CHAPTER IV

CONCLUSION

In this study, three potential methods to prepare optically active 4,6-diamino-1,2-dihydro-1,3,5-triazineformation have been investigated including unsymmetrically substituted formation of diastereomeric salts, chromatography using chiral stationary or mobile phase and by the asymmetric synthesis. It was not possible to prepare enantiomerically enriched dihydrotriazine by formation of diastereomeric salts although many combinations of optically active acids and dihydrotriazines were used in the experiment. Enantiomers of 1-(4′-bromorophenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine and 1-(4′-methylphenyl)-4,6-diamino-1,2-dihydro-1,3,5-triazine have been successfully resolved by chiral reverses phase HPLC. In each case, the two enantiomers showed significants difference in binding affinity to both wild type and A16VS108T mutant pfDHFR. Due to the small quantities of the compound obtained and the case of recemization, their absolute configurations could not be determined. Finally, the asymmetric synthesis method gave optically active 1-(1′-phenylethyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazines trifluoroacetate with known absolute configuration at C_2. Unfortunately, all compounds exhibited poor binding affinity to wild type and A16VS108T mutant of pfDHFR. Therefore the ultimate goal of the research to prove the model of binding between dihydrotriazine and DHFR has not yet been achieved. Nevertheless significant understanding has been made.

A preliminary experiment suggested that enantiomerically enriched 1-(3′,4′-dichlorophenyl)-2-phenyl-4,6-diamino-1,2-dihydro-1,3,5-triazine may be obtained by asymmetric transformation of its D(-)-mandelate salt. This encouraging result brings about the hope that optically active dihydrotriazines might be successfully prepared by this method in sufficient quantity for determination of absolute configuration and further biological study in the future.