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Phosphonium lipocations as antiparasitic agents

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Abstract

Phosphonium lipocations were synthesized and evaluated for inhibition of the development of *Plasmodium falciparum* and *Trypanosoma cruzi*, etiological agents of malaria and Chagas disease, respectively. Optimal phthalimides and 1,4-naphthoquinone-based lipocations were active *in vitro* at mid-high nM concentrations against *P. falciparum* and low μM concentrations against *T. cruzi*.

Keywords

Malaria; Chagas; Antiparasitic drugs; *Plasmodium*; *Trypanosoma*

Malaria and American trypanosomiasis (Chagas disease) are vector-borne infections that cause hundreds of millions of illnesses and nearly a million deaths in the tropics each year.[1] With malaria, clinical illness results when erythrocytes become infected with *Plasmodium* parasites. Effective antimalarial therapies must eliminate erythrocytic parasites while inflicting minimal host toxicity. Older antimalarial therapies such as chloroquine are seriously limited by drug resistance[2]. Newer agents include the artemisinins and the ubiquinone (CoQ) antagonist atovaquone (ATV). Artemisinins are rapidly active components of new combination regimens now widely used to treat malaria[3], although resistance to artemisinins may be emerging[4]. ATV is co-formulated with proguanil (Malarone) for the treatment and prevention of malaria because of synergistic interaction of the two components and high recrudescence rates after monotherapy.[5] ATV acts on the mitochondrion and demonstrates low toxicity due in part to evolutionary dissimilarities between plasmodial and mammalian mitochondria. However, for pharmaceuticals that require internalization by mitochondria, subcellular and therapeutic efficacy can be limited by the physiochemical properties of a compound.

Phosphonium cations are used extensively as molecular probes for studying mitochondrial function[6] and have demonstrated utility as mediators of antioxidant[7], antimicrobial[8], and antineoplastic[9] transport into mitochondria. Mitoquinone[7a] (MitoQ, Fig. 1), a synthetic

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analog of ubiquinone, is the most clinically advanced phosphonium cation, and it has progressed to phase II trials in the U.S. for the management of Parkinson's disease, hepatitis C, and fatty liver disease. As a positively charged analog of the dietary antioxidant idebenone (Catena/Sovrima, Fig. 1), the enhanced therapeutic efficacy of mitoquinone is conferred by attachment of a triphenylphosphonium group to the decyl side chain. This modification guides the lipocation into energized mitochondria by electrostatic attraction and leads to increased drug concentrations in the mitochondrial matrix.[7d]

A structural feature common to mitoquinone and other CoQ mimics (e.g. ATV) is a lipophilic side chain, which increases permeability in the inner phospholipid bilayers of mitochondria, where electron transport complexes are embedded. We hypothesized that if a phosphonium moiety were bound to the lipid substituent in antagonists of the *Plasmodium* and *Trypanosoma* electron transport chains, higher drug concentrations would be achieved inside the mitochondrion and lead to increased antiparasitic effects. In this initial report, we examine the effects on anti-parasitic activity of phosphonium group attachment to structural analogs of CoQ containing phthalimide and 1,4-naphthoquinone platforms.

The initial molecules chosen for evaluation were derived from phthalimide, which has structural similarities to CoQ, and served as a simple platform to conduct an SAR study on the lipocation chain component. *N*-Alkylphthalimides **1a-c** (Scheme 1) were prepared from dibromoalkanes of various chain lengths and then coupled with a tertiary phosphine under microwave[10] or conventional heating conditions (methods A–C) to afford the phosphonium lipocations.

Minimum inhibitory concentrations (IC_{50}) were determined for the phthalimide-based lipocations **2a-j** against the chloroquine-resistant *P. falciparum* strain W2, using methods as previously described.[11] The IC_{50}s ranged from 134.0 nM to >3.5 μM (Table 1), compared to 66.9 nM for chloroquine (CQ). Analysis of structure-activity relationships revealed that antiplasmodial effects were conferred by the phosphonium moiety, and the presence or absence of the phthalimide group had minimal influence on activity. This conclusion was established by inclusion of phthalimide **3** and triphenylphosphonium cations **4** in the study. Conversely, substituents on the phosphonium moiety and the lipid chain length (n) had a moderate impact on activity. The P-substituent could be either alkyl (e.g. R = cyclohexyl, **2i**) or aromatic (e.g. R = Ph, **2g**), with only a moderate effect on the IC_{50} values. The trimethyl derivative **2a** was an exception having much weaker activity compared to analogs of equal chain length (i.e. **2d-j**). A similar detrimental effect was observed for compounds possessing shorter chain lengths, with the 4- and 6-carbon chain analogs, **2b** and **c** respectively, demonstrating 4–15 fold reduced activity compared to the 10-carbon chain lipocation **2g**.

