New Hybrid Malaria Drugs: Ferrocenyl Amides of 4-Aminoquinolines

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Introduction and Background

Malaria, an infectious disease in many underdeveloped countries, is difficult to prevent and treat because certain strains have grown resistant to common anti-malarial drugs, such chloroquine and artemisinin.[3] To counteract this, malaria patients are treated with a combination of different drugs. Currently hybrid drugs are being created that combine the active moieties of the different drugs onto one compound, called trioxaferroquines, see **Figure 1**. They contain a quinine, a ferrocenyl moiety, and a trioxane.[4] These trioxaferroquines and ferroquines proved effective in both in vitro and in vivo studies on chloroquine resistant malaria strains.[5]

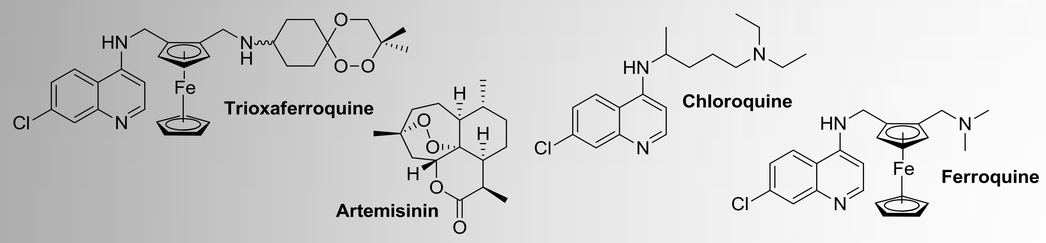
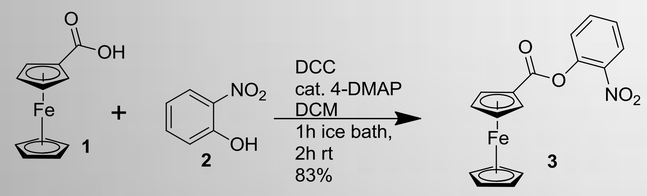


Figure 1. Structures of a trioxaferroquine, artemisinin, chloroquine, and ferroquine.

Experimental and Results

This project worked towards the synthesis of a ferrocenyl amide of chloroquine. The proposed synthetic route[3] is given in **Scheme 1**. The first reaction activated the ferrocene monocarboxylic acid **1** by esterification with 2-nitrophenol **2**. The product was purified by flash column chromatography to give 2-nitrophenyl ferrocenylformate **3** with a good yield (83%). The products were characterized with proton and carbon-13 NMR and IR spectroscopy. [3]



Scheme 1. Proposed Synthetic Route for 2-Nitrophenyl Ferrocenylformate

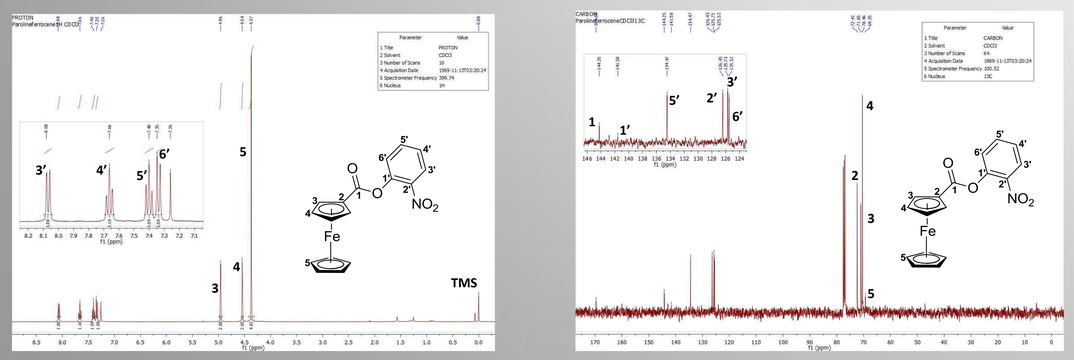


Figure 2. ^{1}H Proton and ^{13}C Carbon NMR Spectra of 2-Nitrophenyl Ferrocenylformate.

Discussion

Metallocenes exhibit a wide range of biological activity. Ferrocene is the most studied organometallic species for its thermal stability and inert character. It is used in these hybrid malaria drugs displays antimalarial activity.[3] In these drugs, the position of the ferrocenyl moiety affects its antiplasmodial activity. It is proposed that the following structure-activity relationships account for this. [3]

1. Interaction with Hematin
2. β-Hematin Inhibition
3. Accumulation in the Food Vacuole
4. Maintenance in Food Vacuole

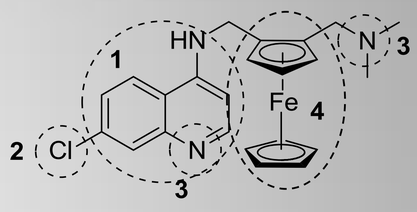
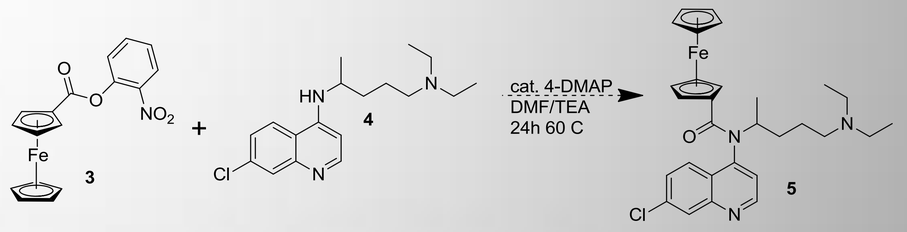


Figure 3. Proposed Activity-Structure Relationship of Ferroquine.

Future Work

The activated ferrocene **3** will then be reacted by amidation with chloroquine **4** to give the target molecule **5**.[3] This reaction was attempted unsuccessfully due to possible decomposition of chloroquine. An NMR spectrum of the chloroquine starting material will be obtained.



Scheme 2. Proposed Synthetic Route for Ferrocenyl Amide of Chloroquine.

Conclusions

The 2-nitrophenyl ferrocenylformate **3** was synthesized by esterification; the NMR and IR spectra were consistent with literature.

Acknowledgments

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References

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