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Synthesis and structure-activity relationship of novel indolizinoindolones with *in vitro* antimalarial activity

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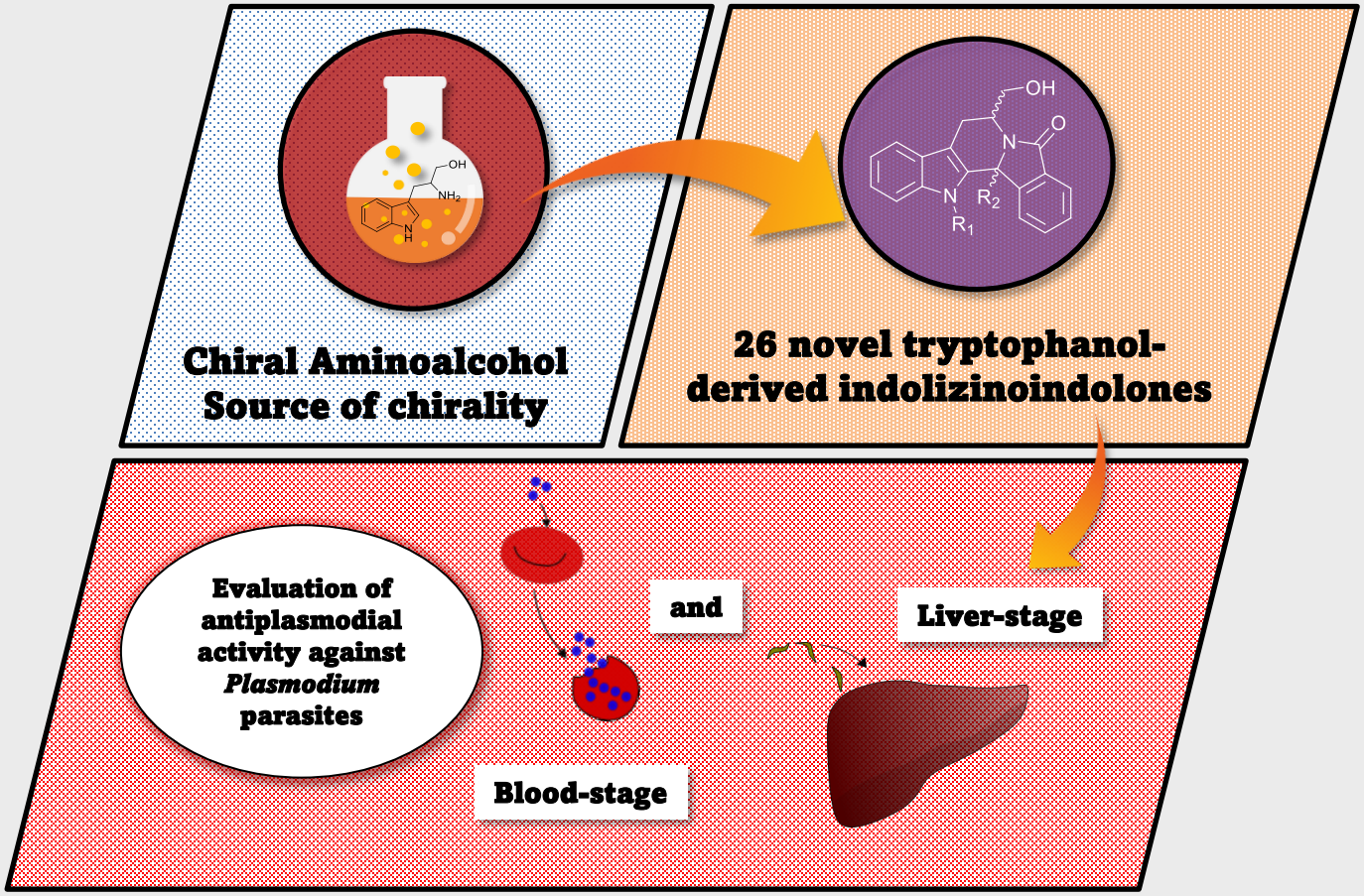
Synthesis and Structure-Activity Relationship of Novel indolizinoindolones with in vitro antimalarial activity



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Abstract:

