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Chapter 2

Perception and Resistance Mechanism of some Metal-drug Complexes and Their Roles as Antibacterial

Joshua A. Obaleye, Nzikahyel Simon, Olufunso O. Abosede, Mercy O. Bamigboye, Abiodun A. Ajibola, Uche B. Eke and Elizabeth A. Balogun

Additional information is available at the end of the chapter

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Abstract

Metal-based drugs have undergone much development and application for therapeutic and diagnostic purposes for many decades since the huge success of cisplatin and other successful metal-drug complexes in the clinical stages. Furthermore, this metal-based drug has come up with a lot of signs of resistance and side-effects in their uses. This review points to some of the resistance natures and mechanisms of previously synthesized complexes in the field of chemistry.

Keywords: metal-drug complexes, antibacterial, mechanism, therapeutics, properties, resistance

1. Introduction

Anti-bacterial are agents that disturb and combat the growth and reproduction of bacteria. They are known as agents used to disinfect surfaces and eliminate potentially harmful bacteria. Some antibacterial agents are contraindicated while some required dosage modification in patients who have renal insufficiency. The use of metal complexes as antibacterial/chemotherapeutic agents against some ailments is a very attractive potential. Some metal complexes including mixed ligand metal complexes have been prepared in our laboratory and that of others. Their effectiveness as antibacterial agents has been revealed. Different synthetic procedures were utilized.

Though development of metallo-pharmaceuticals is met with limitations because of the perception that metals (especially when regarded as heavy metals) are toxic and the relative

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limited expertise of most pharmaceutical companies in Inorganic Chemistry, metals and their compounds are essential to many species of plants and animals. Metal complexes may be useful as research probes of biological function, as intermediary lead compounds in the development of non-metal-containing therapeutics, and as potential diagnostic and therapeutic agents. The unique properties of metal complexes,(e. g., hydrolytic and redox activity, valency, geometry, magnetic, spectroscopic, photo-physical, and radiochemical properties) can be used to measure and/or alter cellular functions. In the recent past, polypyridyl metal complexes are also being tested as chemotherapeutic agents following the first success of cisplatin and the need to discover new drugs to combat the problem of resistance to existing drugs [1-8].

The importance of metal in medicine has been in existence for many years and researchers have explored their uses and advantages to human health, animals and the environment. Some of these metals are content of our day-to-day diets and in varying quantities.

Many researchers have come up with the importance of metals in known drugs or synthesized drugs. Transition metals are involved majorly in the formation of complexes by coordinating with the ligands (i. e. the drugs).

Humans need several metal ions for many vital and important functions in the body in which the lack of some of these metal ions can lead to malfunctioning of the body and development of diseases. Iron deficiency can lead to pernicious anemia while copper deficiency in infants can cause lack of accurate function of the heart.

Medicinal bioinorganic chemistry considers, from a molecular level point of view, how to understand and recognize different diseases that originate from the deficiency of essential metal ions functionality in the body of a living system. This also includes ways of providing solution to these problems. Introduction of heavy metal ions (e. g., Pb and Hg) can be detrimental to living systems [9].

The involvement of the metal ions in most of these potent synthesized complexes has increased their biological activities. In most cases the acceleration of the action of many drugs is mainly caused by metal ion chelation. Therefore many metals are involved in enhancing the efficacy in antimalarial, antitumor and anticancer therapy [10-13].

Drug resistance refers to a situation in which the drugs that usually destroy the bacteria can no longer perform its duty. It implies that the patient can no longer be effectively treated against the bacteria.

Therefore, people become sick for a long time and if the epidemics are extended without a possible solution it results in more people being at risk of becoming infected.

Antimicrobial resistance is the ability of a microorganism to survive at a given concentration of anantimicrobial agent at which the normal population of the microorganism would be killed.

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2. Resistance of some metal-drug complexes of antimalarial

2.1. Resistance to anti-malarials

Resistance to antimalarials could be defined as the tendency by which the parasite is able to thrive and even reproduce itself in the presence of accurate dosage of malaria drug [14].

