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1,4-Naphthoquinone Cations as Antiplasmodial Agents: Hydroxy-, Acyloxy-, and Alkoxy-Substituted Analogues

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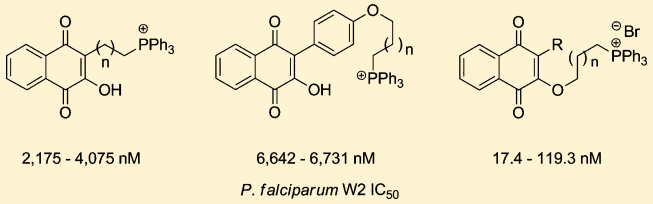
Supporting Information

ABSTRACT: Cations of hydroxy-substituted 1,4-naphthoquinones were synthesized and evaluated as antiplasmodial agents against *Plasmodium falciparum*. The atovaquone analogues were found to be inactive as antagonists of parasite growth, which was attributed to ionization of the acidic hydroxyl moiety. Upon modification to an alkoxy substituent, the antiplasmodial activity was restored in the sub-100 nM range. Optimal inhibitors were found to possess IC_{50} values of 17.4−49.5 nM against heteroresistant *P. falciparum* W2.

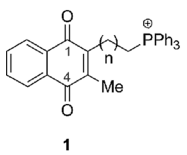


KEYWORDS: *malaria, Plasmodium, 1,4-naphthoquinones, phosphonium cations*

Malaria, particularly that caused by *Plasmodium falciparum*, remains one of the most important infectious diseases in the world.[1,2] As malaria control is seriously limited by resistance to most available drugs,[3−5] it is critical that new chemotherapeutics are developed to replace those now limited by drug resistance (e.g., chloroquine and antifolates) and toxicity (e.g., primaquine, amodiaquine, and mefloquine). Antimalarials that inhibit mitochondrial function such as atovaquone (ATV), which is available as a component of Malarone (ATV/proguanil), have particular clinical importance[6−8] due to their ability to eradicate both liver and blood stages of the malarial parasite. Structural features common to ATV and related inhibitors are lipophilic substituents,[9] which aid in permeability in the mitochondrial matrix membranes where the electron transport complexes are embedded. As a consequence, the physiochemical properties conferred by the hydrophobic groups have detrimental effects on the pharmacokinetic parameters, presenting a significant challenge in the development of mitochondrion-acting treatments of malaria.

Recently, we reported a new class of 1,4-naphthoquinone-based antiparasitic agents believed to be mitochondriotropic antagonists of electron transport.[10] The inhibitory capacity of the compounds is thought to be conferred by a phosphonium group that facilitates passive transport of the lipophilic cations across plasma membranes into the energized plasmodial mitochondria. Electrostatic attraction[11] is rationalized as the driving force for directed movement into the mitochondrion where the antagonists localize until the membrane potential collapses. This drug design strategy to enhance intracellular bioavailability is the subject of current investigations for improving the in vivo performance of antimalarials that target the *Plasmodium* mitochondrion.

The most potent of the identified antiplasmodial cations are 4- and 5-hydrocarbon analogues of vitamin K, **1a** and **1b** (Figure 1). The 1,4-naphthoquinone platform from which the



	n	*Pf* W2 IC_{50} (nM)
1a	3	18.7
1b	4	48.3
1c	9	143.4
2	8	>10,000

Figure 1. Antiplasmodial activities of naphthoquinone-based phosphonium cations against chloroquine-resistant *P. falciparum* W2.[10]

inhibitors were constructed is found in many known antagonists of *Plasmodium* ubiquinone[9,12] including ATV. The binding site of ATV and related naphthoquinone-based inhibitors is the cytochrome bc_1 complex, which has been demonstrated in yeast to be mediated by the C-2 hydroxyl of the quinone ring.[13] The significance of this alcohol as a H-donor in ATV and on antiplasmodial activity gave reason to examine 1,4-naphthoquinone cations containing a C-2 hydroxyl. Moreover, if the compounds possess potency similar to ATV against cultured *P. falciparum*, this result will provide evidence that the cations are acting on the bc_1 complex. On this basis, we set forth to evaluate phosphonium cations of 2-hydroxy 1,4-naphthoquinone, which demonstrated unexpected

