Chemical Approach to Studying the Role of Quinoline-Based Antimalarials in Inhibiting Hemozoin Formation

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Development Day - May 18, 2021

Impetus for our work

- Malaria is still a public health problem
- Treatment medications for malaria are limited
- Drug resistance a major challenge

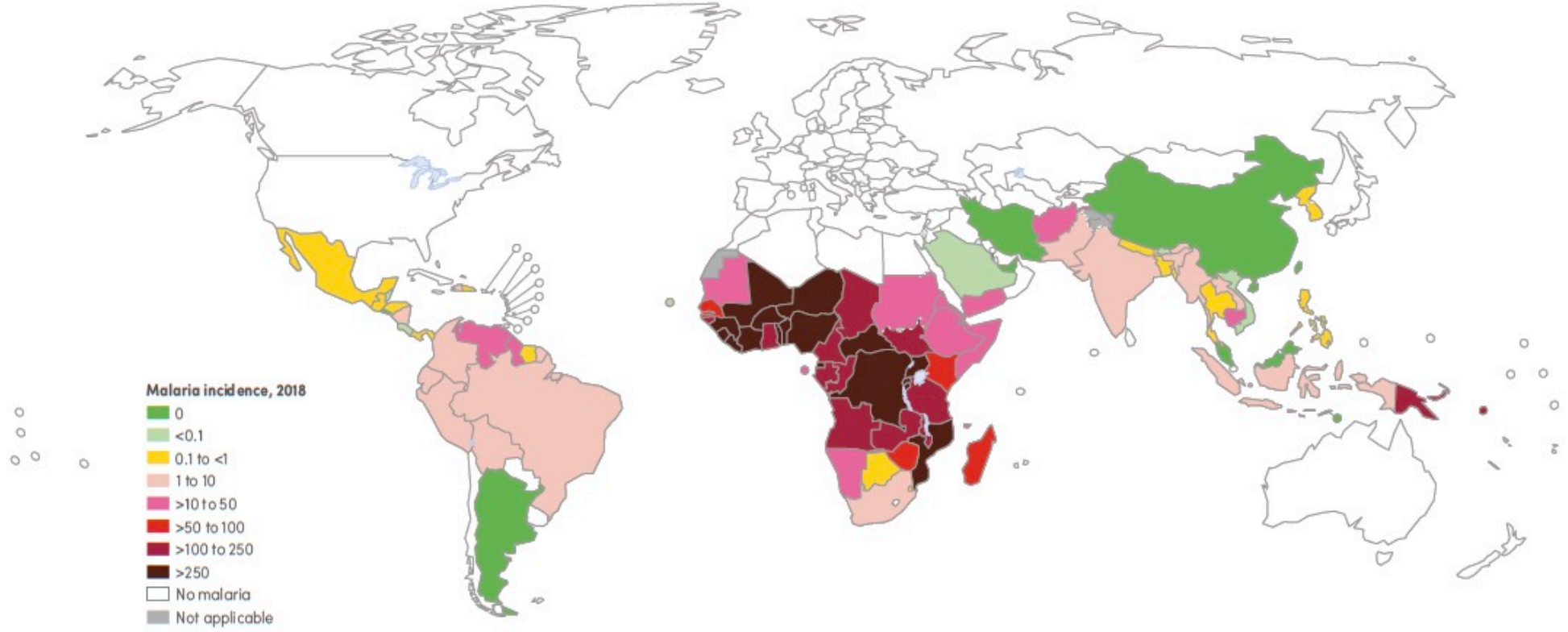


Fig. 1 Map of malaria case incidence rate (cases per 1000 population at risk) by country in 2018

REF. World Health Organization. 2018. World Malaria Report 2018; Geneva, 2018.