In 2006, the World Health Organisation (WHO) stated that, resistance has arisen to all classes of anti-malarials except the artemisinins. This has increased the malaria burden globally and is a most important threat to malaria control. Extensive and indiscriminate uses of antimalarial drugs impose a strong selective stress on *Plasmodium falciparum* and other malaria parasites to acquire higher resistance levels. This can be prevented at its onset or mellowed down significantly, through combination therapies of the anti-malarial drugs with differing modes of actions thereby achieving maximum cure rates by strict adherence to proper drug prescriptions [13].

The data acquired can be of assistance in treatment choices and forecasts concerning future resistance patterns. The most difficult with drug resistance arises from *P. falciparum*. Resistance due to *P. falciparum* is of special interest since the huge burden of disease arises from this class, as well as its deadly potential, the tendency for epidemics, and the cost implication of replacement with candidate drugs in places with well-known drug resistance. Chloroquine resistance does occur in *P. vivax*, particularly in Western Oceania. However, there is very scanty information on resistance in *P. ovale* and *P. malariae* [14].

Malaria is a deadly disease that affect both children and adult and is mostly caused by the protozoan parasite *Plasmodium*, and is transmitted by an Anopheline mosquito vector [15]. The five Plasmodia species affecting humans are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. *Plasmodium falciparum* is a common species commonly affecting the population and therefore its resistance to many drugs. Today, the available therapeutic drugs for malaria are limited; new anti-malarial drugs, preferably with new structures and/or modes of action, are urgently needed [16, 17].

The emergence of resistance in *Plasmodium* depends on parasite mutation rate and their total parasite load. Treatment response and drug selection strength also contributed to these factors.

Increase in the rates of mutation enhances the speed of resistance emergence which subsequently leads to harmful mutations [17].

3. Some metal-drug complexes resistance and their mechanism

3.1. Metal complexes of antimalarial drugs

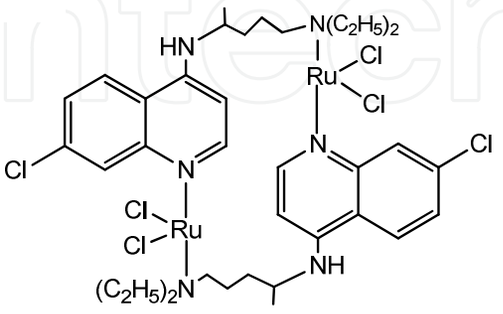
Metal–drug synergism has been exploited to obtain effective antimalarial metal agents [18-20].

The use of chloroquine (CQ) as a major reference drug of all antimalarial drugs has enabled many scientists to develop more potent drugs in combating malaria. Resistance against CQ is

now prominent. The incorporation of metals into CQ and similar drugs has been yielding more positive results with little or no toxicity. Some examples of synthesized metal- drug complexes including their various resistances are also cited in the table below:

For Ruthenium and Rhodium complexes of chloroquine:

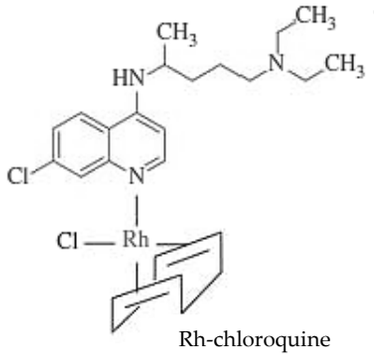
(A)



Ru-chloroquine

$[RuCQCl_2]_2$

(B)

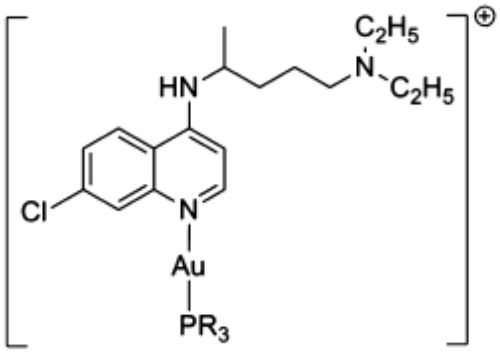


Rh-chloroquine

RhCl(COD)CQ

Compound	CQ-Sensitive strains	CQ-Resistance strains	Reference
A	*P. berghei*	FcB1, FcB2	[21]
B	Reduction of parasitemia by 73%	FcB1	[21]

