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RESEARCH ARTICLE

Drug-derived surface-active ionic liquids: a cost-effective way to expressively increase blood-stage antimalarial activity of primaquine

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Supporting information for this article is given via a link at the end of the document.

Abstract: Inspired by previous disclosure of room-temperature ionic liquids derived from primaquine and cinnamic acids, which displayed slightly enhanced blood-stage activity compared to the parent drug, we have now combined this emblematic antimalarial with natural fatty acids. This affords surface-active ionic liquids whose liver-stage antiplasmodial activity is either retained or slightly enhanced, while revealing blood-stage antiplasmodial activity at least one order of magnitude higher than that of the parent compound. These findings open new perspectives towards the cost-effective recycling of classical drugs that are either shelved or in decline, and which is not limited to antimalarial agents.

Introduction

Most available active pharmaceutical ingredients (API), including antimalarials, are available as salts, e.g., chloroquine phosphate, mepacrine hydrochloride, sodium artesunate, or primaquine phosphate. Although the preparation of saline forms of API is indeed a key step in drug development and formulation, most so-called conventional salts are solids frequently associated to undesirable features, such as polymorphic conversion or low bioavailability, among others. In order to avoid these limitations, ionic liquids (IL) derived from API (API-IL) have recently attracted much attention, since IL are organic salts with low melting points, often below 100 ºC, and usually below room temperature (room temperature ionic liquids - RTIL). Formulating API as IL may not only minimize bioavailability and polymorphism-related issues, but also offer the possibility to fine-tune the biological and physico-chemical properties of the API-IL, through convenient combination of selected organic cations and anions. As such, development of API-IL emerges as an attractive tool for cost-effective rescuing of drugs with limited bioavailability, possibly also improving their therapeutic effects.[1] In view of this, and in line with our long term research focused on the rescuing of classical antimalarial drugs[2], we have previously developed IL derived from primaquine (PQ) that were active against liver- and blood-stage forms of *Plasmodium* parasites.[3] Biophysical studies using model membranes suggested that the observed enhancement of the blood-stage activity of these IL, as compared to the parent drug, might arise from a better interaction of the IL with the membranes of *Plasmodium*-infected erythrocytes.[3] Hence, we hypothesized that PQ's blood-stage activity might be further enhanced upon its acid-base pairing with amphiphilic carboxylic acids, e.g., natural fatty acids, likely able to efficiently interact with membranes of *Plasmodium*-infected red blood cells (PiRBC).

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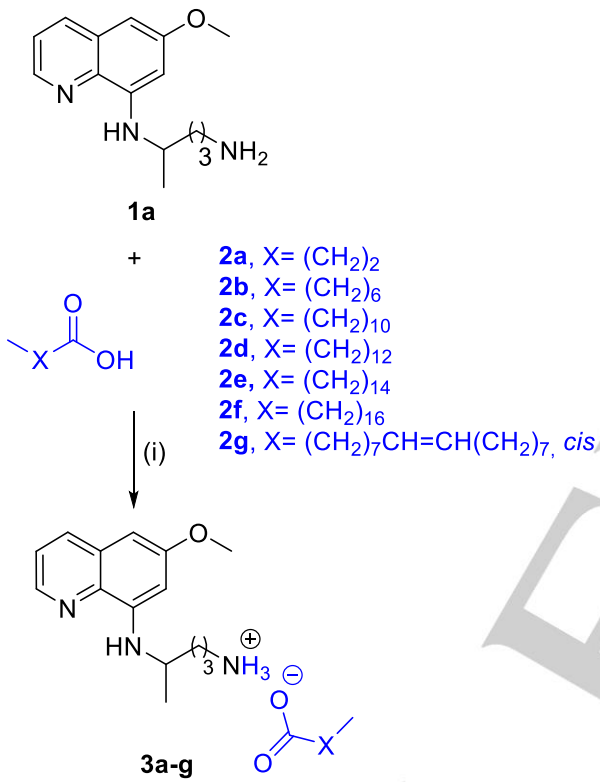
Results and Discussion