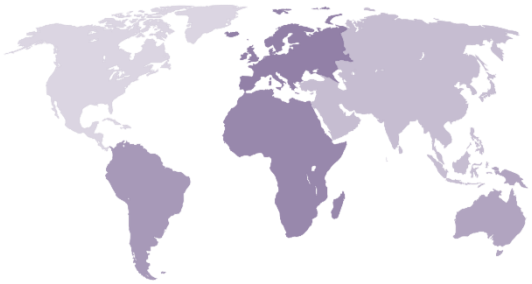
Malaria is a vector-borne parasitic disease that continues to pose a serious public health issue worldwide, despite all effort made towards prevention and control. The etiological agent are parasites of the species *Plasmodium spp*. that are transmitted to humans by the bite of infected *Anopheles* mosquitoes. The emergence of drug-resistant parasites has challenged the goal of eradicating malaria in near future. In addition, current malaria therapy needs to address problems such relapse and recrudescence events due persistence of exo-erythrocytic forms in hepatocytes and erythrocytic forms. Thus, it is still necessary to develop therapeutic options that are effective against drug-resistant strains and active against all stages of parasite life cycle. Recently, our group has reported the dual-stage antimalarial activity of a series of benzoindolizinoindolones. As part of our continuous effort to identify more potent antiplasmodial compounds, we synthetized 26 novel indolizinoindolones, through stereoselective cyclocondensation of a racemic keto-acid with enantiopure *S*- or *R*-tryptophanol, followed by stereocontrolled cyclization on the aromatic ring. Subsequently, we performed structure-activity studies and identified some compounds with higher activity (nanomolar range) than our previous hit compound against *Plasmodium spp*. parasites. Together, this study corroborates our previous results that indicated the indolizinoindolone scaffold as a promising tool for malaria treatment.

Keywords: Malaria, inhibitor, tryptophanol, indolizinoindolones, treatment

Malaria

Life-threatening infectious disease caused by protozoan of the genus *Plasmodium* spp and transmitted to human by infected anopheles mosquitoes

87 Endemic countries



229 million new cases in 2019

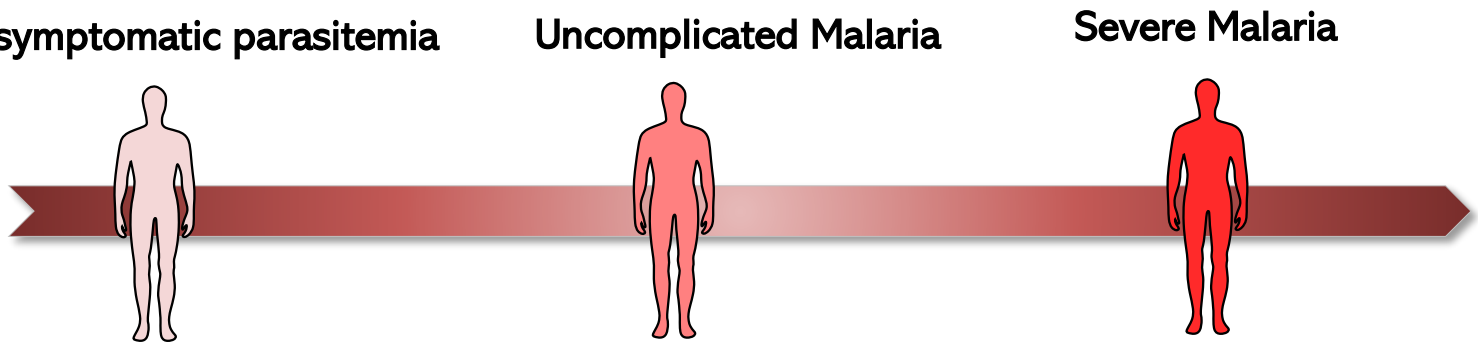
409 000 deaths globally in 2019

94% deaths in Africa

82% cases in Africa

Source: World malaria report 2020: 20 years of global progress and challenges. Geneva: World Health Organization; 2020

CLINICAL MANIFESTATIONS



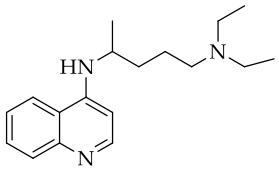
- Fever
- Chills and Sweat
- Nausea and vomiting
- General malaise

- Cerebral Malaria
- Severe anemia
- Acute Kidney injury
- Acute respiratory distress syndrome

