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Graphical Abstract

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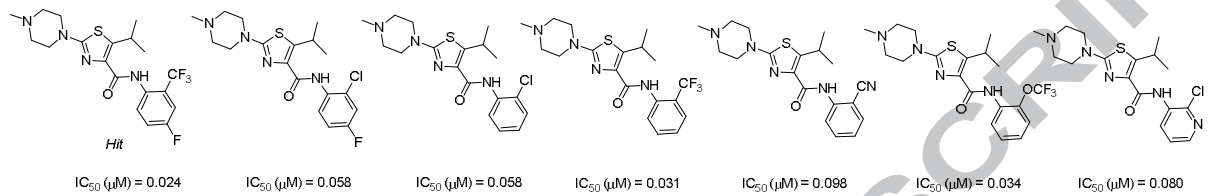

Design, synthesis and antimalarial evaluation of novel thiazole derivatives

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Keywords: *malaria; antimalarials; synthesis; thiazoles; structure-activity relationship.*

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.

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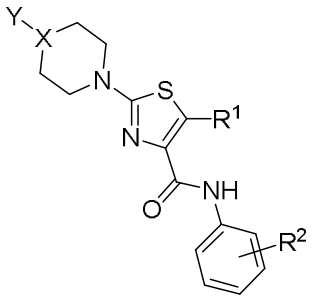
Malaria, the most lethal human parasitic infection,[1,2] is transmitted by female mosquitos of the genus *Anopheles* infected with parasites of the genus *Plasmodium.*[3] Of the latter, *P. vivax* and *P. falciparum* are the most relevant.[4,5] Although several drugs can be used to treat this disease, the rise of drug-resistant strains of *Plasmodium* is a growing cause for concern.[6-8] For this reason, the need for new drugs for those already infected with malaria has acquired a new urgency,[9,10] 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).[11,12] More than 8,000 of these compounds show activity against the Dd2 strain, which is multi-drug resistant.[11-12] GSK has published these results in the form of a data base with free public access through the European Bioinformatics Institute,[13] 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.[14]

The thiazole ring is a well-known component of many biologically active compounds with demonstrated antimicrobial, antifungal and anti-inflammatory properties,[15] as well as potential antitumoral activity.[16-21] Numerous synthetic approaches have been used in their preparation, but the classic methods of Hantzsch[22-27] and Cook-Heilbron[28] still constitute valid strategies for the introduction of chemical diversity around the thiazole scaffold.

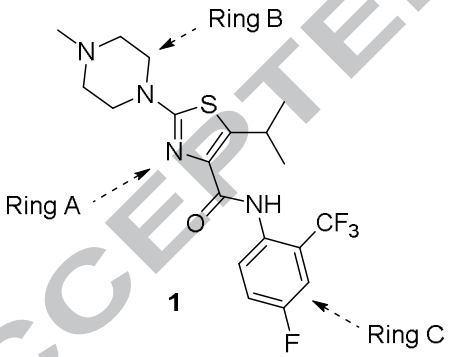
In order to identify a suitable *hit* from the TCAMS Dataset (https://www.ebi.ac.uk/chemblntd/compound/activity_home),[13] we focused our search on thiazoles that showed a high percentage of inhibition of *P. falciparum* at a concentration of 2μM (>98% for both 3D7 and D2d strains), high potency (XC_{50} 3D7 < 0.3 μM), low cytotoxicity on HepG2 human liver cells (<15% at 10μM) 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.[29]



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 (Figure 2).[30] 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 (Figures 2 and 3).



CHEMBL587278
TCMDC-134300

% 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**)

Once compound **1** had been selected as a *hit*, the next step involved the selection of a series of analogs with suitable structural diversity (Figure 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.

