2. Research Envisaged
As discussed earlier, majority of the antimalarial drugs were discovered during the Second World War when the soldiers of the western countries while fighting in the topical countries started contracting malaria in mosquito infested areas. Over a long period of their usage against malaria caused development of resistance in the parasite against these drugs. The problem got further compounded due to non-enrichment of antimalarial drug inventory as the cash rich western countries were not interested in finding new therapeutics for a disease which was considered to be the disease of the poor third world tropical countries. Unfortunately for these poor malaria infested countries an effective antimalarial vaccine also could not be developed due to fast and constant mutations in the parasite genome. All these factors led to a woefully thin antimalarial drug development pipeline with little chemical diversity. There exist a great potential in the exploration of cysteine proteases falcipain inhibitor and thus might prove to be the most suitable drug target for the chemotherapy of malaria.

Genome mapping of the malaria parasite offered a number of attractive drug targets including plasmepsins and falcipains, the enzymes involved in parasite metabolism and in providing nutrients to the parasite to meet energy requirements. Falcipains 2 and 3 especially were more attractive targets as these enzymes degrade haemoglobin to small sized peptides in the acidic environment of the vacuole and degrade the membrane proteins of the host cells and help the parasite rupture the host cells in the alkaline environment. So, inhibition of FP-2/3 enzymes could effectively contain the growth of the parasite and control their progression in the host system.

A large number of peptidic and non-peptidic motifs like chalcones, (thio) semicarbazones, hydrazides, heterocycles, oxiranes and succinates have been reported in the literature to exhibit FP-2/3 inhibitory activity. Unfortunately none of such compounds have

\[ \text{M} \]

\[ \text{X} = \text{Urea, carbamate, amide} \\
\text{A} = \text{Alkyl/aryl/heteroaryl} \\
\text{R = II, } \text{CII}, \text{ CI, } 4-\text{C}_6\text{II}_4\text{OCII}_3 \]

crossed the clinical phase of evaluation as antimalarial agents. There are some reports of some heterocyclic\textsuperscript{215} and polycyclic\textsuperscript{216} pyridopyrimidines exhibiting antimalarial activity. Taking the basic information from literature about the enzyme inhibitors into consideration, it was planned to synthesize pyrido[1,2-\text{a}]pyrimidin-4-one class of
compounds (M). It is worth noting that the circled pharmacophore may act as Michael acceptor for reversible/irreversible binding to the thiol nucleophile present in the FP-2/3 enzymes. While the groups, X and R were selected in such a way that compounds could exhibit better binding profile in the P2 and P3 binding pockets of the falcipain enzyme that could translate into enhanced potency of the compounds.

It was planned to synthesize the given four (Series-I to IV) of compounds and to evaluate them against FP-2 enzyme in the in vitro tests. FP-3 enzyme having a high degree of homology to FP-2 was presumed to react with all such compounds which would prove to be powerful inhibitors of FP-2.

Where:
- \( R = H, 8-\text{CH}_3, 7-\text{Cl}, 4-\text{C}_6\text{H}_4\text{OCH}_3 \)
- \( R_1 = H, \text{Alkyl} \)
- \( A = \text{Alkyl/heteroaryl or alkyl} \)