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Synthesis and biological activity of diaryl ether inhibitors of malarial enoyl acyl carrier protein reductase. Part 2: 2′-Substituted triclosan derivatives

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Abstract—2′-Substituted analogs of triclosan have been synthesized to target inhibition of the key malarial enzyme *Plasmodium falciparum* enoyl acyl carrier protein reductase (PfENR). Many of these compounds exhibit good potency (EC_{50} < 500 nM) against in vitro cultures of drug-resistant and drug-sensitive strains of the *P. falciparum* parasite and modest (IC_{50} = 1–20 μM) potency against purified PfENR enzyme. Compared to triclosan, this survey of 2′-substituted derivatives has afforded gains in excess of 20- and 30-fold versus the 3D7 and Dd2 strains of parasite, respectively.
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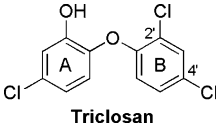
Treatment of *Plasmodium falciparum* malaria has depended for decades on the use of the aminoquinoline chloroquine or the antifolate combination pyrimethamine-sulfadoxine. *P. falciparum* infection is the most widespread and the deadliest form of malaria—a disease that afflicts 300–600 million people worldwide resulting in 1–3 millions deaths per annum.[1] The occurrence and spread of drug-resistance necessitates new, highly potent antimalarials that are not encumbered by existing resistance mechanisms and are orally biovailable, affordable, and safe.

The inhibition of fatty acid synthesis in *P. falciparum* has been a recent focus of drug discovery efforts to find novel antimalarials.[2] This synthetic pathway is believed to be crucial to parasite survival as a result of its key role in membrane construction and energy production. Synthesis of fatty acids is regulated within the apicoplast—an organelle derived from a cyanobacterial endosymbiont.[3] Given the prokaryotic nature of the apicoplast, its metabolic machinery differs significantly from that of mammalian cells.[4] For example, higher eukaryotes and yeast utilize fatty acid biosynthetic machinery residing on a single multifunctional polypeptide (FAS-I), whereas fatty acid synthesis in *Plasmodium* is reliant on a dissociative process that utilizes a set of distinct enzymes composing a FAS-II pathway. This observation hints at selectivity with regard to the human host in a therapeutic strategy.

The enoyl reductase enzyme (PfENR) is responsible for the final step in fatty acid synthesis: NADH-dependent reduction of *trans*-2-enoyl-ACP to acyl-ACP (ACP = acyl carrier protein). Triclosan (Fig. 1) is a known



Triclosan

Figure 1. Chemical structure of triclosan with demarcation of key B-ring sites.

Keywords: Antimalarial; Diaryl ether; Phenol.
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inhibitor of PfENR, as determined with native enzyme purified from *P. falciparum* or recombinant enzyme expressed in *Escherichia coli*.[5,6] Furthermore, triclosan is potent in the low micromolar range against *P. falciparum*[5,7–10] and is reported to effectively treat *P. berghei* in vivo infections in mice.[5] A direct relation between triclosan binding to and inhibition of PfENR in vitro and its whole cell properties is supported by the demonstration that triclosan also inhibits fatty acid synthesis with cultured parasites or parasite extracts.[5] Given triclosan's abundance (U.S. annual production $> 1 \times 10^6$ lbs),[11] its safety as demonstrated by its widespread use in personal care and household products, and the absence of a lipid synthesis inhibitor in the antimalarial arsenal, we and others have chosen to pursue the discovery of a triclosan-derived therapeutic for malaria.[6,8,10,12–16]

This work recently culminated in the X-ray crystal structure of triclosan and NAD^+ co-factor bound to PfENR.[8] The structure demonstrated the critical binding element of triclosan to be the phenol moiety, while suggesting vectors off the triclosan A and B rings where additional functionality could be placed to enhance binding affinity. We have pursued a strategy to build off these aromatic ring positions to enhance enzymatic and anti-parasitic activity. A significant gain in potency could facilitate replacement or removal of the phenol, due to its metabolic liability.[17] Previously, we reported efforts to explore SAR at the 4′-position which resulted in minor improvements in enzyme and anti-parasite potency.[16] This report details our further exploration of the triclosan B-ring, focusing specifically on the 2′-position.

