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Metal complexes as antimalarial potential: A review

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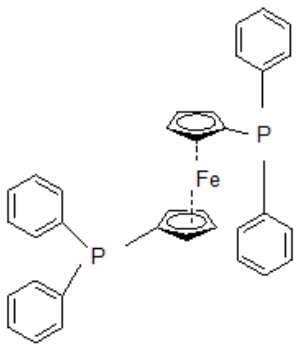
Abstract
Malaria, a parasitic disease which occurs mainly in tropical zones of the world, has contributed greatly to health burden of the global population. Malaria treatment is becoming more challenging due to rising resistance against the antimalarial drug, chloroquine. Novel compounds that target aspects of parasite development are being explored in attempts to overcome this wide-spread problem. Anti-malarial drugs target specific aspects of parasite growth and development within the human host. Organometallic chemistry is of growing interest especially in the recent decades due to its wide applications in the biological and medicinal field, this application leads to a new area called bioorganometallic chemistry. Metal complexes are used in bioorganometallic chemistry since they exhibit a wide range of biological activities against various diseases. In this study we will focus on the antimalarial activities of metal complexes.

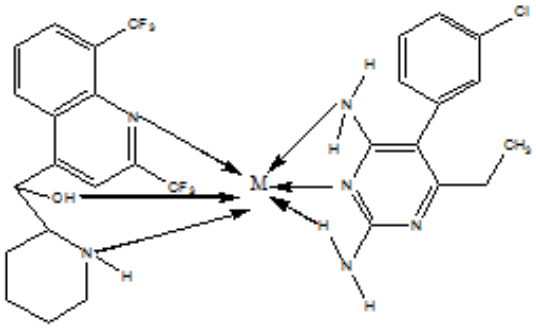
Keywords: Metal complexes, antimalarial activity, bioorganometallic chemistry

Introduction
Malaria, the disease of poor, is among the world's most prevalent infectious diseases, affecting the health and developmental growth of the developing countries. Malaria is one of the rising transmittable diseases, needs strong efforts for controlling it worldwide. It is a tropical parasitic disease that now remains globally extended to more than 40% population and is one of the major causes of mortality and morbidity from the class of infectious diseases worldwide(after tuberculosis, HIV/AIDS, respiratory infections and diarrheal diseases. The disease is unstable with frequent outbreaks affecting the population of all the age groups and thus, currently regarded as a life-threatening deadly disease [1].
Metal-based chemotherapies have existed for centuries, but in recent years there has been an increasing interest in the application of transition metal complexes or organometallic complexes in medicine and in other areas of biological sciences. Metal complexes have been used as drugs in a variety of diseases, as exemplified by the continued success of the platinum complex, cis-$PtCl_2$ $(NH_3)_2$ (cisplatin), as an anticancer drug. This important breakthrough has indeed stimulated a renewed interest in metal complex based chemotherapy. Today, other metal-containing drugs have been developed in a variety of therapeutic areas including malaria [2].

Antimalarial potential of metal complexes
Sofyan *et al* synthesized five silver complexes containing a mixed ligand system of phosphine and thiazolidine were successfully synthesized. The antiplasmodial properties of all synthesized complexes were investigated on chloroquine-resistant P. falciparum parasite via HRP2 assays and cytotoxicity tests on Vero cells. Of all the synthesized complexes, complex 1 showed the highest SI value (more than 12.4) followed by complex 5 (6.6) [3].



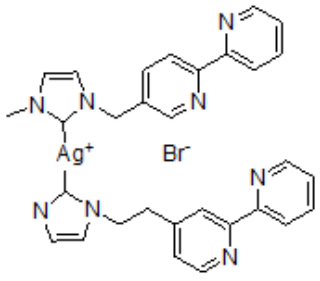
Adediji *et al*. synthesized the Nickel (II) chloride hexahydrate complex of mefloquine and pyrimethamine and performed their antimalarial activities using mice infected with *P. berghei*. Metal complexes formed do not show any toxicity against alkaline phosphate activities of enzymes from the homogenates of serum, liver and kidney homogenates of experimental rats. The metal chloride salt was reacted with the parent compounds according to the equation. The synthesized complex was found to be non-hygroscopic solids with lemon green colour. The results showed that the metal chelate exhibited higher activity against malaria with high percentage inhibition of 70.3% at 25mg/kg dosage and hence overall metal complexes exhibited better properties as compared with that of parent compounds [4].