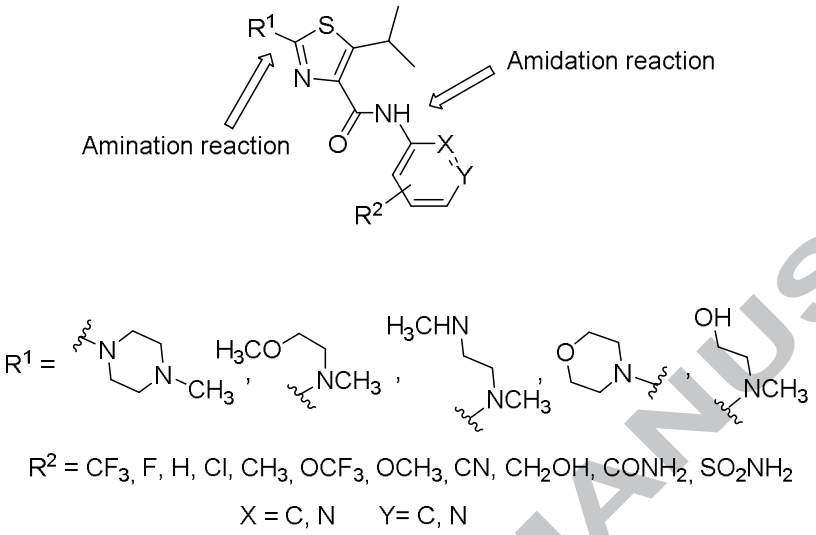
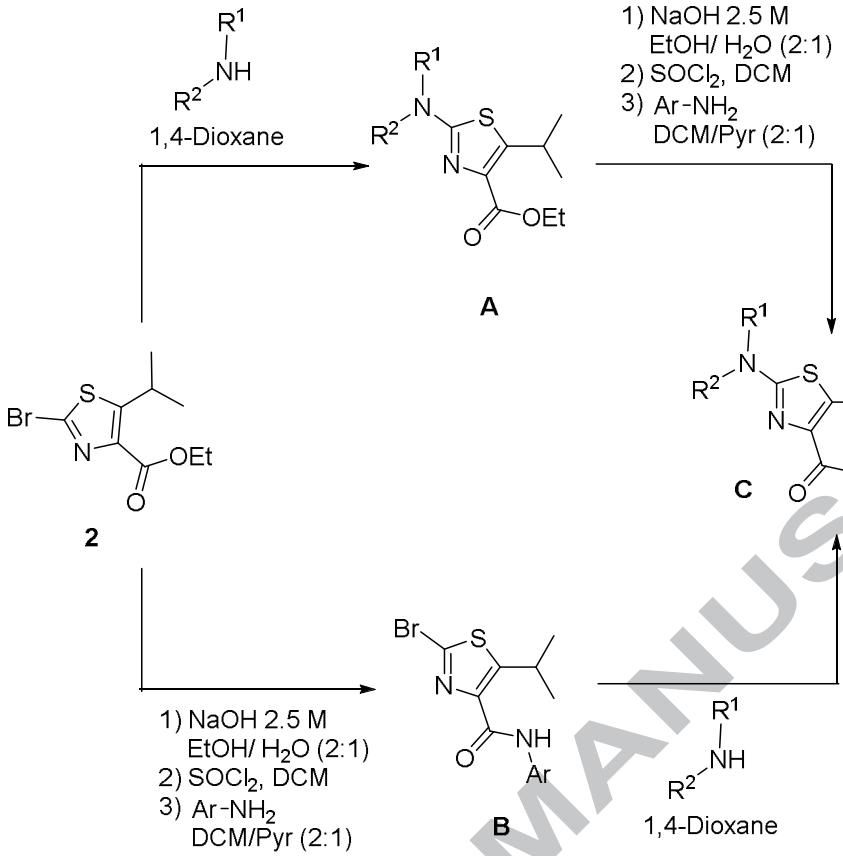


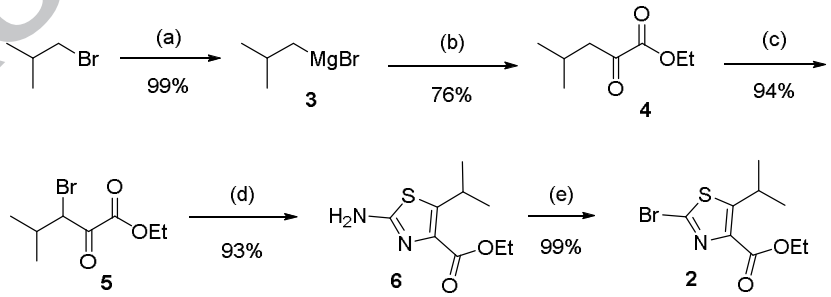
Figure 3: Proposed thiazole analogs of compound **1**

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). 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.



