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New route to the 5-((arylthio- and heteroarylthio)methylene)-3-(2,2,2-trifluoroethyl)-furan-2(5*H*)-ones—Key intermediates in the synthesis of 4-aminoquinoline γ-lactams as potent antimalarial compounds

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ABSTRACT

In this Letter we report on a multi-step synthesis of 5-((arylthio- and heteroarylthio)-methylene)-3-(2,2,2-trifluoroethyl)furan-2(5*H*)-ones starting from γ-keto thiolester or γ-keto carboxylic acid. The key intermediate γ-lactones were then reacted with 4-aminoquinoline-derived amines via ring opening—ring closure (RORC) process affording the corresponding γ-hydroxy-γ-lactams in moderate to good yields. In vitro antimalarial activity of the resulting new 4-aminoquinoline γ-lactams were evaluated against *Plasmodium falciparum* clones of variable sensitivity (3D7 and W2) and were found to be active in the range of 89–1600 nM with good resistance index and did not show cytotoxicity in vitro when tested against human umbilical vein endothelial cells (HUVEC) up to concentration of 50 μM.

Half of the world population is currently at risk of malaria disease. *Plasmodium falciparum* parasite is responsible for almost one million deaths each year affecting mainly children under 5 years and pregnant women.[1] Advances in malaria research have been reviewed,[2–6] including a recent account of interest from a perspective in medicinal chemistry.[7] The widespread resistance of many *P. falciparum* parasites to the most available drugs, as well as the lack of an efficient vaccine, cause an urgent need for new types of antimalarial drugs. 7-Chloro-4-aminoquinoline derivatives, especially chloroquine (CQ), amodiaquine (AQ) and also modified CQ side-chain analogs,[8–11] have been a representative class of such antimalarial drugs. But the use of CQ and others first generation antimalarial drugs is now very limited due to the widespread of resistance. Therefore the current malaria treatment of choice involves artemisinin-based combined therapies (ACTs),[12] but nevertheless chemical exploration and structural modification of CQ is still an attractive approach to propose new chemical entities that are equally active against CQ-sensitive and CQ-resistant strains.

In the course of our medicinal chemistry project devoted to the synthesis of new antimalarials, we have previously prepared a set of compounds of general structure **1**. All these compounds have two major structural subunits, a 7-chloro-4-aminoquinoline core and a 1*H*-pyrrole-2(5*H*)-one connected with a spacer. Based on some difference in substitution patterns, they were divided in two series **A** ($R^2 = CH_2S(O)_mAr$, $R^4 = CF_3$, $R^{4'} = R^5 = H$) and **B** (R^2 = Alk, Ar, $R^4 = CF_3$, $R^{4'} = H$, R^5 = SEt) (Fig. 1).[13,14] Incorporation of 1*H*-pyrrole-2(5*H*)-one unit into the side chain of quinoline and synthetic antimalarials has been scarcely explored despite the fact that natural products such as codinaepsin[15] and ascosalipyrrolidinone A[16] displayed promising antimalarial activity.

Compounds **1** in both series show high in vitro activity against *P. falciparum* strains of variable sensitivity (3D7 and W2) and good resistance index (in the range 1.0–2.5). Activity of the most potent molecules was in the range of 40–50 nM (Fig. 2)[13] and for most of them correlated with high lipophilicity (*c* log*P* close to 4.5–6.6) and *c* log*D* at pH 7.4 usually in the range of 1.2–2.8, except for two molecules with values higher than 5.0. Moreover, they were

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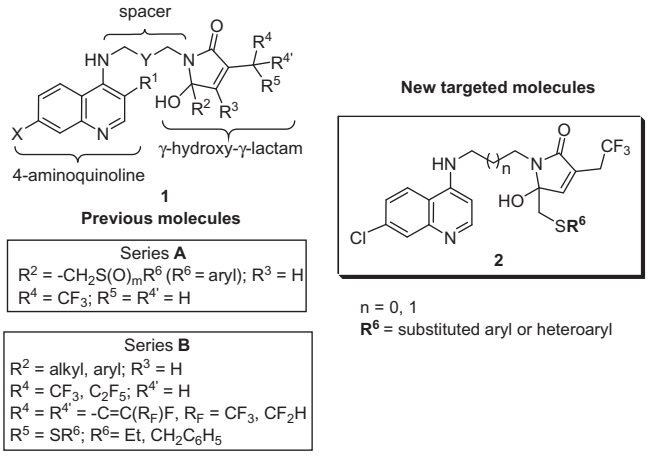
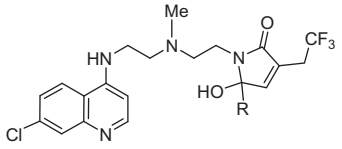


Figure 1. Structures of our previous 4-aminoquinoline-γ-hydroxy-γ-lactams[13] and our new targeted molecules.



