Bioorganic & Medicinal Chemistry Letters 26 (2016) 5308–5311

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

7-Chloro-4-aminoquinoline γ-hydroxy-γ-lactam derived-tetramates as a new family of antimalarial compounds

Nicolas Chopin [a,†], Shinya Iikawa [a,†], Julien Bosson [a], Adeline Lavoignat [a], Guillaume Bonnot [a], Anne-Lise Bienvenu [a], Stéphane Picot [a], Jean-Philippe Bouillon [b,*], Maurice Médebielle [a,*]

[a] Université Claude Bernard Lyon 1, Université de Lyon, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires ICBMS (UMR 5246), Equipe "Synthèse de Molécules d'Intérêt Thérapeutique (SMITh)", 43 bd du 11 Novembre 1918, F-69622 Villeurbanne, France
[b] Normandie Université, UNIROUEN, INSA Rouen, CNRS, COBRA (UMR 6014), Equipe "Biomolécules Fluorées", F-76821 Mont Saint Aignan Cedex, France

ARTICLE INFO

Article history:
Received 26 July 2016
Revised 12 September 2016
Accepted 14 September 2016
Available online 15 September 2016

Keywords:
Antimalarial
Tetronate
Tetramate
Lactam
Aminoquinoline

ABSTRACT

In this Letter we report on an efficient and short 2–3 steps synthesis of γ-hydroxy-γ-lactam derived-tetramates bearing a 7-chloro-4-aminoquinoline skeleton and their evaluation as potent antimalarials. These molecules were obtained through ring opening-ring closure (RORC) process of γ-ylidene-tetronate derivatives in the presence of 7-chloro-4-aminoquinoline-derived amines. In vitro antimalarial activity of these new γ-lactams was evaluated against *Plasmodium falciparum* clones of variable sensitivity (3D7 and W2) and they were found to be active in the range of 14–827 nM with generally good resistance index. A preliminary SAR study is also presented to explain these results. Finally, the most active compounds did not show in vitro cytotoxicity when tested against Human Umbilical Vein Endothelial Cells (HUVEC) up to concentration of 50 μM and they were stable at pH 7.4 for at least 48 h.

Malaria is a serious disease endemic in tropical and subtropical parts of the world. Despite recent progress toward malaria elimination in few endemic areas, it is estimated that half of the world population is currently at risk of malaria disease, and *Plasmodium falciparum* parasite is responsible for almost half million deaths each year affecting mainly children under 5 years.[1] The widespread resistance of many *P. falciparum* parasites to current drugs, as well as the lack of an efficient and safe vaccine, cause an urgent need for new classes of antimalarial drugs that are either derived from known drugs[2–5] or that operate by novel mechanism of actions.[6] The current recommended first-line malaria treatment in most endemic areas are artemisinin-based combined therapies (ACTs).[7]

In our current research program directed toward the synthesis and biological evaluation of new antimalarials, we have previously reported on the synthesis of a set of γ-hydroxy-γ-lactams of general structure **1**, having two major structural subunits, a 7-chloro-4-aminoquinoline core and a 1*H*-pyrrole-2(5*H*)-one (also called γ-hydroxy-γ-lactam) bearing a fluoroalkyl substituent, connected with a spacer (Fig. 1).[8] Despite that compounds **1** show high in vitro activity against *P. falciparum* strains of variable sensitivity (3D7 and W2) (activity of the most active compounds were in the range of 40–50 nM) and good resistance index (in the range 1.0–2.5), their synthesis required at least 6–7 steps, with some lack of diversity. Synthetic antimalarials having a γ-lactam or a pyrrolone skeleton have been scarcely explored[9] but it is worth to mention that some acylated non tetramic γ-hydroxy-γ-lactams[10] natural products such as Codinaepsin[11] and Ascosalipyrrolidinone A[12] displayed promising antimalarial activity. Based on our previous studies,[8] we have recently initiated a program aiming at the synthesis of novel γ-hydroxy-γ-lactams especially structures derived from tetramates[13] (Fig. 1) with the goal to generate in only few steps molecules with molecular diversity and with promising in vitro activity against *P. falciparum* clones. Tetramate derivatives have never been described as new chemotherapeutic agents against malaria. Herein we present our preliminary results in this direction.