The Life Cycle of the *Plasmodium* Parasite

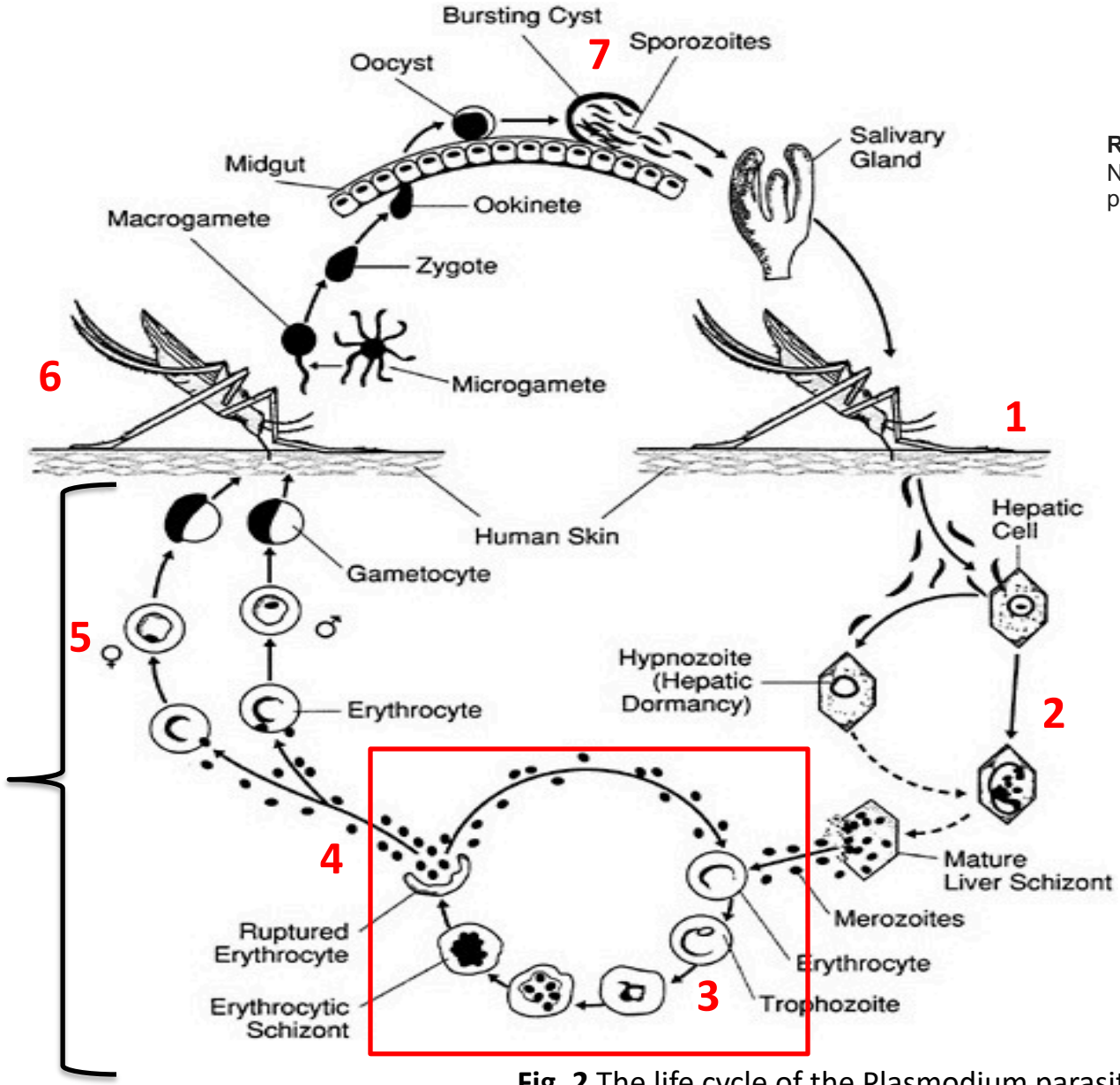


Fig. 2 The life cycle of the Plasmodium parasite

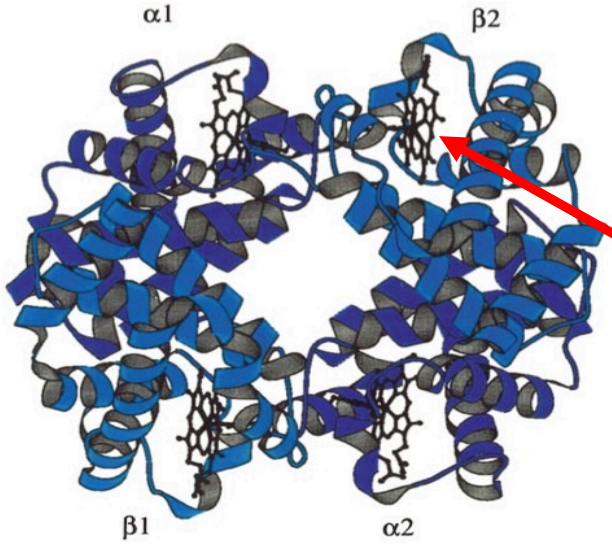
REF. Oaks, et al., Malaria, Obstacles and Opportunities", National Academy Press: Washington, DC, 1991. Used with permission

