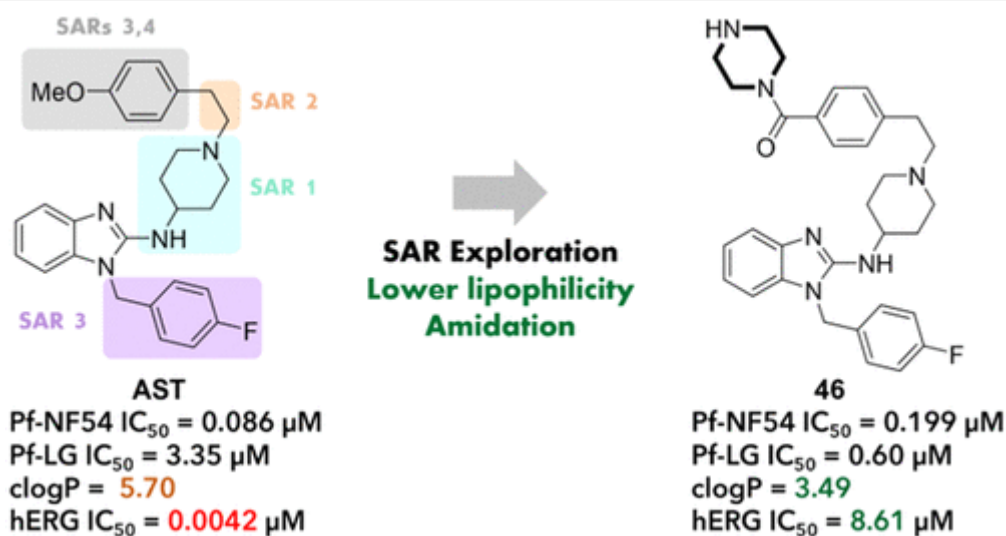


Abstract



In the context of drug repositioning and expanding the existing structure–activity relationship around astemizole (AST), a new series of analogues were designed, synthesized, and evaluated for their antiplasmodium activity. Among 46 analogues tested, compounds **21**, **30**, and **33** displayed high activities against asexual blood stage parasites (*Pf*NF54 IC_{50} = 0.025–0.043 μ M), whereas amide compound **46** additionally showed activity against late-stage gametocytes (stage IV/V; *Pf*LG IC_{50} = 0.6 ± 0.1 μ M) and 860-fold higher selectivity over hERG (**46**, SI = 43) compared to AST. Several analogues displaying high solubility (Sol > 100 μ M) and low cytotoxicity in the Chinese hamster ovary (SI > 148) cell line have also been identified.