Where (COD: 1,5-Cyclooctadiene), Ru- Ruthenium, Rh= Rhenium,

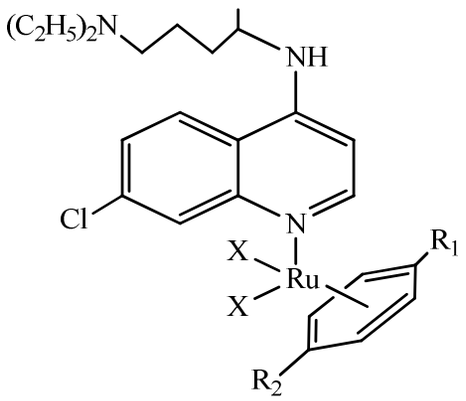


1. **R = CH_3, X= PF_6 (Au-CQ)**
2. **R = C_6H_5, X = PF_6**
3. **R = C_6H_5, X = NO_3**
4. **R = C_2H_5, X = PF_6**

Compound	CQ-Sensitive strains of P. berghei	CQ-Resistance strains of P. falciparum	Reference
1. $[Au(PMe_3)(CQ)]PF_6]$	F32	W2, K1, FcB1	[23]
2. $[Au(PPh_3)(CQ)]PF_6$	F32	FcB1, FcB2	[22]
3. $[Au(PPh_3)(CQ)]NO_3$	F32	W2, K1, FcB1	[23]
4. $[Au(PEt_3)(CQ)]PF_6$	F32	W2, K1, FcB1	[22]

From the conclusion that was drawn from the mechanism of $[Au(PPh_3)(CQ)]PF_6$ and its antimalarial action, $[Au(PPh_3)(CQ)]PF_6$ has high propensity to haem than chloroquine diphosphate. The same complex also shows high ability to inhibit β-haematin formation.

The mechanism of antimalarial action of $[Au(CQ)(PPh_3)]PF_6$ has been clearly defined [22]. Structural effects and increased drug lipophilicity enhance haem aggregation inhibition at lipid/water interfaces [24].



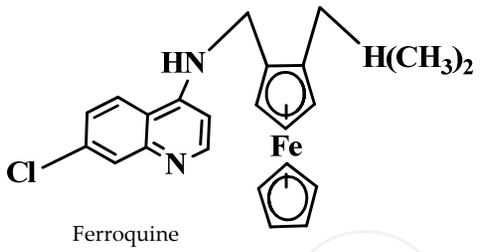
1. R_1 = -CH_3, R_2 = -$CH(CH_3)_2$, X = Cl^-

2. R_1=R_2 = H, X = Cl^-

Compound	CQ-Sensitive strains	CQ-Resistance strains	Reference
6	FcB1, 3D7, PFB, F32	W2, Dd2, K1	[25]
7	FcB1, 3D7, PFB, F32	W2, Dd2, K1	[25]

The description of CQ derivatives with Arene–metal complexes and half-sandwich complexes are shown above, where some of them showed high antiplamodial activity and some showed different modes of binding with CQ.

Ferroquine (FQ) shows higher biological and structural activity than any other antimalarial drugs in the market including chloroquine (CQ). The reaction of FQ and CQ against *P.*



Ferroquine

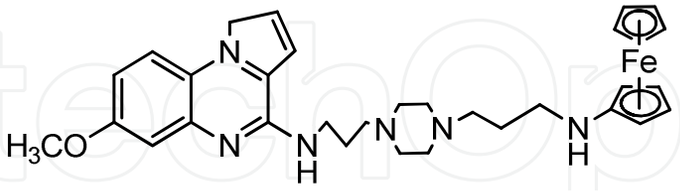
falciparum strains is quite unique and different in which FQ reveal some high potency in chloroquine-resistant and chloroquine-sensitive *P. falciparum* strains[26-32].

