The burgeoning global problem of malaria is largely due to the emergence of parasite resistance to our limited armamentarium of antimalarial drugs. The prevalence of resistance to known antimalarial drugs has resulted in the expansion of antimalarial drug discovery efforts. The isolation in 1972 of artemisinin by Chinese scientists, and their development of all the derivatives now used in the treatment of malaria today, were of outstanding importance. The results which have accumulated both from the Chinese work and from that subsequently conducted on a worldwide basis provide for a relatively comprehensive understanding of the chemistry, pharmacological profiles, toxicology, metabolism, and effects on the malaria parasite. The optimal regimens for use in the field are also apparent, particularly in combinations with longer half-life quinoline antimalarials. Thus the future use of the artemisinin class of drug appears assured. However, the mechanism of action needs to be clarified. More importantly from a clinical viewpoint, problems inherent in the current derivatives must be addressed, particularly that of neurotoxicity, if new artemisinin derivatives are to be introduced in a normal drug regulatory environment.

The most important artemisinin derivatives like artesunate, artemether, arteether and dihydroartemisinin are fast acting drugs but they are eliminated quickly as they have short plasma half life. Their rapid onset makes them especially effective against severe malaria. Their rapid disappearance may be a key reason why artemisinin resistance has been so slow to develop, and may also explain reason of recrudescence when used in monotherapy, so WHO has now recommended use of artemisinin derivatives in combination which classical drugs that have long plasma half life.

Efforts have been made to understand the mechanism of action and pharmacokinetics of artemisinin derivatives so as to synthesize compounds that have reduced neurotoxicity, better bioavailability, good solubility and large plasma half life.

Although artemisinin and its derivatives are still the best known antimalarials but it suffers real problem of poor natural abundance, high cost, poor bioavailability and high rate of recrudescence.

The identification of 1,2,4-trioxane moiety as principal pharmacophore of artemisinin has led to the development of several synthetic peroxides that have shown potential antimalarial activity and have gone up to clinical stages.
Central Drug Research Institute (CDRI), Lucknow is also one of the leading institutions in the World that have given huge contribution towards the development of artemisinin based antimalarials together with synthetic peroxides. The main objective of CDRI malaria research programme is to develop antimalarials that are effective against multi-drug resistant malaria and are commercially viable.

As a part of this programme in search for better antimalarials, an attempt has been made to synthesize synthetic as well as semisynthetic analogues of artemisinin that have high antimalarial potency. In this thesis synthesis of structurally diverse synthetic 1,2,4-trioxanes, their antimalarial activity and chemistry have been reported. The present thesis also covers the synthesis and antimalarial assessment of several semisynthetic derivatives of artemisinin as well. The results of these studies are discussed in five chapters as summarized below:

The first chapter includes a brief review on malaria, historical perspectives in development of malarial chemotherapy especially in the field of artemisinin and its related peroxides and a brief note of their mode of action.

The second chapter describes the details of synthesis and antimalarial assessment of new class of synthetic 1,2,4-trioxanes in search for better substitutes for artemisinin analogues.

The third chapter covers the synthesis and antimalarial activity of novel hydroxy-functionalized 1,2,4-trioxanes that have enhanced oil and water solubility.

The fourth chapter describes the chemistry of 1,2,4-trioxanes, which involves a novel and unprecedented acid catalyzed rearrangement.

The fifth chapter covers the details of synthesis and antimalarial assessment of a new class of artemisinin derivatives having free amino functionality.