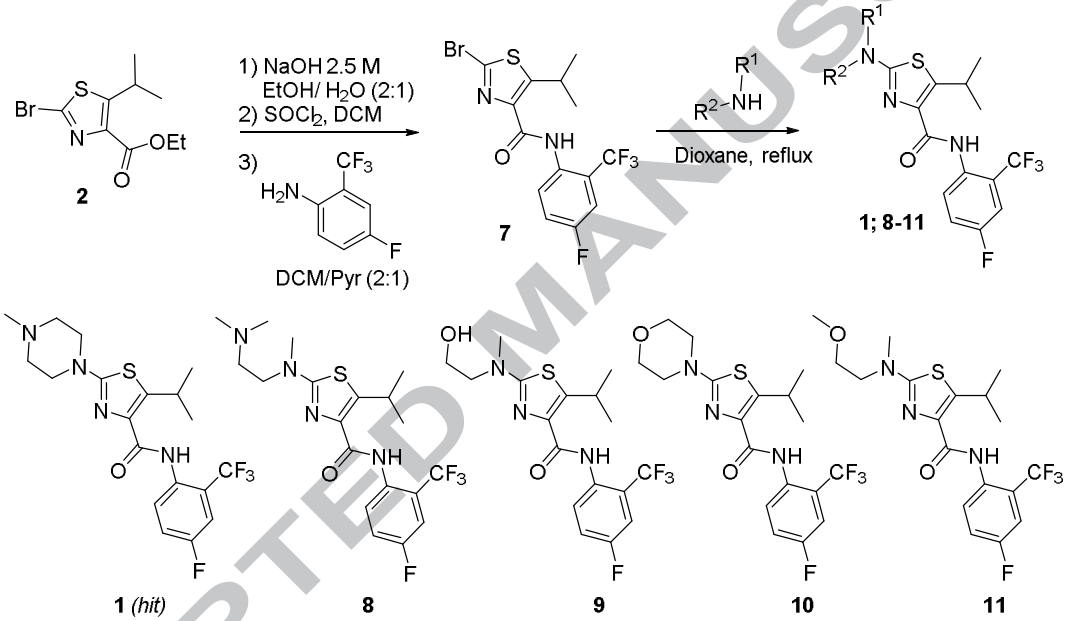
Scheme **1**: Two possible approaches for the synthesis of novel antimalarial thiazoles **C**.

Compound **2** was prepared by means of a Hantzsch synthesis[22] 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).[31] In turn, compound **4** reacted with $CuBr_2$ to yield the brominated derivative **5**,[32-35] which then reacted with thiourea in EtOH to afford thiazole **6** in high yield.[36] 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).[37]



Scheme 2: Preparation of intermediate **2**. Conditions: (a) Mg, I_2, 30 Min. reflux. (b) Diethyl oxalate, Et_2O, -78°C to rt, 1h. (c) $CuBr_2$, EtOAc-DCM 2:1, 18h. reflux. (d) Thiourea, EtOH, 5 h. reflux. (e) $CuBr_2$, *t*-BuONO, CH_3CN

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).



Scheme 3: Preparation of compounds **1** and **8**-**11** from intermediate **2**

Table 1.

