NEW PYRROLE DERIVATIVES WITH MULTI-STAGE ANTIPLASMODIAL ACTIVITY AND TRANSMISSION-BLOCKING POTENTIAL

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Abstract

Introduction: The spread of *Plasmodium falciparum* resistant to artemisinin-based combination therapies threatens recent advances in malaria control and highlights the need for new chemical classes with distinct mechanisms. Compounds able to act on multiple parasite targets and life stages are particularly attractive to limit resistance selection. In this context, we identified pyrrole derivatives as promising chemical platforms due to their structural versatility and association with essential *Plasmodium* targets.

Objectives: To identify pyrrole derivatives with multi-stage antiplasmodial activity and investigate the molecular targets involved in their mechanism of action.

Methods: A library of 92 compounds was screened against *P. falciparum* chloroquine sensitive 3D7 and multidrug-resistant Dd2. Active compounds were evaluated for cytotoxicity in mammalian cells, gametocytocidal activity, mitochondrial depolarization (TMRE) and bc_1 inhibition. Recombinant PfDHODH was expressed, purified by affinity and size-exclusion chromatography and analyzed by thermal shift assay (DSF), using DSM265, a validated PfDHODH inhibitor, as control.

Results: Four pyrrole derivatives showed EC_{50} values around 50 nM and high selectivity. LDT-818 fully inhibited mature gametocytes, while LDT-802 inhibited about 80% of immature gametocytes. All compounds caused mitochondrial depolarization without significant bc_1 inhibition versus atovaquone. LDT-802 showed an ~11-fold EC_{50} increase in pfdhodh-amplified strains versus the parental line. In DSF, DSM265 stabilized PfDHODH, whereas LDT-802 induced a curve shift consistent with enzyme conformational perturbation; LDT-818 had no effect.

Conclusion: These data indicate that pyrrole derivatives act through a multi-target mechanism involving PfDHODH and additional parasite pathways yet to be elucidated. For LDT-802, genetic resistance, mitochondrial dysfunction and PfDHODH thermal modulation support a non-classical target engagement consistent with interference in multiple critical parasite processes.