Pathogenic blood stage

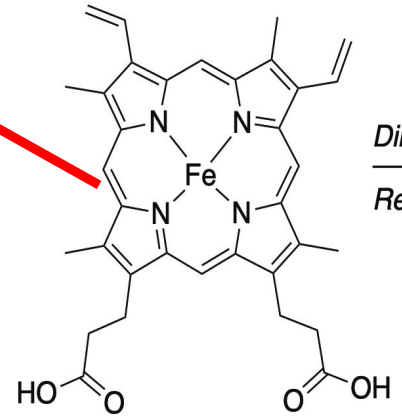
Heme is a target for antimalarials

Current Literature

- The plasmodium parasite feeds on the protein portion of heme
- Mechanism of hemozoin formation debated
- Antimalarials inhibit hemozoin formation



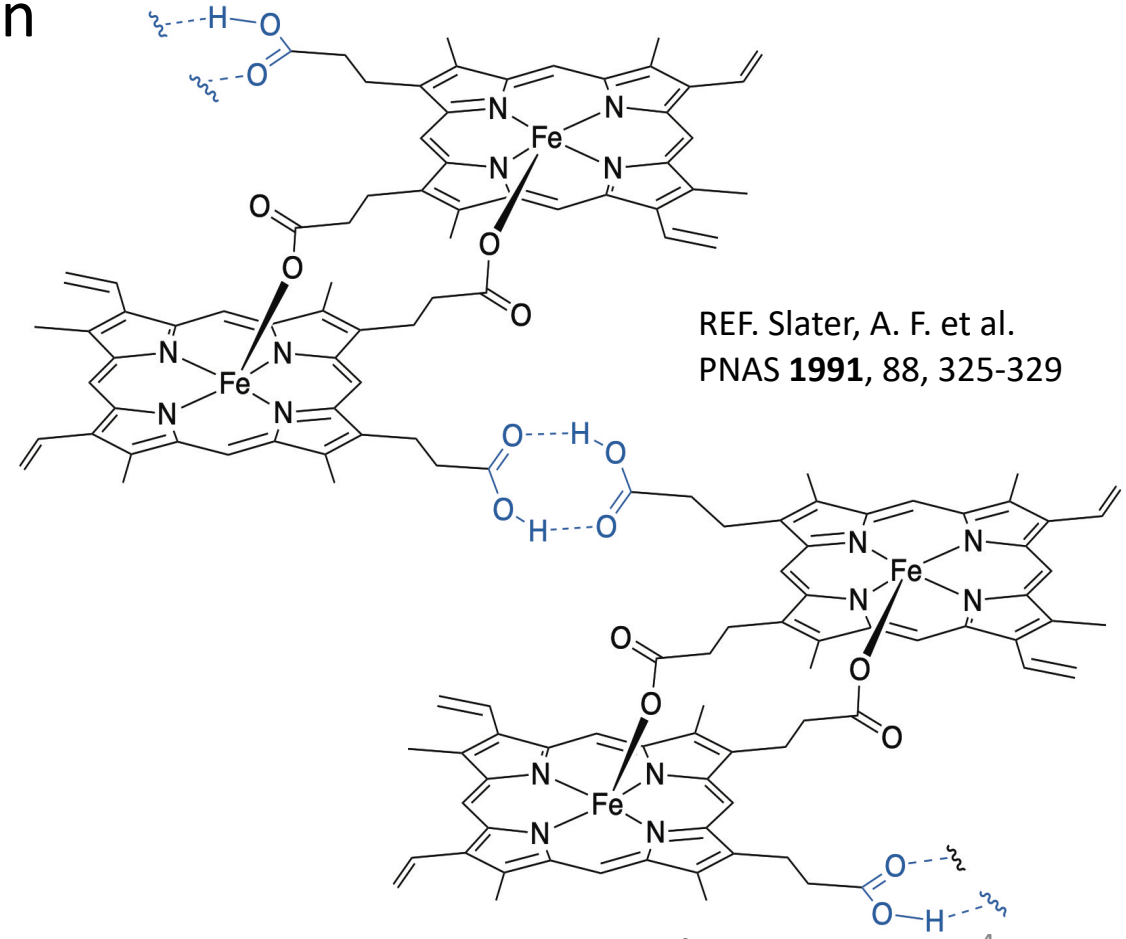
Hemoglobin



(PPIX)Fe

Dimerization, cryst.