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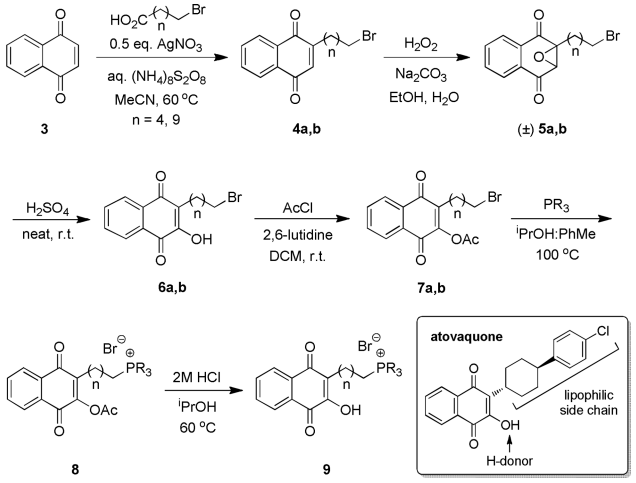
antiplasmodial activities that led to the investigations of O-linked acyloxy and alkoxy derivatives of quinone **1**.

The synthetic plan to prepare hydroxyl analogues of naphthoquinone **1** involved first the installation of a *n*-bromoalkyl side chain to which the phosphonium substituent will subsequently be bound. The hydrocarbon linker was attached by the Kochi–Anderson radical decarboxylation procedure[14,15] using 1,4-naphthoquinone **3** as the base material (Scheme 1). The alkylated product **4** was then oxidized to

Scheme 1. Synthesis of 2-Hydroxy 1,4-Naphthoquinone Phosphonium Cation 9 (Table 1)

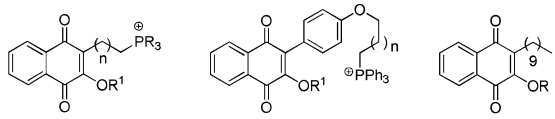


epoxide **5** and treated with sulfuric acid[16] to give the 2-hydroxy naphthoquinone **6**. Subsequent attempts to directly convert the naphthoquinone to phosphonium cations **9** were unsuccessful and resulted in the formation of complex mixtures of highly polar products. To overcome this problem, the hydroxyl was acetylated prior to the alkylation reaction with a tertiary phosphine (PR_3). The phosphonium salts **8** were successfully generated at 100 °C from the acylated quinone **7** in 3:1 ^{i}PrOH:PhMe, a solvent combination that was found to minimize thermal degradation of the products during the sluggish reaction. In the final step, acid-catalyzed hydrolysis of the acetyl group provided the desired 2-hydroxy naphthoquinone product **9** (Table 1).

For comparison, a second series of 2-hydroxy 1,4-naphthoquinone cations were synthesized with a benzene ring linking the phosphonium hydrocarbon chain to the platform (Scheme 2). The analogues were prepared from phenyliodonium ylide **11**[17] utilizing the BF_3-mediated arylation procedure developed by Spyroudis and co-workers.[18] The ylide was obtained in high yield from lawsone (**10**) and (diacetoxy)iodobenzene and then coupled with 4-(bromoalkoxy)-benzaldehydes **13** under reflux in $CHCl_3$. Acetylation of the C-2 hydroxyl followed by alkylation of PPh_3 and O-deprotection afforded the aryl-linked cations **17** (Table 1).

Determination of antiplasmodial activities was performed by assessing 50% inhibitory concentrations (IC_{50}) against chloroquine-resistant *P. falciparum* (W2 strain) according to methods previously described.[19] Surprisingly, each of the 2-hydroxy 1,4-naphthoquinone cations (**9** and **17**) possessed weak activity with IC_{50} values between 2175 and 6731 nM (Table 1). Similarly, the *O*-acetyl analogues (**8** and **16**) performed poorly as antiplasmodial agents in the medium–low micromolar range. On comparison with the uncharged controls

