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# Synthesis of functionalized 3-, 5-, 6- and 8-aminoquinolines *via* intermediate (3-pyrrolin-1-yl)- and (2-oxopyrrolidin-1-yl)quinolines and evaluation of their antiplasmodial and antifungal activity

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ABSTRACT

(3-Pyrrolin-1-yl)- and (2-oxopyrrolidin-1-yl)quinolines were prepared *via* cyclization of diallylaminoquinolines and 4-chloro-*N*-quinolinylbutanamides, respectively, as novel synthetic intermediates *en route* to *N*-functionalized 3-, 5-, 6- and 8-aminoquinolines with potential biological activity. (3-Pyrrolin-1-yl)quinolines were subjected to bromination reactions, and the reactivity of (2-oxopyrrolidin-1-yl)quinolines toward lithium aluminum hydride and methyllithium was assessed, providing an entry into a broad range of novel functionalized (pyrrolidin-1-yl)- and (hydroxyalkylamino) quinolines. Antiplasmodial evaluation of these novel quinolines and their functionalized derivatives revealed moderate micromolar potency against a chloroquine-sensitive strain of the malaria parasite *Plasmodium falciparum*, and the two most potent compounds also showed micromolar activity against a chloroquine-resistant strain of *P. falciparum*. Antifungal assessment of (hydroxyalkylamino)quinolines revealed three compounds with promising MIC values against *Rhodotorula bogoriensis* and one compound with potent activity against *Aspergillus flavus*.



## 1. Introduction

Quinoline or benzo[*b*]pyridine is an azaheterocyclic aromatic compound and a weak tertiary base that can undergo both nucleophilic and electrophilic substitution reactions. The quinoline moiety is nontoxic to humans on oral absorption and inhalation and therefore occurs in several pharmacologically active compounds, displaying a wide range of biological activities. In particular, quinoline derivatives have been found to exhibit antimalarial [1–4], antibacterial [5–7], antiprotozoal [8–11], anti-HIV [12–14], anticancer [15–17] and antifungal activity [18–20], pointing to their versatility as templates in drug discovery.

The majority of known quinoline drugs have a side chain on the 4- or 8-position of the quinoline building block. However, recently, it has been reported that moving a functionalized side chain around the quinoline core to the 3-, 5- or 6-position can result in retention of biological (*in casu* antiplasmodial) activity [21,22], providing new opportunities for the design of bioactive compounds. Therefore, the combination of the privileged quinoline scaffold (bearing a varied substitution pattern) with a synthetically and biologically interesting heterocyclic moiety (like pyrrolidine derivatives) in a conjugate system might reveal new perspectives in bioactive compound development. Thus, antiplasmodial and antimicrobial evaluation of novel pyrrolidinyl-quinoline chimeras and their functionalized derivatives could potentially provide new hit compounds in this field of research. Hence, the objective of this study consists of the design, synthesis and biological evaluation of a range of novel (3-pyrrolin-1-yl)quinoline and (2-oxopyrrolidin-1-yl)

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quinoline intermediates and their derivatives.

## 2. Results and discussion

### 2.1. Chemistry

A first synthetic approach envisioned the initial synthesis of (3-pyrrolin-1-yl)quinolines starting from aminoquinolines. Diallylaminoquinolines had to be prepared as intermediates, but since they have only been reported as (minor) side products of the monoallylation of aminoquinolines [23–26], optimization of the reaction conditions was required to realize selective diallylation. Complete diallylation of aminoquinolines could be accomplished by sequentially adding lithium bis(trimethylsilyl)amide to a mixture of aminoquinoline **1** and allyl bromide in tetrahydrofuran, affording the desired diallylaminoquinolines **2a**–**d** in good to excellent yields (50–99%) and purities (Scheme 1 and Table 1). Diallylamines **2a**–**d** were subsequently treated with 1st or 2nd generation Grubbs catalyst in tetrahydrofuran or dichloromethane yielding the desired new (3-pyrrolin-1-yl)quinolines **3a**–**d**. 1st Generation Grubbs catalyst was preferred over 2nd generation since it was shown to be more active toward 3-diallylaminoquinoline derivatives. However, 1st generation Grubbs catalyst was unable to effect ring closure of 8-diallylaminoquinolines, and it appeared that 2nd generation Grubbs catalyst was required in that case. Conversion rates of diallylaminoquinolines **2a**–**d** to (3-pyrrolin-1-yl)quinolines **3a**–**d** varied between 50 and 100%, but 3-pyrrolines **3a**–**d** could be isolated in pure form in yields of 16–82% by preparative thin layer chromatography (Scheme 1 and Table 1). The reactivity of (3-pyrrolin-1-yl)quinoline intermediates **3a**–**c** was then evaluated by adding bromine to a solution of quinolines **3a**–**c** in tetrahydrofuran or dichloromethane. Surprisingly, next to the anticipated *anti*-addition of bromine across the pyrroline double bond, bromination of the quinoline core occurred as well. The position of quinoline bromination was dependent on the substitution pattern; seemingly bromination of the quinoline core took place in the α-position with respect to the pyrrolidinyl side chain. Electron donation by the nitrogen atom into the aromatic quinoline ring enhanced electrophilic aromatic substitution at the neighboring positions. For the 3- and 5-substituted quinolines **3a**–**b**, this resulted in additional bromination at the 4-and 6-position of the quinoline core, respectively. 6-Substituted quinoline **3c**, however, yielded two products in a 3/1 ratio, with the major product brominated at the 5-position and the minor product brominated at the 7-position of the quinoline core. Only the major product **4c** could be isolated. The small scale synthesis and troublesome purification step(s) affected the overall yields (14–34%) of the final obtained products (Scheme 1 and Table 1).

