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Synthesis, Antimalarial Activity, and Structure–Activity Relationship of 7-(2-Phenoxyethoxy)-4(1*H*)-quinolones

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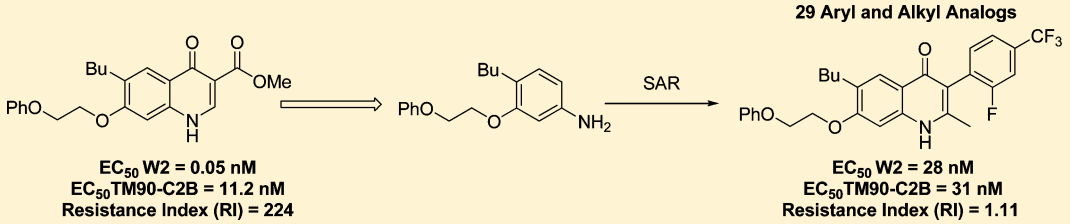
Supporting Information



ABSTRACT: ICI 56,780 (**5**) displayed causal prophylactic and blood schizonticidal activity (ED_{50} = 0.05 mg/kg) in rodent malaria models but produced rapid acquisition of parasitological resistance in *P. berghei* infected mice. Herein we describe the synthesis of analogues of **5** with EC_{50} as low as 0.15 nM against multidrug resistant *P. falciparum*. Optimal activity with low cross-resistance indexes (RI) to atovaquone was achieved by introducing ortho-substituted aryl moieties at the 3-position of the 7-(2-phenoxyethoxy)-4(1*H*)-quinolone core.

INTRODUCTION

Malaria is among the most significant public health problems in the world. The disease occurs in tropical and subtropical climates and affects over 243 million people annually while claiming nearly one million lives in 2009.[2,3] *P. falciparum* and *P. vivax* are the two most prevalent species responsible for causing disease in humans.[4] The development of curative antimalarial agents is difficult because of the various developmental stages of the parasite within the host. Following inoculation of sporozoites by an infected female Anopheles mosquito, the parasite must first undergo a proliferation period within the liver before the pathogenic infection of red blood cells ensues. The most effective drug for liver stage infections is primaquine, an 8-aminoquinoline that acts on actively growing liver stages and on the dormant forms known as hypnozoites. Hypnozoites of *P. vivax* can lay dormant in a host for weeks to years and upon reactivation cause a relapse. Discovery and development of drugs active against hypnozoites are limited by the lack of reliable high or medium throughput assays.[5] In 2007 the Bill and Melinda Gates Foundation set an agenda for the elimination of malaria.[2] Before this lofty goal can be achieved, new drugs are required that are safe and effective against liver and blood stage parasites simultaneously within the same host.

An additional difficulty for malaria drug development is the rapid emergence of multidrug resistance. Many of the common antimalarials such as atovaquone, chloroquine, and more recently the artemisinin combination therapies (ACTs) have suffered from parasitological resistance being developed in many regions of the world, especially in Southeast Asia.[6] Advances in drug discovery such as high-throughput screening, physicochemical property assessment, synthetic methodologies, and improved in vivo efficacy protocols have allowed for re-examining old chemotypes or hits and for optimizing them to a more appropriate lead clinical candidate.[7−12] Recently, endochin (**1**), a 4(1*H*)-quinolone, and its related tetrahydroacridone analogue (THA) floxacrine (**2**) were successfully optimized for antimalarial activity by substituting various benzenoid ring features and aryl moieties (**3** and **4**) while simultaneously assessing the physicochemical properties (Figure 1).[9,10] Another such example is the 4(1*H*)-quinolone ester ICI 56,780 (**5**), which was found in 1970 to have antimalarial activity by Ryley and Peters (Figure 1).[1] This compound possesses blood schizontocidal activity against *P. berghei* and prophylactic activity against *P. cynomolgi* sporozoite challenge assays. It was shown that rhesus monkeys inoculated intravenously with *P. cynomologi* sporozoites and subsequently treated with **5** for 7 consecutive days had no relapse after 120 days of exposure, confirming potency against hypnozoites.[13] Compound **5** was found to be curative at 15 mg/kg. Unfortunately, rapid selection of resistance was obtained after one passage in *P. berghei* infected mice, leading to an abandonment of the compound.[1]

