Efforts to develop an effective malaria vaccine are yet to be successful and thus chemotherapy remains the mainstay of malaria control strategy. Plasmodium falciparum, the parasite that causes about 90% of all global malaria cases is increasingly becoming resistant to most antimalarial drugs in clinical use. This dire situation is aggravated by reports from Southeast Asia, of the parasite becoming resistant to the "magic bullet" artemisinins, the last line of defense in malaria chemotherapy. Drug development is a laborious and time consuming process, and thus antimalarial drug discovery approaches currently being deployed largely include optimization of therapy with available drugs--including combination therapy and developing analogues of the existing drugs. However, the latter strategy may be hampered by crossresistance, since agents that are closely related chemically may share similar mechanisms of action and/or targets. This may render new drugs ineffective even before they are brought to clinical use. Evaluation of drug-resistance reversers (chemosensitizers) against quinoline-based drugs such as chloroquine and mefloquine is another approach that is being explored. Recently, evaluation of new chemotherapeutic targets is gaining new impetus as knowledge of malaria parasite biology expands. Also, single but hybrid molecules with dual functionality and/or targets have been developed through rational drug design approach, termed as "covalent bitherapy". Since desperate times call for radical measures, this review aims to explore novel rational drug-design strategies potentially capable of revolutionizing malaria therapy. We thus explore malaria apoptosis machinery as a novel drug target, and also discuss the potential of hybrid molecules as well as prodrugs and double prodrugs in malaria chemotherapy.