Partnership with Malaria Libre for Antimalarial Drug Discovery; Compound Synthesis and Evaluation

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INTRODUCTION:

- The Medicines for Malaria Venture launched the Malaria Libre program as an open-access drug discovery program.[1]
- The program actively recruits academic/student participants and holds monthly online project meetings to disseminate information.
- PharmD research students participated as part of their elective coursework and APPE rotations.

GOALS & OBJECTIVES:

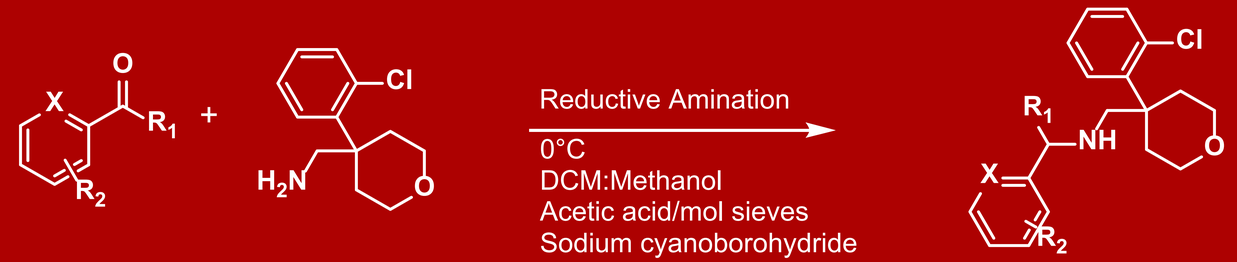
- Engage PharmD students as critical contributors to an international drug discovery project.
- Synthesize novel aminopyridinol compounds and develop SAR to optimize activity against sensitive and chloroquine-resistant malarial strains.
- Address the metabolic instability of early lead aminopyridinols to enhance compound stability and improve efficacy.

METHODS:

- Selected high-priority synthetic targets through collaboration and discussion with Malaria Libre.
- Synthesized twelve (12) new aminopyridinol analogs. Each was purified using standard methods, and their structures were confirmed via ^{1}H NMR, ^{13}C NMR, and elemental analysis.
- Compounds were assayed by the MMV using an asexual blood stage test for potency against the 3D7 strain of *Plasmodium falciparum* (72-hour lactate dehydrogenase assay.)
- Compounds that showed activity were subsequently also assayed against a chloroquine-resistant Dd2 malarial strain.
- The activity (pIC_{50}) values generated from the assays are reported for all compounds.

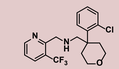
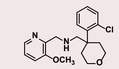
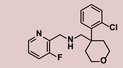
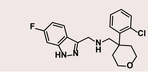
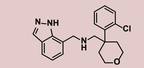
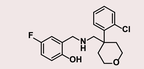
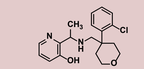
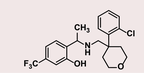
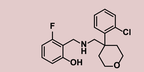
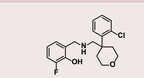
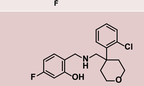
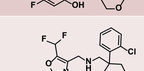
Interested in curing Malaria?

Malaria Libre is accepting new academic partners to synthesize compounds.



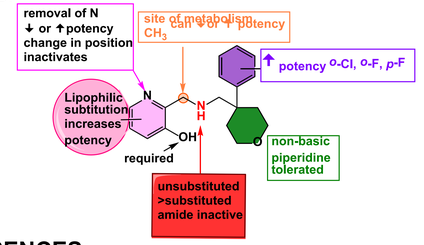
MALARIA LIBRE

RESULTS:

Compound	Structure	3D7 pIC_{50}	Dd2 pIC_{50}
KR-3-1-C		inactive	
KR-5-1-G		inactive	
IN-6-1-C		inactive	
HK-5-1		inactive	5.07
KR-4-1		inactive	
HK-4-1		6.3	6.4
HK-3-1		5.5	5.7
HK-6-1		7.2	7.5
BC-5-1B		5.9	6.0
HK-1-1B		6.2	6.3
HK-2-1		6.7	6.8
HK-7-1		inactive	inactive

CONCLUSIONS:

- Four PharmD students participated, synthesizing 12 compounds with yields ranging from 24-81%.
- HK-6-1 exhibits excellent potency and holds promise to address the metabolic liabilities of the series.



REFERENCES:

1. https://www.mmv.org/mmv-open/malaria-libre/malaria-libre-open-innovation-platform

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