The in vivo antirelapse activity in combination with the excellent blood stage activity of **5** shows great promise in developing a viable multistage antimalarial agent.[1,13]A related set of 4-oxo-3-carboxyl analogues (**6**) were recently developed

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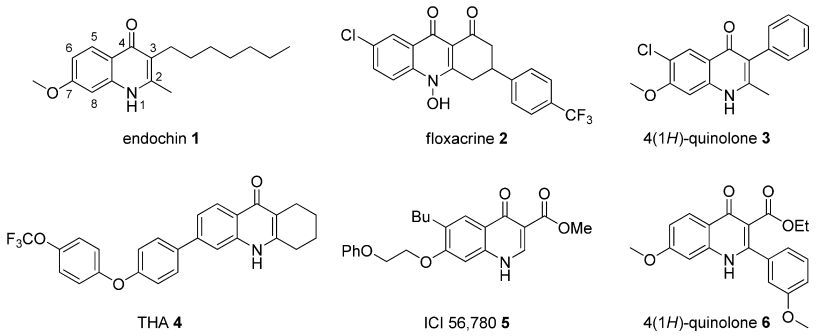
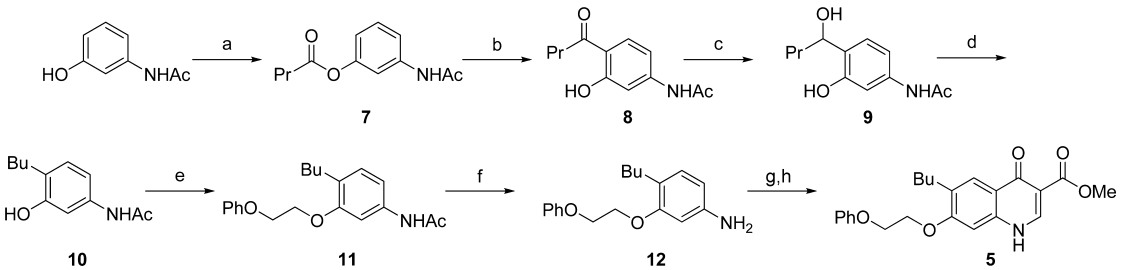


Figure 1. Structures of historic and modern antimalarial compounds **1**–**6**.

Scheme 1. Synthesis of the PEQ 5 via Key Intermediate Aniline 11[a]



[a]Reaction conditions: (a) butyryl chloride, pyr, rt; (b) $AlCl_3$, 150–175 °C 45 min, then 3 h; (c) $NaBH_4$, THF anhyd, 0 °C; (d) AcOH, 10% Pd/C, 60 psi, 36 h; (e) NaH, DMF, 30 min, then (2-bromoethoxy)benzene, 3 h; (f) KOH (14 equiv), EtOH/H_2O (9:1), reflux, 4 h; (g) dimethyl 2-(methoxymethylene)malonate, EtOH, reflux; (h) Ph_2O, reflux, 12 min.

by using a parallel approach of SAR and pharmacologic characterization to design quinolones that were less prone to cross-resistance with atovaquone.[12] Given the sparse number of chemotypes with proven antirelapse activity, we have explored the 7-(2-phenoxyethoxy)-4(1*H*)-quinolones (PEQs) scaffold to optimize SPR and blood stage antimalarial activity. Since the rapid induction of resistance reported in *P. berghei* was likely due to cytochrome b mutations, we also optimized the scaffold for potency against clinically relevant atovaquone resistant *P. falciparum*.