Ashley EA, Pyae Phyo A, Woodrow CJ. Malaria. Lancet. 2018

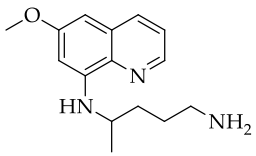
CLASSES OF ANTIMALARIAL DRUGS

4-aminoquinolines



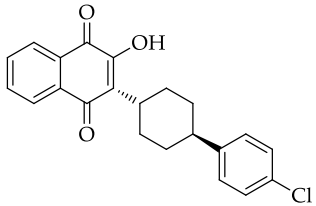
Chloroquine

8-aminoquinolines



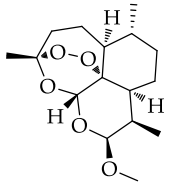
Primaquine

Hydroxynaphthoquinones

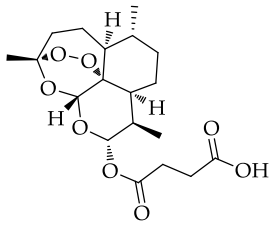


Atavaquone

Artemisinin derivatives

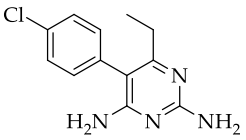


Artemether



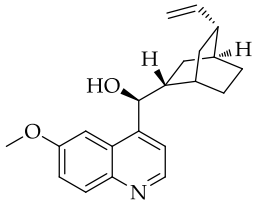
Artesunate

Diaminopyrimidines



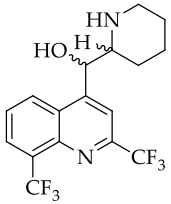
Pyrimethamine

Quinolines-based cinchona alkaloids



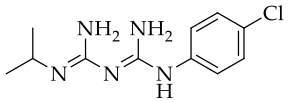
Quinine

4-quinolinemethanols



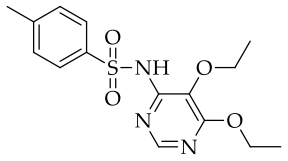
Mefloquine

Biguanides



Proguanil

Sulfonamides



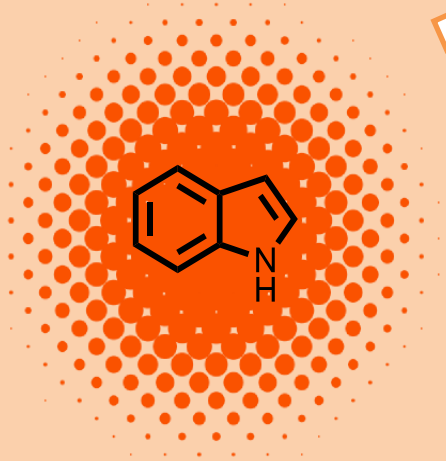
Sulfadoxine

Emergence of drug resistance challenges Malaria control

Urgency to develop new antimalarials

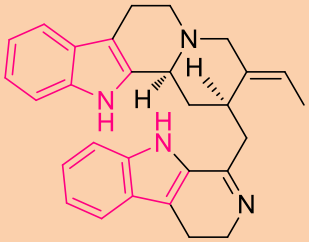
Kokwaro G. Ongoing challenges in the management of malaria. Malar J. 2009, 8 Suppl 1.

Indole

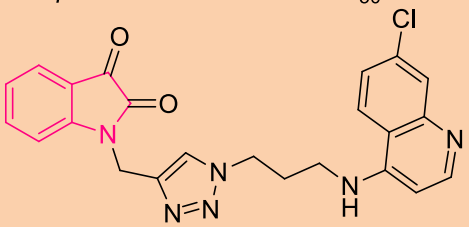


Privileged scaffold in Medicinal Chemitry

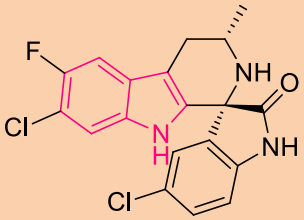
Several indole-based natural products and synthetic compounds demonstrate biological activities



Dihydrousambarensine
P. falciparum W2 CQR-strain IC_{50} = 32 nM



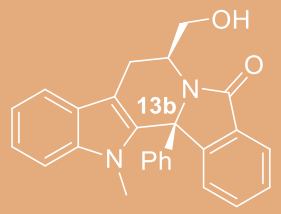
Isatin-chloroquine conjugated
P. falciparum W2 CQR-strain IC_{50} = 1.2 μM