Redox rxn

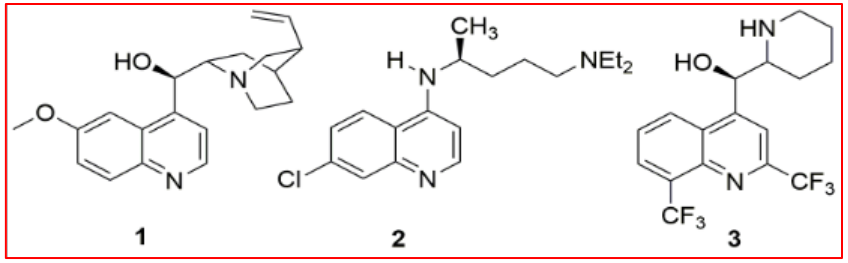


Hemozoin

REF. Slater, A. F. et al.
PNAS **1991**, 88, 325-329

+

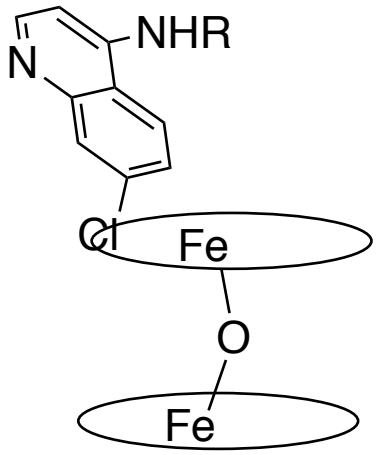
Quinoline-based antimalarials



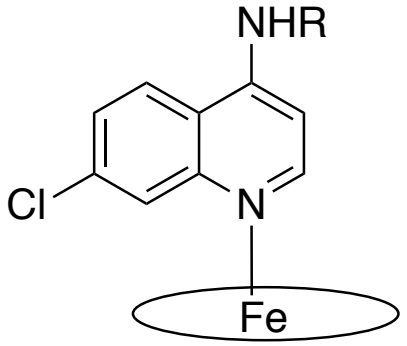
Scheme 1 Hemozoin formation

Current Literature

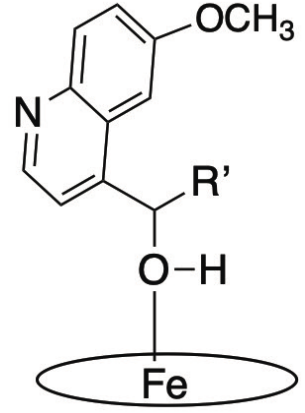
- Quinoline-based drugs inhibit hemozoin formation by interacting with heme or hemozoin
- Few solid state structures of heme-drug adducts have been reported, although several adducts have been characterized by spectroscopy



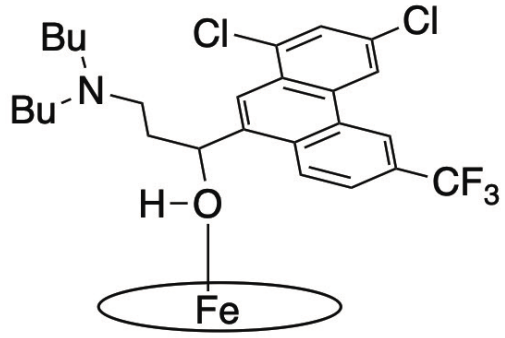
CQ/AQ—μ-oxo-dimer complex (π—π stabilized)
*Roepe (Biochem. **2002**; Inorg. Chem. **2004**)*



CQ-complex (N-bound)
*Roepe (J. Phys. Chem. A. **2003**)*



QN/QD-complex (O-bound)
*Villiers (ACS Chem. Biol. **2012**)*
*Roepe (J. Inorg. Biochem. **2011**)*