1a: R = CH_2SPh: IC_{50}(3D7) = 47nM, IC_{50}(W2) = 55nM
1b: R = $CH_2SC_6H_4pCl$: IC_{50}(3D7) = 55nM, IC_{50}(W2) = 57nM
1c: R = $CH_2SC_6H_4pBr$: IC_{50}(3D7) = 45nM, IC_{50}(W2) = 42nM

Figure 2. Representative structures of our most active compounds.

found to have no cytotoxicity when tested against HUVEC cells in concentrations up to 100 μM. These preliminary data demonstrate that structures in both series have some potential for generation of new antimalarials, but one major concern is their relatively low solubility due to high lipophilicity which is a potential issue when progressing further potential hits. Our results presented herein are directed to reduce the lipophilicity of the most active phenyl derivatives keeping good potency against 3D7 and W2 strains with low cytotoxicity in order to provide structures that will be more appropriate for in vivo oral assessment.

Generally, compounds in series **A** were more active than those obtained in series **B**. Further structure diversification of compounds in series **A** was then explored in order to reduce the *c* log P of the most active molecules and this may be achieved by judicious choice of the aryl substitution or by changing aryl substituent (R^6) to heteroaryl one (Fig. 1). A series of new heterocyclic variants were thus identified based on their compliance with the Lipinski's 'rule of five' criteria (Table 1);[17,18] all the new targeted γ-lactams have the following calculated values: (a) *c* log*P* lower than 5.0 in contrast to most of the previous active molecules (Fig. 2)[13], (b) molecular weight in the range of 508–524 g/mol which is only slightly higher than the accepted 500 g/mol, (c) *c* log*D* at pH 7.4 in the range of −1.10 to +0.45 and (d) are compliant with hydrogen bonding properties.

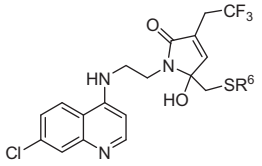
During initial studies only three lactones **5a–c** with Ar = –Ph,[19] $-C_6H_4-p$Cl,[19] and $-C_6H_4-p$Br[13] substituents were successfully obtained and used to prepare target compounds. Our well established synthetic methodology starts from commercially available heptafluorobutyraldehyde and leads in five-steps to the key intermediate lactones **5a–c** as depicted on Scheme 1.

Unfortunately this methodology was totally fruitless when trying to use heterocyclic thiols in the first thioacetalization step. Particularly, no reaction was observed with 2- or 4-pyridine thiols both under Lewis acid ($TiCl_4$) or protic (H_2SO_4) conditions, which may be probably explained by pyridine complexation with Lewis acid or its protonation. Moreover, thioacetalization also failed with thiols bearing electron donating substituents such as *p*-methoxy thiophenol.

Taking into account the lack of versatility (linear five-step sequence) and the above mentioned drawbacks of heteroaryl thiols, a new improved synthesis of the lactone precursors from readily available starting material and utilizing less number of steps was urgently needed in order to support our antimalarial project.

γ-Keto thiolester **6** is one of the easy accessible fluorinated building blocks efficiently used in our previous syntheses of nitrogen containing heterocycles.[20–22] It was prepared in large quantities and with good overall yield using cheap EtSH in the same synthetic path as shown in Scheme 1 (steps a–d). When γ-keto thiolester **6** was treated with SO_2Cl_2 in CH_2Cl_2,[23–25] smooth quantitative conversion into corresponding acid chloride took place, and the latter was immediately isomerized into its cyclic 'pseudo acid chloride' **7** (Scheme 2). It is worth noting that compound **7** was

Table 1
Calculated physicochemical properties of the targeted γ-lactams **2** using MarvinSketch 5.11 from ChemAxon[17]



R^6	MW (g/mol)	*c*log*P*/*c*log*D* (pH 7.4)	Polar surface area (PSA)	H-bond donors	H-bond acceptors	Violation parameters (MW)
Ph	507.96	4.68/1.07	65.46	2	5	>500
	508.94	3.46/−0.15	78.35	2	6	>500
	508.94	4.05/0.45	78.35	2	6	>500
	524.94	2.80/−0.80	90.92	2	7	>500
	509.93	3.43/−0.18	91.24	2	7	>500
	512.94	2.50/−1.10	96.17	2	8	>500