RESULTS AND DISCUSSION

Synthetic Chemistry. Compound **5** was first synthesized to obtain preliminary data on the PEQ scaffold. This compound was patented in 1968 by Bowie as an antimalarial[14] and in 1970 reported to have coccidiostatic activity by Mizzoni et al.[15] The goal was to prepare more than 100 g of the intermediate aniline **12** to funnel into Conrad–Limpach reaction sequences to generate analogues of **5**. Iodination of a PEQ scaffold to prepare 3-aryl analogues would be achieved using our recently developed protocol.[16] Furthermore, aniline precursors would be used in several iterative sequences to prepare structurally diverse analogues in the 6- and 7-positions.

The route to generate **5** began with 450 g of commercially available *N*-(3-hydroxyphenyl)acetamide that was transformed to **7** with butyryl chloride in pyridine (Scheme 1). Next a Fries rearrangement was employed to arrive at **8** using $AlCl_3$. Compound **8** was directly reduced to the butyl analogue **10** in the original report; however, without access to a large-scale 500 psi hydrogenation apparatus and with the reaction failing to work at 75 psi, an alternative route was employed.[15] Conjugated ketones are much more stable to hydrogenolysis compared to a benzylic alcohol.[17] Therefore, **8** was reduced using $NaBH_4$ to obtain benzylic alcohol **9** in moderate yield and high purity. Compound **9** was now much more prone to hydrogenolysis compared to the conjugated ketone **8**, and the hydrogenation in acetic acid at 60 psi occurred relatively smoothly to yield **10**. Compound **11** was prepared through a simple alkylation using (2-bromoethoxy)benzene in high yield. The key aniline intermediate **12** was prepared via hydrolysis of the acetamido moiety in **11**. Finally, **5** was synthesized in a two-step Gould–Jacobs sequence from **12**.[18] The compound was isolated via precipitation; however, the resulting material was not pure enough for accurate in vitro and in vivo tests. The solid was recrystallized in DMF/methanol (4:1).

Starting from aniline **13**, prepared as in a previous report, a 6-chloro-7-methoxy-4(1*H*)-quinolone bearing the *β*-dicarbonyl moiety (**14**) was synthesized using 1-ethyl 3-methyl 2-acetylmalonate.[9] A subset of **5** was prepared to determine the necessity of the methyl 3-benzoate substituent (Scheme 2, Table 1). The placement of a proton or ethyl group in the 3-postion compared to a methyl 3-benzoate substituent would determine the importance of the *β*-dicarbonyl motif present in **5**. Compound **12** was subjected to Conrad–Limpach conditions using two different 2-substituted *β*-ketoesters to generate **15** and **16**.

Next, a set of 3-ethyl-4(1*H*)-quinolones substituted at the 6- or 7-position were prepared. In contrast, the 3-benzoate 4(1*H*)-quinolones were not prepared to avoid structural overlap with antimicrobial *β*-dicarbonyl containing quinolones,[19] which have been shown to possess weak intrinsic potency as antimalarials.[20] The 6- or 7-substitution contained various solubilizing groups with different linker lengths. Starting from 5-amino-2-chlorophenol, 4(1*H*)-quinolones **17**–**24** were prepared (Scheme 2, Table 1). N-Acylation of 5-amino-2-substituted phenols produced an intermediate acetamide, which could be alkylated using various alkyl halides. These intermediates were then hydrolyzed using KOH to arrive at the necessary anilines. The anilines were then cyclized using 2-