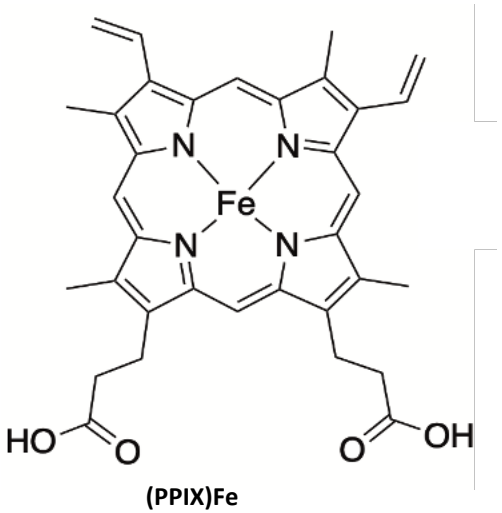


Hf-complex (O-bound)
*Egan (J. Inorg. Bichem. **2008**)*

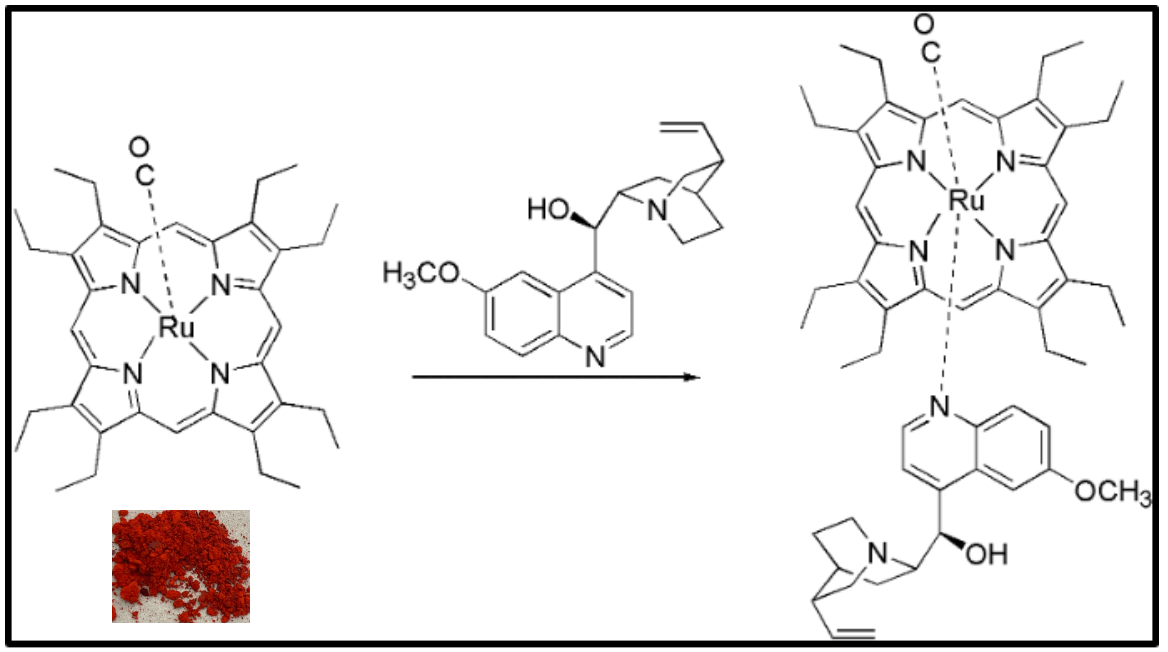
Fig. 3 Some heme-drug adducts

Our Work

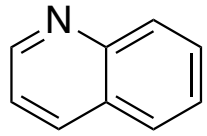
- Study the spectroscopic properties of heme-antimalarial adducts
- Understand features of the solid-state structures of the adducts
- Learn more about the redox behavior of the adducts
  - Use stable synthetic models such as (OEP)Ru(CO)



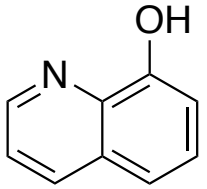
(PPIX)Fe



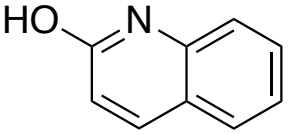
Scheme 2 Synthesis of the (OEP)(Ru(CO)(QN) adduct



Qnl



8-HOQ

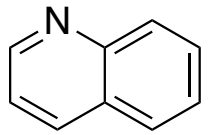


2-HOQ

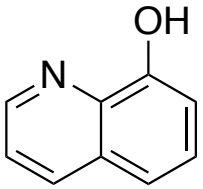
QN = quinine; Qnl = quinoline, 8-HOQ = 8-hydroxyquinoline; 2-HOQ = 2-hydroxyquinoline; OEP - octaethylporphyrinato

Infrared Spectroscopy

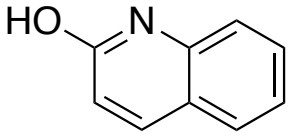
- Infrared (ATR) spectral data suggest adduct formation



Qnl



8-HOQ



2-HOQ

Table 1 IR spectral data of the (OEP)Ru(CO)(Q) complexes

Entry	Compound	υ_{CO} (cm^{-1})	$\Delta\upsilon_{CO}$ (cm^{-1})*
1	(OEP)Ru(CO)(H_2O)	1918	-
2	(OEP)Ru(CO)(Qnl)	1938	20
3	(OEP)Ru(CO)(QN)	1931	13
4	(OEP)Ru(CO)(8-HOQ)	1916	-2
5	(TPP)Ru(CO)(H_2O)	1938	-
6	(TPP)Ru(CO)(Qnl)	1965	27
7	(TPP)Ru(CO)(QN)	1963	25

**Obtained by subtracting the* υ_{CO} value of the precursor (OEP)Ru(CO)(H_2O) complex from that of the (OEP)Ru(CO)(Q) complex