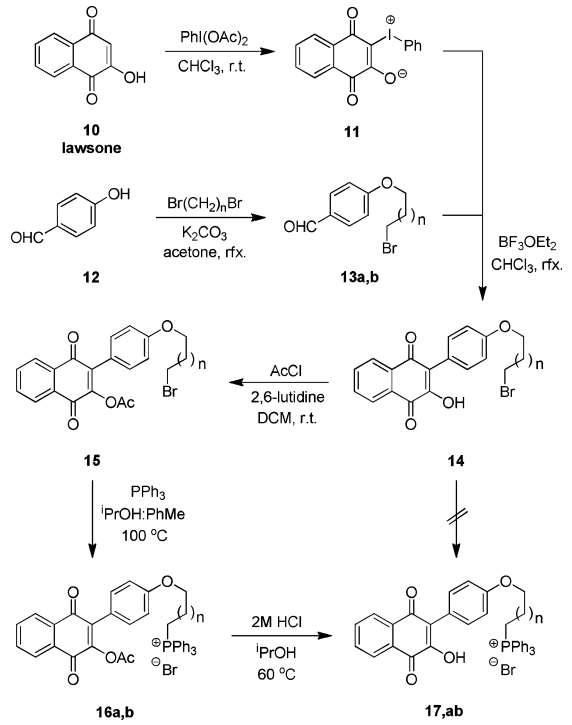
Table 1. Comparisons of IC_{50} Values for *P. falciparum* W2 Growth



8, 9 (Table 1) | **16, 17** (Table 1) | **18** (R = Ac) IC_{50} 392 nM; **19** (R = H) IC_{50} 339 nM

compd	*n*	R	R^1	IC_{50} (nM)
16a	8	Ph	Ac	7123
17a	1	Ph	H	6731
17b	8	Ph	H	6642
16b	2	Ph	Ac	5440
9a	4	Ph	H	4075
9b	9	n-Bu	H	3865
8a	9	Ph	Ac	3592
9c	9	Bn	H	3282
9d	9	Ph	H	2175
8b	4	Ph	Ac	1896
chloroquine				142.7 ± 0.8
artemisinin				18.1 ± 2.2

Scheme 2. Synthesis of 1,4-Naphthoquinone-Based Phosphonium Cations 16 and 17 (Table 1)



18 and **19** (IC_{50} 339–392 nM), it was confirmed that the phosphonium moiety had an adverse effect on the IC_{50} values. With the unexpected results that the phosphonium modification to the 2-hydroxy 1,4-naphthoquinones did not enhance the activity as previously observed for cations **1**, the possible rationale behind the reduced efficacy was investigated.

The vast majority of 2-hydroxy 1,4-naphthoquinones, including lawsone (pK_a = 3.98[20]) and phthiocol (pK_a = 5.08[21]), are weak acids that undergo ionization at physiological pH. Depending on the adjacent substituents, anion formation may result in delocalization of the negative charge over the C-2 and C-4 oxygen atoms, which can be ascertained as a

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bathochromic (red) shift in the UV−vis spectrum.[22] In the case of the phosphonium cations **7** and **17**, ionization was thought to have occurred in *Plasmodium* growth medium (pH 7.4), resulting in neutralization of the cationic charge of the inhibitors (Figure 2). The loss of charge needed to facilitate

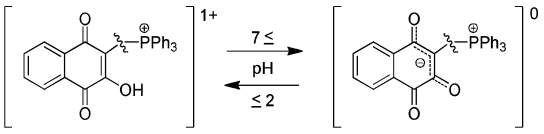


Figure 2. Ionization of naphthoquinone cations.

movement into the cell might therefore explain their lack of antiplasmodial activity. To probe if ionization occurred, UV−vis spectroscopy was employed to detect pH-dependent changes in electron delocalization levels of quinone cation **9a** and its methyl analogue **1b**.

On comparison of the UV−vis absorbance spectra of **9a** (IC_{50} = 4075 nM) in buffers ranging from pH 2 to 10, the ionization of the 2-hydroxy residue at neutral pH was confirmed (Figure 3a). Under acidic conditions (pH 2), the