In view of the above, we first converted PQ phosphate into the compound's deprotonated form, PQ (**1**), which was next reacted with natural fatty acids **2a-g** to afford a small set of PQ-derived organic salts **3a-g** (Scheme 1). These salts were obtained in near-quantitative yields, with **3a-d** and **3g** being isolated as yellow-orange RTIL, and 3e-f as orange IL. Spectroscopic data supplied in the Supporting Information (SI) were in agreement with the expected structures, and complete transfer of the carboxylic acid proton to the 8-aminoquinoline drug was confirmed by proton nuclear magnetic resonance (^{1}H-NMR), as shown for **3b** in Figure S1 (SI).



Scheme 1. Synthesis route to PQ-derived organic salts **3a-g**. (i) **1** (1 molar equivalent, eq), **2a-g** (1 eq), methanol (MeOH), room temperature (RT), 30 min.

As thermal stability is an important issue for all API used in the treatment of diseases that mainly affect tropical and sub-tropical regions of the world, all compounds were first submit-ted to simultaneous thermal analysis (STA). The IL present at least two major thermal decomposition events (Table 1), at temperature values that increase alongside with the size of the fatty acid hydrocarbon chain. Relevantly, data in Table 1 show that, despite the IL **3a-c** and **3f** are somewhat less thermally stable than the commercial PQ phosphate salt, they remain undegraded up to temperatures as high as 82 ºC (**3a**) or even higher (**3b-c and 3f**). The compounds were screened *in vitro* for their activity against blood-stage forms of the chloroquine-sensitive 3D7, and the chloroquine-resistant Dd2 strains of P. falciparum. The antiplasmodial activity of IL **3** was ca. one order of magnitude higher than that of the parent drug against both strains (Table 1).

Despite the fact that there are many well-known antimalarials with more potent blood-stage activity[4] than that displayed by these compounds, this is an important outcome for PQ-based compounds, which typically act as tissue shizontocidals and gametocytocidals.[4b,5] Moreover, the IC_{50} values displayed by IL **3** do not merely reflect the activity of their parent compounds, i.e., PQ and fatty acids **2**, either alone or in a 1:1 mixture, as inferred from comparison of PQ laurate salt **3c** with PQ or lauric acid (**2c**) alone or in an equimolar mixture (Table 1). Indeed, the clearly distinct behaviour of **3c** as compared to the 1:1 mixture of PQ with lauric acid shows that these IL have their own identity as chemical entities, not being the simple sum of their parts.

Table 1. Synthesis yields, thermal degradation data, and *in vitro* activity of IL **3a-f**.

Compound	Synthesis Yield / %	Temperature of observed degradation events (Td) / ºC	Half maximal inhibitory concentration (IC_{50}) ± SD / nM (95% confidence intervals)	
			P. falciparum 3D7 strain	*P. falciparum* Dd2 strain
3a	87	81.8; 189.6	432 ± 162 (92-757)	204 ± 37 (117-304)
3b	99	138.5; 203.4	225 ± 142 (125-325)	225 ± 33 (87-341)
3c	99	161.7; 297.0	510 ± 142 (249-657)	356 ± 3 (323-389)
3d	36	-	164 ± 64 (117-212)	127 ±39 (93-162)
3e	99	-	247 ± 118 (158-336)	127 ± 40 (90-163)
3f	95	186.9; 328.9	n.d.[a]	n.d.[a]
2a	-	75.5	n.d.	n.d.
2b	-	131.0	n.d.	n.d.
2c	-	172.3	> 3000	> 3000
2f	-	218.5	n.d.	n.d.
PQ[b]	-	301.7	> 3000	> 3000
PQ + 2c	-	-	> 3000	> 3000
CQ[b]	-	-	45 ± 15 (33-55)	660 ± 104 (442-888)