Indeed it has been observed that a number of drugs that are active against CQ-resistant strains, including metal-based CQ derivatives, such as the iron-containing ferroquine [21,28,33] and the gold-CQ complex [Au(CQ)(PPh3)]PF6 [34], are considerably more lipophilic than CQ and this could be an important factor in the reduction of resistance.

Antiplasmodial activity of the synthetic products of chloroquine-bridged ferrocenophane analogues of ferroquine were reported by Salas *et. al*. (2013) [35]. All the disubstituted bridged ferrocenyl compounds were observed to be active against all the tested parasite strains.

The activities of some of the compounds under investigation were observed to be sensitive to the drug resistance level of the parasite strains. It was noted that:

- FQ was twenty times or more potent or operative against chloroquine-resistant parasite strains than CQ;
- FQ also displayed high level of potency *in vivo* in some experiments against *P. berghei*, *P. vinckei* and *P. yoeli;*
- Due to the different formulation and structure, there were no expected differences.



ferrocene−pyrrolo[1,2-α]quinoxaline compounds

This drug has shown lower resistance than chloroquine, therefore making their derivatives a good contender for chloroquine-resistant malaria. [36]. The most potent of this derivative contains a methoxy group just like the above.

Compound	CQ-Sensitive strains	CQ-Resistance strains	Reference
F	F32	FcB1, PFB	[36]

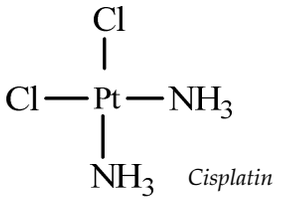
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4. Multiple drug resistance mechanisms in cancer

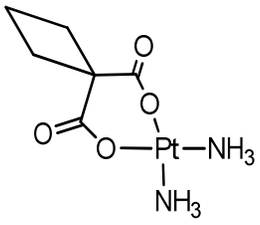
The process and system whereby resistance to one drug is accompanied by resistance to drugs whose structures and mechanisms of action may be completely different is called multiple drug resistance (MDR). [37-42]

4.1. Platinum anticancer agents

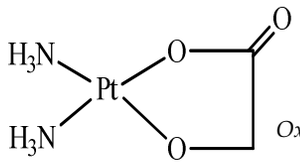
One of the most effectively used drugs in cancer and for its treatment is the family called Platinium (II) complexes. The following compounds have been clinically approved for treatment universally.



Cisplatin



Carboplatin



Oxaliplatin

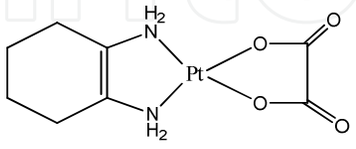
Consideration of the toxic reduction of platinum complexes in living cells has been of special interest over the years. This happened so as to have a wider range of cure over other types of cancer that have come to light, hereby avoiding being stopped by some resistance. [43-45]

The usefulness of Platinum complexes in the clinical stage is limited by:

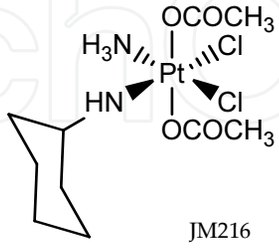
i. the spectrum of its anticancer activity (not active enough against several types of cancer),

ii. the development of resistance after continued treatment, and

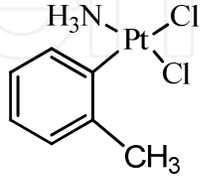
iii. its high toxicity to some normal cells.



