## Rational design of guanylthiourea derivatives as antimalarial agents

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*Plasmodium falciparum* dihydrofolate reductase (P*f*DHFR) enzyme is one of the validated targets for antimalarial drug discovery. The quadruple mutant of P*f*DHFR is resistant to the known anti-P*f*DHFR drugs (e.g. proguanil, pyrimethamine and trimethoprim). Recently, P218 was identified as a potential lead molecule. In this work, a rational drug design strategy was adopted to identify guanylthiourea (GTU) derivatives as a potential P*f*DHFR inhibitor. Electronic structure analysis of the GTU moiety was carried out to determine the correct tautomeric form which was 11.99 kcal/mol more stable than the previously reported structure in the literature. Once acceptable structure was established; *in silico* investigations on the wild type/quadruple mutant P*f*DHFR and various ligands (including MESP analysis, molecular docking studies) were performed to design novel GTU derivatives as potential P*f*DHFR inhibitors. Three series of GTU derivatives were synthesised, by reacting bromides with GTU under reflux and microwave condition. The synthesized compounds were first evaluated for *in vitro* P*f*DHFR inhibitory activity, resulting in the identification of two compounds (100 µM and 0.4 µM). Further, *in vivo* studies recognized six compounds with high mean survival time, out of which one compound was identified to be curative. This work reports a systematic rational approach for the structure-based design of potential antimalarial agents.

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