Although investigation of the phthalimide-based lipocations was beneficial in confirming activity and examining SAR, it was apparent that the phthalimide group was not serving as an antagonist of CoQ, as supported by similarities in the IC_{50} values of phosphonium salts **2f-j** and **4a**. Attention was turned to lipocations containing the 1,4-naphthoquinone platform which is found in ATV and many other known inhibitors of the *Plasmodium* cytochrome bc_1 complex[12]. The analogs were synthesized from quinones **5** using 3 different approaches to install the lipocation chain (Scheme 2). The first method was by nucleophilic addition[13] of straight-chain amino alcohols to 1,4-naphthoquinone (R = H), followed by mesylation of the corresponding alcohol, and generation of the phosphonium salts under microwave irradiation. The second approach introduced the cation by chloroalkylation[14] of naphthoquinone **5** (R = Me) with formaldehyde and subsequent conversion to triphenylphosphonium salt **9f**. The final method was by alkylation of naphthoquinones **5** (R = H, Me) via radical decarboxylation.[15] The resulting bromides were then converted to the lipocations by methods A–C (Scheme 1), which often resulted in substantial amounts of

reduced products (i.e. 1,4-naphthalenediols) being formed. When this occurred, re-oxidation to the quinone was accomplished with nitric oxide generated *in situ* from $NaNO_2$[16] and subsequent counterion exchange to the mesylate salt form to ensure chemical conformity of the product.

Susceptibility testing of the naphthoquinone-based lipocations against W2-strain *P. falciparum* revealed an SAR profile similar to that of the phthalimide series (Table 2). Antiplasmodial activity was conferred by the installation of a phosphonium-containing hydrocarbon chain, and a variety of P-substituents could be utilized without significant deviations in the IC_{50} values (i.e. **9i-m**). The activities for many of the 10-carbon chain analogs were once again comparable to the lipocation control **4a** (IC_{50} 141.6 nM), suggesting that the inhibitory effects were due not to a specific mechanism (e.g. cytochrome bc_1 inhibition), but rather to a non-specific action such as disruption of plasma membrane integrity. The two apparent exceptions were lipocations **9n** (IC_{50} 48.3 nM) and **9o**[17] (IC_{50} 18.7 nM), which displayed 3–7 fold greater activity than control **4a**. The 5- and 4-carbon chain analogs were also more active than their 10-carbon chain counterpart **9k** (IC_{50} 143.4 nM), a reversal in the SAR profile observed with the phthalimide series. In addition, a comparison of analog **9o** to its 4-carbon chain control **4b** and phthalimide **2b** (IC_{50}s 3.5 μM) established that the naphthoquinone platform had a role in achieving sub-50 nM activities.

The naphthoquinone-derived lipocations were additionally evaluated as growth inhibitors against *Trypanosoma cruzi*, the etiological agent of Chagas disease. Like *P. falciparum*, *T. cruzi* has a complex life cycle which includes infective, non-replicating bloodstream trypomastigote forms and intracellular amastigotes that infect cardiac and other cells, leading to disease.[18] The compounds were assessed for efficacy against Vero cell-infected *T. cruzi* amastigotes[19]. The IC_{50}s for inhibition of parasite development ranged from 1.6 to 5.4 μM and variable degrees of Vero cell toxicity was observed (Table 3). For comparison, benznidazole was used as a positive control (IC_{50} 2.1 μM) and was non-toxic at the concentrations indicated.

As with *P. falciparum*, the lipocation analogs were more effective antitrypanosomal agents than their uncharged naphthoquinone counterparts **11** and **12**. Chain length and P-substituent type appeared to have little effect on the activity but, were influential on Vero cell cytotoxicity and may have resulted in the increased efficacy observed for lipocations **7e** and **9k** (IC_{50}s 1.6 μM). The most potent compound not displaying toxicity at 25 μM was the 4-carbon chain analog **9o** (IC_{50} 2.7 μM) which also possessed the highest antiplasmodial activity at 18.7 nm. Additional testing of lipocation **9o** further revealed therapeutic index values {TI = [IC_{50}(Vero)]/[IC_{50}(parasite)]} of 19.5 and 2,818 for *T. cruzi* and *P. falciparum*, respectively.

