

## PROBLEM STATEMENT

### Background

*Plasmodium falciparum* (*P. falciparum*), the most virulent of the human malaria parasites, causes a major global health problem. Malaria was the underlying cause of death for 1.24 million individuals in 2010, of which 57% were children below the age of five (Murray *et al.*, 2012). The widespread resistance of *P. falciparum* to most antimalarial drugs is a major obstacle in the elimination of the disease. Consequently, there is an urgent need for new drugs.

The discovery and development of artemisinin and its clinical derivatives have provided a new class of highly effective antimalarials, and these have become the most important class of drugs because *P. falciparum* displayed resistance to all classic antimalarial drugs. Artemisinin-based combination therapy (ACT) is therefore used to overcome the problem of resistance. The recently reported potential emergence of resistance to artemisinin (Carrara *et al.*, 2009; Dondorp *et al.*, 2010) is a major threat, highlighting the need for new chemotherapeutic approaches in the treatment of *P. falciparum* infections. The major drawback of artemisinin and its derivatives, despite their rapid antimalarial action, is the very short half-lives (less than 1 h) that are due to the drugs' capacity for autoinduction of metabolism (Ashton *et al.*, 1998; Asimus & Gordi, 2007). Artemisinin itself has also been shown to influence cytochrome P450 (CYP)-mediated metabolism of other drugs, increasing the risk of drug-drug interactions when ACTs are used (Asimus *et al.*, 2007).

When an artemisinin and longer half-life quinoline moiety is combined chemically in the same molecule, the risk of treatment failure is reduced, and partner drugs are substantially protected against resistance. Aminoquinoline is the pharmacophore of all classic quinoline antimalarials *e.g.* mefloquine, amodiaquine, primaquine, etc., which are currently used as part of ACTs. Long-acting quinoline antimalarials possess half-lives of 10 hours to 10 days (White, 2004). Therefore, by chemically combining artemisinin with aminoquinoline, dual pharmacological action could result in synergism, which in turn would allow lower doses and a potentially wider safety margin. Drug-drug interactions, which are becoming an increasing concern when using ACT in malaria treatment, would thus be avoided when adopting hybrid chemotherapy.

## Aims and Objectives

The aims and objectives of this thesis were, therefore, to:

- I Design hybrids, consisting of dihydroartemisinin and aminoquinoline attached *via* various linkers
- II Synthesise hybrids chemically, purify and characterise the compounds
- III Determine the *in vitro* antiplasmodial activity and cytotoxicity of the series of compounds
- IV Determine the *in vivo* antimalarial activity of the promising compounds
- V Perform a snapshot pharmacokinetic analysis to determine the pharmacokinetic profile of this class of drugs

## References

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