[a] Compound was insoluble in assay conditions; [b] phosphate salt (commercial formulation of this API);

These *in vitro* data support our initial assumption that formulation of PQ as a fatty acid-derived organic salt might enhance its blood-stage antiplasmodial activity. This expectation was based on the amphipathic nature of fatty acids, which suggested that IL **3** might behave as surface-active ionic liquids (SAIL),[6] with enhanced ability to internalize PiRBC. Accordingly, we carried out surface tension studies (*cf*. SI for experimental details) on IL **3** to gain further insight into the effect of the fatty acid chain's length on

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surface activity. Although the test IL **3** exhibit low solubility in pure water, their surface activity is demonstrated by saturated aqueous solutions of **3b**, **3c** and **3e**. The surface tension value measured at 25.0 °C for 3b, 3c and 3e was 37.3 mN·m-1, 28.9 mN·m-1 and 26.0 mN·m-1, respectively. These values are much lower than that the surface tension of ultra-pure water (72.0 mN·m^{-1}, at 25 °C), indicating that these ILs have a strong adsorption at the air-liquid interface. Mixing with surfactant cetyltrimethylammonium bromide (CTAB) improves the solubility of IL **3b-e** and **3g**. This enabled the assessment of the effect of adding each of **3b-e** and **3g** on the critical micelle concentration (*cmc*) and on the surface tension at the *cmc* (γ_{cmc}) of CTAB solutions at a constant SAIL molar fraction, defined as $x_{SAIL} = n_{SAIL}/(n_{SAIL} + n_{CTAB})$, of 0.10. All tested salts **3** are SAIL, as they form mixed micelles with CTAB and cause a significant decrease in the mixture *cmc* as compared to neat CTAB (Table 2 and Figure 1A). Moreover, our data suggest that there may be an unusual relationship between *cmc* and the length of the fatty acid chain, highlighting the dodecanoate (laurate) salt **3c** as the SAIL with strongest surface activity (Table 2). Indeed, the *cmc* of the CTAB + **3c** mixture is ca. 13 times smaller than that of neat CTAB and the γ_{cmc} for the mixture with **3c** is quite low, reaching 24.4 mN·m^{-1}, consistent with a strong surface adsorption. We further assessed the dependence of the mixture *cmc* on the molar fraction of **3c** (cf. Figure S3, in the SI), and it was observed that the *cmc* decreases with increasing molar fraction of SAIL (Figure 1B).

Table 2. Critical micellar concentration (*cmc*) and surface tension at the cmc (γ_{cmc}) for CTAB and different CTAB/SAIL mixtures with a molar fraction of SAIL, xSAIL, equal to 0.10. Typical uncertainties are: cmc, ± 5%, and γ_{cmc}, ≤ ± 2%.

System	*cmc* / mmol·kg^{-1}	γ_{cmc} / mN·m^{-1}
CTAB	0.84	33.0
CTAB + **3b**	0.41	31.8
CTAB + **3c**	0.061	24.4
CTAB + **3d**	0.67	30.0
CTAB + **3e**	0.60	25.4
CTAB + **3g**	0.12	27.2

