CHAPTER 1

1 INTRODUCTION AND PROBLEM STATEMENT

1.1 Introduction

Malaria affects an estimated 250 million people each year and is the most wide-spread parasitic disease encountered (Grimberg & Mehlotra, 2011). The disease has a worldwide distribution and is found throughout the tropics, sub-Saharan Africa, South East Asia, the Pacific islands, India, Central and South America (Figure 1) (Ashley et al., 2006). Malaria caused by *Plasmodium falciparum* predominates in Africa where the mortality attributed to it approaches 1 million annually, and accounts for 90% of the global malaria burden (Breman *et al.*, 2004). The majority of these deaths are children under the age of 5 years. Thus, one child dies of malaria in Africa every 30 seconds, which translates into a tragic 3000 children each day (WHO 2010; Grimberg & Mehlotra, 2011). Many of the children who survive an episode of severe malaria suffer from brain damage and cognitive disability, consequently crippling these families with its debilitating aftermath (Oh & Chishti, 2005).

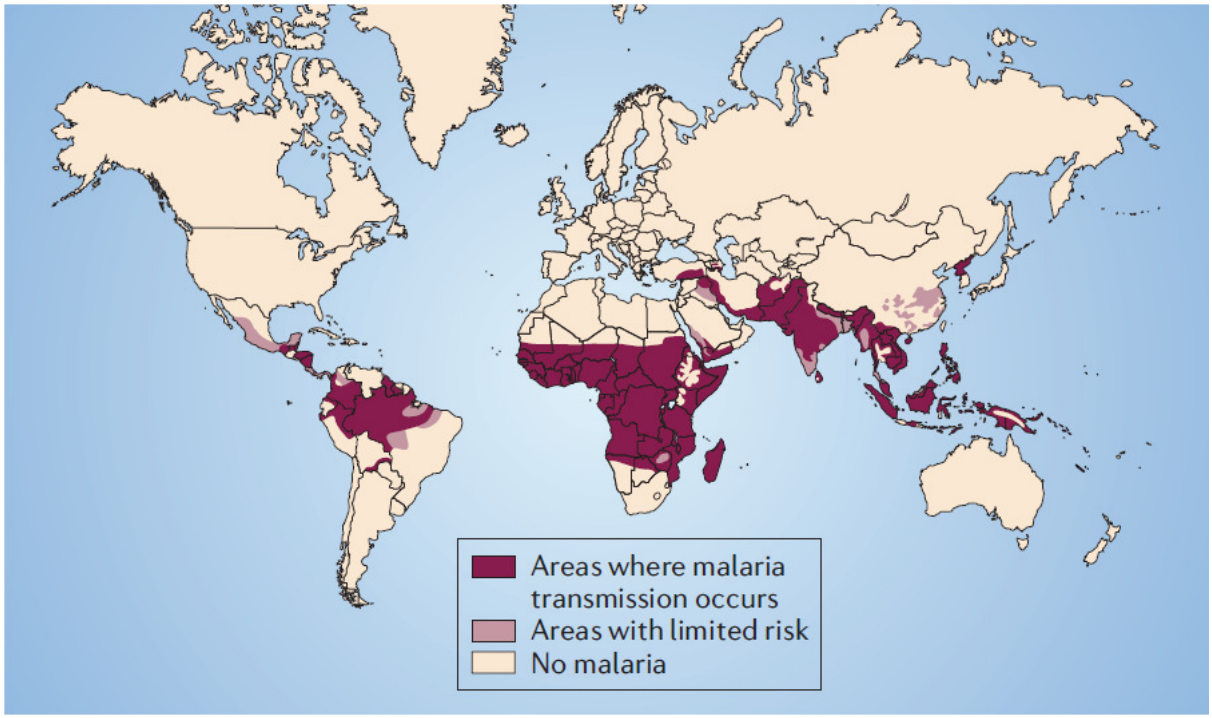

Figure 1 The distribution of *Plasmodium falciparum* malaria (Bell *et al.*, 2006).

The emergence of *P. falciparum* resistance to chloroquine, mefloquine, sulphadoxine and pyrimethamine, as well as insecticide resistance in *Anopheline* mosquito vectors have led to a dramatic resurgence of the disease (Vangapandu *et al,* 2006). The demise of chloroquine's antimalarial efficacy has contributed directly to the doubling of malaria specific mortality over the last 15 years (Breman *et al*., 2004). The above mentioned considerations highlight the importance of developing new drugs that might circumvent parasite resistance.

The quinoline antimalarial drugs inhibit the formation of hemozoin, allowing haematin released during haemoglobin degradation to accumulate to toxic concentrations. The 4-aminoquinoline drug, chloroquine used to be a flagship drug against malaria because of its low cost, excellent clinical efficacy and low toxicity. However, the development of resistance has now limited its use to resistance free areas of the world. Nevertheless the 4- and 2-aminoquinoline scaffolds remain an attractive template for design of new drugs, because of their unique affinity for haematin compared to the 3-, 5-, 6- and 8-aminoquinoline scaffolds (Egan *et al.,* 2000; Egan, 2003). The haemoglobin degradation pathway poses difficulty for the parasite in developing drug resistance, since the detoxification process is not enzyme mediated and therefore not susceptible to mutation. This delays the appearance of drug resistance to the hemozoin formation inhibitors (Dorn *et al.,* 1998; Egan, 2003).

Subsequently the mechanism of resistance in *P. falciparum* to chloroquine is mainly associated with reduced drug accumulation inside the digestive vacuole. This is achieved through a *Plasmodium falciparum* chloroquine resistance transporter (PfCRT) or ATP-dependant P-glycoprotein efflux pump (Pgh1), which actively pumps or transports drug out of the parasite vacuole (Fidock *et al*., 2000). The chloroquine side chain was identified as the primary recognition motif for chloroquine resistance due to structural specificity of this PfCRT protein (Bray *et al*., 2005). It is possible that new drugs with structural modifications that result in reduced affinity for the PfCRT may be able to retain activity against chloroquine resistant strains, therefore avoiding reduced drug accumulation due to recognition of the chloroquine tertiary amine. Furthermore, the quinoline antimalarial drugs are weak bases which traverse down the pH gradient between the extracellular matrix (pH 7.3) and the digestive vacuole (pH 4.5 - 5.5) of the malaria parasite. In the acidic environment they become protonated and membrane-impermeable, increasing the accumulation of the drug *via* a pH-trapping mechanism.

1.2 Aim and objectives of the study

In light of the aforementioned considerations, the aim of this study was to synthesise series of bisquinoline and bispyrrolo[1,2*a*]quinoxaline compounds containing the 4- and 2-aminoquinoline nucleus and polyamine bridges with secondary/tertiary amines, which may act as potential protonation sites, to determine the physicochemical properties of the synthesised compounds and evaluate their antimalarial activity in comparison with chloroquine.

In order to achieve the aim of this study, the following objectives were set:

- Synthesise bisquinoline and bispyrrolo[1,2*a*]quinoxaline compounds and confirm their chemical structures.
- Experimentally determine the aqueous solubility and the partition coefficients.
- Evaluate the *in vitro* the antimalarial activity of the synthesised compounds against a chloroquine-sensitive D10 strain and chloroquine-resistant Dd2 strain of *Plasmodium falciparum*.
- Test compounds for *in vitro* cytotoxicity against a mammalian cell-line, Chinese Hamster Ovarian (CHO) cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)-assay.
- Anti-cancer screening of the most promising compounds against a panel of TK10 (renal), UACC62 (melanoma) and MCF7 (breast) cancer cells using a Sulforhodamine B assay.