Malaria is one of the major global health problems with high mortality rates especially in children below five years of age. The interventions in place to control the disease worldwide include vector control and chemotherapy. Chemotherapy has developed crippling limitations due to malaria drug resistance to the effective, available and affordable anti-malarials. The emergence of parasite resistance has limited the armory of effective anti-malarials. Resistance is developing faster than the development of new and effective anti-malarials. This has raised a need of therapy optimization using the already existing anti-malarials. Combination therapy has been shown to effectively delay the onset of resistance and improve the efficacy of two or more anti-malarials when in combination. The objective of this study was to establish the activity of cAMP modulators on a few selected anti-malarials in vitro. The CAMP modulators were tested in combination with chloroquine, quinine, mefloquine, amodiaquine and doxycycline against Plasmodium falciparum in vitro against chloroquine sensitive strain (D6) and the chloroquine resistant strain (W2). Parasite susceptibility testing was carried out using semi automated micro dilution technique. The Inhibitory Concentration at 50% (IC₅₀) was calculated for each drug and for the drugs in fixed combination (1:1, 1:3, 3:1, 1:4, 4:1, 1:5). These data were used to calculate the Fractional Inhibitory Concentration at 50% (FIC₅₀) and to plot isobolograms. Quinine-AC inhibitors combination assays showed synergistic interactions in all the levels of concentration ratios against both the D6 and W2. The other anti-malarials-AC inhibitor combination assays showed a range of response, additivity, synergism and antagonism at different levels of concentration ratios. Anti-malarials-AC activators mainly exhibited antagonistic interactions. These findings suggest that quinine-AC inhibitors combination should be considered for evaluation as possible new anti-malarial combinations.