$M+L_1+L_2=ML_1L_2$

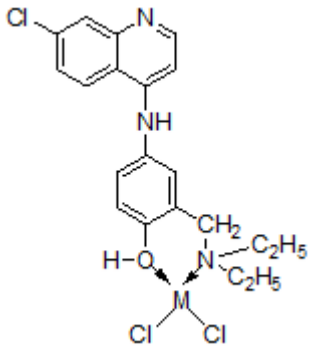
Hamza *et al*., synthesized 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one, as well as the Fe(III), Ni(II) and Mn (II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one. The uncomplexed 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one as well as the Fe(III), Ni(II) and Mn (II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one were subjected to in-vitro antimalarial screening using Plasmodium berghii cysteine enzyme inhibition assay at concentrations of 1000 ug/ml, 500 ug/ml, and 250 ug/ml. 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one shows promising activity for inhibiting the cysteine enzymes. The antimalarial activity of Fe(III) and Mn(II) complexes of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one was found to be much higher that of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one. However, the Ni (II) complex of 3-(4-nitrophenyl)-1-phenylprop-2- ene -1-one did not show enhanced antimalarial activity [5].

Hemmert *et al*., synthesized a series of mono and dinuclear silver (I) and mononuclear gold (I) complexes containing bis (N-heterocyclic carbene) or non functionalised NHC. The *in-vitro* antiplasmodial and antifungal activities of a family of N-functinalized bis (imidazolium) proligands and their corresponding complexes were investigated against chloroquine-resistant strain of *P. falciparum* and against two *Candida* strains. Antifungal tests were performed against *Candida albicans* and *Candida glabrata* of molecules [6].

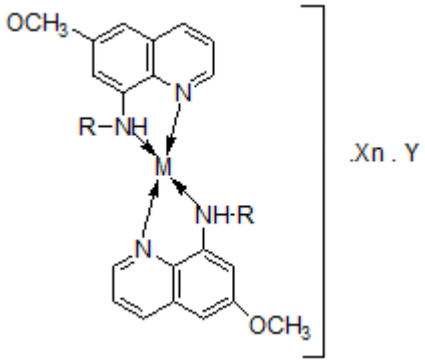


Structure of silver complex

Wasi and Singh synthesized the metal complexes of amodiaquine and primaquine with different metal salts. Amodiaquine hydrochloride and primaquine diphosphate were complexed with Oxovanadium(II), Chromium(III), Iron(III), Copper(II), Cobalt(II), Nickel(II), Zinc(II), Cadmium(II), Mercury(II), Rhodium(III), Palladium(II), Gold(II), Silver(I), Manganese(II), Tin(II). All the synthesized metal complexes were screened by an *in-vitro* micro technique for their schizonticidal activity.



Structure of amodiaquine metal complex



Structure of Primaquine metal complex

The inhibitory activity of drug was studied against *P. falciparum* strain of malaria parasite. The antimalarial activity of synthesized metal complexes was found to be shown same activity as that of parent compound. The minimum inhibitory activity of amodiaquine and its metal complex were found to be 10^{-7} M while of primaquie was found to be 10^{-6} M. However metal salts of mercuric complex showed minimum inhibitory activity of 10^{-10} M, cadmium complex exhibited 10^{-10} M inhibitory activity while the tin complex and silver complex exhibited minimum inhibitory activity of 10^{-8} M [7].

A series of 2-phenylbenzimidazoles and their corresponding Ru (II), Ir (III) and Rh (III) cyclometallated complexes were synthesized by Rylands *et al*. and evaluated for antiplasmodial activity against the chloroquine-sensitive (NF54) strain of the human malaria parasite Plasmodium falciparum. Selected metal complexes were further screened against the multidrug-resistant (K1) strain. In general, the 2-phenylbenzimidazole ligands showed weak antiplasmodial activities (IC ~ 17.66-22.32 μM) while an enhancement of antiplasmodial activity was observed upon coordination of the ligands with either ruthenium, iridium or rhodium. The new cyclometallated complexes were found to be active against both parasite strains, with IC values in the low to submicromolar range (0.12-5.17 μM). In addition, the metal complexes have relatively low cytotoxicity against mammalian Chinese Hamster Ovarian (CHO) cells [8].

Patti *et al*., synthesized 2-ferrocenylquinoline derivatives and evaluated their antimalarial activity. The antimalarial activity of ferrocenyl derivatives were *in-vitro* evaluated for the chloroquine-resistant W2 strains of *P. falciparum*. The ferrocenyl derivatives showed increased potency of antimalarial drugs [9].