Modifications in the B ring of the *hit*.[a]

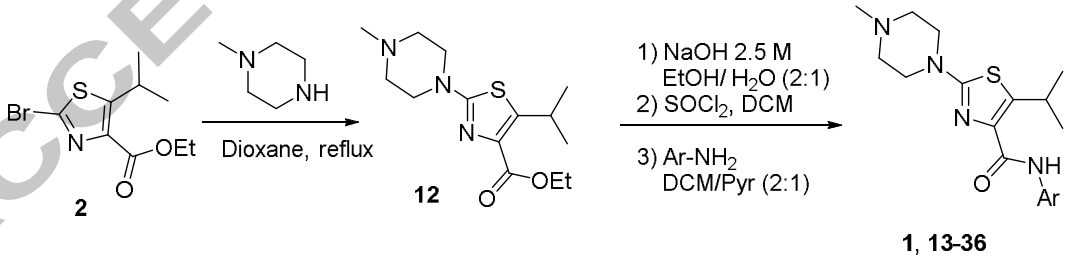
Entry	**Compound**	**Yield (%)**	**IC_{50} (µM) after 48 h**
1	**1 (*hit*)**	99%	0.024
2	**8**	95%	3.150
3	**9**	96%	3.260

4	**10**	99%	0.102
5	**11**	93%	0.590

[a] IC_{50} values for the commercially available drugs Atovaquone and Artesunate were 0.0005 μM and 0.014 μM, respectively.

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** *vs.* **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.[38] 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.

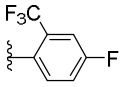
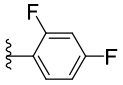
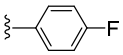
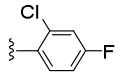
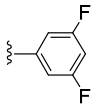
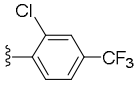
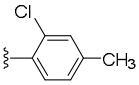
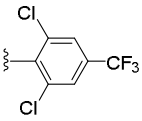
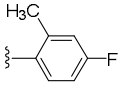
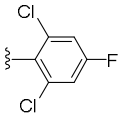
After having determined that changes to the B ring of **1** do not significantly alter its activity, we focused our attention on modifications to the C ring while keeping the B ring of the *hit* unchanged. This allowed us to study the influence of the aryl group with a range of substituents. Diversity 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 the latter with several different anilines yielded amides **13**-**36** as analogs of **1** (Schemes 1 and 4 and Table 2, entries 1-25).

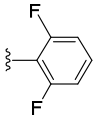
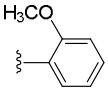
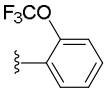
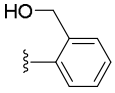
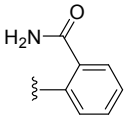
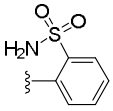


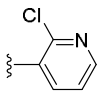
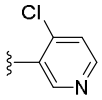
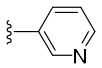
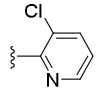
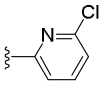
Scheme 4: Preparation of compounds **1** and **13**-**36** from intermediate **2**

Table 2.

Modifications on the amide *N*-phenyl ring substitution in **1** with several different groups.[a]

Entry	Compound	Ar	Yield (%)	IC_{50} (μM) after 48 h
1	**1 (*hit*)**		80%	0.024
2	**13**		80%	1.194
3	**14**		79%	>5
4	**15**		90%	0.058
5	**16**		99%	>5
6	**17**		88%	>5
7	**18**		73%	3.270
8	**19**		77%	>5
9	**20**		80%	0.72
10	**21**		68%	>5

11	**22**		75%	0.058
12	**23**		83%	0.031
13	**24**		42%	0.260
14	**25**		46%	>5
15	**26**		84%	0.350
16	**27**		76%	0.098
17	**28**		57%	0.034
18	**29**		87%	>5
19	**30**		82%	>5
20	**31**		65%	>5

21	**32**		76%	0.08
22	**33**		82%	1.7
23	**34**		63%	>5
24	**35**		75%	>5
25	**36**		82%	0.35

[a] See footnote to Table 1.

