Since antiquity malaria has been a curse on humanity and is responsible for taking lives of millions of human beings, especially children under the age of five and expectant women. As an estimate, nearly half of world’s population is under constant threat of malaria and the persons of under-developed countries, where the resources to combat such diseases are extremely limited are most severely affected. Around 627,000 deaths have been reported due to malaria in year 2012 only. Continuous fight to tackle this infectious disease has led to the development of various treatment regimens as well as therapeutic agents but the efforts have not been sufficient to check the widespread threat of this disease. Most of the one-time very successful drugs such as chloroquine 1 have suffered resistance owing to a variety of reasons and many others such as artemisinin and its derivatives, which function against multidrug-resistant parasites, might also attain resistance owing to their excessive and/or exclusive use. Thus, malaria has been acknowledged as a global health priority. Further, primaquine 2, which is almost an exclusive drug to counter infections of P. vivax and P. ovale, is limited owing to toxicity to patients with glucose-6-phosphate dehydrogenase deficiency in the malaria-endemic regions. This also implies that owing to the complexity of malaria, it might be more difficult to eradicate it compared to other successful events such as eradication of smallpox, owing to the non-availability of efficacious vaccines. This issue has, in part, been discussed in Chapter 2 of this thesis. The efforts invested by various research groups around the globe, especially in the direction of inventing new antimalarial drugs and/or antimalarial vaccines has not gained much success, but there is always a hope as some agents are currently under advanced stages of pre-clinical/clinical testing. Even a vaccine (RTS,S/AS01) may become available in 2016.

Out of the prevalent drug therapies, the concept of hybrid drugs has rapidly gained attention and owing to their efficacy, these have been purported to be the drugs of the future.
Chapter 1

Different classes of hybrid drugs have been synthesized and tested for their antimalarial activity against a variety of chloroquine resistant as well as chloroquine sensitive strains and this area of investigation is continuously being expanded. Consequently, the search for new antimalarial drugs, their efficacious synthesis, understanding of structure-activity relationships, mode of action, cytotoxicity, physico-chemical characteristics, continues unabated. Almost all of the hybrid antimalarials target blood-stage parasites in their mode of action. Therefore, new drugs, which may act on a new target or act synergistically against the different stages of life-cycle of the parasite offer effective replacements for the drugs facing resistance.

Keeping in view the above developments and in order to develop new antimalarials, in this thesis, we present results of our investigation on the design, synthesis, structure-activity relationships, physico-chemical properties, antiplasmodial activity and cytotoxicity of new pyrimidine based hybrid antimalarials. Additionally, we have undertaken studies related to the understanding of the mode of action of these hybrid antimalarial compounds. In Chapter 2, we have presented a review on different aspects such as life cycle of plasmodium species, symptoms and complications of malaria, prevention, diagnosis and treatment, drug targets, mode of action, resistance of antimalarial drugs and strategies of design of antimalarial hybrid drugs. Additionally, as many antimalarial drugs are also potent antituberculosic agents, we have evaluated the efficacy of selected compounds against *mycobacterium tuberculosis* also. It is hoped that the results of the current investigation shall pave way for shaping future research in the direction of hybrid antimalarial drugs as well as antituberculosis drug therapy.