Examination of the triclosan:co-factor:PfENR structure showed the 2′-chloro is pointed toward the pyrophosphate portion of NAD^+ and is approximately 4 Å from two of the negatively charged oxygens (Fig. 2). We hypothesized that a properly placed positively charged amine off the 2′-position could favorably interact with one or both of these oxygens. In addition, a hydrophobic substituent on the amine could participate in favorable interactions with proximal enzyme residues such as Ala-319 and Arg-318. Compared to triclosan, 2′-analogs with these features could have enhanced interactions with both the bound co-factor and enzyme, thus conferring greater binding affinity for the co-factor:enzyme complex and potentially enhanced anti-parasitic activity. Amino derivatives off the 2′-position could also have improved physiochemical properties.

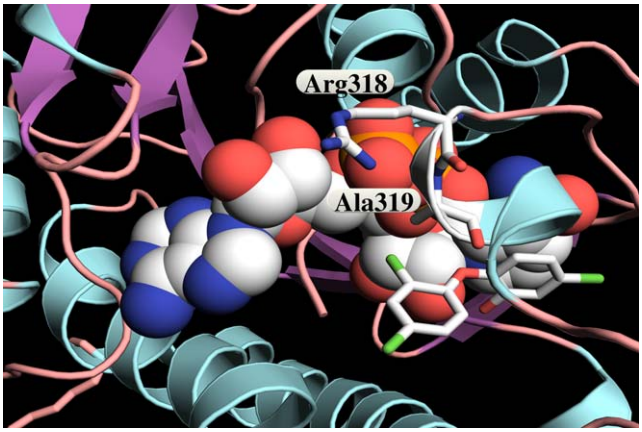


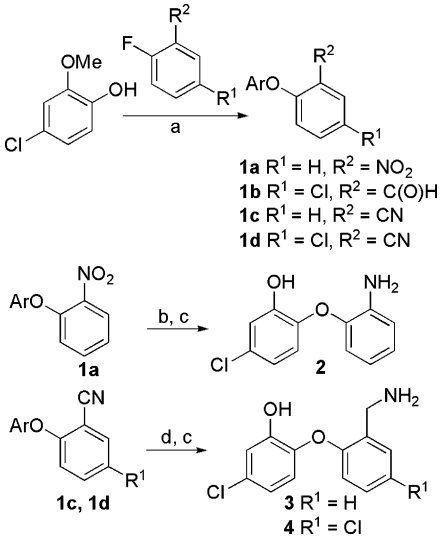
Figure 2. X-ray crystal structure of triclosan (stick drawing) bound to PfENR (ribbon and tube with key residues in stick format) in the presence of NAD^+ (space-fill). The 2′-chloro is shown pointing towards Ala-319 and Arg-318.

The synthesis of triclosan analogs began with diaryl ether anisoles **1a–d**, prepared from commercially available materials via nucleophilic aromatic substitution (Scheme 1). Aniline **2** was synthesized via hydrogenation of nitroarene **1a** followed by boron(III) bromide-mediated cleavage of the methyl ether. Benzonitriles **1c** and **1d** were converted to the 2′-aminomethyl compounds **3** and **4** via reduction with lithium aluminum hydride and then methyl ether cleavage. In all cases, final compounds were characterized by ^1H NMR and LC–MS.

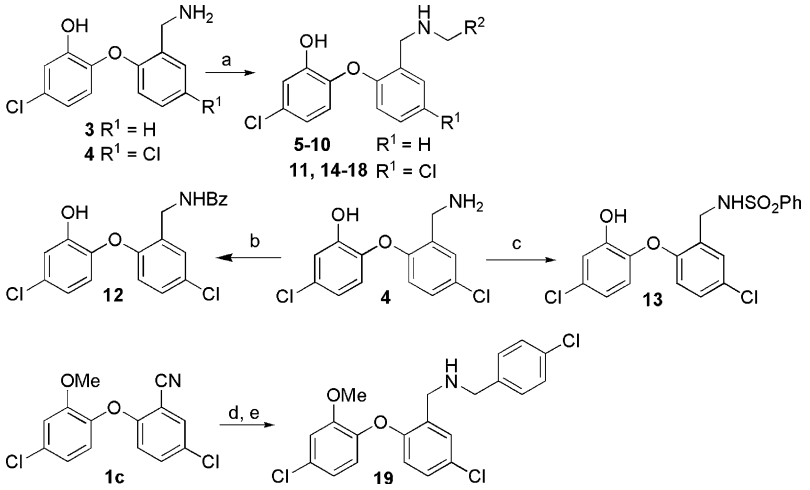
As shown in Scheme 2, reductive amination, utilizing solid-phase reagents/scavengers[18] and various aldehydes, allowed the functionalization of aminomethyl derivatives **3** and **4** to provide **5–10**, **11**, and **14–18**. Interestingly, the reductive aminations proceeded more cleanly (i.e., less dialkylation) with the corresponding phenol than with the anisole (free base or hydrochloride salt). Compound **4** was also coupled with benzoic acid to afford amide **12** and sulfonylated with benzenesulfonyl chloride to yield sulfonamide **13**.