Bjelosevic *et al*., synthesized the Platinum (II) and Gold (I) complexes based on 1, 1'-bis (diphenylphosphino) metallocene derivatives. The antimalarial activity was performed on *P. falciparum* strains W2 by culturing in human erythrocytes. Cytotoxic activity were performed on a cervical carcinoma cell line(Hela)(CCL-2) and antiviral activity were performed on T-lymphoblastoid cell line CEM-SS. Synthesized gold(I) complexes, {1-[1-(dimethylamino)ethyl]-1, 2-bis (diphenylphosphino) ruthenocene-κ^2P,P'} bis[chlorogold(I)] with inhibitory concentration of 1.40 μM (IC_{50} = 1.40 μM), {1-[1-(acetoxyethyl)-1′,2-bis(diphenylphosphino)ferrocene-κ^2P,P']bis[chlorogold(I)] with inhibitory concentration of 0.50 μM (IC_{50} = 0.51 μM), {1-[1-(3-carboxypropanamido)ethyl]-1′,2 bis (diphenylphosphino) ruthenoceneκ^2P,P'}bis[chlorogold(I)] with inhibitory activity of 1.784 μM (IC_{50} = 1.784 μM), have the best activities against cancer, HIV and malaria respectively [10].

Lam and Geiger synthesized anodic electrochemistry of cymanquine and related compounds. Cymaquine is the analogue of ferroquine in which the FeCp group is replaced by a Mn $(Co)_3$ group. Three compounds of 4-aminochloroquinoline moiety were prepared by covalent linkage to a cyclopentadienyl manganese tricarbonyl moiety. The new compounds exhibited a rich set of oxidative electrochemical reactions [11].

Phopin *et al*., synthesized 8-Aminoquinoline (8AQ) derivatives and screened their antimalarial, anticancer, and antioxidant activities. This study investigated the potency of 8AQ-5-substituted (iodo and nitro) uracils metal (Mn, Cu,Ni) complexes as antimalarial and antimicrobial agents. Interestingly, all of these metal complexes showed fair antimalarial activities. Moreover, Cu complexes 2 (8AQ-Cu-5 Iu) and 5 (8AQ-Cu-5Nu) exerted antimicrobial activities against Gram-negative bacteria including *P. shigelloides* and *S. dysenteriae*. The results reveal application of 8AQ and its metal complexes as potential compounds to be further developed as novel antimalarial and antibacterial agents [12].

Chopin *et al*., synthesized novel 1, 4-disubstituted-[1, 2, 3]-triazole-derived β-aminovinyl trifluoromethylated ketones and their copper (II) complexes. (Z)-4-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-1,1,1-trifluorobut-3-en-2-one and (Z)-4-(((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)-1,1,1-trifluoro-4-phenylbut-3-en-2-one were synthesized. They had been screened for as potential antifungal agents and the antimalarial activity against two *P. falciparum* strains (3D7 and W2) and showed the good activity [13].

Niculescu *et al*., synthesized the Novel 2, 3-disubstituted 1, 4-napthoquinone derivatives and their metal complexes. The potential cytotoxic activity of novel 2, 3-disubstituted 1, 4-napthoquinone and their metal complexes were studied against L929 murine fibroblasts cells grown *in-vitro*. The two new napthoquinonic ligands containing S, N as donor atoms were: 2-acetamino-3-mercapto-1, 4-napthoquinone (AMNQ) and 2-mercapto-3(5-nitrobarbituro)-1, 4-napthoquinone (MNBNQ). The IC_{50} of ligands were 0.0088mg/ml for AMNQ and 0.0022 mg/ml for MNBNQ [14].

Summers, synthesized Metal-thiosemicarbazone (TSC) complexes and tested for antimalarial efficacy against drug-sensitive and drug-resistant strains of *P. falciparum*. An array of TSC complexes with numerous transition metals, including ruthenium, palladium, and gold has displayed antiplasmodial activity. Au I) - and Pd (II) -TSC complexes displayed the greatest potency; 4-amino-7-chloroquine moieties were also found to improve antiplasmodial activity of TSCs. Although promising metal-TSC drug candidates have been tested against laboratory strains of P. falciparum, problems arise when attempting to compare between studies [15].