Oxaliplatin



JM216



AMD473

Some of the current thinking on the chemical basis for the mechanism of action of cisplatin as an anticancer drug is summarized below:

In 2000, Pe´rez *et. al.* [46], were able to report the first crystal structure of a biologically active *trans*-platinum compound *trans*-[$PtCl_2$(dimethylamine)(isopropylamine) containing different

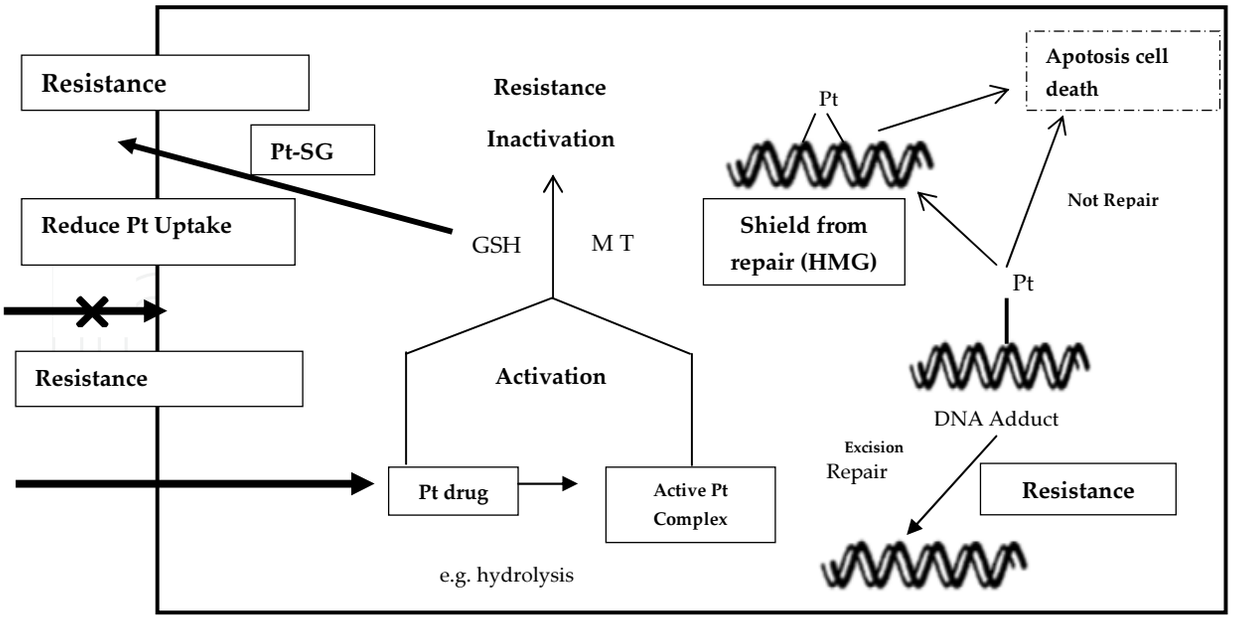
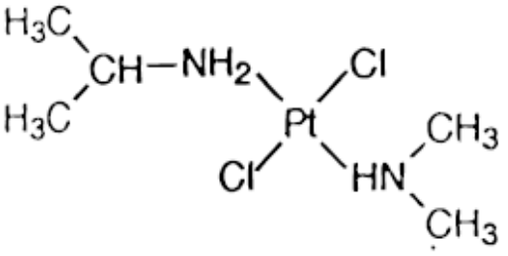
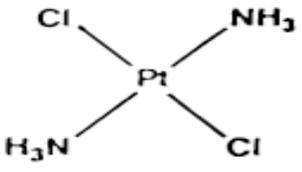


Figure 1. A summary of some of the processes that are thought to be involved in the cytotoxicity of platinum anticancer agents

aliphatic amines where *trans*-$PtCl_2$(dimethylamine)-(isopropylamine)] readily form DNA inter-stand crosslinks.



