INTRODUCTION TO TRIOXANES
Countries around the world are funding various research organisations as well
\(^1\) WHO has taken up the initiative for promoting research on antimalarials in order to
irradicate malaria. More than half the world's population lives in areas where there is
a potential risk of malaria, and programs for controlling malaria in cities and other
areas of developing countries have broken down for many reasons. \(^1\)

There are several antimalarials available in the market but due to prolonged
use of these drugs; the malarial parasite is steadily becoming resistant to most of them
or there have been reports of serious side effects by the use of some antimalarials,
which has limited their use. During past years, parasites have developed resistance to
several drugs and also by development of resistance in mosquito vector to currently
available insecticides, the situation has worsened. Discovering new drugs in this field
is therefore a healthy priority. \(^2\)

Understanding the mode of action of and mechanism of resistance to drugs is
central to optimizing their use, and discovering new therapeutics with novel targets.
We have limited understanding of how antimalarial drugs work and how resistance
emerges. \(^3\) Thus there arises a need for new and better drugs, which can meet the
requirements of less or no side effects and more effective in eliminating the malarial
parasite from blood as well as from the organs like liver. Several workers are
synthesizing molecules taking the existing drugs as lead molecules.

Artemisinin, obtained from Artemisia annua L. is an endoperoxide
sesquiterpene lactone. \(^4\). Artemisinin and its derivatives are a promising new class

\(^{1}\) [Reference]
\(^{2}\) [Reference]
\(^{3}\) [Reference]
\(^{4}\) [Reference]
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of antimalarial drugs, which have become important due to their impressive activity against multi-drug resistant forms of Plasmodium [5].

There are various reference articles available on the progress achieved during the last years in the production, structure, biosynthesis and analysis of artemisinin and its mode of action. Also focus is given to clinical studies, toxicity studies, pharmacokinetics and activity of related compounds. [6] HPLC method of analysis for artemether has been developed and validated [7].

Many workers like JN Cumming et.al [8], GH Posner et.al [9,10], PM O'Neil et.al. [11], P Christen et.al. [12], and M Liu et. al. [13, 14] have synthesized derivatives of artemisinin and evaluated there activity. Artemisinin and its derivatives, artemesunate and artemether show excellent efficacy in both severe and uncomplicated malaria, dosage regimens still need to be optimized and pharmacokinetic profiles defined, and all have comparable efficacy. They are well tolerated in both adults and children, with no evidence to date of serious clinical toxicity.[15]

In presence of intra-parasitic iron, these drugs are converted into free radicals and other electrophilic intermediates which then alkylate specific proteins [16].

Artemisinin is believed to act via a two-step mechanism. It is first activated by intraparasitic heme-iron, which catalyzes the cleavage of artemisinin, and the resulting free radical then kills the parasite. No clinically relevant artemisinin-resistant human malaria has yet been reported [17].

There is great need to identify and characterize drug targets and chemotherapeutic strategies against malaria. A vacuolar-network induced by the human malarial parasite *P falciparum* is a major import pathway for artemisinin.[18]
In a study two cases of complicated falciparum malaria, who had poor response to artesunate with delayed parasite clearance times was reported. The host factors, the parasitemia count, the quality of antimalarial chemotherapy and blood level of the antimalarial drugs must be considered in relation to the causes of the delayed clearance of parasitemia. [19]

The insight into structure-toxicity relationships and the progress made in the synthesis of artemisinin analogs and finally the contribution of these efforts towards rational drug design in order to access potent, non-toxic antimalarial drugs based on artemisinin have been of interest to some workers. [20].

One of the pharmacophor present in the Artemisinin is trioxane ring. Some trioxanes have been synthesised as potent antimalarials, which are simple and easy to synthesize [21].

Our institute has taken up this project to develop new antimalarials as well as to test their activity against Plasmodium. Several compounds have been launched in the market and several are still in preclinical phase. Chemists in our institute have also synthesizing several trioxane derivatives. CDRI compound no. 97/63 [C₂₄H₃₂O₅] and 97/78 [C₂₈H₃₆O₈], (figure-1& 2), are trioxane derivative, which have shown promising antimalarial activity and have been patented. These compounds have been taken up for further drug development studies at our institute.

Figure-1: Structure of compound no.97/63-
The present study was undertaken to develop various physicochemical parameters of the compound 97/63 and 97/78. As physicochemical parameters play a very important role in deciding the transport of the drug in the body [22]. In order to achieve this, first it was required to develop an easy, reliable and reproducible estimation procedure. A HPLC estimation method for this compound was developed for the quality control of the various batches of both the compounds 97/63 and 97/78 and its formulations. This method was also used for study of its physicochemical properties and stability studies conducted on the compounds.