Mohamed and Gad-Elkreem synthesized metal complexes of new azo compounds derived from sulfa drugs. Four new azo compounds of sulfa drugs have been prepared. These azo ligands coordinate via the azo N, carbonyl O, enolic sulphonamide OH, and pyrazole or thiodiaza N groups forming two binding chelating agents. The ligands were $[MX_2$ (L1) $(H_2O)_m].nH_2O$, $[(MX_2)_2(HL_2$ or $HL_3)$ $(H_2O)_m].nH_2O$ and $[M_2\ X_3(L_4)(H_2O)].nH_2O$. Metal salts used for ligands formation were Cobalt (II), Nickel (II), Copper (II) and Zinc (II) [16].

Pandey *et al*., synthesized and evaluated novel 4-aminoquinoline-tetrazole derivatives as potent antimalarials agents. These derivatives were screened for their antimalarial activities against both chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *P. falciparum* as well as cytotoxic activity against VERO cell lines Compounds with significant *in-vitro* antimalarial activity were evaluated for their *in-vivo* efficacy in Swiss mice against *P. yoelii* by both intraperitoneal as well as oral administration [17].

Chellan *et al*., synthesized the cyclopalladated complexes containing tridentate thiosemicarbazone and performed their antimalarial activity. The C-H activation reaction of two aryl-derived thiosemicarbazones with K_2 $[PdCl_4]$ forms a cyclopalladated complexes where thiosemicarbazone act as a tridentate donor coordinated to palladium via the *ortho*-carbon of the aryl ring, imine nitrogen and thiolate sulfur. Different palladium complexes were [Pd(3,4-dichloroacetophenone thiosemicarbazone)], $[Pd(3,4\text{-dichloropropiophenone thiosemicarbazone})]_4$, $[Pd(3,4\text{-dichloroacetophenone thiosemicarbazone})]_4$, $[Pd(3,4\text{-dichloroacetophenone thiosemicarbazone})(PPh_3)]$, $[Pd(3,4\text{-dichloropropiophenone thiosemicarbazone})(PPh_3)]$, $[Pd_2(3,4\text{-dichloroacetophenone thiosemicarbazone})_2(dppf)]$, $[Pd_2$ $(3,4\text{-dichloroacetophenone thiosemicarbazone})_2(trans\text{-}dppe)]$, $[Pd_2$ $(3,4\text{-dichloropropiophenone thiosemicarbazone})_2(trans\text{-}dppe)]$, $[Pd_2$ $(3,4\text{-dichloroacetophenone thiosemicarbazone})_2(dppb)]$. These palladium complexes along with their free ligands were evaluated as bioorganometallic antimalarial agents against two *P. falciparum* strains, 3D7 (chloroquine sensitive) and K1 (chloroquine and pyrimethamine resistant) [18].

Belloti de souza *et al*., synthesized the 4-aminoquinoline metal complexes and their antimalarial activities were performed. 4-amino quinolones derivatives were the most potential sources of antimalarial drugs. 1, 2, 4-aminoquinolone derived drugs were obtained and some of them were used to form platinum complexes. These compounds were tested *in-vivo* in murine model and showed remarkable inhibition of parasite multiplication. These drugs act by the inhibition of iron-protoporphyrin IX (FP-IX). The 25 mg/kg dose of platinum complex showed greater activity than ligands against antimalarials. It showed 50-80% inhibition of parasite multiplication and in addition they showed no cytotoxic effects [19].

Macedo *et al*., reported the pharmacological activity of organoruthenium complexes containing chloroquine (CQ) as a chelating ligand. The complexes displayed intraerythrocytic activity against CQ-sensitive 3D7 and CQ-resistant W2 strains of *Plasmodium falciparum,* with potency and selectivity indexes similar to those of CQ. Complexes displayed activity against all intraerythrocytic stages, but moderate activity against *Plasmodium berghei* liver stages. However, unlike CQ, organoruthenium complexes impaired gametocyte viability and exhibited fast parasiticidal activity against trophozoites for *P. falciparum*. This functional property results from the ability of complexes to quickly induce oxidative stress. The parasitaemia of *P. berghei*-infected mice was reduced by treatment with the complex [20].

Conclusion

Malaria is a potentially life-threatening disease, affecting approx. 214 million people worldwide. Malaria is caused by a protozoan, Plasmodium falciparum, which is transmitted through the Anopheles mosquito. Malaria treatment is becoming more challenging due to rising resistance against the antimalarial drug, chloroquine. Novel compounds that target aspects of parasite development are being explored in attempts to overcome this wide-spread problem. Researchers have progressed from simple "synthesis/activity" to complex insights into their mechanisms of action. A better understanding of these mechanisms will represent the essential requirement in new generations of metal-based agents. This perspective outlines a unique strategy for that purpose through the development of metal-based antimalarial agents.

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