

ANTIMALARIAL ACTIVITY OF DICYCLIC AND TRICYCLIC 2,4-DIAMINOPYRIMIDINE DERIVATIVES AGAINST *PLASMODIUM FALCIPARUM* IN VITRO.

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Due to the rapid increase in resistance to most antimalarial drugs currently in use, there is an urgent need for new drugs that are potent against *Plasmodium falciparum*. Many antifolate agents that are anti-Dihydrofolate reductase (DHFR) an enzyme in the folate pathway have been synthesized as targets for cancer cells in human cancer chemotherapy. Most of them have not been developed further due to their lack of potency.

Since the folate pathway is essential for *P. falciparum* survival, we hypothesized that some of these anti-DHFR agents initially developed for cancer chemotherapy could also inhibit this enzyme in *P. falciparum*.

In this respect, we tested the *in vitro* antimalarial activity of twenty-eight dicyclic and tricyclic 2,4-diaminopyrimidine derivatives that were developed by the Dana-farber cancer institute. We investigated the activities of these anti-DHFR agents on *P. falciparum* in relation to their structure i.e. structure activity relationship (SAR). Laboratory isolate V1/S that is multidrug and antifolate resistant was used. *In vitro* culture tests in physiological folate concentrations were carried out for 48 hrs. Growth rate of *P. falciparum* was then assessed by the incorporation of tritium labeled hypoxanthine. From our results, the Inhibitory concentration (Ic50) values of the compounds ranged from 6.88nM to 200µM and this depended on their SAR. These results are promising for the synthesis of more potent antimalarials based on their SAR and for drug development of potent compounds in malaria combination therapy.