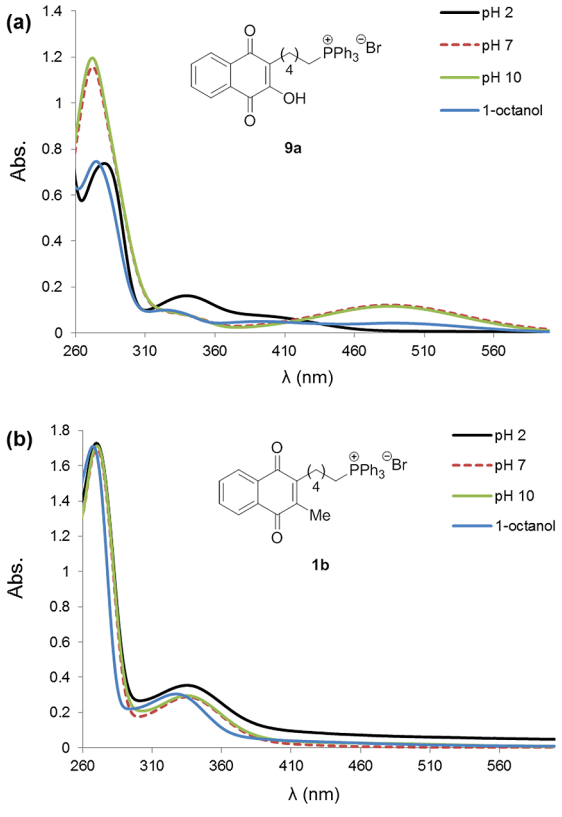


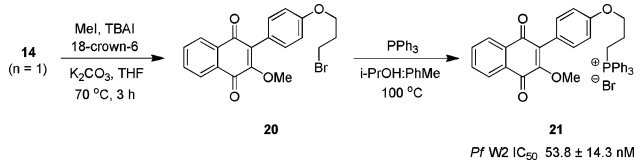
Figure 3. UV−vis absorption spectra of phosphonium cations **9a** and **1b** in 1-octanol and acidic−basic phosphate buffers.

quinone gave rise to quinoid transition bands centered at 280 and 335 nm for benzenoid.[22] When contrasted with the spectra obtained in neutral and basic pH buffers, the quinoid bands were repositioned at 270 nM and as a broad emission peak at 485 nm. Similar results, albeit of lesser intensity, were observed in 1-octanol, a medium that mimics the physiochemical properties of biological membranes.

The quinoid absorbance at the higher λ represents an increase in π electron delocalization.[23] This was attributed to ionization of the hydroxy group and distribution of the resulting anionic charge into the quinone. The nearly identical emission spectra for quinone **9a** at pH 7 and 10 was evidence that the deprotonated form exists in cells and the physiological environment. The cationic feature, which is believed to direct the molecules to the mitochondrion, would thereby be suppressed by the ionization, rendering the compounds inactive. As further confirmation of the pH-dependent change in the ionization state of hydroxy-substituted analogues, the UV−vis absorbance spectra of the C-2 methyl analogue **1b** were compared, and little variability in pH 2−10 buffers was observed (Figure 3b).

On the basis of these results, it is concluded that in order for the naphthoquinone cations to function as growth antagonists, an acidic moiety cannot be present in the molecule. To test this hypothesis, the 2-methoxy analogue **21** of quinone cation **17a** (IC_{50} = 6731 nM) was synthesized from 2-hydroxy naphthoquinone **14** and tested against *P. falciparum* W2 (Scheme 3). As expected, potent activity was restored (IC_{50} =

Scheme 3. Synthesis of 2-Methoxy 1,4-Naphthoquinone Phosphonium Cation 21

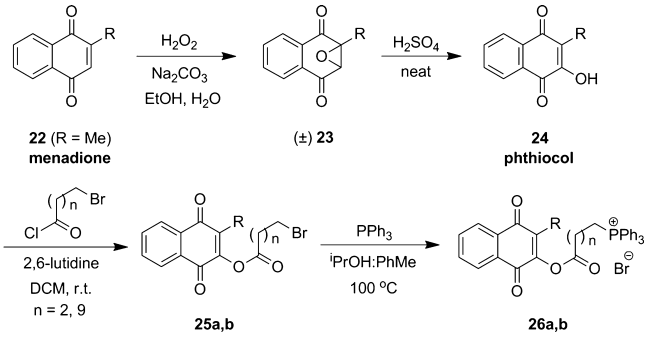


58.3 ± 14.3 nM) upon removal of the acidic hydroxy substituent on the quinone ring. With this finding, additional O-substituted quinone cations were synthesized for evaluation as antiplasmodial agents.

