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Thai malaria drug targets resistance causing mutation

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Singapore: Professor Yongyuth Yuthavong and colleagues at the National Center for Genetic Engineering and Biotechnology (BIOTEC), Thailand, along with scientists from across the world, developed a technique for creating highly efficient drugs that target specific enzymes present in different pathogens. Using this technique, they have produced a new antimalarial drug candidate, P218.

The main target for many antimalarial drugs is a form of dihydrofolate reductase (DHFR); in the malaria parasite Plasmodium it is called PfDHFR. Since PfDHFR constantly mutates, it has become resistant to antimalarial treatments. Using the x-ray structures as a guide, the team designed P218 as an inhibitor that envelops the enzyme and binds so tightly that there is no space left for mutation.

Furthermore, P218 is shaped so that it will bind only to malarial PfDHFRs if they are present in the body, not human DHFRs, meaning it is less toxic to humans. The research has shown that the mutations that cause PfDHFR lead to change in its geometry, thereby restricting the drug molecule's activity.

Professor Yuthavong said that, "We studied the x-ray structure of mutant forms of the PfDHFR enzyme to understand how resistance arises."