Anisole **1c** could be converted to benzylic amine **19** via nitrile reduction with lithium aluminum hydride followed by reductive amination using the protocol of Bhattacharyya.[19]

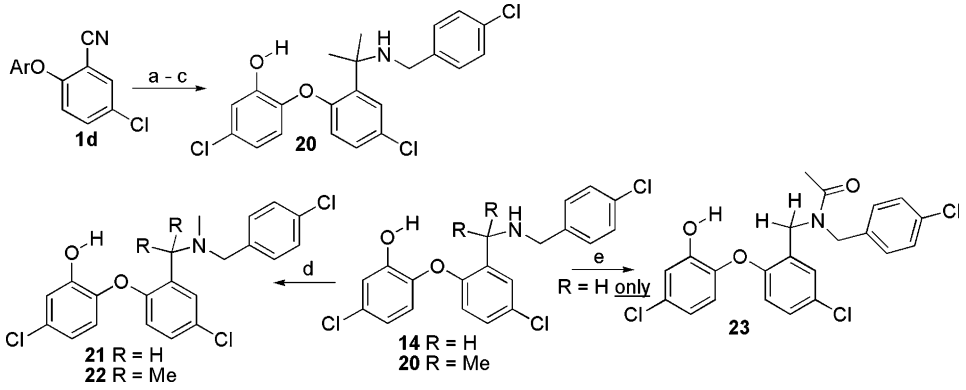
Analogs of **14** were prepared as shown in Scheme 3. Benzonitrile **1d** was transformed to α,α-dimethylamino derivative **20** via a three-step sequence, featuring reduc-



Scheme 1. Reagents and conditions: (a) K_2CO_3, DMSO, Δ; (b) Ra-Ni, H_2, EtOH/EtOAc; (c) BBr_3, DCM, 0 °C to rt; (d) $LiAlH_4$, THF. Ar = 4-chloro-2-methoxyphenyl.



Scheme 2. Reagents and conditions: (a) i—MP-Triacetoxyborohydride, RCHO, THF; ii—PS-PhCHO; iii—MP-TsOH; (b) $PhCO_2H$, ACTU, PS-HOBt, DIEA, DMF; (c) $PhSO_2Cl$, pyridine, DCM/THF; (d) $LiAlH_4$, THF; (e) i—$Ti(O\text{-}i\text{-}Pr)_4$, $p\text{-}ClC_6H_4CHO$, THF/EtOH; ii—$NaBH_4$, EtOH.

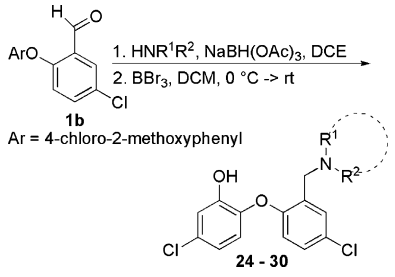


Scheme 3. Reagents and conditions: (a) $CeCl_3$, MeLi, THF, −78 °C to rt; (b) BBr_3, DCM, 0 °C to rt; (c) i—$Ti(O\text{-}i\text{-}Pr)_4$, $p\text{-}ClC_6H_4CHO$, THF/EtOH; ii—$NaBH_4$, EtOH; (d) $Ti(O\text{-}i\text{-}Pr)_4$, $NaBH_4$, $(HCHO)_n$, EtOH; (e) Ac_2O, DCM. Ar = 4-chloro-2-methoxyphenyl.

tive alkylation of the nitrile using an excess of in situ prepared methylorganocerium reagent.[20] N-methylation of **14** and **20** was achieved via a $Ti(O\text{-}i\text{-}Pr)_4/NaBH_4$ mediated reaction with paraformaldehyde to provide **21** and **22**, respectively.[21] N-acetylation, however, was only attainable with **16** to afford acetamide **23**.

