CHAPTER IV
CONCLUSION

Three series of 4,6-diamino-1,2-dihydro-1,3,5-triazine derivatives were successfully prepared by Three-component condensation or Two-component condensation (1-aryl substituent, 65 compounds), the reaction of protonated Schiff base with dicyanodiamide (1-alkyl substituent, 44 compounds), and the alkylation of 1-hydroxy-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine with alkyl bromides (1-alkyloxy substituent, 28 compounds). The products have been prepared in the form of crystalline hydrochloride, trifluoroacetate, hydrobromide or *p*-toluenesulfonate salt and were characterized by NMR, MALDI-TOF MS and in some cases, elemental analysis.

The products were tested against both the wild-type and the cycloguanil-resistant mutant (A16V+S108T) pfDHFRs to study the binding affinities and the relationship between the structure and biological activities of 4,6-diamino-1,2-dihydro-1,3,5-triazine derivatives. The result of inhibition constant (K_i) values indicated that the substituents at 4- and 3-position of the benzene ring at N-1 were important for binding to wild-type and A16V+S108T mutant enzymes respectively. In addition to 3-chlorophenyl and 3,4-dichlorophenyl groups, flexible alkyl and alkyloxy groups at N-1 showed improved binding affinity to A16V+S108T mutant pfDHFRs. The length of at least more than a few carbon atoms of the substituents was important factor to this binding. The substituents at position C-2 was another major factor for achieving effective inhibition of the wild-type and A16V+S108T mutant enzymes. The study revealed that at least one substituents at position C-2 should be H and the other was long chain alkyl group or phenyl or 3- or 4-phenoxyphenyl groups in order to achieve effective inhibition against both enzymes. The information obtained could have profound implications for the development of new and effective inhibitors against dihydrofolate reductase of *Plasmodium falciparum*.

Finally, a number of dihydrotriazine analogues which are more active than cycloguanil against both wild-type and A16V+S108T mutant pfDHFRs have been identified in this study. These are potential lead compounds to be further developed into antimalarial agents in the future.