Since **1** has two halogenated groups in the C ring (*o*-CF_3 and *p*-F), the first round of compounds explored the effect of the presence of halogen atoms or CF_3 groups in several positions on the phenyl ring. Our initial results showed highly significant changes in the potency of these analogs (Table 2, entries 1-6). For example, the substitution of a CF_3 group (compound **1** (*hit*)) by a fluorine atom (compound **13**, entry 2) caused a marked loss of activity (IC_{50} from 0.024 µM to 1.194 µM). Similarly, when two F atoms were introduced in *meta* position (compound **16**, entry 5) or when the *ortho* position was not substituted (compound **14**, entry 3), a complete loss of activity was observed (>5 µM for each compound). Only compound **15** (*o*-Cl, *p*-F, entry 4) had a potency similar to that of **1**. As these results all seemed to indicate the importance of substitution in the *ortho* position, we prepared additional analogs **17-25**, all of which have at least one *ortho* substituent (Table 2, entries 7-25). The activity of **23** (*o*-CF_3, entry 12) (IC_{50} = 0.031 µM), which has a free *para* position, is similar to that of **1** (*o*-CF_3, *p*-F, entry 1) (IC_{50} = 0.024 µM). At the same time, while the activities of **15** (*o*-Cl, *p*-F, entry 4) and **22** (*o*-Cl, entry 11) are the same (IC_{50} = 0.058 µM for both compounds), **17** (*o*-Cl, *p*-CF_3, entry 6) is inactive. These findings not only confirm that substitution in the *ortho* position is essential for activity, but also that the *para* position should preferably be kept free or occupied by a fluorine atom. Indeed, the presence of a bulkier group such as CF_3 in compound **17** (entry 6) or CH_3 in **18** (*o*-Cl, *p*-CH_3, entry 7) rendered these compounds practically inactive. Additionally,

CF_3 and Cl groups in *ortho* position are almost interchangeable in terms of their effects on potency, as shown by the data for **1** (entry 1) *vs.* **15** (entry 4) and **22** (entry 11) *vs.* **23** (entry 12). Taken together, our findings point to Ring C as the most important component of these compounds in their interaction with possible biological targets; we therefore focused most of our later synthetic efforts here.

In a second round of experiments we decided to prepare several analogs with two substituted *ortho* positions. In all cases, the antimalarial activity was completely lost (IC_{50} > 5 μM), as in **19** (*o*-Cl, *o*-Cl, *p*-CF_3, entry 8), **21** (*o*-Cl, *o*-Cl, *p*-F, entry 10) and **25** (*o*-F, *o*-F, entry 14).

In a third round, several additional monosubstituted analogs with the *ortho* position occupied by either an electron-rich or an electron-withdrawing group were prepared and assayed (entries 15-20, Table 2). The results showed that when the substituent position is electron-rich, as in **26** (*o*-OCH_3), the activity is lower (IC_{50} = 0.350 μM) in comparison to analogs in which electron-withdrawing groups are present, such as **27** (*o*-CN) and **28** (*o*-OCF_3), with IC_{50} activities of 0.098 μM and 0.034 μM, respectively. Additionally, in *ortho* monosubstituted compounds **29** (*o*-CH_2OH), **30** (*o*-$CONH_2$) and **31** (*o*-SO_2NH_2), all of which display stronger steric and lower lipophilic effects, the antimalarial activity is likewise lost.

Finally, compounds **32-36** include a pyridine instead of a benzene ring (Table 2, entries 21-25). Although compounds **22** (*o*-Cl, entry 11) and **32** (with a 2-chloropyridin-3-yl group, entry 21) have similar substitution patterns and potencies, the introduction of pyridyl C rings as in **33-36** did not generally improve the potency of these analogs. This might, however, have an effect on other important properties. In fact, a significant decrease in lipophilicity was observed in compound **32** (chlogD=7.8) compared to the *hit* **1** (chlogD=9.06).

The toxicity of the most active compounds in our series against HepG2 human cells was also determined (Figure 4). Preliminary results seem to indicate that toxicity might not be an issue of concern in this series of compounds.

