# Chloroquine-organoruthenium compounds are fast-acting multistage antimalarial agents

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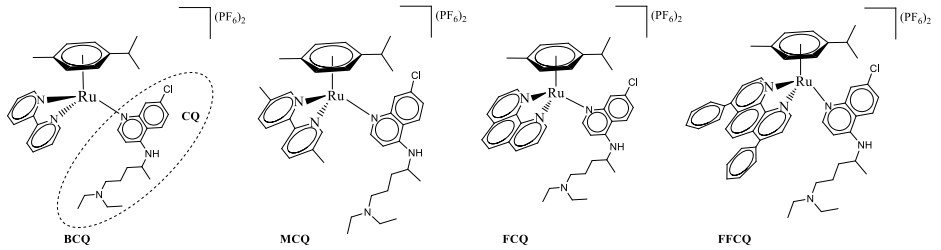
Malaria remains a major health problem in the world. Chemotherapy has long been a mainstay in the combat against malaria, but increasing emergence of drug resistance is limiting malarial control.[1,2] Therefore, we examined here the pharmacological activity of four organoruthenium complexes containing chloroquine (CQ). These complexes were characterized by conductivity, I.R., cyclic voltammetry, $^{1}H$, $^{13}C$, $^{15}N$ and $^{31}P$ NMR.[3]




The complexes displayed intraerythrocytic activity against CQ-sensitive 3D7 and CQ-resistant W2 strains of *P. falciparum*, with potency and selectivity indexes similar to those of CQ. Like CQ, complexes displayed activity against all intraerythrocytic stages, interacted to ferriprotoporphyrin and inhibited polymerization of hemin into β-hematin. But, unlike CQ, organoruthenium complexes impaired gametocyte viability and exhibited fast parasiticidal activity against trophozoites of *P. falciparum*.

**Table.** Activity against *P. falciparum* and mammalian cell cytotoxicity.

| Comp. | *P. falciparum*, $IC_{50}$ ±S.E.M.(μM)[a] | | J774 lineage, $CC_{50}$±S.E.M.(μM)[b] | Gametocytes $IC_{50}$±S.D.(μM)[c] |
|---|---|---|---|---|
| | CQ-sensitive 3D7 | CQ-resistant W2 | | |
| (**BCQ**) | 0.34±0.13 | 0.52±0.04 | 153.9±6.3 | 0.78±0.24 |
| (**MCQ**) | 0.30±0.007 | 0.30±0.1 | 42.6.±1.6 | > 14.5 |
| (**FCQ**) | 0.30±0.03 | 0.31±0.01 | 154.0±6.9 | 4.28±1.05 |
| (**FFCQ**) | 0.21±0.039 | 2.1±0.3 | 2.4±0.2 | 1.43±0.24 |
| CQ | 0.11±0.035 | 0.43±0.09 | 37.6 ±3.6 | > 20 |

[a] Determined 48 h after incubation with compounds. [b] Determined 72 h after incubation with compounds.

Mechanistically, antiparasitic activity is due to the ability of complexes to impair with β-hematin formation and quickly induce oxidative stress. Treatment with BCQ complex reduced parasitemia in *P. berghei*-infected mice. In conclusion, we demonstrated that using chloroquine for the synthesis of organoruthenium complexes retains potency and selectivity while leading to an increase in the spectrum of action and parasite killing rate relative to CQ.

[1]Lin, J. W.; Spaccapelo, R. *J. Exp. Med.* **2015**, *212*, 893. [2]Petersen, I.; Eastman, R.; Lanzer, M. *FEBS Lett.* **2011**, *585*, 1551. [3] Colina-Vegas L, Villarreal W, Navarro M, de Oliveira CR, Graminha AE, Maia PI, Deflon VM, Ferreira AG, Cominetti MR, Batista AA. *J. Inorg. Biochem.* **2015**, *153*, 150.

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