With these findings, a question to be addressed is whether pharmacological activity is conferred by charge-mediated accumulation of the lipocations inside the mitochondrion. As with mitochondrial-targeted modulators of similar design,[7,20] subcellular internalization of the antagonists is thought to be governed by their physiochemical properties. It is hypothesized that the lipid character of the cations combined with electrostatic forces facilitates non-carrier-mediated transport through the cytoplasmic membranes of the host cell and parasite. Their lipophilic properties results from distribution of the cation charge across the molecules however, guiding movement of the inhibitors toward regions of negative charge within parasitized cells (Fig. 2).

In the case of plasmodia, the inward cytoplasmic membrane potential ($\Delta\psi_p$) of erythrocytes and *P. falciparum* are reportedly ≤−35 mV[21] and −95 ± 2 mV[22], respectively, which offers a rational basis for a $\Delta\psi$-directed route into the parasite. Further, with the absence of

mitochondria in uninfected erythrocytes, the *Plasmodium* mitochondrion would be the site of highest negative charge in an infected erythrocyte, and thereby be the primary location where the lipocations would be expected to accumulate. Conversely, mammalian cells usually possess hundreds of mitochondria also capable of taking up the lipocations, which may have led to the reduced efficacy observed against Vero cell-infected *T. cruzi*. Although host mitochondria will cause a decrease of lipocation concentrations in the parasite, *T. cruzi* amastigotes have only a single mitochondrion[2]. Lower drug concentrations would therefore likely be required to collapse the $\Delta\psi_m$ and confer lethal effects on the trypanosome compared to host cells.

In summary, phosphonium lipocations were found to be efficacious inhibitors of the development of cultured *P. falciparum* and *T. cruzi*. Preliminary SAR profiles were established for lipocations derived from phthalimide and 1,4-naphthoquinone platforms. In both series, antiparasitic activity was greater for compounds containing a phosphonium group. The P-substituent could be either aromatic or alkyl without significant deviations in the IC_{50}s, while a lipid chain of 4-carbons appeared to be the optimal length for 1,4-naphthoquinone-based inhibitors. Current research efforts are focused on evaluating the antiparasitic activity of lipocations containing various platform types of known electron transport antagonists. The goal will be to identify compounds that are equipotent to other mitochondrion-acting agents (e.g. ATV) and demonstrate minimal cytotoxicity. Ideally, the lipocations will also have good distribution in tissues most susceptible to damage by the infection (erythrocytes for malaria parasites and cardiac and intestinal myocytes for *T. cruzi*) and cost-effective, orally active agents to merit their development as antiparasitic drugs.

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17. (4-(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butyl)triphenyl-phosphonium methanesulfonate (**9o**): orange oil; TLC (SiO_2) R_f 0.27 (9:1 DCM:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04-8.02 (m, 1H), 7.97-7.96 (m, 1H), 7.81-7.68 (m, 17H), 3.69-3.63 (m, 2H), 2.68-2.66 (m, 5H), 2.17 (s, 3H), 1.86-1.80 (m, 2H), 1.76-1.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 184.9, 146.0, 144.4, 135.09, 135.06, 133.64, 133.56, 133.5, 133.4, 132.1, 131.9, 130.6, 130.5, 126.3, 126.2, 118.6, 117.9; ^{31}P NMR (202 MHz, $CDCl_3$) δ 24.9; ESI-HRMS calcd for $C_{33}H_{30}O_2P$ [M^+] 489.1977, found 489.1982.
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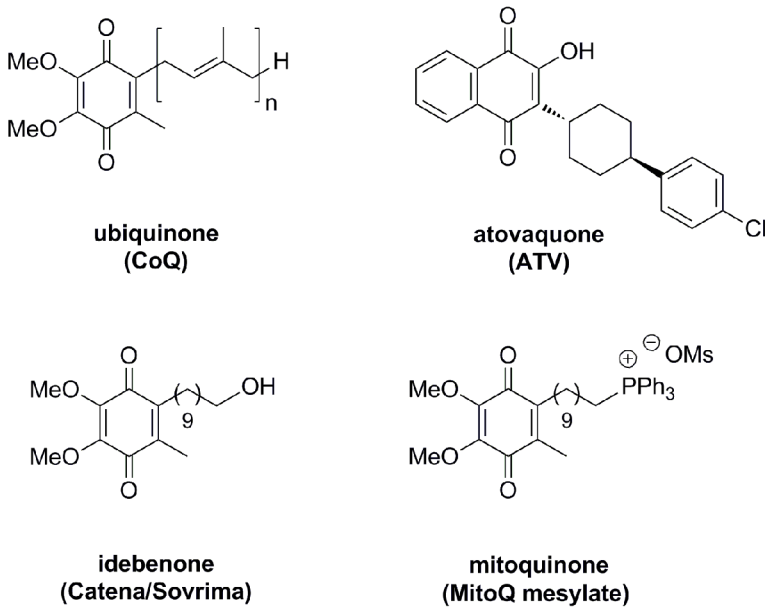