For the preparation of 3-acyloxy- and 2-alkoxy-linked naphthoquinone cations, methyl-1,4-naphthoquinone (menadione, **22**, Scheme 4) was used as the initial base material. Installation of the C-2 hydroxyl was achieved by acid-mediated cleavage of the corresponding menadione epoxide **23**.[16] Acylation of phthiocol (**24**) with 4-bromobutanoyl and 11-bromoundecanoyl chlorides followed by alkylation of PPh_3 afforded the 3-acyloxy-linked cation derivatives **26a** (n = 2) and **26b** (n = 9).

Both phthiocol (**24**) and lawsone (**10**) were similarly employed as base materials for the synthesis of 2-alkoxy naphthoquinone cations **28** (Scheme 5). The *n*-bromoalkyl chain linkers were attached to the quinone platform under THF reflux with K_2CO_3, 18-crown-6, and tetrabutylammonium

Scheme 4. Synthesis of 3-Acyloxy 1,4-Naphthoquinone Cations 26 (Table 2)



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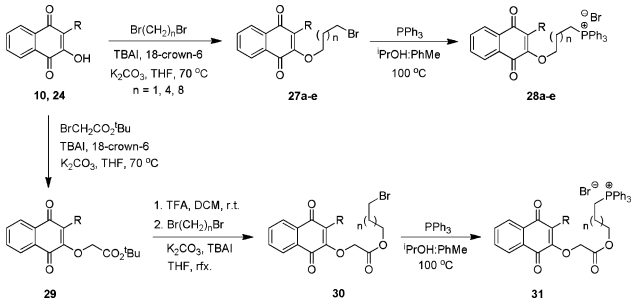
Scheme 5. Synthesis of 2-Alkoxy Naphthoquinone Phosphonium Cations 28a−e and 31 (Table 2)



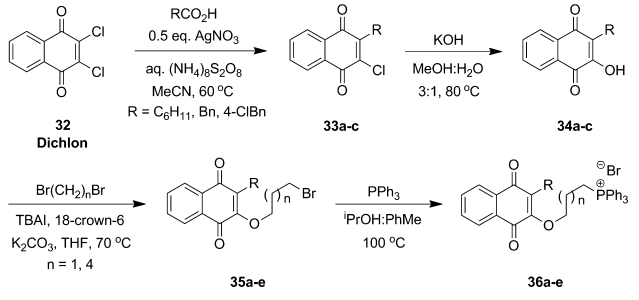
iodide (TBAI). Supplementing the reaction with two phase-transfer catalysts was found to enhance nucleophilicity of the C-2 oxygen and hinder formation of K^+-naphthoquinone chelation complex.[24] Alternatively, a *n*-bromopropyl chain was attached to phthiocol via a glycolic spacer prior to installation of a phosphonium group in quinone **30**. In the final step, the naphthoquinone cations **28a−e** (Table 2) and **31** were generated by the alkylation of PPh_3 in 3:1 ^{i}PrOH:PhMe at 100 °C.

Table 2. Comparisons of IC_{50} Values for *P. falciparum* W2 Growth

compd	*n*	R	IC_{50} (nM)
26a	2	Me	4604
26b	9	Me	1377
31	1	Me	1230
28a	8	Me	119.3 ± 11.3
28b	4	Me	42.7 ± 1.4
28c	1	Me	41.9 ± 4.0
28d	1	H	40.0 ± 0.8
28e	4	H	28.5 ± 3.0
36a	4	4-ClBn	49.5 ± 7.8
36b	4	Bn	49.1 ± 6.3
36c	4	C_6H_{11}	47.9 ± 6.3
36d	1	Bn	46.7 ± 4.4
36e	1	C_6H_{11}	42.3 ± 0.0
ATV			0.50 ± 0.2

For further comparison, additional 2-hydroxy-3-alkyl-naphthoquinones prepared from the algaecide Dichlon (**32**) were used to synthesize 2-alkoxy linked cation analogues **36** (Scheme 6). Derivatization of the C-3 position with cyclohexyl, benzyl, and 4-chlorobenzyl substituents was again achieved by radical decarboxylation.[14,15] Following methanolysis of the remaining

Scheme 6. Synthesis of 1,4-Naphthoquinone-Based Phosphonium Cations 36a−e (Table 2)

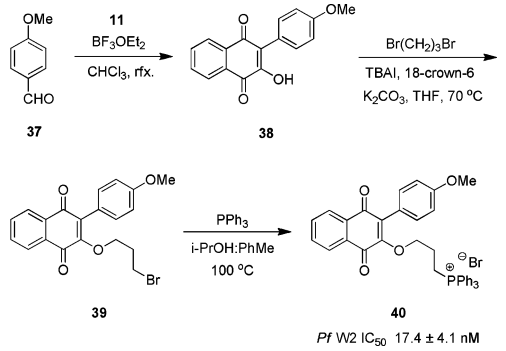


chlorine atom, the hydrocarbon linkers were attached to the C-2 hydroxyl, and the corresponding triphenylphosphonium bromides **36a−e** (Table 2) were prepared as previously described.