Qnl = quinoline; QN = quinine; 8-HOQ = 8-hydroxyquinoline
OEP – octaethylporphyrinato
TPP – tetraphenylporphyrinato

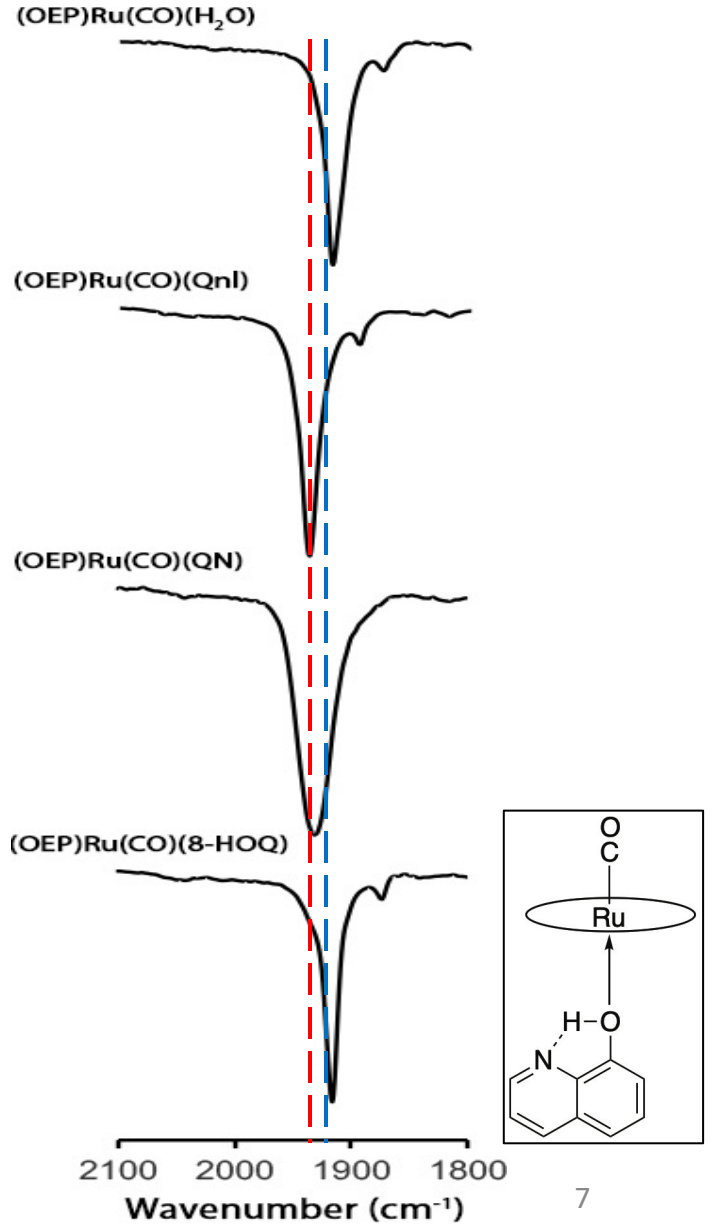
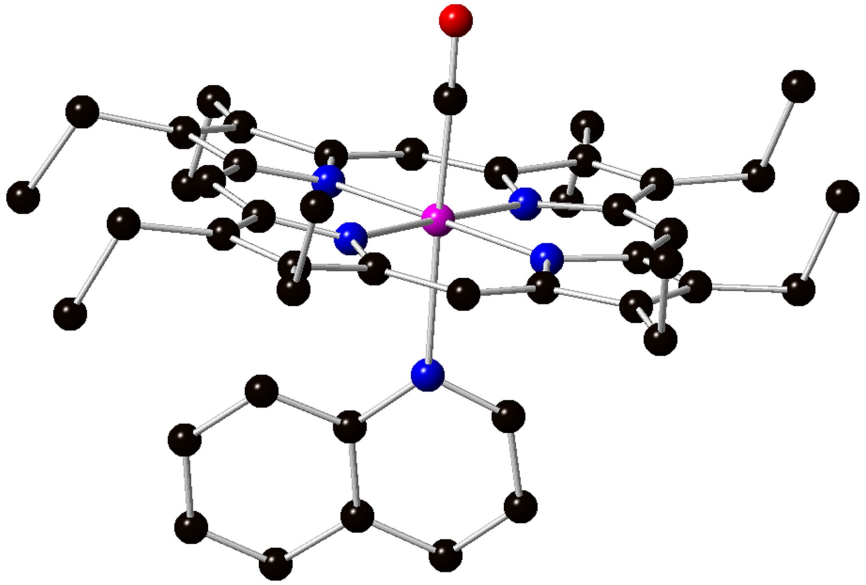


