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Expanding the SAR of Nontoxic Antiplasmodial Indolyl-3-ethanone Ethers and Thioethers

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Despite major strides in reducing *Plasmodium falciparum* infections, this parasite still accounts for roughly half a million annual deaths. This problem is compounded by the decreased efficacy of artemisinin combination therapies. Therefore, the development and optimisation of novel antimalarial chemotypes is critical. In this study, we describe our strategic approach to optimise a class of previously reported antimalarials, resulting in the discovery of 1-(5-chloro-1*H*-indol-3-yl)-2-[(4-cyanophenyl)thio]ethanone (**13**) and 1-(5-chloro-1*H*-indol-3-yl)-2-[(4-nitrophenyl)thio]ethanone (**14**), whose activity was equipotent to that of chloroquine against the *P. falciparum* 3D7 strain. Furthermore, these compounds were found to be nontoxic to HeLa cells as well as being non-haemolytic to uninfected red blood cells. Intriguingly, several of our most promising compounds were found to be less active against the isogenic NF54 strain, highlighting possible issues with long-term dependability of malarial strains. Finally, compound **14** displayed similar activity against both the NF54 and K1 strains, suggesting that it inhibits a pathway that is not compromised by K1 resistance.

Introduction

Plasmodium falciparum induced malaria remains one of the most prevalent parasitic disease worldwide.[1] The WHO reported 212 million new cases of malaria and 429 000 deaths in 2015, with children under five years of age and severely disadvantaged populations being particularly vulnerable.[2-4] Chemotherapeutics have formed a cornerstone of efforts to decrease the burden of malaria, but have been hampered by the continuous emergence of resistance to first-line treatments.[5-8] The rapid and efficacious nature of artemisinin combination therapies (ACT) against multidrug-resistant parasites coupled with widespread adoption of ACT as a first-line treatment in most malaria-endemic countries[10] has contributed to the significant progress made in decreasing the rates of malarial transmission.[11] However, reports of delayed parasite clearance after standard ACT dosing regimens indicate that the current trends in decreasing the malaria burden may be under threat,[12-14] and highlights the urgent need to discover chemotypes that disrupt vital malarial biochemical processes, either via new targets, or by overcoming resistance pathways in current validated targets. The post-genomic era of drug discovery has provided stunning insight into biological pathways and has facilitated target-based drug discovery against human derived diseases.[15] However, targeted screening approaches have proven more challenging against infectious disease.[16] Conversely, phenotypic screening takes advantage of the greater chemical space sampled in the complex cellular environment, thereby increasing the probability of unearthing new classes of biological targets, or the discovery of active compounds that act against multiple targets.[17-20]

Recent studies conducted by our research group, focusing on indole-based antimalarials,[21,22] identified a new class of compounds, two members of which (**1** and **2**, Figure 1) were found to possess good antimalarial activity in an in vitro phenotypic screening campaign against the chloroquine-sensitive

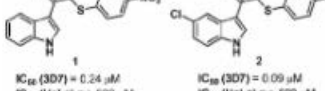

Figure 1. Promising early antimalarial compounds identified through phenotypic screening against the 3D7 *P. falciparum* strain.

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