Antiplasmodial testing revealed that the 2-alkoxy analogues **28** and **36** possessed significantly higher activity than their 3-acyloxy counterparts **26**. The IC_{50} values of ester-linked derivatives including quinone **31** ranged from 1230 to 4604 nM, suggesting that the lipid chains with the triphenylphosphonium group bound were susceptible to intracellular hydrolysis. Conversely, the alkoxy-linked quinones (**28b−e** and **36a−e**), which would be stable to esterase degradation possessed sub-50 nM IC_{50} values. Although few correlations between structure and activity could be ascertained for these analogues, compounds with shorter alkoxy linkers appeared to be slightly more effective antagonists of parasite growth. Little variability was also observed between analogues with different C-3 substituents with the nominal exception of the lawsone-derived cation **28e** (IC_{50} = 28.5 ± 3.0 nM).

A structural feature lacking in each of the cations listed in Table 2 is a rigid substituent attached to the quinone ring. To compare the effect of restricted rotation of the C-3 residue on activity, an analogue bound with a *p*-anisyl group was synthesized (Scheme 7). Ylide **11** was once again employed

Scheme 7. Synthesis of 3-(4-Anisyl)-1,4-naphthoquinone Phosphonium Cation 40



as the base material to construct the 2-hydroxy naphthoquinone **38** via the BF_3-mediated arylation procedure.[18] Attachment of a *n*-propyl chain linker and installation of a triphenylphosphonium moiety afforded the *p*-anisyl quinone cation **40**. Subsequent antiplasmodial testing revealed that the incorporation of rigidity at C-3 resulted in nearly a 2-fold increase in activity (IC_{50} = 17.4 ± 4.1 nM) as compared with analogues **28** and **36**. An additional property of cation **40** that could be contributing to the enhanced efficacy is molecular planarity. With this finding, the correlation between planarity and antiparasitic activity of the cationic inhibitors will be a subject of future studies.

In summary, O-linked phosphonium cations of 1,4-napthoquinones were discovered to be effective growth inhibitors of cultured *P. falciparum* with IC_{50} values in the nanomolar range. The activity was greatest for quinones that did not possess an acidic functionality and were bound to the phosphonium moiety via a short hydrocarbon chain linker. Little variability in the IC_{50} values was observed for the 2-alkoxy cation analogues **28** and **36** with a H or sp^3-hybridized carbon residue bound at the C-3 position. Alternatively, when a rigid aromatic group was attached to the C-3 position of the

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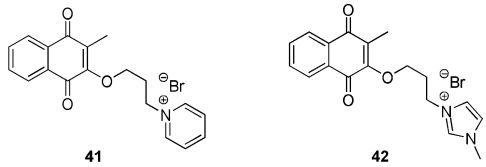
quinone, a definitive increase in inhibitory activity was observed.

Future investigations will continue to examine the effect of rigidity and planarity on activity. In addition, analogues possessing nitrogen-based cations will be evaluated as antiparasitic agents. Preliminary studies have revealed that the pyridinium (**41**) and imidazolium (**42**) derivatives of quinone **28c** demonstrate weaker antiplasmodial activity than their phosphonium counterpart (Figure 4). Although the initial



IC_{50} 167.0 ± 0.2 nM IC_{50} 164.7 ± 23.5 nM

Figure 4. Antiplasmodial activity comparisons of pyridinium and imidazolium analogues of triphenylphosphonium cation **28c** against *P. falciparum* W2.

results have shown them to be several fold less active, cationic inhibitors containing a quaternary amine may possess better pharmaceutical properties and ultimately prove to have greater in vivo efficacy than the phosphonium analogues.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic procedures and characterization data of reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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