Discovery of arylpyridine derivatives as new Plasmodium falciparum inhibitors

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Introduction: The global emergence of *Plasmodium falciparum* resistance to current antimalarials necessitates the development of novel therapeutic agents. Arylpyridine derivatives, specifically pyridylpiperazines, have emerged as an attractive series for antimalarial drug discovery due to their potent antiplasmodial activity and structural versatility.
Objective: To investigate the *in vitro* antiplasmodial profile of arylpyridyl carboxamide derivatives against *P. falciparum* strains.
Methods: A series of 23 derivatives were designed, synthesized, and evaluated for antiplasmodial activity (IC_{50}) against the *P. falciparum* 3D7 strain (SYBR Green I assay) and cytotoxicity (CC_{50}) against HepG2 cells (resazurin assay). Compounds exhibiting high selectivity indices (SI = CC_{50}/IC_{50}) were further characterized regarding their speed of action and cross-resistance against multi-resistant strains.
Results: Structure-Activity Relationship (SAR) analysis showed that a trifluoromethyl pyridine substituent at the arylpyridyl core (R1) increased potency, particularly when combined with a cyclopropane group at the carboxamide substituent (R2), as seen in **17** (1.7 ± 0.1 μM; SI > 59) and **177** (0.8 ± 0.2 μM; SI > 125). The inhibitory activity was maintained when the pyridyl was replaced with pyrimidine (**53**, 1,1 ± 0,1; SI > 91) or phenyl (**194,** 1,0 ± 0,2, SI > 25) groups. The highest potency and selectivity were achieved with a phenyl group at R1 and a hydroxypyridinyl substituent at R2 (**182,** 0.6 ± 0.1 μM; SI > 166). **177** and **182** displayed a non-fast acting profile and retained potency against multi-resistant strains, indicating no cross-resistance.

Conclusion: Substituents at R1 and R2 modulated the antiplasmodial activity. The most promising candidates were **177** and **182**, exhibiting sub-micromolar activity, high selectivity, and efficacy against resistant strains, supporting the potential of pyridylpiperazine derivatives as candidates for antimalarial drug discovery.

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