Fig. 4 IR spectra of the compounds

X-ray Crystallography

- X-ray crystal structure of the (OEP)Ru(CO)(Qnl) confirms binding of Qnl to Ru through the quinolinyl N
- Possible that mode of binding is similarly quinolinyl N in the (OEP)Ru(CO)(QN) adduct



*(OEP)Ru(CO)(Qnl) S*elected bond lengths (Å) and angles (°): Ru–C = 1.8081(15), Ru–N(Qnl) = 2.3408(13), C–O = 1.155(2), ∠RuCO = 176.51(14),

Fig. 5 Molecular structure of *(OEP)Ru(CO)(Qnl)*

Cyclic Voltammetry

- All 4 compounds have two oxidations

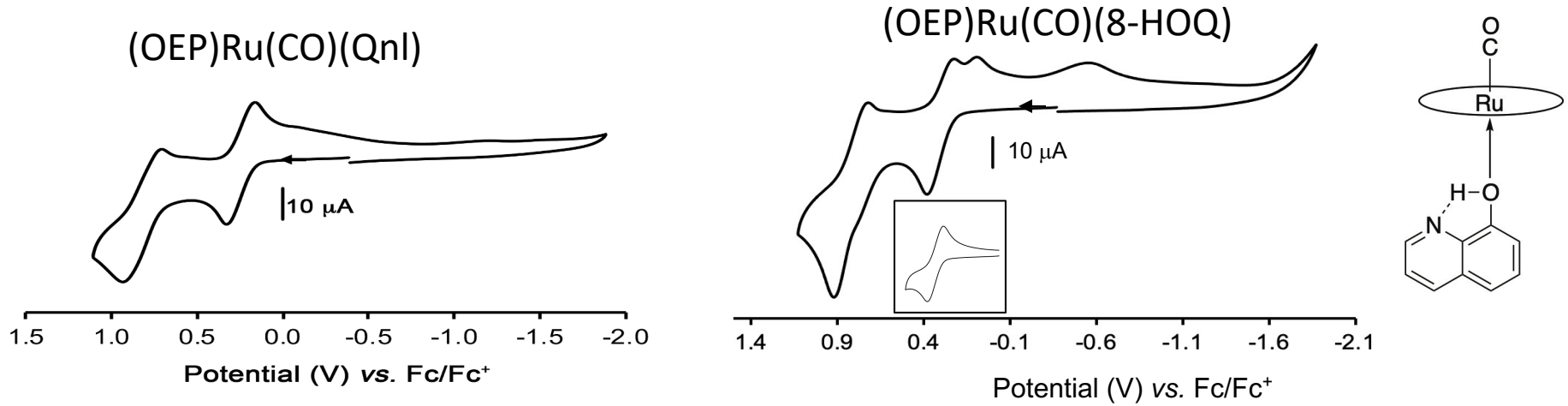


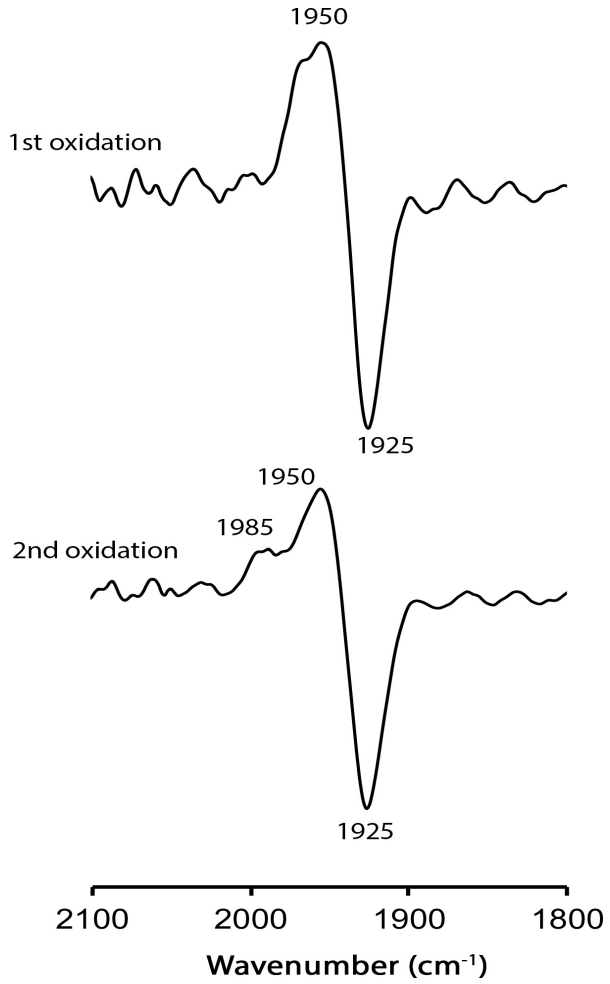
Fig. 6. CV of (OEP)Ru(CO)(Qnl) & (OEP)Ru(CO)(8-HOQ) in CH_2Cl_2 at 200 mV/s, 1 mM analyte, 0.1 M NBu_4PF_6 @ RT