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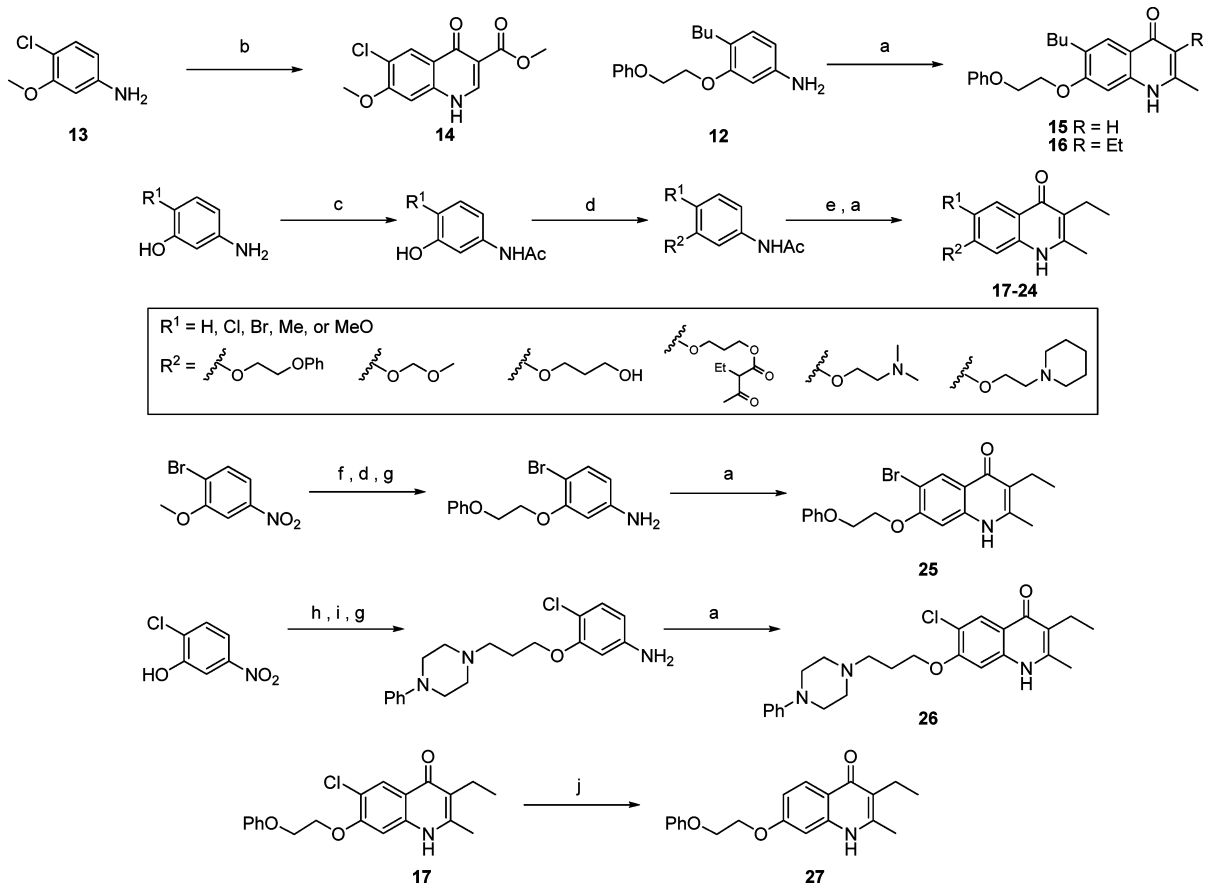
Scheme 2. Synthesis of 4(1*H*)-Quinolones 13−27[a]



[a](a) Ethyl acetoacetate or 2-ethyl acetoacetate, AcOH, benzene, Dean−Stark trap, reflux, overnight, then Ph_2O, reflux, 15 min; (b) 1-ethyl 3-methyl-2-acetylmalonate, AcOH, benzene, Dean−Stark trap, reflux, overnight, then Ph_2O, reflux, 15 min; (c) Ac_2O, AcOH; (d) corresponding alkyl halide, Cs_2CO_3, DMF, 4−8 h; (e) KOH, EtOH/H_2O (9:1), reflux; (f) BBr_3; (g) Zn, AcOH, rt, 4 h; (h) 1,3-dibromopropane, Cs_2CO_3, rt; (i) *N*-phenylpiperazine, K_2CO_3, DMF, rt; (j) $Pd_2(dba)_3$, SPHOS, K_3PO_4, DMF, mesitylboronic acid, 130 °C.