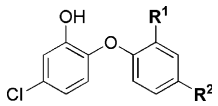
Reductive aminations to afford tertiary amines were initiated from benzaldehyde **1b**. In contrast to reductive aminations with aminomethyl analogs **3** and **4**, **1b** and various amines were observed to react most smoothly with regard to a reductive amination pathway in the presence of two equivalents of sodium triacetoxyborohydride in 1,2-dichloroethane (Eq. 1).[22] This synthetic protocol, followed by boron(III) bromide-promoted methyl ether cleavage, afforded tertiary amines **24**–**30**.

Final compounds **2**–**30** were tested in two assay systems to determine their inhibition of PfENR enzymatic activity and inhibition of parasite whole cell growth. For both assays, the reported inhibitory concentrations are tabulated as means ± standard error, taking into account three independent determinations performed in duplicate. Two parasite strains were utilized: 3D7, which is drug-sensitive, and Dd2, which is resistant to chloroquine and pyrimethamine-sulfadoxine. Both systems were previously described in detail.[8,16] To date, fourteen independent determinations of the IC_{50} of triclosan have been made in the biochemical screen with purified PfENR, resulting in a mean of 73 nM with a standard error of 21 nM. For the parasite whole-cell assay, 46 independent runs of triclosan have been conducted. Against the 3D7 strain, the EC_{50} was determined to have a mean value of 2.9 μM and a standard error of 0.2 μM versus the Dd2 strain, the EC_{50} mean value for triclosan was 3.8 μM with a standard error of 0.2 μM.



(1)

Table 1. Inhibitory properties of selected 2′-substituted derivatives



Compound	R^1	R^2	EC_{50}[a] 3D7/Dd2 (μM)	PfENR[a] IC_{50} (μM)
Triclosan	Cl	Cl	2.9 ± 0.2/3.8 ± 0.2	0.073 ± 0.021
2	NH_2	H	83 ± 15/140 ± 20	7 ± 2
3	CH_2NH_2	H	9.7 ± 1.5/7.2 ± 0.8	>50

[a] Values reported as means ± standard error.

The first set of 2′-derivatives prepared is shown in Table 1 where the 4′-position was chosen to be hydrogen. Although aminomethyl **3** is much less potent than aniline **2** against the purified enzyme, it is significantly more efficacious against the cultured parasites.

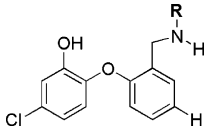
In keeping with our design hypothesis, we examined the effect of placing hydrophobic groups off the amine terminus of **3** in order to improve its enzyme and anti-parasitic potencies over those of triclosan. As shown in Table 2, compounds **5**–**10** achieve approximately an order of magnitude increase in potency over **3** in the parasite assay. The 1-naphthyl **9**, phenylpropyl **8**, and *p*-Cl-benzyl **6** derivatives are the most potent members of this series against the parasite. In general, the compounds also display an improvement in enzyme activity over **3**, although their micromolar level IC_{50} values against PfENR appear incongruent with their nanomolar level anti-parasitic potencies. It is interesting to note that of the 2′-substituted derivatives prepared to date, phenethyl analog **7** is the most potent against purified enzyme (IC_{50} = 2.5 μM).

Subsequently, triclosan derivatives with a 4′-chloro were prepared in an effort to improve enzyme and anti-parasitic potency while adhering more strictly to the triclosan scaffold (Table 3). While **4** is observed to be more potent than **3** against cultured parasites, it fails to offer an observable improvement in the enzyme assay. Surprisingly, introduction of the 4′-chloro group does not consistently improve the performance of these analogs in both assay systems. Phenylamide **12** and phenylsulfonamide **13** derivatives are less active than **11** versus the enzyme and parasite. Whereas utilization of polar moieties was not tolerated, proper placement of hydrophobic functionality off the phenyl ring of **11** generally afforded more potent anti-parasitic compounds while leading to reduced enzyme inhibition. For example, the 2-naphthyl derivative **17** exhibits EC_{50} values of 210 and 140 nM against the two parasite strains, while the 5-(2,3-dihydrobenzofuranyl) analog **18** displays EC_{50} values of 180 and 110 nM against 3D7 and Dd2. Compound **18** exhibits the most potent activity against Dd2 in the 2′-substituted class.

