ATP gatekeeper of Plasmodium protein kinase may provide the opportunity to develop selective antimalarial drugs with multiple targets

ABSTRACT

Malaria is one of the most devastating infectious diseases that caused millions of clinical cases annually despite decades of prevention efforts. Recent cases of Plasmodium falciparum resistance against the only remaining class of effective antimalarial (artemisinin) in South East Asia may soon pose a significant threat. Hence, the identification of new antimalarial compounds with a novel mode of action is necessary to curb this problem. Protein kinase has been implicated as a valid target for drug development in diseases such as cancer and diabetes in humans. A similar approach is now recognized for the treatment of protozoan-related disease including malaria. Few Plasmodium protein kinases that are not only crucial for their survival but also have unique structural features have been identified as a potential target for drug development. In this review, studies on antimalarial drug development exploiting the size of Plasmodium protein kinase ATP gatekeeper over the past 15 years are mainly discussed. The ATP-binding site of Plasmodium protein kinases such as Pf CDPK1, Pf CDPK4, Pf PKG, Pf PK7, and Pf PI4K showed great potential for selective and multi-target inhibitions owing to their smaller or unique ATP-gatekeeper amino acid subunits compared to that of human protein kinase. Hence it is a feasible solution to identify a new class of active antimalarial agents with a novel mode of action and longer clinical life-span.