ethyl-*β*-ketoester to yield the corresponding 4(1*H*)-quinolones **17**−**24** (Scheme 2). An alternative route was used to prepare **25**−**27** utilizing a commercially available disubstituted nitro precursor (Scheme 2). Compound **26** was initially synthesized via an acetamide intermediate as in Scheme 2 (**17**−**24**). Unfortunately, usage of 1,3-dibromopropane (condition h) led to inseparable mixtures of the aniline required to prepare **26** and an *O*-allyl side product generated from elimination using Cs_2CO_3. Employment of 2-chloro-5-nitrophenol as the starting material led to overall improved yields and easier separation of elimination side products. The synthesis of **27** was initially attempted starting from **17** using several standard Pd hydrogenation conditions; however, a mixture consisting of **27** and a 4(1*H*)-quinolone product containing a partially reduced benzenoid ring was obtained. Previously, we observed that cross-couplings of 3-halo-4(1*H*)-quinolone with mesitylboronic acid yield mainly the protodehalogenated 4(1*H*)-quinolone.[16] On the basis of these findings, **17** was heated in a Schlenk tube for 36 h with several additions of mesitylboronic acid until the chlorine was all consumed generating **27** in high yield.

A small library of 3-aryl PEQs **31**−**44** was prepared by cyclizing aniline **12** using a Conrad−Limpach protocol followed by a regioselective iodination to generate 4(1*H*)-quinolone **28** (Scheme 3, Table 1), which was subjected to Suzuki−Miyaura cross-coupling conditions. The 3-halo-4(1*H*)-quinolone core can tolerate couplings with or without alkyl protection; however, depending on the nature of the boronic acid used, better yields are achieved starting from alkylated quinolones.[16] Therefore, using *O*-methyl or *O*-ethyl-3-iodo-quinoline **29** or **30**, the coupling could be employed successfully followed by chemoselective dealkylation using HBr in refluxing acetic acid.[21,22] Note that this dealkylation is a time sensitive reaction and unwanted bromination or dealkylations may occur depending on the substituents of the 6- or 7-position. For example, when the 7-(2-phenoxyethoxy) group is present, a bromine replaces the phenoxy moiety when the reaction is left to reflux too long. A variety of boronic acids including ones containing an ortho substituent were utilized to generate 3-arylquinolones.

Antimalarial Activity and Cytotoxicity. All synthesized quinolones were tested as previously reported for in vitro antimalarial activity against the clinically relevant multidrug resistant malarial strains W2 (chloroquine and pyrimethamine resistant) and TM90-C2B (chloroquine, mefloquine, pyrimethamine, and atovaquone resistant) and for cytotoxicity against J774 mammalian cells.[9,23] Generally, the PEQs do not display signs of cytotoxicity at less than 20 μM, rendering cytotoxicity indices (CI = EC_{50}(J774)/EC_{50}(TM90-C2B)) of 100 or more. These results indicate that most of the PEQs are selective and nontoxic agents.

The emergence of resistance and cross-resistance with atovaquone is a concern for new antimalarials that target the parasite's mitochondria (e.g., atovaquone). For the structure−activity relationship study, the resistance index (RI), calculated as

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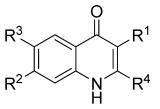
Table 1. EC_{50} of PEQ Analogues[a]



Compound	R^1	R^2	R^3	R^4	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)
5	-CO_2Me		-Bu	-H	0.05	11.2	223	46
14	-CO_2Me	-MeO	-Cl	-H	134	765	5.7	37
15	-H		-Bu	-Me	216	44.1	0.20	28
16	-Et		-Bu	-Me	1.92	0.15	0.08	1
27	-Et		-H	-Me	104	71.3	0.79	4
17	-Et		-Cl	-Me	256	72.1	0.28	>28
25	-Et		-Br	-Me	203	43.5	0.21	>25
18	-Et		-Me	-Me	255	27.7	0.11	>30
19	-Et		-MeO	-Me	184	19.5	0.11	>29
20	-Et		-Cl	-Me	908	79.7	0.09	19
21	-Et		-Cl	-Me	8450	776	0.09	N.D.
22	-Et		-Cl	-Me	6130	6130	1.0	N.D.
23	-Et		-Cl	-Me	5090	726	0.14	N.D.
24	-Et		-Cl	-Me	5050	604	0.12	N.D.
26	-Et		-Cl	-Me	976	91.7	0.09	>23

