Introduction
Ever since the discovery of very first chemotherapeutic drug, questions were raised regarding its not so popular and almost ubiquitous side effects. There always exists a delicate balance between efficacy, tolerability and undesirable effects for any particular drug, depending mainly upon its dosages and duration of its therapeutic regime. The success of a drug thus not only depends upon its potential to combat the impeding diseased state but also in its ability to refrain from any undesired toxicity. Not surprisingly, the reason for withdrawal of nearly 70% of marketed drugs and failure of new drug entities in pre-clinical and clinical trials is indeed due to drug induced toxicity (Lee, 2003). This has bestowed pharmaceutical companies with much financial burden resulting in the quest for more profound and thorough toxicological investigations for candidate drugs.

The toxicological investigations are primarily concerned with defining the potential of natural and synthetic substances to produce adverse health effects and to determine their nature, incidence, mechanism of action and reversibility. However recent advances in genome-scale sequencing have enabled the development of methods for quantitatively comparing the expression levels of all potentially expressed genes between different toxicological samples [Brown & Botstein, 1999]. The application of such technology to toxicology is known as toxicogenomics. Toxicogenomics has proved to be a powerful tool for the direct monitoring of patterns of cellular perturbations in specific pathways through identification and quantification of global shifts in gene expression resulting from pathological alterations within cells and tissues. In particular, toxicogenomic technologies using a DNA microarray profile the cell-wide changes in gene expression following exposure to a toxin. This creates the potential of a characteristic gene expression profile termed a ‘molecular signature’ or ‘fingerprint’ of exposure for toxicological response to specific classes of toxic compounds. The molecular signatures of cellular responses offer the opportunity to: (a) provide mechanistic information about the cellular perturbations, pathways and responses elicited by specific exposures (in comparison with responses associated with previously characterized mechanisms), (b) allow classification of compounds based on the biological responses they elicit and (c) identify biomarkers specific to particular classes of
molecular damage (Murata et al., 1999; Pennie, 2000; Steiner & Anderson, 2000; Waring 2001; Hamadeh et al., 2002).

Malaria remains to be the major killer disease in the developing countries that affects lives of more than 500 million people annually and killing not less than 2 million of them (Snow et al., 2005). The four species of Plasmodium, a protozoan parasite that causes malaria are P. falciparum, P. ovale, P. malariae, and P. vivax. However major episodes of the disease are caused by P. falciparum and P. vivax. Most of the drugs that are used to treat malaria can be broadly grouped into 4-aminoquinilines, 8-aminoquinilines, anti folates, and artemisinin derivatives. Drugs that are used to treat the acute attack of malaria acts as blood schizonticidal agents and includes 4-aminoquinilines, antifolates and artemisinin derivatives. 8-aminoquinilines are tissue schizonticidal agents and offers a radical cure for malaria by acting on the parasite in liver (Newton et al., 1999). 4-Aminoquiniline derivatives such as Chloroquine and Amodiaquine are the first line drugs against malaria for last several decades. Development of resistance against these drugs in several parts of world necessitated the use of other drugs along with it for efficient treatment. Sulphadoxine-Pyrimethamine and Chloroquine/Amodiaquine combination is shown to be very effective against Chloroquine resistant uncomplicated malaria. (Sowunmi, 2002; Lederman et al., 2006). However, some reports have shown that certain antimalarial compounds are responsible for toxicities of different organs. In this regard antimalarial compounds such as quinidine (Dzur, 1976), quinine (Farver and Lavin, 1999) and chloroquine (Pari and Murugavel, 2004) have been reported to show hepatotoxicity and nephrotoxicity in different experimental animals. There have been no studies till date to envisage the toxicity profile of co-exposure of 4-aminoquinilines and anti-folates in experimental animals.

Liver and kidney are the two vital organs of body linked directly with drug metabolism and their biotransformation. Their unique position and crucial link with gastro-intestinal tract renders them highly vulnerable to drug induced toxicity. It has been observed that certain therapeutics whose bio-transformation take place in liver and kidney often results in the production of toxic by-products. These unwanted by-products often attain considerable concentration in hepatic and renal tissue, consequently resulting in target organ toxicity with a number of debilitating effects and breakdown of general
body homeostasis. Furthermore, drug-induced toxicity may show exaggerated symptoms in certain populations due to idiosyncratic behavior (Lee, 2003). Due to these reasons, drug-induced hepatotoxicity and nephrotoxicity are great clinical problem and a significant cause of drug withdrawal from marketplaces. To address these issues, robust screening assays with high predictive capacity are desirable that may be utilized throughout the drug discovery and development phases in conjunction with traditional in vivo methods, for decision making during drug selection and risk assessment.

The present endeavor is thus taken to delineate the toxicity and genomic scale changes in gene expression in mice models exposed with therapeutic equivalent dosages of antimalarials- amodiaquine and sulfadoxine -pyrimethamine combination. The idea was to generate antimalarial drug specific toxicity gene expression profile of liver and kidney tissues capable enough for toxicology class prediction and deciphering mechanism of antimalarial drug toxicity. Attempts were also made to explain the dose dependent toxicity of another widely used 4-Aminoquiniline antimalarial drug Chloroquine in Swiss albino mice. Markers of oxidative stress and changes in gene expression of major antioxidant enzymes in target organs were studied in light of previous reports of Chloroquine induced oxidative stress in liver and kidney. Furthermore, there have been several reports of multi-organ failure including damage to liver and kidney tissues during malarial infections (Newton & White, 1999; Guha et al., 2006; Guha et al. 2007). The reasons for these damages are not yet clearly understood. Hence, efforts were also made to understand the probable mechanism of this toxicity in liver and kidney tissue of host organism. Mouse model has been utilized extensively in the malaria research to study the pathogenesis, host- parasite interaction, vaccine development and drug toxicity (Lamb et al., 2006; Wykes & Good, 2009; Langhorne et al., 2002). I infected the mouse model with Plasmodium vinckei petteri a rodent’s malaria parasite and studied the toxicity and global gene expression alteration with rising level of percent parasitemia. Plasmodium vinckei petteri infected mice exhibit symptoms and physiological characteristics similar to human malaria, hence used extensively as good model for human malaria (Puri et al., 2006).