Abstract. The drug resistance condition of *P. falciparum* pose a major challenge in the fight against malaria. This prompts a comprehensive research in an effort to discover new drug candidates. Therefore, chalcone was modified into 24 new compounds, including indolyl-benzodioxyl-chalcone, pyrrolyl-benzodioxyl-chalcone, and thiophenyl-benzodioxyl-chalcone in the course of this study. Moreover, these compounds are commercial malaria mediciations screened for their inhibitory activity using molecular docking simulations. Subsequent results of combined indolyl-benzodioxyl-chalcone and *Pf*DHFR-TS showed the intrinsic indolyl components produced stronger interactions referenced to pyrrolyl-benzodioxyl-chalcone, thiophenyl-benzodioxyl-chalcone, and chloroguanide. Under these circumstances, intense *Pf*DHFR-TS-indolyl-benzodioxyl-chalcone complex was produced with lower binding affinity values (-7.32 to -8.43 kcal/mole) referenced to *Pf*DHFR-TS-pyrrolyl-benzodioxyl-chalcone (-6.38 to -6.68 kcal/mole), *Pf*DHFR-TS-Thiophenyl-benzodioxyl-chalcone (-6.47 to -6.52 kcal/mole), and *Pf*DHFR-TS-chloroguanide (-6.75 kcal/mole). Furthermore, the hydrogen bond interactions developed by indolyl-benzodioxyl-chalcone *(7-10)* are observably similar to standard chloroguanide compounds and WR99210. These compounds also possess a binding affinity similar to WR99210 (native ligand) and are expected to be potentially anti-malarial candidates.