γ-Ylidenetetronates **6**–**12** obtained through the condensation of methyl and benzyl tetronates **1a**–**b** (**1a** being commercially available) with aryl aldehydes **2**–**5**, in a 2-steps aldolisation/dehydration sequence disclosed recently in our laboratory,[14] represent our key intermediates in the synthesis of the targeted γ-hydroxy-γ-lactam derived-tetramates **16**–**26** (Scheme 1). Indeed, lactones **6**–**12** were engaged in a RORC (Ring Opening-Ring Closure) lactamization reaction with a series of 4-aminoquinoline-derived amines **13**–**15** (Scheme 1).[8] The transformation was conducted in anhydrous MeOH, in a sealed tube at 80 °C, until complete

* Corresponding authors. Tel.: +33 2 35522422 (J.P.B.), +33 4 72431989 (M.M.).
E-mail addresses: jean-philippe.bouillon@univ-rouen.fr (J.-P. Bouillon), maurice.medebielle@univ-lyon1.fr (M. Médebielle).
† These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.bmcl.2016.09.038
0960-894X/

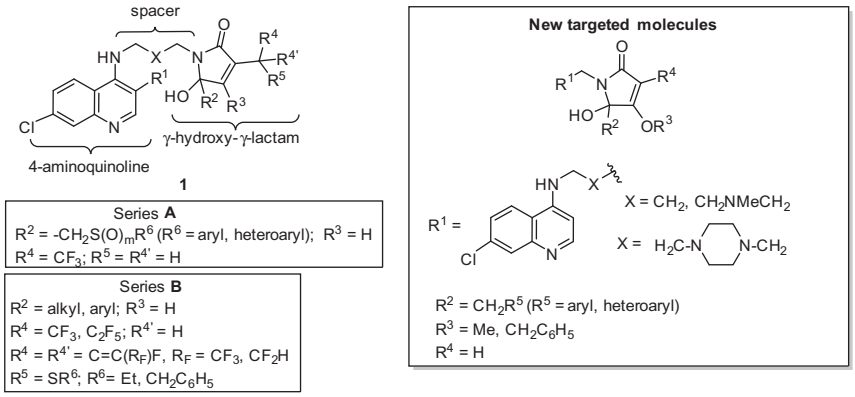
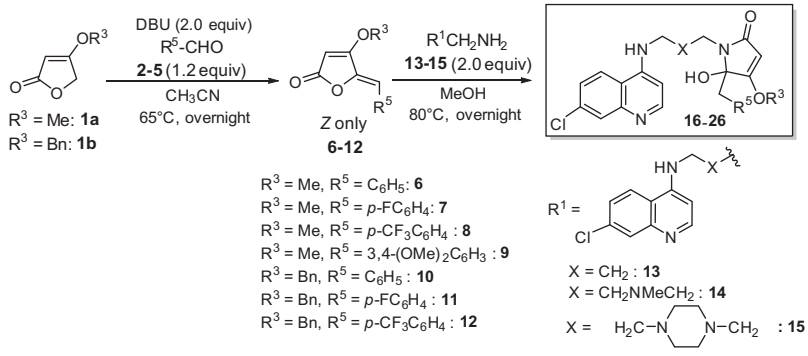


Figure 1. Structures of our previous 4-aminoquinoline-γ-hydroxy-γ-lactams[8] and our new targeted molecules.