Figure 1.
Chemical structures of ubiquinone analogs atovaquone, idebenone, and mitoquinone.

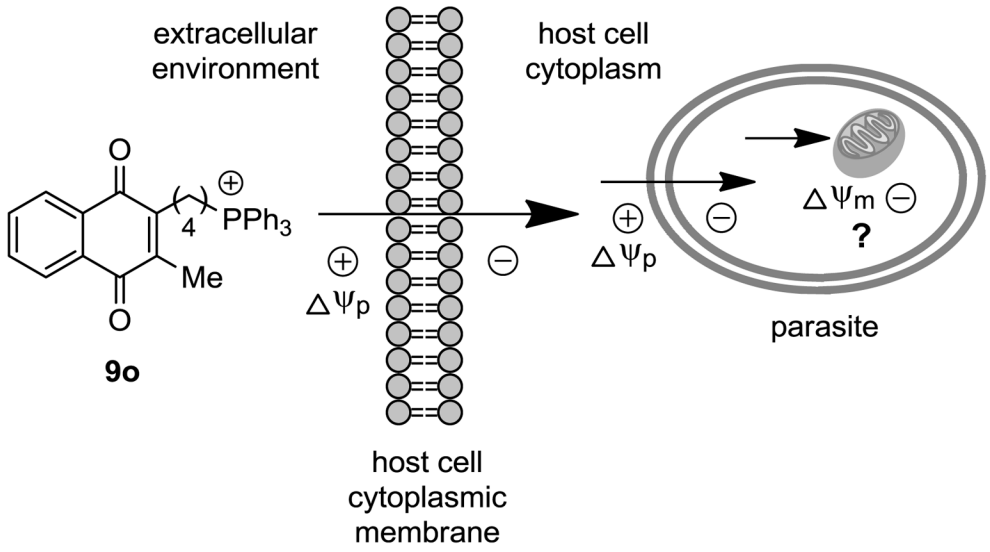
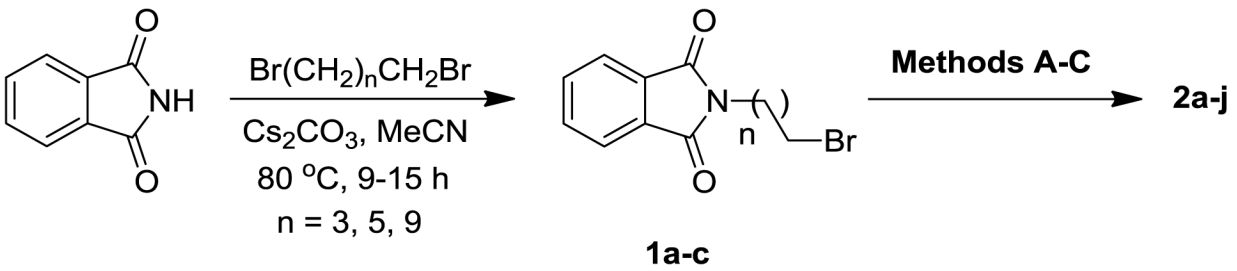
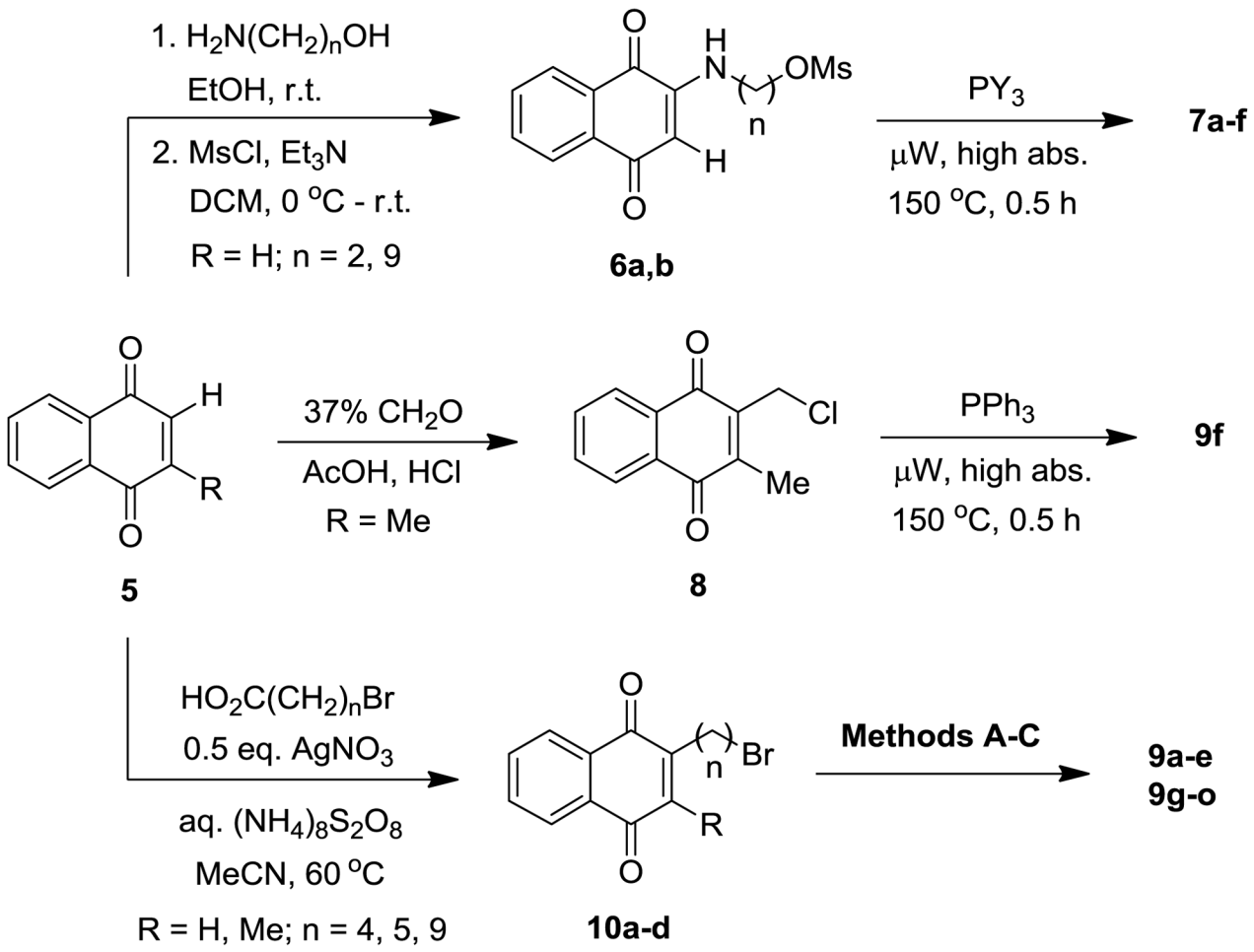


