrocenyl carbohydrate conjugate](image)

The complex of gold with chloroquine having formula Au(PPh\textsubscript{3})(CQ)\textsubscript{2}PF\textsubscript{6} (Figure 13) consider more active against two chloroquine-resistant strains of Plasmodium falciparum in vitro than CQ and besides active against Plasmodium berghei in \textit{vitro} and in \textit{vivo}\textsuperscript{27}.

![Figure 13 Gold chloroquine [Au(CQ)(PPh\textsubscript{3})\textsuperscript{+}](image)

**Anti-Alzheimer:** Metal complexes exhibited ability to blocking $\beta$-amyloid aggregation and scavenging its toxicity. Some complexes for ruthenium (III) exhibited significant role as anti-Alzheimer agents such as NAMI A, KP1019, and PMRU20 (Figure 14)\textsuperscript{28}. In the same manner, some copper (II) and vanadium complexes exhibited remarks role in the \textit{vitro} as anti-Alzheimer\textsuperscript{29,30}.

![Figure 14 Ruthenium compounds as anti-Alzheimer](image)

**Antihypertensive:** Sodium nitroprusside (Figure 15) uses a drug for arterial and venous vasodilation. It interacts with the sulfhydryl groups to deliver nitric oxide which causes fast vasodilation and acute lowering blood pressure\textsuperscript{31-33}. Some studies mentioned to the capability of sodium nitroprusside to restrain platelet aggregation in \textit{vivo} and \textit{vitro}\textsuperscript{34}. Pharmacists prefer the therapeutic results of
nitroprusside, but it is accompanied by the release of cyanide, so it is currently preferable only in severe cases.

![Figure 15 Structure of sodium nitroprusside](image)

### Cosmetics

Chlorophyll is a complex for magnesium for porphyrin derivative and is hence a metal complex dye. It is key component in the leaves of green plants and is very crucial in the process of photosynthesis. Chlorophyll has very good solubility in fats and oils, also it is used essentially for dyeing and bleaching oils and soaps, and also for coloring mineral oils, waxes, essential oils and ointments. Water-soluble chlorophyll exhibited many applications in the food stuffs industry for colouring confectionery, gelatine products and beverages. In the cosmetics industry they are added to creams and soaps. Copper chlorophyllin (Figure 16) is a complex for copper producing by replace Mg$^{2+}$ by Cu$^{2+}$. This complex is a good food colorant, cosmetics and possibility anti carcinogenic and antioxidant. The great majority use of azo dyes and their complexes is in hair colouring, leather and fur especially coordination compounds of cobalt and chromium based azo dye.

![Figure 16 Structure of copper chlorophyllin](image)

### Release bioactive ligands:

Small ligands such as nitric mono oxide and carbon mono oxide are toxic when we take them by nose while the body produces little amounts of them and they play large role biology in the body. Nitric mono oxide play a critical role as vasorelaxant, inhibitor of platelet aggregation, sexual dysfunction. We can get high concentration of nitric mono oxide locally to treat the cancer by photo-irradiation of metal nitrosyl like ruthenium nitrosyl complexes with pyridine, bipyridine, and terpyridine.

### Photosensitizers for photodynamic therapy:

Photodynamic therapy (PDT) uses to therapy many diseases for instance cancer, microbial infections, fungal, skin diseases and esthetic. Recently this type of treatment has more interest to treat the viruses such as coronavirus (SARS-CoV-2), Ebola
virus, Middle East Respiratory Syndrome and anti-HIV. The PDT depends on the photosensitizer (PS) which is a compound acting by irradiation to form ROS and/or radicals leading to cell death. The PS is stable in dark conditions and not or so lower toxicity. Many PSs are coordination compounds and they showed favourable physico-chemical properties. They absorb in visible area and it is possible in the NIR area by absorption two-photon such as coordination compounds of bacteriochlorin and iridium dye (Figure 17) that means that less harmful and more penetration in the tissue of the body.

Conclusion: In this review, we have selected the reports containing application of coordination compounds (metal-based drug) in field of their application in medicine and drug discovery. We classified the metal based complex compounds depending on their application in the therapy of diverse diseases. We have shown the utilisation metal containing compounds in various biomolecules and their vital role in living systems. The use of metal based drug molecules are summarized against Cancer, Malaria, Anaemia and Alzheimer diseases. The essential roles of metal complexes in the field of cosmetics have also been incorporated. We believe that our review is very comprehensive and specific for the researchers who are working in the area of application of metal complexes in various fields.

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