Scheme 1. Synthetic approach to prepare the targeted γ-hydroxy-γ-lactam derived-tetramates **16**–**26**.

consumption of the starting γ-lactone, as checked by TLC. Corresponding γ-lactams were usually obtained in moderate to good yields in only 2–3 steps (Scheme 1, Table 1) after evaporation of solvent and purification by silica gel chromatography.[15] Most of our targeted γ-hydroxy-γ-lactam derived-tetramates have a methylene spacer (Table 1: X = CH_2) but, some of them bear also a basic nitrogen in order to potentially increase food vacuole accumulation, to generate a hydrogen bond acceptor as well as to induce better solubility via possible salt formation (Table 1: compounds **20**, **21** and **25**, **26**).

The 4-aminoquinoline γ-lactams (Table 1) have the following calculated values: (a) *c*log*P* in most cases lower than 5.0 in contrast to most of the previous active molecules[8], (b) molecular weight in the range of 438–625 g/mol which is below or slightly higher than the accepted 500 g/mol according to Lipinski's rules,[17] (c) *c*log*D* at pH = 7.4 in the range of 2.09–5.25 and (d) are compliant with hydrogen bonding properties.

Compounds **16**–**26** were then evaluated against CQ-sensitive (3D7) and CQ-resistant (W2) clones of *P. falciparum* (Table 2).[18] All experiments were carried out twice with wells in triplicate. Data are reported as IC_{50} values.

The derivatives are for most of them more active than chloroquine (CQ) on W2 clone with two of them having low nanomolar activity with approximatively equal activity on both clones (Table 2: **20** and **21**). They are usually equally or more active than our previous active molecules with a 1*H*-pyrrole-2(5*H*)-one bearing a fluoroalkyl substituent.[8]

Derivatives having the *p*-trifluoromethylphenyl (R^5) substitution in combination with a basic nitrogen in the spacer (Table 2: **20**, **21** and **26**) are the most active molecules. It is interesting to note that an electron-withdrawing group in R^5 is generally preferred for the activity. Indeed, when R^5 is a phenyl (Table 2: **16**) or an electron-rich aromatic (Table 2: **19**), activity against both clones is diminished. Furthermore, with methyl or benzyl tetramates, a *p*-$CF_3C_6H_4$ moiety induced a better activity than a *p*-FC_6H_4 substituent (Table 2: **17** vs **18** and **23** vs **24**). When comparing methyl and benzyl tetramates (Table 2: **16** vs **22**; **17** vs **23** and **18** vs **24**), the benzyl derivatives are generally more active. For these derivatives, comparing the *c*log*P*/*c*log*D* values, it appears that the activity is probably due to the highest lipophilicity generated by the benzyl group (Tables 1 and 2: **23**, **24**, **25** and **26**). That study revealed that the antimalarial activity of these compounds is linked to a good balance between the lipophilicity and the presence of specific groups, as electron-withdrawing moiety on R^5 and basic nitrogen within the spacer.

Selected most active compounds (**20**, **21**, **23**–**26**) were evaluated against Human Umbilical Vein Endothelial Cells (HUVEC) using final concentrations ranging from 0.01 to 50 μmol/L.[18] We did not detect significant cytotoxicity and no relevant EC_{50} could be obtained in the concentration range tested. Based on these data, we extrapolate a minimum cytotoxicity value over 10–50 μmol/L for these compounds, leading to an excellent selectivity against parasites (for both clones).

In conclusion, a series of new mixed 4-aminoquinoline γ-hydroxy-γ-lactam tetramates were prepared via RORC process from the corresponding γ-ylidenetetronates **6**–**12** in a 2 or 3 steps synthesis. Most 4-aminoquinoline γ-lactams **16**–**26** exhibited good in vitro antimalarial activity against *P. falciparum* clones of variable sensitivity (3D7 and W2) with good resistance index. The tetramate derivative **20** with a piperazine moiety in the linker, was equally active on both strains and is more active than the reference chloroquine. Compounds **20** and **21** may serve as a good starting hits for further optimization since they possess overall very good activity on both clones, and good calculated physicochemical properties. Since the γ-ylidenetetronate key intermediates can be easily modified through, for example, metal cross coupling