Table 2 CV data of the compounds

Compound	Redox Potentials, V (vs. Fc/Fc⁺)	
	E_1^o	E_2^o
(OEP)Ru(CO)(H_2O)	0.23	0.72
(OEP)Ru(CO)(Qnl)	0.22	0.79
(OEP)Ru(CO)(QN)	0.20	0.69
(OEP)Ru(CO)(8-HOQ)	0.36	0.82

IR Spectroelectrochemistry

- IR spec. echem. suggests porphyrin-centered oxidations



$$[(OEP)Ru(CO)(Qnl)] \rightleftharpoons [(OEP^{\bullet})Ru(CO)(Qnl)]^{+} + e^-$$

$$[(OEP^{\bullet})Ru(CO)(Qnl)]^{+} \rightleftharpoons [(OEP^{\bullet})Ru(CO)(Qnl)]^{2+} + e^-$$

Fig. 7 Difference IR of (OEP)Ru(CO)(Qnl) after 1st & 2nd oxidation

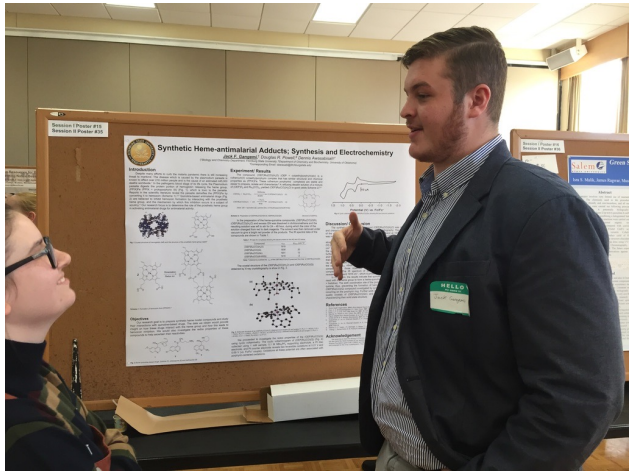
Cell Design:

Shaw, M. J.; Henson, R.; Houk, S. E.; Westhoff, J. W.; Jones, M. W.; Richter-Addo, G. B. *Electroanal. Chem.* **2002**, *534*, 47.

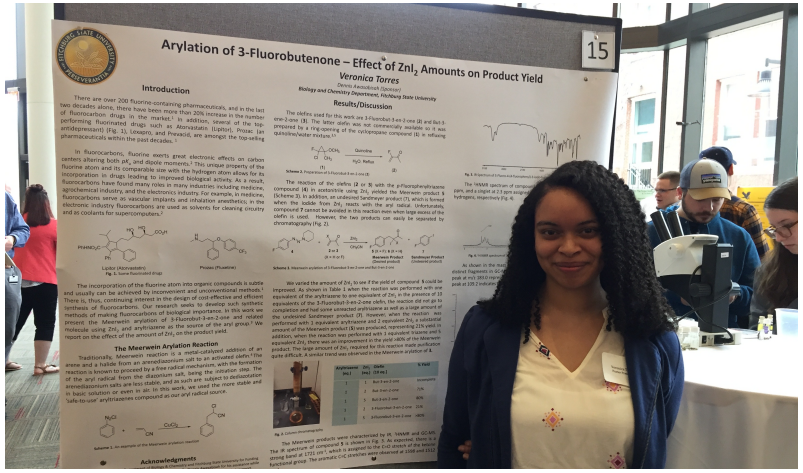
Conclusion

- Ru adducts of quinoline-based molecules have been prepared as structural models for the interactions of selected antimalarial drugs with heme
- The X-ray crystal structure of (OEP)Ru(CO)(Qnl) displays N-binding of the quinoline to the metal center
- The quinoline-based antimalarials bind directly to the Ru center of the heme model
- Work is currently underway to obtain X-ray quality crystals of (OEP)Ru(CO)(QN) and (OEP)Ru(CO)(8-HOQ) adducts to assist in characterizing their solid state structures.

Acknowledgement



Jack Gangemi (BS Chemistry)*



Veronica L. Torres (BS Biology, 2019)

Kyle Robbins (BS Chemistry, 2020)*

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Thank You!