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Research paper

Discovery and optimisation studies of antimalarial phenotypic hits

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ABSTRACT

There is an urgent need for the development of new antimalarial compounds. As a result of a phenotypic screen, several compounds with potent activity against the parasite *Plasmodium falciparum* were identified. Characterization of these compounds is discussed, along with approaches to optimise the physicochemical properties. The *in vitro* antimalarial activity of these compounds against *P. falciparum* K1 had EC_{50} values in the range of 0.09–29 μM, and generally good selectivity (typically >100-fold) compared to a mammalian cell line (L6). One example showed no significant activity against a rodent model of malaria, and more work is needed to optimise these compounds.

1. Introduction

Malaria is a serious endemic disease and is a major threat to public health in more than 100 countries [1,2]. It affects about 200 million people per year, with approximately 580,000 associated deaths [3,4]. In addition malaria exerts a huge economic toll in endemic countries [3]. The need for a continual supply of new antimalarial therapeutics is still as relevant as ever.

Malaria is caused by protozoan parasites of the species *Plasmodium* [5], with *Plasmodium falciparum* being responsible for most malaria-related deaths. In many areas malaria parasites have developed resistance to chemotherapeutic agents such as chloroquine, mefloquine, and sulfadoxine/pyrimethamine. Therefore, an urgent need exists to develop new classes of antimalarial drugs that operate by novel mechanisms of action.

We have recently reported the identification of a hit (**TDR32750**) [6,7] from a screen of the ChemDiv5000 'maximally structurally diverse' compound collection against *P. falciparum*. This screen was carried out by the World Health Organisation Programme for Research and Training in Tropical Medicine (Fig. 1). **TDR32750** showed potent activity against *P. falciparum* (EC_{50} = 9 nM), and good selectivity compared to L6 mammalian cells (>2000-fold). In order to follow up on the hit, other analogues from ChemDiv and PrincetonBio were screened. This led to identification of two more hits, **TDR45024** and **TDR45033** (Fig. 1), which shared the *N*-aryl-pyrrole found in **TDR32750**.

In this paper we report the follow up of these compounds, **TDR45024** and **TDR45033**; systematic structure-activity relationship studies were undertaken with the aim of improving antiparasitic activity, and to generate compounds with drug-like physicochemical and pharmacokinetic properties. The studies encompassed variation of the phenyl ring attached to the pyrrole, modification of the pyrrole and modification of the thiazolidinedione ring. The activity of compounds against the chloroquine and pyrimethamine resistant (K1) strain of *P. falciparum* is reported, as well as a counter-screen (EC_{50}) against the L6 murine cell line, to provide an indication of selectivity (Table 1, Fig. 2).

2. Results and discussion

2.1. Synthesis of cyclohexyl-2-(phenylimino)-4-thiazolidinedione analogues (*20*–*32*)

The thiazolidinedione core [8,9] (**3**) was prepared by condensation of the commercially available 1-cyclohexyl-3-phenyl-2-thiourea (**1**) with monochloroacetic acid (**2**; Scheme 1). This was

Abbreviations: DMPK, drug metabolism and pharmacokinetics; SAR, structure-activity relationship; WHO, World Health Organisation; WHO-TDR, World Health Organisation Programme for Research and Training in Tropical Diseases.

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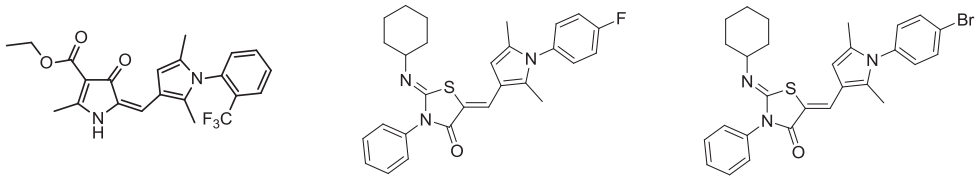
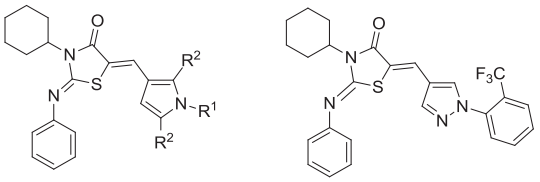
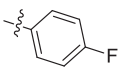
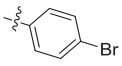
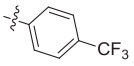
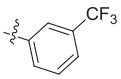
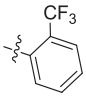
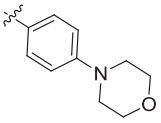
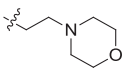
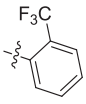
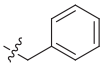


Fig. 1. The hit TDR32750 and follow-up compounds.

Table 1
In vitro activity of phenyliminothiazolidinones against *P. falciparum* and L6 cells.



Compound *(Z,Z-isomers)*	R^1	R^2	*P. falc.*[a] EC_{50}(μM)	L-6 cells[b] EC_{50}(μM)	cLogP	cLogD pH 7.4
20		Me	2.0	>190	6.6	2.7
21		Me	0.42	>170	7.2	3.1
22		Me	0.25	>200	6.6	2.6
23		Me	0.25	>170	7.5	3.2
24		Me	1.9	>170	7.5	3.2
25		Me	0.78	>170	7.5	3.2
26		Me	0.09	>170	6.5	3.1
27		Me	0.61	71	5.4	1.9
28		H	2.3	>180	6.7	2.9
29		H	1.6	>200	6.1	2.2
30		Me	3.4	23	5.1	1.5
31		Me	1.9	>230	5.6	1.5
32	–	–	1.9	>180	6.1	2.6

[a] *Plasmodium falciparum*.
[b] Measure of cytotoxicity; nd: not determined. Controls: for *P. falciparum* K1, chloroquine, $EC_{50} = 0.1$ μg/ml; for cytotoxicity (L6 cells), podophyllotoxin, $EC_{50} = 0.005$ μg/ml. The EC_{50} values are the data are means of two independent assays run in singleton. Yields for compounds **20**–**32** are 40–80%.