Scope and Plan of Present Work
According to the recent estimates, about 300 to 500 million people suffer from malaria each year and more than one million die of it. Mosquitoes are becoming resistant to chemical insecticides that have been used for decades to control malaria. Moreover, insecticides are expensive, can pose a threat to human health and cause environmental contamination. Filariasis, another debilitating and concurrently disfiguring scourge, is one of most major public health problems in Africa and many of the Southeast Asian countries. Though the disease is not fatal, it is responsible for considerable morbidity causing social stigma among men, women and children. It afflicts poor people in both the urban and rural areas as well.

The continuing demand for novel antiparasitic agents of these two most debilitating diseases has augmented an ever-widening search for novel biochemical targets that could provide foundation for rational drug design and development. The great evolutionary distance between mammals and filarial/malaria parasites suggests the possibility that differences among individual enzymes or functional pathways may allow specific inhibition of the parasite. The oversimplified pathways in a number of parasites, including filariae and malaria parasites, are usually indispensable for their survival and thus represent points of vulnerability (Wang, 1983; Jaffe, 1980a,b).

Since for both parasitic diseases the defence against oxidative damage is essential, the interference with their glutathione metabolism seemed promising for the rational approach for chemotherapeutic strategies against both parasitic infections. In support of this interpretation, the most relevant enzymatic antioxidant devices of the mammalian host are either lacking, partially present, or expressed at low level in the parasites (Flohe et al., 1999). The design and synthesis of specific inhibitors of these physiologically important enzymes are of critical importance for the development of therapeutic agents as well as for use as mechanistic and physiological probes in GSH metabolism (Meister and Anderson, 1983). Based on the leads from the literature and the fact that interference of GSH biosynthesis may have drastic consequences in parasitic protozoa as well as helminths, needs for the characterization of the enzymes involved in GSH biosynthesis (GCL) and regeneration (GR) in one species of filarial worms i.e. *S. cervi* and multi-drug resistance strain of malaria parasites i.e. *P. yoelii nigeriensis* was felt. It was planned to partially purify and characterize GCL and GR from *S. cervi* and *P. yoelii*, search towards the inhibitors of these two enzymes and
validation of the same for serving as targets for the primary screening of antimalarial and antifilarial drugs in the present investigation.

Studies made during the period have been divided into four chapters.

Chapter I deals with the partial purification and characterisation of GCL (which catalyses the rate limiting step of the de novo synthetic pathway of Glutathione), in filarial worms and malaria parasites.

Chapter II deals with partial purification and characterisation of GR (the enzyme which catalyses the regeneration of the tripeptide Glutathione (GSH) from its disulfide (GSSG)), in filarial worms and malaria parasites.

Chapter III delineates evaluation of rationally designed synthetic compounds as inhibitors of GCL and GR from filarial worms and malaria parasites and their application in chemotherapy. This chapter details the effect of synthetic compounds that may serve as substrate analogs for GSH biosynthesis and hamper its de novo synthetic and salvage pathways. The compounds, belonging to various chemical series were looked for their in vitro on filarial and malarial GCL and GR. Identification of few lead compounds is one of the main achievements of this section.

Chapter-IV details attempts to measure GSH levels and its metabolizing enzymes GCL and GR in hepatic and splenic tissues of P. yoelii nigeriensis infected mice and in the same tissues after treatment with known antimalarial drugs.

The straightforward perspective of the present dissertation was to characterize and validate GCL and GR of malaria parasites and filarial worms as target for antimalarial and antifilarial drug development. Besides studies on characterization of both GCL and GR from the above said organisms, the specificities of the chemical compounds have been assessed and evaluated on the protein level in vitro, the whole parasite in culture and in the animal model in the present dissertation.