Malaria is still one of the major health problem in the whole world along with tuberculosis and AIDS. The parasite responsible for the vast majority of fatal malarial infections is *P. falciparum*. The first effective antimalarial drug was quinine, which was isolated from the bark of Cinchona. Since then malaria has been treated with quinoline-based drugs such as quinine, chloroquine, mefloquine and primaquine. Unfortunately, many *Plasmodium* strains have now become resistant to these drugs. Almost 35 years ago, the major breakthrough in malaria chemotherapy occurred when a new antimalarial structural prototype with a pharmacophoric peroxide bond in a unique 1, 2, 4-trioxane heterocycle i.e. artemisinin was isolated from *Artemisia annua* and brought great attention to the whole world in malaria chemotherapy. It met the dual challenges posed by drug-resistant parasites and rapid progression of malarial illness.

Available evidence proves that artemisinin and related peroxidic antimalarial drugs exert their parasiticidal activity subsequent to reductive activation by haem, released as a result of haemoglobin digestion by the malaria-causing parasite *Plasmodium*. This irreversible redox reaction produces carbon-centred free radicals, leading to alkylation of haem and proteins (enzymes), one of which-the sarcoplasmic endoplasmic reticulum ATPase PfATP6-may be critical to parasite survival. Notably, there is no evidence of drug resistance to any member of the artemisinin family of drugs. The chemotherapy of malaria has benefited greatly from the semi-synthetic artemisinin derivatives such as dihydroartemisinin, artemether, arteether and artesunate as they rapidly reduce parasite burden, have good therapeutic indices and provide successful outcomes for the treatment of malaria. However, as a drug class, the artemisinins suffer from chemical (semisynthetic availability, purity and cost), biopharmaceutical (poor
bioavailability and limiting pharmacokinetics) and treatment (non-compliance with long
treatment regimens and recrudescence) issues that limit their therapeutic potential.

For malaria researchers, sequencing of genome of *P. falciparum* has provided an
unprecedented opportunity. The analysis of the genome sequence should provide valuable
information to identify promising new leads for vaccine development. A number of new
potential target pathways have already been identified and efforts to develop lead
compounds for these putative targets hopefully will allow treatment of malaria infections
in a uniform sustained way.

Since the Central Drug Research Institute, Lucknow, has an avowed objective of
developing new drugs; it is running a research programme in malaria chemotherapy since
late 70's. This programme had two major objectives: (a) to develop new antimalarials and
especially effective against resistant malaria and (b) to develop efficient technologies for
existing antimalarial drugs.

As part of this programme and in search for better artemisinin analogues, an
attempt has been made to improve the antimalarial activity of artemisinin analogues better
than β-arteether In this thesis, the structure, conformation and stereochemistry of
artemisinin skeleton by utilizing several synthetic strategies has been explored.
Furthermore, synthesis and antimalarial testing of several new artemisinin analogues,
exploring the antimalarial potency of artemisinin by carrying out structure-activity
relationship, development of new biologically active scaffolds in artemisinin skeleton and
the study towards the preparation of optically pure 1,2,4-trioxanes taking
dihydroartemisinin as chiral template were taken up. The present thesis covers the result
of these studies and is divided into five chapters as summarized below:

The **first Chapter** presents a concise review on artemisinin and accommodates
some of the most significant historical achievement and development observed during the
past 35 years in the discovery of antimalarial drug artemisinin and its related antimalarial peroxides. This review also highlights about the current scenario of malaria chemotherapy.

The second Chapter describes the synthesis and antimalarial activity of several new analogues of artemisinin in search for better analogue than β-arteether.

The Chapter third of the thesis describes the development of new synthetic strategy for the conversion of artemisinin into diastereomeric ozonides and deals with the chemistry, stereochemical assignment and X-ray crystallography studies of these stable ozonides. In this chapter we cover antimalarial as well as antitubercular activity of these stable ozonides.

The fourth chapter deals with the possible exploration for the preparation of optically pure 1, 2, 4-trioxanes using DHQ as chiral auxiliary.

The chapter five of the thesis describes the development of novel route for the synthesis of hydroxy-functionalized tricyclic 1, 2, 4-trioxane from artemisinin and their evaluation for antimalarial activity. Structure-activity relationship of several analogues of this novel tricyclic 1, 2, 4-trioxanes are also described.