Analogs of **6** and **14**, containing a *p*-chlorobenzyl-2′-aminomethyl substituent, were investigated further and the biological data are shown in Table 4. The importance of the phenol is underscored by the observation that anisole **19** is much less potent than phenol **6** against both the enzyme and parasite. Comparison of the data for **6** and **14** shows that alteration of the 4′-substituent from hydrogen to chloride confers slightly more potency against PfENR, while not significantly affecting anti-parasitic activity. Interestingly, α,α-dimethylation of the 2′-benzylic carbon (cf. **20**) slightly reduces the parasite potency, while having no effect in the enzyme assay. N-methylation (cf. **21**) leads to a slight gain in the parasite assay and a loss in enzyme inhibition. The combination of these two structural alterations in **22** leads to increased anti-parasitic potency against the 3D7 strain but not the Dd2 strain, with a slight loss in enzyme activity. **22** exhibits the most potent activity in the 2′-substituted chemotype against the 3D7 strain of parasite (EC_{50} = 140 nM). N-acetylation to afford **23** produces losses in efficacy in both assay systems.

In light of the enhanced anti-parasitic activity of **21** due to its N-methylation, a series of 2′-*N*-methylamines was synthesized and evaluated in both screening assays (Table 5). Mono- and dimethylamino analogs **24** and **25** show enhanced activity compared to that of parent amino **4** in both assays. The two *N*-methyl substituents were next constrained in a ring system. Cyclic analogs (**26**–**27**) display slight losses in parasite activity and are inactive against PfENR. The N4-substituent of piperazines **28**–**30** modulates potency against both cultured parasites

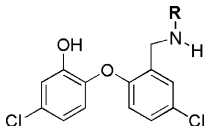
Table 2. Effect of secondary amine substituent with 4′-hydrogen

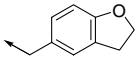


Compound	R	EC_{50}[a] 3D7/Dd2 (μM)	PfENR IC_{50}[a] (μM)
3	H	9.7 ± 1.5/7.2 ± 0.8	>50
5	CH_2Ph	0.49 ± 0.02/0.42 ± 0.03	10 ± 3
6	$CH_2(p\text{-}ClC_6H_4)$	0.33 ± 0.04/0.30 ± 0.04	35 ± 4
7	$(CH_2)_2Ph$	0.78 ± 0.05/0.75 ± 0.07	2.5 ± 0.9
8	$(CH_2)_3Ph$	0.32 ± 0.08/0.39 ± 0.08	19 ± 5
9	1-Naphthyl	0.30 ± 0.02/0.37 ± 0.07	11 ± 4
10	2-Naphthyl	0.45 ± 0.05/0.33 ± 0.09	46 ± 14

[a] Values reported as means ± standard error.

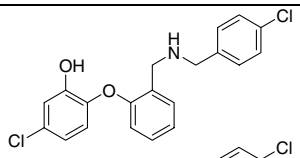
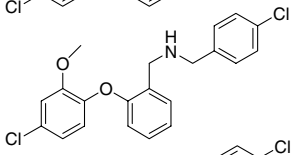
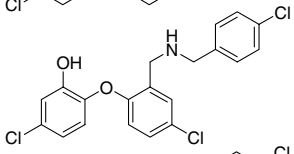
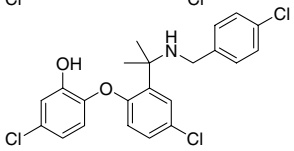
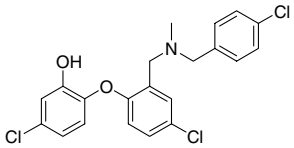
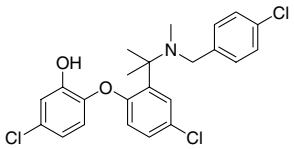
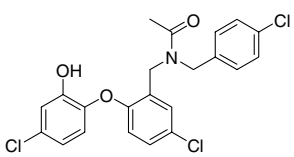
Table 3. Effect of secondary amine substituent with 4′-chloride