Cipargamin
Phase 2 clinical trial
subnanomolar potency

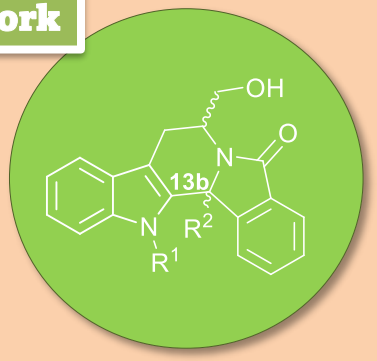
Previous Work

Hit compound



P. falciparum W2 IC_{50} = 1.2 μM
P. berguei IC_{50} = 0.6 μM

This Work



Study the influence of other substituents in the C-13b position and *N*-indole

Chauhan M, Saxena A, Saha B. An insight in anti-malarial potential of indole scaffold: A review. Eur J Med Chem. 2021;218:113400. Pereira NA, Monteiro Â, Machado M, Gut J, Molins E, Perry MJ, Dourado J, Moreira R, Rosenthal PJ, Prudêncio M, Santos MM. Enantiopure Indolizinoindolones with in vitro Activity against Blood- and Liver-Stage Malaria Parasites. ChemMedChem. 2015, 12, 2080

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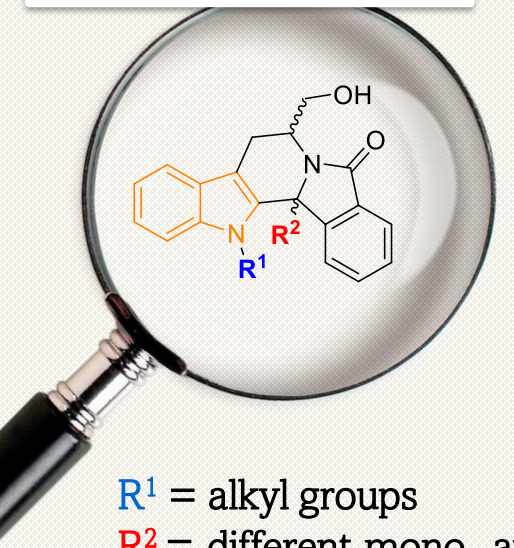
Synthesis of the chemical library