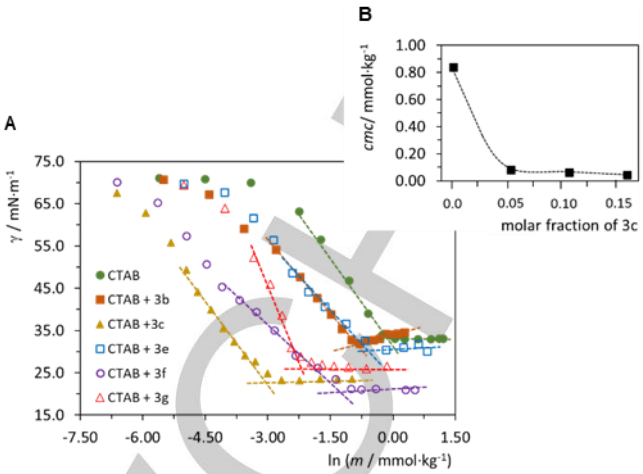

Figure 1. Surface tension plots and *cmc* determination, at 25 ºC, of aqueous CTAB/SAIL mixtures: **(A)** surface tension vs. the logarithm of total CTAB+SAIL concentration, expressed in molality; the *cmc* values are obtained from the intersection points of the linear fit in each system; **(B)** *cmc* vs. molar fraction of **3c** in mixtures with CTAB, showing the marked effect of **3c** in reducing *cmc*.

In summary, surface tension studies confirm the behavior of **3** as SAIL, which may be associated to the significant improvement of *in vitro* activity against blood-stage malaria parasites. Despite the relatively low number of compounds **3** studied thus far, and the fact that solubility issues limit the size of the fatty acids that can be used, these findings highlight a new path for antimalarial drug development that is worthy of further exploration. Indeed, other biocompatible amphiphilic acids may be useful to produce novel PQ-derived SAIL with promising blood-stage antiplasmodial activity. Nevertheless, this will be worthless if such SAIL are toxic to human cells or devoid of the valuable liver-stage antiplasmodial activity that characterizes PQ-based compounds. Consequently, we further screened SAIL **3a-f** *in vitro* for their activity against liver forms of *P. berghei* and for their toxicity to human Huh-7 cells. Our results show that all six SAIL **3a-f** display dose-response dependence (Figure 2 - bars) and **3b-f** are more active than both the parent drugs, in free form **1a** and in bisphosphate form **1b**, with **3c** being the most active compound evaluated. SAIL **3c** also displays higher activity than the original fatty acid **2c** and than the mixture **1b** + **2c**. Additionally, none of the compounds is cytotoxic up to 10 μM, as shown by the cell confluence data displayed (Figure 2 - dots). To the best of our knowledge, this works constitutes the first report of PQ-derived SAIL acting as dual-stage antiplasmodial hits.

Conclusion

In conclusion, we advance PQ-derived SAIL as a new dual-stage antiplasmodial chemotype. We are aware that *in vitro* activity of these SAIL against blood-stage *P. falciparum* is not as high as those of first-line antimalarials like artemisinin or artesunate,[7] but the considerable activity increase relative to that of the parent drug suggests that a similar cost-effective approach can be explored for both antimalarial and other API. Likewise, the preliminary assessment of the hepatic-stage antiplasmodial activity of these SAIL indicates that, although they are not as potent as reference drug atovaquone,[8] their potency is higher than that of the parent PQ, which is a reference drug for all liver forms of *Plasmodium*, including hypnozoites, against which atovaquone is inactive.

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Although further studies are required to gain deeper insight into these systems and fully test our hypothesis, the first-time disclosure of PQ-derived SAIL that are active against both blood- and liver-stage *Plasmodium* parasites, while having the ability to co-assemble into colloidal nanostructures (micelles), is of undeniable impact in the medicinal chemistry field. In-deed, drug-derived SAIL enclose the remarkable potential of being exploitable, in the near future, as new bioactive chemo-types able to act both as drug and drug delivery systems. Ongoing studies in our lab, using similar SAIL derived from other antimalarial and anti-infective agents, will hopefully contribute to the establishment of API-derived SAIL as a cost-effective and simple approach towards the rescuing of classical drugs that are either shelved or in decline.