Trans-[$PtCl_2$(dimethylamine)(isopropylamine)]



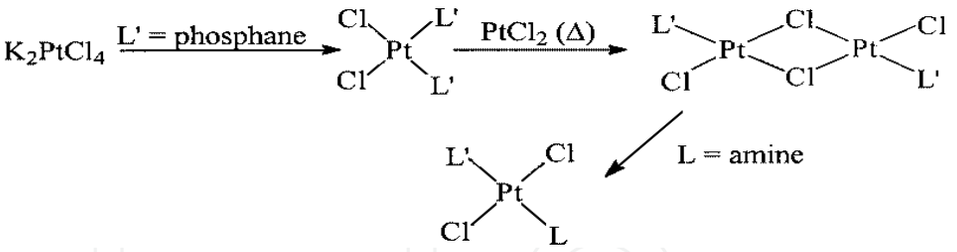
Transplatin

*tra*CC)(Cisopropy Transplatin lamincce)

But in the year 2003, Ramos-Lima *et al*, were able to replace two amine groups of transplatin with aliphatic amine and phosphane group, which resulted in circumvention of cisplatin resistance [47-48].

The synthesis pathway for the novel complexes is shown below;

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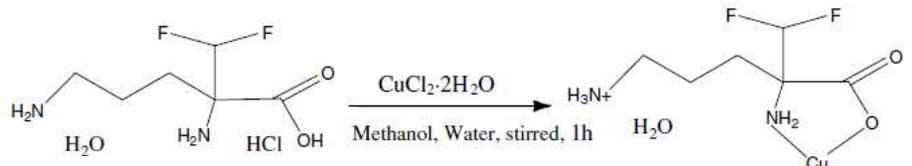


In 2014, Obaleye and co-workers synthesized and characterized a novel –M–X–M–X– type infinite chain 1D Cu(II) complex with eflornithine hydrochloride hydrate as ligand where their biological evaluation were examined and the results of the antibacterial screening show appreciable activity of the metal-drug complexes compared to the ligand when challenged with test organisms at varying concentrations. Copper complex was effective at virtually all concentrations used except against *E. coli* and *P. aeruginosa* at 0. 0001 gL^{-1} [49].

Highest susceptibility to Copper complex was recorded by S. aureus with clearance zone of 4. 2 mm at 1. 0 gL^{-1}. The results show that the metal-drug complex possesses a measure of antibacterial activity against all the organisms tested. The results also agree with the findings of other researchers [50-51] that antibacterial potency is usually concentration dependent.

The data also revealed that the activity of the Ligand EFL was bacteriostatic against all the organisms tested, while the activity of the copper (II) complex was bacteriostatic against *E. coli* and *P. aeruginosa* but bactericidal against S. aureus at 0. 0001 g/L concentration.

The Scheme of the reaction is shown below:



Eflornithine Hydrochloride Hydrate

Ligand EFL

5. Conclusion

For a couple of years now, some bacteria are becoming resistant to antibiotic drugs during this era of chemotherapy. This has been the main cause of morbidity and mortality worldwide. Many reasons had been attached to this drug resistance of the organism. Some of these proposed reasons are (i) the over-prescription of the drugs by physicians,(ii) self-medication, (iii) premature discontinuity of the medication by the patients as they start to regain strength and (iv) difficulty in affording the full course of the therapy. Other factors such as the transmission of the drug-resistant organism among patients through air or by direct contact with contaminated person or environment have been identified. It is also attested that a long period is usually needed to complete the treatment of individuals infected by the organisms. Modes

of action of some of the potent antibiotic drugs are sometimes tagged as unknown. Hence, there is urgent need for continuous research in the development of drugs in order to have more effective drugs than the already available less potent drugs that will combat these dangerous microbes.

Although several metal-drug complexes have been synthesized to date, there are few of them at the final clinical stage due to their resistance capacity. Many researches are ongoing to circumvent this drug resistance, from this review, it is clear that some of the existing organic ligands or their derivatives are observed to be more potent when complexed with metals. These metal-drug complexes are *in vitro* and *in vivo* efficient.

In the aspect of antimalarial, antitumor, and anticancer drugs, more profitable researches are gradually emerging, yielding positive products with decent potency, stability, and reduced side effects. In this review resistance mechanisms of some synthesized metal-drug complexes were highlighted based on the investigations of various researchers.

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