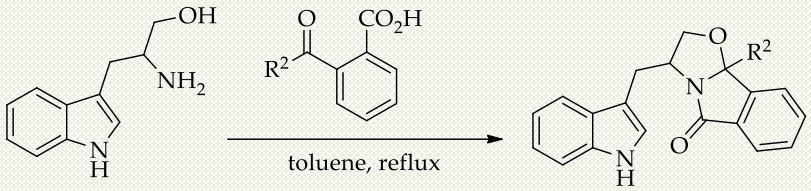
Target compounds



R^1 = alkyl groups
R^2 = different mono- and disubstituted phenyl rings

Synthetic route

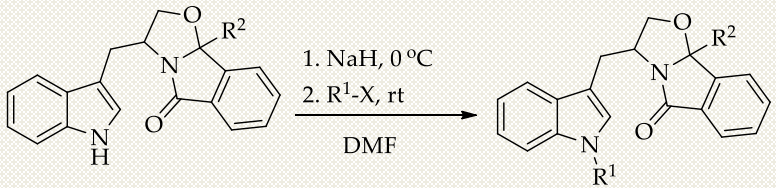
1) Stereoselective cyclocondensation



(R)- or (S)- tryptophan

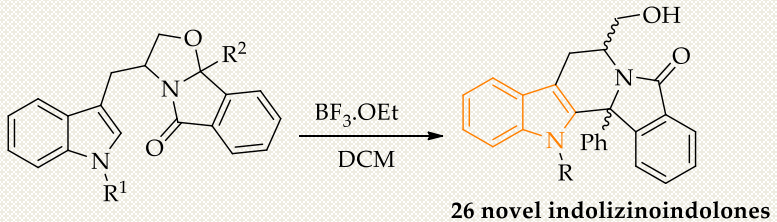
44.5 % - 97%

2) N-indole protection



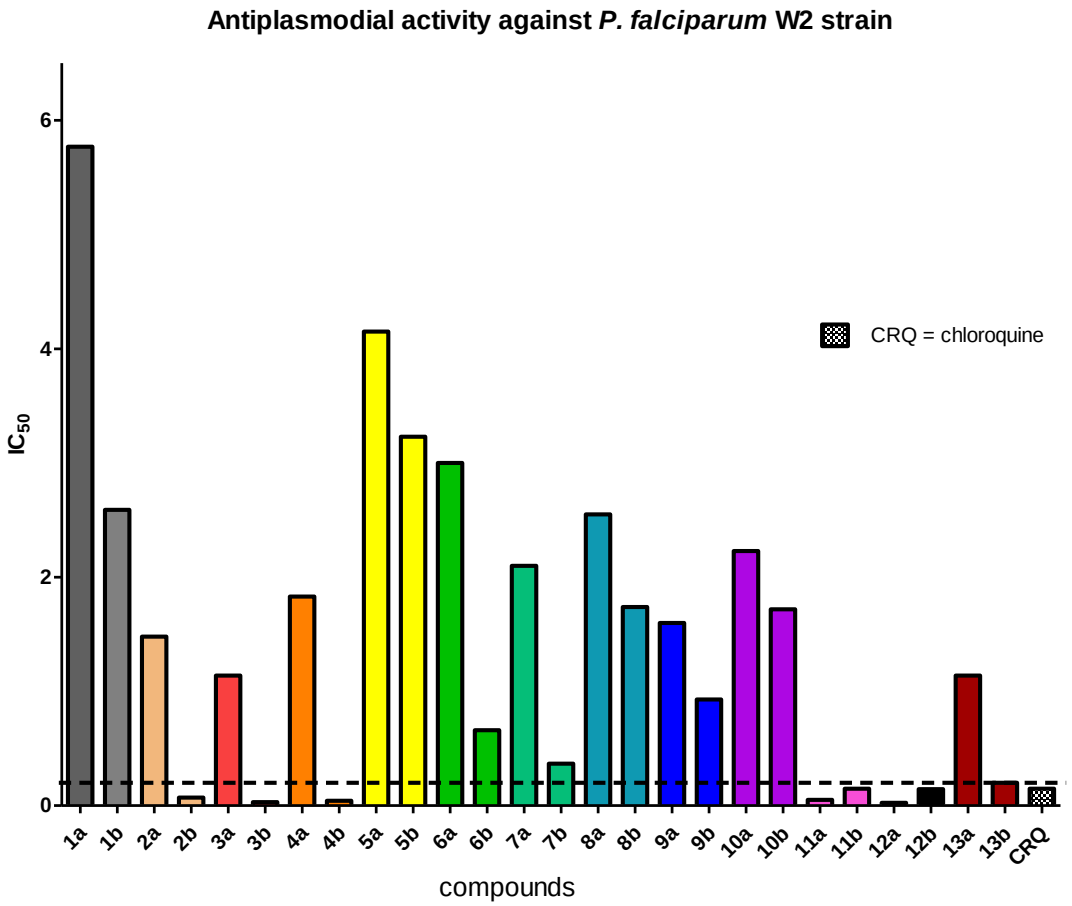
70 % - 94%

3) Pictet–Spengler cyclization



26 novel indolizinoindolones synthetized

Structure-Activity Relationship studies



26 novel indolizinoindolones evaluated against *P. falciparum* W2 strain

↓

9 compounds with IC_{50} lower than our previous hit compound (in a low micromolar range)

↓

Trends observed:

1. (*R*)-tryptophanol derived indolizinoindolones exhibited higher potency
2. Stereochemistry and substituent nature in the position C-13b are important for activity
3. Bulky groups in *N*-indole and C-13b position also affect the activity

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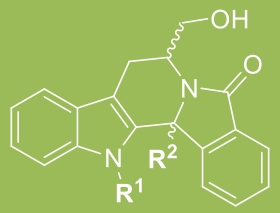
Conclusions



- 26 novel indolizinoindolones synthetized by through stereoselective cyclocondensation of a racemic keto-acid with enantiopure *S*- or *R*-tryptophanol, followed by stereocontrolled cyclization on the aromatic ring
- 9 compounds with good activity against blood-stage *P. falciparum* W2 strain
- The compounds are under evaluation for antiplasmodial activity against *P. berguei* (liver stage)

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