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Design, synthesis and antimalarial evaluation of novel thiazole derivatives

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ABSTRACT

As part of our medicinal chemistry program's ongoing search for compounds with antimalarial activity, we prepared a series of thiazole analogs and conducted a SAR study analyzing their in vitro activities against the chloroquine-sensitive *Plasmodium falciparum* 3D7 strain. The results indicate that modifications of the *N*-aryl amide group linked to the thiazole ring are the most significant in terms of in vitro antimalarial activity, leading to compounds with high antimalarial potency and low cytotoxicity in HepG2 cell lines. Furthermore, the observed SAR implies that non-bulky, electron-withdrawing groups are preferred at *ortho* position on the phenyl ring, whereas small atoms such as H or F are preferred at *para* position. Finally, replacement of the phenyl ring by a pyridine affords a compound with similar potency, but with potentially better physicochemical properties which could constitute a new line of research for further studies.

Malaria, the most lethal human parasitic infection,[1,2] is transmitted by female mosquitos of the genus *Anopheles* infected with parasites of the genus *Plasmodium*.[3] Of the latter, *P. vivax* and *P. falciparum* are the most relevant.[4,2] Although several drugs can be used to treat this disease, the rise of drug-resistant strains of *Plasmodium* is a growing cause for concern.[5–7] For this reason, the need for new drugs for those already infected with malaria has acquired a new urgency,[8,9] especially considering that in the last 10 years, no effective new candidates have been found to treat this disease. Recently, a significant contribution to the eventual solution of this problem has been made by *GlaxoSmithKline* (GSK). Using its corporate collection of over two million compounds as a starting point, GSK carried out a High-Throughput Screening (HTS) against the *P. falciparum* 3D7 strain, which is chloroquine sensitive, to reduce the original number to around 13,000 confirmed *hits*; these are known as the Tres Cantos Antimalarial Set (TCAMS).[10,11] More than 8,000 of these compounds show activity against the Dd2 strain, which is multi-drug resistant.[10,11] GSK has published these results in the form of a data base with free public access through the European Bioinformatics Institute,[12] thus offering academic institutions the opportunity to join the effort in the *hit to lead* development of antimalarials. To this end, a collaboration was established between GSK and our two universities with the aim of selecting a *hit* from the TCAMS with a thiazole scaffold to conduct SAR studies based on its antimalarial activity.[13]

The thiazole ring is a well-known component of many biologically active compounds with demonstrated antimicrobial, antifungal and anti-inflammatory properties,[14] as well as potential antitumoral activity.[15–20] Numerous synthetic approaches have been used in their preparation, but the classic methods of Hantzsch[21–26] and Cook-Heilbron[27] still constitute valid strategies for the introduction of chemical diversity around the thiazole scaffold.

In order to identify a suitable *hit* from the TCAMS Dataset (https://www.ebi.ac.uk/chemblntd/compound/activity_home),[12] we focused our search on thiazoles that showed a high percentage of inhibition of *P. falciparum* at a concentration of 2 μM (>98% for both 3D7 and D2d strains), high potency (XC_{50} 3D7 < 0.3 μM), low cytotoxicity on HepG2 human liver cells (<15% at 10 μM) and a low inhibition frequency index (<10). As a result, a cluster of nine structurally related thiazole derivatives with promising antimalarial activity was selected. The main structural features of these nine compounds are shown in Figure 1.[28]

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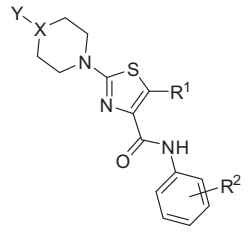


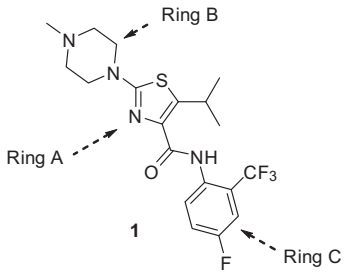
R^1 = Me, Et, *i*-Pr
X = N, C
Y = Me, H
R^2 = CF_3, F, fused cyclohexyl ring

Figure 1. Significant common structural features of the nine thiazoles included in the TCAMS chemical cluster # 300.

From the selected compounds, thiazole **1** was chosen as the starting point for a SAR study on the basis of its potency against both sensitive *P. falciparum* 3D7 (XC_{50} 3D7 = 190 nM) and resistant Dd2 strains to the commercially available antimalarial drugs chloroquine and pyrimethamine (Fig. 2).[29] At a concentration of 2 μM, **1** was found to inhibit both the 3D7 and Dd2 strains by 100% and 99%, respectively. Additionally, compound **1** displays low toxicity against the HepG2 cell line (3% inhibition at 10 μM). Finally, the amenable chemistry involved in its synthesis allows for the introduction of a number of substituents not only at the thiazole ring, but also around the B and C rings (Figs. 2 and 3).