[a]Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay. DHA (1.8 nM W2 and 0.9 nM TM90-C2B), CQ (131 nM for TM90-C2B and 162 nM for W2), and ATO (0.53 nM W2 and >170 nM TM90-C2B). N.D.: not determined.

the ratio of the effective concentrations for TM90-C2B and W2 (RI = EC_{50}(TM90-C2B)/EC_{50}(W2)), was also taken into account.[9] Compounds with RI = 0.3−3.0 are considered acceptable in regards to risk of cross-resistance with atovaquone, whereas compounds with RI > 10 or RI < 0.1 are likely to have clinically relevant levels of cross-resistance with atovaquone.[24,25]

Structure−Activity Studies. First, **5** was shown to have excellent activity against W2 and TM90-C2B with EC_{50} of 0.05 and 11.17 nM, respectively (Table 1). However, the potency difference between the two strains yielding RI = 223 is a concern, as the atovaquone resistance mutations in cytochrome *b* can be rapidly selected in vivo.[24] Therefore, a small series of PEQs were designed to examine the 3-, 6-, and 7-susbtitutents of **5** to improve potency against atovaquone sensitive and resistant *P. falciparum*. Interestingly, the 6-chloro-7-methoxy analogue **14** led to a 70-fold or larger decrease in antimalarial activity for both strains, while PEQ **15** displayed a 4000-fold loss in activity for W2 compared to only a 4-fold potency decrease for TM90-C2B. Conversely, introduction of an ethyl group at the 3-position in **15** provided PEQ **16** with restored EC_{50} values of 1.92 nM against W2 and 150 pM against TM90-C2B. The potency of **16** shows a reversed preference for TM90-C2B with RI = 0.08, which stands in sharp contrast to **5** that inhibits W2 approximately 220-fold more than TM90-C2B. This result led us to prepare a series of 6- and 7-substituted 2-methyl-4(1*H*)-quinolones containing an ethyl group in the 3-position.

First, a subset was prepared to probe the role of the 6-butyl group of **16**. Complete removal of the butyl group generated compound **27** with EC_{50} of 104 and 71.3 nM against W2 and TM90-C2B, respectively. In comparison to **27**, 6-chloro- or 6-bromo-substituted PEQs **17** and **25** displayed slightly reduced activities against W2, while their potencies for TM90-C2B were unaffected or slightly improved. PEQs **18** and **19** substituted with a methyl or a methoxy group in the 6-position were also shown to be less active against W2, but ∼3-fold more potent against TM90-C2B compared to **27**. Next, a

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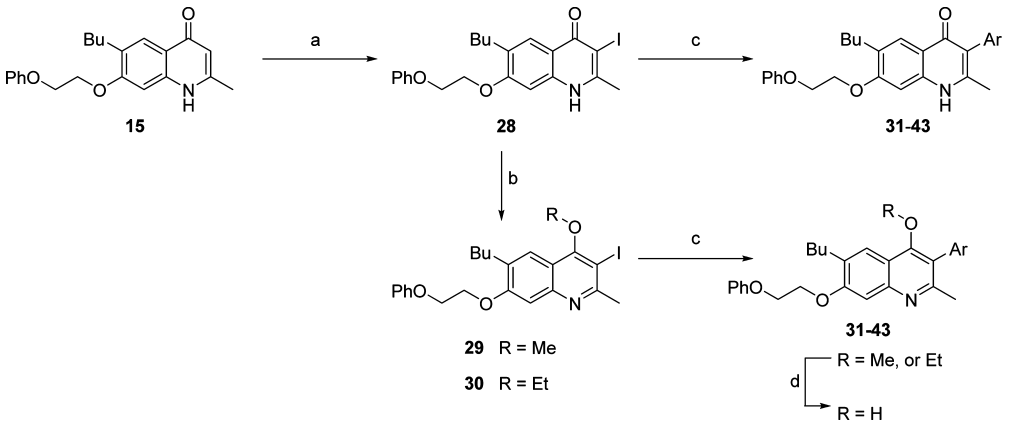
Scheme 3. Synthesis of 3-Aryl PEQs[a]