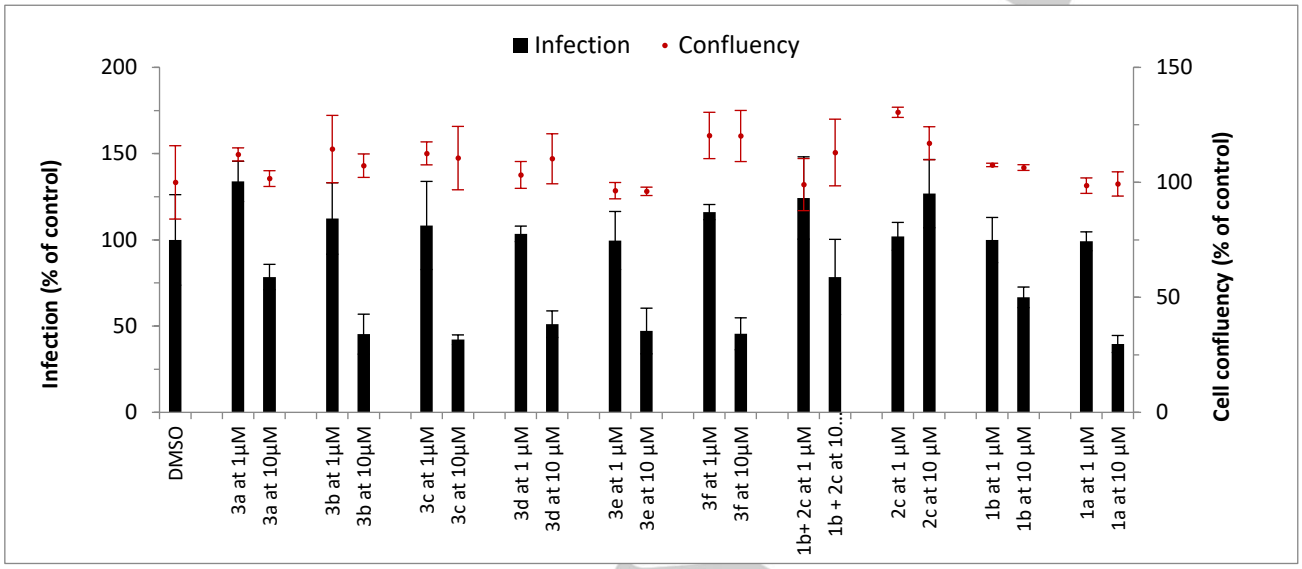

Figure 2. *In vitro* screening of the effect of SAIL **3a-f**, at 1 and 10 μM, on growth of liver forms of *P. berghei* parasites (bars), and confluency of their host cells, Huh-7 hepatocytes (dots).

Experimental Section

Chemistry

Conversion of primaquine phosphate into 1a: Conversion of commercial primaquine phosphate into its free base form 1a was performed as previously described by us Ferraz *et al.*[3a] Briefly, triethylamine was added to a suspension of chloroquine biphosphate in dichloromethane (DCM), and the mixture was stirred for 30 minutes. The organic layer was washed with water (x3), dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure, to afford 1 with correct ^{1}H-NMR spectral data.

Synthesis of ionic liquids 3: 1 molar equivalent (1eq) of primaquine (1a) was dissolved in methanol. In parallel, 1 eq of fatty acid was dissolved in methanol. The methanolic solution of the drug was placed under magnetic stirring and the methanolic fatty acid solution was added dropwise. Upon addition of the acid, the reaction mixture was kept under stirring for 30 min, at room temperature. The solvent was removed by evaporation under reduced pressure in the rotary evaporator, and finally dried at high vacuum. The residue obtained was analyzed by ^{1}H-NMR and ^{13}C-NMR, allowing to verify the identity of the desired salt, with an anion / cation stoichiometry of 1:1, according to the structural data presented in the Supporting Information.

Simultaneous thermogravimetric analysis: In this work, the compounds under study were subjected to heating from room temperature to 500 ºC, at a speed of 5 ºC/min, obtaining the thermograms shown in the Supporting Information. For a better visualization of the degradative events, the derivatives of the thermogravimetric curves are also present in the thermograms. The thermal stability of the compounds was evaluated in a simultaneous thermal analyzer (STA) from Scancsi, model 7200RV.