Once compound **1** had been selected as a *hit*, the next step involved the selection of a series of analogs with suitable structural diversity (Fig. 3). Several different R^1 groups were chosen to explore the importance of the B ring. As for R^2 groups, we chose to examine halogenated, electron-rich and electron-withdrawing groups in several positions on the benzene C ring. Finally, the substitution of benzene with a pyridine as C ring was also considered.

Brominated thiazole **2** was identified as a key intermediate for the preparation of the desired analogs of *hit* **1**. After building the thiazole core, two different synthetic routes can be used to obtain these analogs. As a first option, reaction of **2** with suitable amines would yield amino-thiazole derivatives **A**, which could be then transformed into the corresponding amides **C**. Alternatively, **2** could be transformed into amides **B**, whose subsequent reaction with suitable amines would lead to a set of analogs **C** (Scheme 1).



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% Inhibition 3D7 (2μM) = 100
% Inhibition Dd2 (2μM) = 99
pXC50 3D7 = 6.72 (189.62nM)
% Inhibition HepG2 (10μM) = 3
Inhibition Frequency Index = 5.77
MW = 430.46
A LogP = 3.96

Figure 2. Structure and properties of the *hit* (**1**).

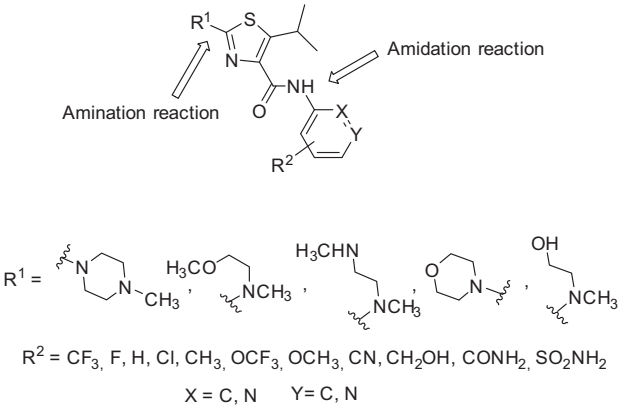

Figure 3. Proposed thiazole analogs of compound **1**.

Indeed, an initial synthetic trial showed that both **A** and **B** pathways yielded the same compound **C** in comparable yields. We thus concluded that both synthetic routes would be suitable for the preparation of a small library of thiazole derivatives with appropriate chemical diversity, based on the *hit* compound.

Compound **2** was prepared by means of a Hantzsch synthesis[21] in which α-bromoketone **5** (Scheme 2) was an intermediate for the preparation of the thiazole moiety. We were able to prepare **5** in three steps and with good yield from the Grignard reagent **3**. Thus, reaction of **3** with diethyl oxalate afforded α-oxoester **4** (Scheme 2).[30] In turn, compound **4** reacted with $CuBr_2$ to yield the brominated derivative **5**,[31–34] which then reacted with thiourea in EtOH to afford thiazole **6** in high yield.[35] Compound **2** was then obtained in one step by means of a Sandmeyer reaction, which involved the formation of an intermediate diazonium salt, followed by reaction with $CuBr_2$ (Scheme 2).[36]

With compound **2** in hand, we started our SAR study by introducing diversity in the B ring. Thus, several different cyclic and open secondary amines were introduced in position 2 of the thiazole ring while retaining the amide moiety of the *hit* (route **B**, shown in Scheme 1). To that end, ester hydrolysis of **2** to the corresponding carboxylic acid followed by reaction with thionyl chloride provided an acyl chloride which, upon reaction with 4-fluoro-2-trifluoromethylaniline, yielded amide **7**. This amide then reacted with several secondary amines to afford compounds **1** and **8**–**11** (Scheme 3 and Table 1).

Our initial results (Table 1) showed that open chain compounds **8**, **9** and **11** have a markedly lower potency than **1**, especially in the case of the first two compounds. Furthermore, substitution of an *N*-methyl group by an O atom in the B ring (as in **1** versus **10**) only causes a slight decrease in activity. Moreover, similar compounds in the initial thiazole cluster, which include piperidine, 4-methylpiperidine and *N*-methylpiperazine B rings also display similar potency values.[37] We therefore concluded that the presence of an additional basic nitrogen in the B ring is not essential for activity as long as a six-membered ring attached through a N atom is present at position 2 of the thiazole. This seems to point to the need for steric hindrance in this part of the molecule.

After having determined that changes to the B ring of **1** do not significantly alter its activity, we focused our attention on modifications to the C ring while keeping the B ring of the *hit* unchanged. This allowed us to study the influence of the aryl group with a range of substituents. Diversity in the C ring was introduced in position 2 of the thiazole through reaction of **2** with *N*-methylpiperazine in refluxing dioxane (Scheme 4). The resulting ester **12** was then hydrolyzed to the corresponding carboxylate which, upon reaction with thionyl chloride, provided an acyl chloride. Finally, reaction of