Figure 2.
The antiparasitic effects of phosphonium lipocation **9o** is believed to be due to electrostatic forces that increase subcellular (mitochondrial) concentrations of the inhibitor.



Method A: PY_3, μW, 0.5 h; **B:** $P(2\text{-}PhMe)_3$, 110 °C, 16-40 h; **C:** PMe_3, 2-PrOH:PhMe, 90 °C, 48-72 h.

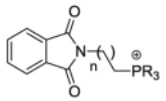
Scheme 1.
Synthesis of phthalimide-based phosphonium lipocations **2** (Table 1).



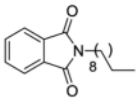
Scheme 2.
Synthesis of 1,4-naphthoquinone-based phosphonium lipocations **7** and **9** (Table 2).

Table 1

Comparisons of IC_{50}s for *P. falciparum* growth.



2a-j
(Table 1)



3
>10,000 nM

4a (n = 8) 141.6 ± 3.5 nM
4b (n = 2) 3,500 nM

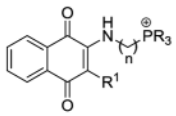
compd	n	R	IC_{50} (nM)	Log D^a	MW^b
2a	9	Me	>10,000	−0.08	362.5
2b	3	Ph	3,500	0.01	464.5
2c	5	Ph	1021 ± 93.2	1.14	492.6
2d	9	4-PhF	345.6 ± 15.3	2.13	602.6
2e	9	Bn	288.5 ± 35.2	1.37	590.8
2f	9	n-Bu	194.2 ± 3.8	3.68	488.7
2g	9	Ph	172.7 ± 4.0	1.67	548.7
2h	9	2-PhMe	143.4 ± 7.0	−0.75	590.8
2i	9	C_6H_{11}	140.6 ± 0.7	4.50	566.8
2j	9	4-PhOMe	134.0 ± 1.7	3.19	638.7
CQ			66.93 ± 2.3		319.9

[a] measured by 1-octanol–water partition at pH 7.4

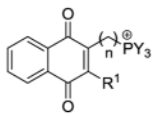
[b] molecular weights of lipocations **2** minus the counterion

Table 2

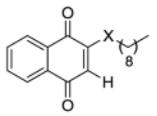
Comparisons of IC_{50}s for *P. falciparum* growth.



7a-f
(Table 2)



9a-o
(Table 2)



11 (X=NH) >10,000 nM
12 (X=CH_2) >10,000 nM

compd	n	R	R^1	IC_{50} (nM)	Log *D*[a]	MW[b]
7a	1	Ph	H	519.9 ± 61.2	−1.08	462.5
7b	10	4-PhF	H	292.0 ± 53.2	1.67	628.7
7c	10	Bn	H	214.6 ± 0.5	2.80	616.8
7d	10	4-PhOMe	H	134.2 ± 10.5	4.37	664.8
7e	10	Ph	H	113.9 ± 7.6	3.60	574.7
7f	10	C_6H_{11}	H	94.4 ± 35.2	3.41	592.9
9a	10	Bn	H	1303.5 ± 13.4	5.32	601.8
9b	10	4-PhF	H	846.3 ± 0.7	1.66	613.7
9c	10	Ph	H	259.2 ± 18.7	4.08	559.7
9d	5	Ph	H	156.6 ± 6.5	1.00	489.6
9e	5	Me	Me	955.6 ± 2.5	0.21	317.4
9f	1	Ph	Me	543.4 ± 79.2	1.89	447.5
9g	10	Me	Me	404.2 ± 16.7	1.95	373.5
9h	10	Bn	Me	212.0 ± 27.2	6.64	615.8
9i	10	n-Bu	Me	155.8 ± 9.0	5.10	513.8
9j	10	2-PhMe	Me	143.4 ± 7.0	3.58	615.8
9k	10	Ph	Me	143.4 ± 6.3	3.97	573.7
9l	10	C_6H_{11}	Me	134.3 ± 1.8	3.64	591.9
9m	10	4-PhOMe	Me	130.9 ± 6.6	3.52	663.8
9n	5	Ph	Me	48.3 ± 1.5	2.15	503.6
9o	4	Ph	Me	18.7 ± 0.3	1.91	489.6

compd	n	R	R^1	IC_{50} (nM)	Log D^a	MW[b]
ART[c]				7.31 ± 0.14		262.3
ATV				0.28 ± 0.19		366.3

[a] measured by 1-octanol–water partition at pH 7.4

[b] molecular weights of lipocations **7** and **9** minus the counterion

[c] artemisinin

Table 3

Comparisons of IC_{50}s for *T. cruzi* growth and Vero cell toxicity.

compd	n	R	*T. cruzi* IC_{50} (μM)	Vero cell toxicity (μM)[a] 25	12.5	6.25
11			17.3 ± 7.1	−	−	−
12			9.3 ± 1.3	−	−	−
9n	5	Ph	5.4 ± 0.1	+	−	−
9i	10	n-Bu	4.0 ± 3.6	+	+	−
9h	10	Bn	3.7 ± 1.8	+	+	−
9a	10	Bn	3.0 ± 1.3	−	−	−
9o	4	Ph	2.7 ± 1.0	−	−	−
9l	10	C_6H_{11}	2.4 ± 0.7	+	+	−
7e	10	Ph	1.6 ± 0.5	+	+	+
9k	10	Ph	1.6 ± 0.5	+	+	+
BNZ[b]			2.1 ± 0.4	−	−	−

[a] + cytotoxicity observed; − cytotoxicity not evident

[b] benznidazole