Efforts to develop an effective malarial vaccine are yet to be successful and thus chemotherapy remains the mainstay of malaria control strategy. Unfortunately, Plasmodium falciparum, the parasite that causes about 90% of all global malaria cases is increasingly becoming resistant to classical antimalarials, necessitating a search for new chemotherapeutics preferably with novel modes of action. Today, rational drug discovery strategy is gaining new impetus as knowledge of malaria parasite biology expands, aided by the parasite genome database and improved bioinformatics tools. Drug development is a laborious, time consuming and costly process, and thus the "useful therapeutic lives" (UTLs) of new drugs should be commensurate with the resources invested in their development. Historical evidence on development and evolution of resistance to classical antimalarial drugs shows that the mode of action of a drug influences its UTL. Drugs that target single and specific targets such as antimalarial antifolates and atovaquone (ATQ) are rendered ineffective within a short time of their clinical use, unlike drugs with pleiotropic action such as chloroquine (CQ) and artemisinins (ART) with long UTLs. Unfortunately, almost all new targets currently being explored for development of novel drugs belong to the "specific target" other than the "multiple target" category, and is plausible that such drugs will have short UTLs. This review relates the pleiotropic action of CQ and ART with their long UTLs, and discusses their relevance in rational drug development strategies. Novel targets with potential to yield drugs with long UTLs are also explored.