Preface

Malaria is one of the most common infectious diseases and an enormous public health problem. The disease is caused by protozoan parasites of the genus *Plasmodium* and affects over 100 countries of the tropical and subtropical regions of the world including South-East Asia, Sub-Saharan Africa and South America. Every year, around 300 to 500 million clinical cases of malaria are reported, of which nearly 1 to 3 million people, mostly children, die due to complicated cases of malaria. As per an estimate, every 30 seconds a child dies of malaria. Malaria is commonly associated with poverty, but is also a cause of poverty and hence an economic burden on the affected countries. The situation is getting worse with the emergence and spread of multidrug-resistant parasites.

Four identified species of the *Plasmodium* parasite responsible for human malaria are *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Of these, *P. falciparum* and *P. vivax* account for more than 95% of malaria cases in the world. The female anopheles mosquito is a vector for transmitting malaria parasites.

Malaria is reemerging as the biggest infectious killer and is currently the first priority tropical disease of the WHO (World Health Organization). The widespread development of resistance by *P. falciparum* to chloroquine, the cheapest, efficacious and most widely used drug, has posed a major challenge to combat malaria. Artemisinin, isolated from *Artemisia annua* and its semisynthetic derivatives e.g. artemether, arteether, and artesunic acid are the only class of antimalarials, which are effective against multidrug-resistant malaria. The peroxide bond in the form of 1,2,4-trioxane is essential for the antimalarial activity of this class of drugs. Ever since the isolation of artemisinin and establishment of the peroxide bond as its active pharmacophore, synthesis and antimalarial assessment of structurally simple 1,2,4-trioxanes has become an area of hot pursuit.

The thesis entitled “Structurally Simple Synthetic Peroxides: Synthesis and Antimalarial Assessment” describes a part of our efforts for developing organic peroxides as newer antimalarial agents. The thesis has been organized under five main chapters as summarized below:

The first chapter presents a concise review that accommodates some of the most significant historical achievements and developments observed in the discovery of antimalarial drugs, with particular emphasis on the last 35 years.
The **second chapter** describes synthesis and antimalarial activity of novel amino-functionalized 1,2,4-trioxanes in search for an analog, better than β-arteether.

The **third chapter** of the thesis describes synthesis and antimalarial activity of novel lipophilic ether- and ester-functionalized 1,2,4-trioxanes and hydrophilic hemisuccinate derivatives.

The **fourth chapter** deals with synthesis and antimalarial assessment of novel nitrogen-containing peroxides having entirely different pharmacophore than 1,2,4-trioxanes.

The **fifth chapter** describes synthesis and antimalarial assessment of novel dihydroartemisinin derivatives, which include dihydroartemisinin derived esters and hetero-dimers.
List of Abbreviations

anhyd  anhydrous
aq     aqueous
ATP    adenosine triphosphate
bm     broad multiplet
bs     broad singlet
cat    catalytic amount
CDCl₃  deuterated chloroform
compd  compound
concd  concentrated
°C     degree celsius
d      doublet
DCM    dichloromethane
dd     doublets of a doublet
ddd    doublets of doublets of a doublet
DMAP   N,N-dimethyl amino pyridine
DME    1,2-dimethoxyethane
DMF    dimethylformamide
DMSO   dimethylsulphoxide
ESI-MS electron spray ionization mass spectrum
EI-HRMS electron impact high resolution mass spectrum
EtOAc  ethyl acetate
FAB-MS fast atom bombardment mass spectrum
FT-IR  fourier transform infrared spectroscopy
g     gram
h     hour(s)
hv    quantum of light/photon
HPLC  high performance liquid chromatography
Hz     hertz
IC₅₀   50% inhibitory concentration
im    intramuscular
ip    intraperitoneal
iv    intravenous
J     coupling constant
LAH   lithium aluminium hydride
m     multiplet
MDR   multidrug-resistant
MHz   mega hertz
MIC   minimum inhibitory concentration
min   minute(s)
 mL   milliliter
mp    melting point
m/z   mass per unit (+ve) charge
µg    microgram
mmol  millimole
NMR   nuclear magnetic resonance
p-TSA p-toluenesulphonic acid
q     quartet
rt    room temperature
s     singlet
t     triplet
THF   tetrahydrofuran