**Table 1**
Substitution pattern and isolated yields of quinolines **2**, **3**, **4** and **5**.

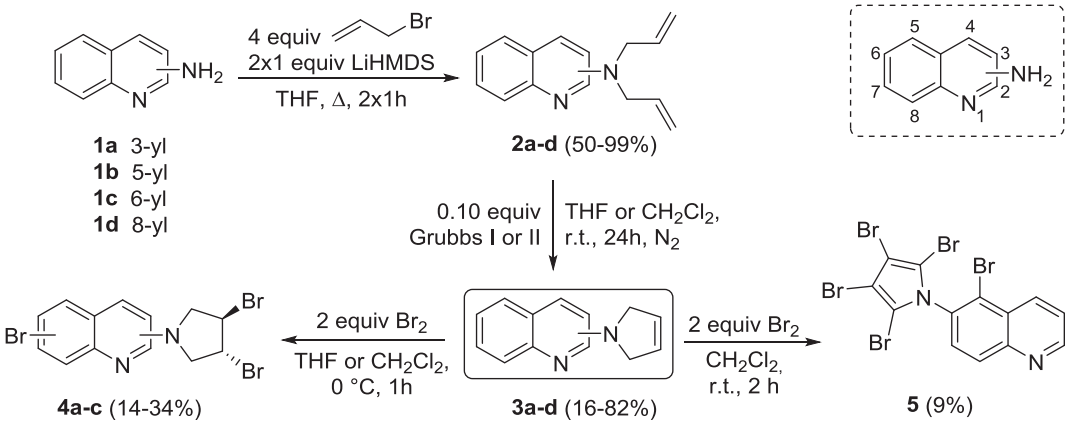
| Compound | Quinolin- | Position Br | Yield (%) |
|---|---|---|---|
| **2a** | 3-yl | – | 90–99[a] |
| **2b** | 5-yl | – | 79–95 |
| **2c** | 6-yl | – | 50–70[a] |
| **2d** | 8-yl | – | 71 |
| **3a** | 3-yl | – | 20–53 |
| **3b** | 5-yl | – | 48–82 |
| **3c** | 6-yl | – | 50–80 |
| **3d** | 8-yl | – | 16–53 |
| **4a** | 3-yl | 4-Br | 28 |
| **4b** | 5-yl | 6-Br | 28–34 |
| **4c** | 6-yl | 5-Br | 14 |
| **5** | 6-yl | 5-Br | 9 |

[a] Crude yields, purity >90% (NMR).

In order to increase the yield of the reaction, 6-(3-pyrrolin-1-yl) quinoline **3c** was treated with bromine in dichloromethane and stirred at room temperature. However, in that case a complex reaction mixture was obtained, but after two purification steps over silica gel (column chromatography followed by preparative TLC), a pure fraction could be isolated. Further analysis proved that 1-(5-bromoquinolin-6-yl)-2,3,4,5-tetrabromopyrrole **5** was obtained in 9% yield (Scheme 1 and Table 1). The very low yield of the reaction can be attributed to the small scale of the reaction (0.5 mmol), the cumbersome purification steps and the fact that insufficient bromine was added to the reaction to achieve full conversion to compound **5**.

A second approach commenced with the synthesis of 1-quinolinylpyrrolidin-2-ones from the aminoquinoline building blocks **1**. The first step in the synthesis of these intermediates comprised the *N*-acylation of aminoquinolines **1** with 4-chlorobutyryl chloride in the presence of potassium carbonate in dichloromethane. This approach afforded the required *N*-(quinolinyl)butanamides **6a**–**d** in excellent yields (71–99%) and high purities (Scheme 2 and Table 2). The crude products **6a**–**d** were subjected to an intramolecular ring closure by adding potassium *tert*-butoxide to an acetonitrile solution of butanamides **6a**–**d**, this yielded the desired novel (2-oxopyrrolidin-1-yl)quinolines **7a**–**d** in good yields (60–62%) (Scheme 2 and Table 2).

Subsequently, various strategies for further derivatization of the pyrrolidin-2-one moiety were evaluated. Firstly, lithium aluminum hydride was added to lactams **7a**–**c** and reaction at refluxing




**Scheme 1.** Synthesis and bromination of (3-pyrrolin-1-yl)quinolines **3**.