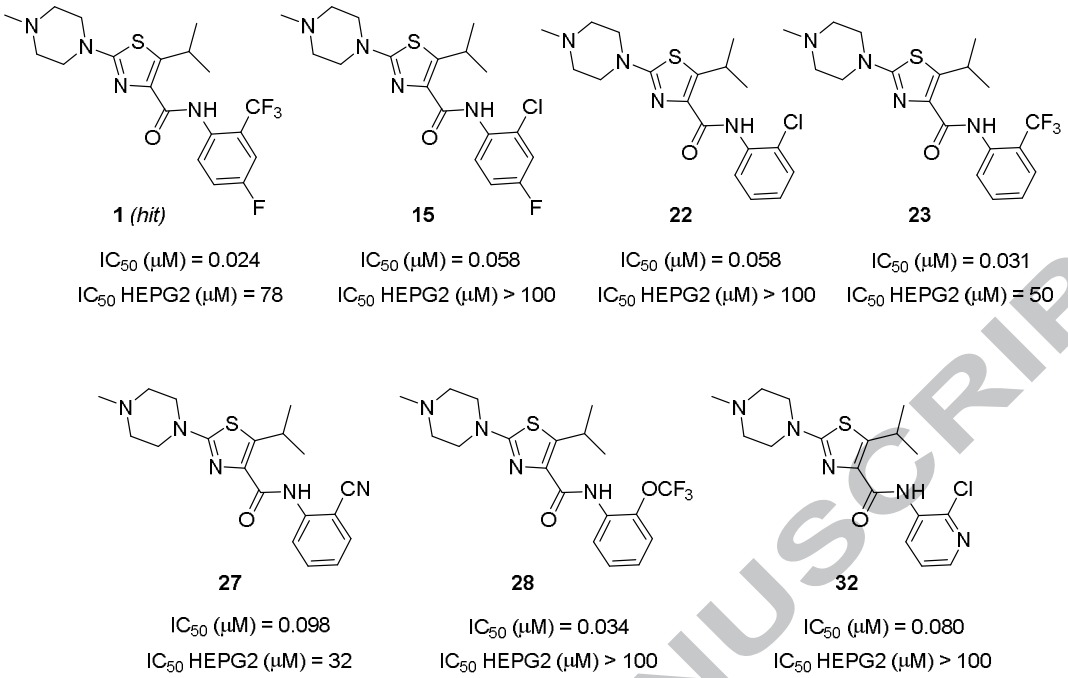


Figure 4: *In vitro* antimalarial activity (IC_{50} for *P. falciparum* 3D7 strain) and toxicity (IC_{50} for HepG2 human liver cells) of the *hit* and the most active analogs prepared in this study.

In conclusion, starting from the Tres Cantos Antimalarial Set (TCAMS), a previously published antimalarial data base with free public access, we were able to find a cluster of thiazoles from which we identified a suitable *hit* **1**. From this compound, we prepared a series of analogs which allowed us to build a SAR study, analyzing their *in vitro* activities against the 3D7 strain of *P. falciparum*. The results led to several conclusions. First, modifications to the B ring of the molecule do not significantly affect its activity as long as position 2 of the thiazole is directly bound by a nitrogen atom from a piperidine, piperazine, or *N*-methylpiperazine moiety. However, opening the B ring significantly lowers the potency of the corresponding analogs. Secondly, position 5 of the thiazole must be occupied by an ethyl or isopropyl group, as a methyl group makes it lose most of its activity.[24] Third, and most importantly, ring C is the most significant in this series, greatly affecting antimalarial activity. The most potent compounds have one electron attractor group in *ortho* position and a free *para* position, with only two exceptions: compounds **1** and **15**, in which the *para* substituent is a fluorine atom. Furthermore, when both *ortho* positions are simultaneously substituted, the analogs are inactive. These findings indicate that *ortho* monosubstitution is required for activity, with non-bulky electron-withdrawing groups being preferred. When the *para* position is occupied, the substituent must be a small atom, such as F. Moreover, preliminary assays against HepG2 human liver cells indicate that toxicity does not seem to be a problem in this series of analogs. Finally, replacement of the aryl ring by a pyridine affords a compound with similar potency to **1**, but

with potentially better physicochemical properties which could constitute a new line of work for further studies.

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30. The strain 3D7 is chloroquine resistant while Dd2 is a multidrug resistant strain. The detailed activity data comparison for the compounds in the TCMDC chemical cluster # 300 along with the specifics of the *hit* selection process can be found in the supplementary material section.

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Supplementary material

The supplementary material contains experimental procedures used in the biological work as well as chemical procedures and data.