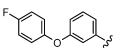
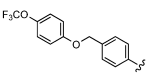
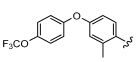


[a]Reaction conditions: (a) KI (20% aq), I_2, 2 M NaOH, MeOH, rt, 2 h; (b) Cs_2CO_3, DMF, EtI/MeI, 0 °C to rt, 5 h; (c) $Pd_2(dba)_3$, SPHOS, K_3PO_4, DMF, $ArB(OH)_2$, 110 °C or $Pd(PPh_3)_4$, 2 M Na_2CO_3, DMF, $ArB(OH)_2$, 110 °C (MW); (d) HBr/AcOH, reflux 1−2 h.

subset of 2-methyl-3-ethyl-6-chloro-substituted PEQs **20**−**26** were examined, in which the group at the 7-position was varied. With the exception methoxymethyl ether **20** and piperazine **26**, all others **21**−**25** were 5−30 times less active against W2 and TM90-C2B in comparison to their reference compound **17**. PEQs **20** and **26** were similar to **17** in potency against TM90-C2B and ∼4-fold less active against W2. These results indicate that the 7-(2-phenoxyethoxy) moiety greatly affects antimalarial activity and that the 3-ethyl-susbtituted PEQs display more favorable RI values in comparison to methyl carboxylate **5**.

While retaining the 6-butyl-7-(2-phenoxyethoxy) moiety, a small series of 3-aryl analogues (**31**−**43**) was prepared and tested against W2 and TM90-C2B (Table 2). Generally, PEQs **38**−**43** containing an ortho-substituted aromatic ring in the 3-position were approximately 10-fold more potent compared to the 3-aryl-substituted analogues **31**−**37**. Ortho-substituted 3-aryl analogues **38**−**43** were also more potent against the W2 strain, whereas the 3-aryl PEQs **31**−**37** were more potent against TM90-C2B. Initially, the 3-phenyl analogue **31** was prepared, which displayed poor EC_{50} of 1072 nM against W2 and 764 nM against TM90-C2B. Next, 3-*p*- and 3-*m*-pyridyl analogues **32** and **33** were shown to have moderate activity in low micromolar or high nanomolar range. Trifluoromethylphenyl and trifluoromethoxyphenyl substituted PEQs **34** and **35** were similar to **32** and **33** in activity. The biaryl and benzylaryl analogues **36** and **37** were inactive. Of the ortho-substituted 3-aryl analogues **38**, **40**, and **42** were the least promising with high EC_{50} against one or both strains, rendering poor RI values. Fluorotrifluoromethylphenyl-substituted PEQ **41** displayed the best antimalarial activities with EC_{50} of 27.9 and 31.0 nM against W2 and TM90-C2B, yielding RI = 1.1. Interestingly, analogue **43** substituted with 3,5-dimethylisoxazolyl in the 3-position was also very potent against W2 with an EC_{50} of 27.0 nM and approximately 5 times less potent against TM90-C2B. Overall, though the 3-aryl series was less potent compared to **5**, several analogues such as fluorotrifluoromethylphenyl-substituted PEQ **41** or isoxazole **43** showed promise in terms of antimalarial activity and acceptable RI value. These findings are similar to our endochin optimization studies, in which the aryl substituent of a different 4(1*H*)-quinolone pharmacophore has been shown to be the best suited for the development of a lead devoid of cross-resistance with atovaquone.[9] Although these new PEQ analogues show promise, additional studies will be required to assess their potential for rapid resistance selection which has been a concern for several cytochrome *b* inhibitors. Additional studies also are required to determine if the improved PEQs maintain the potent activity against liver stages as the lead **5**.