Surface tension measurements: A DCAT11 tensiometer from Dataphysics GmbH with a Pt–Y alloy Wilhelmy plate was used and all measurements were performed at 25.0 ± 0.5 ºC. The measurements for *cmc* determination of the CTAB/SAIL solutions were performed by adding aliquots from a stock mixed solution to the solution in the measuring vessel. No dynamic surface tension effects were observed.

In vitro assays

***Plasmodium* liver stages:** The inhibition of infection in the hepatic stage by the compounds is assessed by measuring the luminescence intensity of lysates of Huh-7 cells infected with a firefly luciferase-expressing *P. berghei* line, as previously described by Ploemen *et al.*[9]

Huh-7 cells, a human hepatoma cell line, were cultured in 1640 RPMI medium supplemented with 10% v/v fetal calf serum, 1% v/v non-essential amino acids, 1% v/v penicillin/streptomycin, 1% v/v glutamine and 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulphonic acid (HEPES), pH 7, and maintained at 37 °C with 5% CO_2. For infection assays, Huh-7 cells (1.2 × 104 per well) were seeded in 96-well plates the day before drug treatment and infection. Medium in the cells was replaced by medium containing the appropriate concentration of each compound approximately 1 h prior to infection with sporozoites freshly obtained through disruption of salivary glands of infected female *Anopheles stephensi* mosquitoes. Sporozoite addition was followed by centrifugation at 1700 g for 5 min.

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The evaluation of the parasitic load was evaluated at 48 h infection by luminescence measurement of cell lysates, following addition of the luciferin substrate.

The effect of the compounds on the viability of Huh-7 cells was assessed by the AlamarBlue assay (Invitrogen, UK), using the manufacturer's protocol.

Blood stage

Parasite cultivation: Laboratory-adapted *P. falciparum* 3D7 (chloroquine and mefloquine sensitive), Dd2 (chloroquine-resistant, mefloquine-resistant) were continuously cultured and sorbitol synchronized, as previously described by Nogueira *et al.*[10]

Determination of IC_{50} values: Staging and parasitaemia were determined by light microscopy of Giemsa-stained thin blood smears. Antimalarial activity was determined using the SYBR Green I assay, as performed by Machado *et al.*[11] Briefly, early ring stage parasites (> 80% of rings) were challenged with a 1:3 serial dilution of each compound, in concentrations ranging from 10,000–0.169 nM. Fluorescence intensity was measured with a multi-mode microplate reader (Triad, Dynex Technologies), with excitation and emission wavelengths of 485 and 535 nm, respectively, and analysed by nonlinear regression using GraphPad Prism to determine IC_{50} values.

The Supporting Information, with structural characterization (NMR, MS spectra) and additional surface tension data, is available free of charge on the European Chemical Societies Publishing website.

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Keywords: Antimalarial • blood-stage • fatty acid • ionic liquid • liver-stage • *Plasmodium* • SAIL • surface activity

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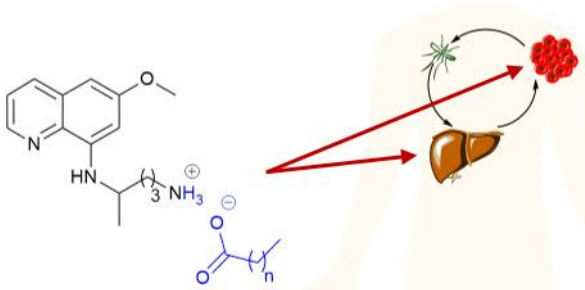
RESEARCH ARTICLE

Surface-active ionic liquids (SAIL) obtained by acid-base combination of primaquine with natural fatty acids are disclosed as antimalarial hits against both liver- and blood-stage parasites. These findings pave the way towards drug-derived SAIL able to act both as drug and drug delivery systems, hence representing an interesting way to rescue drugs either shelved or in decline.



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