Compound	R	EC_{50}[a] 3D7/Dd2 (μM)	PfENR[a] IC_{50} (μM)
4	H	2.7 ± 0.1/2.0 ± 0.5	>50
11	CH_2Ph	0.77 ± 0.05/0.83 ± 0.01	3.3 ± 1.5
12	C(O)Ph	8.6 ± 1.8/12 ± 1	18 ± 8
13	SO_2Ph	11 ± 1/17 ± 1	15 ± 7
14	$CH_2(p\text{-}ClC_6H_4)$	0.32 ± 0.08/0.27 ± 0.10	7.2 ± 1.4
15	$CH_2(p\text{-}PhC_6H_4)$	0.23 ± 0.06/0.15 ± 0.04	35 ± 15
16	1-Naphthyl	2.6 ± 0.1/2.2 ± 0.1	>50
17	2-Naphthyl	0.21 ± 0.06/0.14 ± 0.03	26 ± 7
18		0.18 ± 0.03/0.11 ± 0.01	9 ± 3

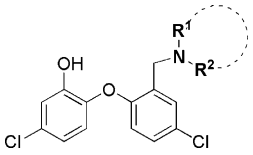
[a] Values reported as means ± standard error.

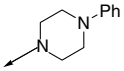
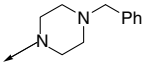
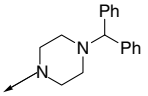
Table 4. Inhibitory properties of *p*-Cl-benzylamine derivatives

Compound	Chemical structure	EC_{50}[a] 3D7/Dd2 (μM)	PfENR[a] IC_{50} (μM)
6		0.33 ± 0.04/0.30 ± 0.04	35 ± 4
19		19 ± 2/24 ± 1	>50
14		0.32 ± 0.08/0.27 ± 0.10	7.2 ± 1.4
20		0.41 ± 0.03/0.35 ± 0.02	7.2 ± 1.6
21		0.25 ± 0.06/0.19 ± 0.03	22 ± 2
22		0.14 ± 0.01/ 0.38 ± 0.02	27 ± 4
23		3.5 ± 0.2/5.9 ± 0.1	28 ± 3

[a] Values reported as means ± standard error.

Table 5. Inhibitory properties of selected amines



Compound	NR^1R^2	EC_{50}[a] 3D7/Dd2 (μM)	PfENR[a] IC_{50} (μM)
24	N(H)Me	0.58 ± 0.09/0.47 ± 0.13	27 ± 9
25	NMe_2	0.18 ± 0.01/0.22 ± 0.01	19 ± 5
26		0.50 ± 0.03/0.45 ± 0.03	>50
27		0.73 ± 0.21/0.48 ± 0.26	>50
28		14 ± 2/15 ± 3	6.1 ± 1.0
29		0.63 ± 0.05/0.62 ± 0.03	11 ± 2
30		2.1 ± 0.1/1.4 ± 0.1	>50

[a] Values reported as mean ± standard error.

and purified enzyme. Compared to piperidine **27**, significant gains in enzymatic potency against the enzyme are realized with **28** (IC_{50} = 6.1 μM). The corresponding anti-parasitic activities of these piperazines do not improve significantly upon that of **27**.

In conclusion, a series of 2′-substituted triclosan derivatives has been prepared and assayed for inhibition of PfENR and intracellular parasite growth. The effort provided a number of compounds that are significantly more potent than triclosan against the cultured parasites. 5-(2,3-dihydrobenzofuranyl) analog **18** was 16 and 34 times more active than triclosan against the 3D7 and Dd2 strains, respectively. Methylated analog **22** displayed anti-parasitic efficacy 21 and 10 times greater than triclosan against 3D7 and Dd2, respectively. Studies are now required to assess whether these compounds are cytotoxic or cytostatic. Preliminary indications that this compound class is cytotoxic come from the study of Waller et al.,[9] who exposed synchronized parasites at different stages to triclosan for 16 h periods. With ring stage parasites, susceptibility to triclosan was similar to that observed when parasites were exposed for the full 48 h of intracellular development, suggesting that the drug action was toxic and not static. Nevertheless, further experiments are required to rigorously address this, including 'washout' experiments and these will be performed with the more potent compounds from the triclosan series.

Given the micromolar activity of these and other 2′-analogs versus purified PfENR, it appears reasonable to suggest the possibility of off-target activity. Future efforts will seek to define the mode of action of these potent antimalarials while further optimizing their activity. These include studies on whether PfENR is the primary target (indeed, it may very well not be the intracellular target for these compounds) and parallel genetic investigations to assess whether this target is essential. This will be done in conjunction with probing other positions along the diaryl ether scaffold of triclosan.

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