Table 2. EC_{50} of 3-Aryl PEQs[a]

Compound	Ar	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)
31		1070	764	0.71	23
32		3150	1016	0.32	23
33		1350	588	0.44	23
34		509	2450	4.82	20
35		3220	2510	0.78	20
36		1390	1002	0.72	19
37		4050	4050	1.00	16
38		58.5	475	8.12	16
39		71.8	140	1.95	20
40		907	1630	1.79	22
41		27.9	30.9	1.11	19
42		68.7	542	7.89	>21
43		27.0	128	4.73	22

[a]Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay. DHA (1.8 nM W2 and 0.9 nM TM90-C2B), CQ (131 nM W2 and 162 nM TM90-C2B), and ATO (0.53 nM W2 and >170 nM TM90-C2B).

CONCLUSIONS

A series of 29 novel PEQ analogues with varying substitution at the 2-, 3-, 6-, and 7-positions were synthesized and assessed for

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antimalarial activity against the clinically relevant strains TM90-C2B and W2, with the objective to improve SAR and reduce cross-resistance with atovaquone. The most potent antimalarial activities were obtained when the 3-position contained an ethyl group or a fluoroaryl moiety. With the exception of compound **5**, most of the PEQ analogues lacking the 7-(2-phenoxyethoxy) substituent showed significant differences in EC_{50} against the two strains, providing unfavorable RIs. For 3-ethyl-substituted PEQs, the best activities and RI values were obtained with compounds containing a 2-phenoxyethoxy moiety in the 7-position, whereas the group in the 6-position produced the activity order Bu ≫ MeO > Me > Br > Cl > H for TM90-C2B and Bu > H > MeO > Br > Me > Cl for W2, providing a strain preference that had minor dependence on the moiety in 6-position. Similarly, 3-aryl-substituted PEQs displaying good potencies against both strains and acceptable RIs contained the butyl in the 6-position and the 2-phenoxyethoxy group in the 7-position. Best activities and acceptable RIs were obtained with PEQs **41** and **43** containing in the 3-position an ortho-substituted aromatic ring such as a fluorotrifluoromethylphenyl or a 3,5-dimethylisoxazolyl.

In summary the 3-aryl or 3-ethyl-substituted PEQs (e.g., **14**, **41**, and **43**) are less potent against W2 and TM90-C2B than compound **5**. Nevertheless these compounds have been improved significantly by reducing cross-resistance in the clinically relevant atovaquone resistant TM90-C2B parasite. Our data therefore suggest that these compounds have potential for further optimization to identify PEQs optimal for in vivo liver stage and blood stage efficacy studies.

EXPERIMENTAL SECTION

Compounds were prepared using general procedures A–J (see Supporting Information). The purity of each compound that was synthesized and tested for antimalarial activity was ≥95% via HPLC analysis.

ASSOCIATED CONTENT

Supporting Information

Details of the synthesis of **7**–**43**; all general procedures; ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR characterizations for all tested compounds; and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS USED

EC_{50}, half-maximal effective concentration; ACT, artemisinin combination therapy; WRAIR, Walter Reed Army Institute of Research; SAR, structure–activity relationship; SPR, structure–property relationship; SPHOS, dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine; DCM, dichloromethane; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium(0); Ph, phenyl; DMF, *N*,*N*-dimethylformamide; RPMI, Roswell Park Memorial Institute; RI, resistance index; Ac, acetyl; rt, room temperature; CI, cytotoxicity index; MW, microwave; ED_{50}, half-maximal effective dose; PEQ, 7-(2-phenoxyethoxy)-4(1*H*)-quinolones

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