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Synthesis of halogenated 4-quinolones and evaluation of their antiplasmodial activity

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ABSTRACT

Treatment of 4-hydroxyquinolines with (2-methyl)allyl bromide in the presence of K_2CO_3 resulted in the formation of novel *N*-[(2-methyl)allyl]-4-quinolones through selective *N*-alkylation. Further reaction of *N*-(2-methylallyl)-4-quinolones with bromine or *N*-bromosuccinimide yielded the corresponding 3-bromo-1-(2,3-dibromo-2-methylpropyl)-4-quinolones and 3-bromo-1-(2-methylallyl)-4-quinolones, respectively. Furthermore, a copper-catalyzed C–N coupling of the latter 3-bromo-4-quinolones with (5-chloro)indole afforded novel 3-[(5-chloro)indol-1-yl]-4-quinolone hybrids. Antifungal and antiplasmodial assays of all new 4-quinolones were performed and revealed no antifungal properties but moderate antiplasmodial activities. All 15 compounds displayed micromolar activities against a chloroquine-sensitive strain of *Plasmodium falciparum*, and the five most potent compounds also showed micromolar activities against a chloroquine-resistant strain of *P. falciparum* with IC_{50}-values ranging between 4 and 70 μM.

Diverse studies in medicinal chemistry research have shown that the presence of halogens in organic molecules often improves their biological activities. A broad variety of halogenated compounds with different biological activities are known to date, such as anticancer,[1] antiviral,[2] antituberculosis,[3] antimalarial[4,5] and antifungal agents.[6] A tangible example is chloroquine (and many of its derivatives) used in malaria treatment, as it contains a chlorine atom at the 7-position of the quinoline core. Next to halogen introduction, another point of attention in medicinal chemistry programs involves the use of 4-quinolones as privileged building blocks. These scaffolds are among the most frequently encountered frameworks in recent drug development and have a broad and potent activity spectrum. 4-Quinolones, and more specifically 4-quinolone-3-carboxylic acid derivatives, are widely used as antibacterial agents,[7–11] but 4-quinolones are also known as second-line drugs in tuberculosis treatment.[12,13] Some lesser known biological activities of 4-quinolones include their anticancer,[14] antiviral,[15–17] and antimalarial activity,[18–20] pointing to the versatility of these structures with regard to bioactive compound development.

The objective of this study comprised the combination of 4-quinolone chemistry and halogen introduction, thus providing access to new 4-quinolones bearing halogens positioned directly on the 4-quinolone core as well as on the side chains. Finally, these novel halogenated 4-quinolones were subjected to biological evaluation.

The synthesis of the premised halogenated 4-quinolones (4(1*H*)-quinolinones according to IUPAC) commenced with *N*-(2-methyl)allylation of 4-hydroxyquinolines **1** using 1.5 equiv of (2-methyl)allyl bromide in acetone in the presence of potassium carbonate (3 equiv) for 24 h under reflux conditions. The reaction mixtures contained the *N*- and *O*-(2-methyl)allyl product as respectively the major and minor compound (ratios 6:4–10:0), and column chromatography on silica gel afforded the pure and novel *N*-[(2-methyl)allyl]-4-quinolones **2a–e** in moderate to good yields (56–85%). This reactivity stands in contrast with the (2-methyl)allylation of other hydroxyquinolines, as demonstrated in a recent study where reaction of 5-, 6- and 8-hydroxyquinolines with (2-methyl)allyl bromide under the same reaction conditions resulted in selective *O*-(2-methyl)allylation.[21] For 4-hydroxyquinolines, *N*-alkylation is known to be favored over *O*-alkylation due to *O* to *N* charge delocalisation.[22] However, the *N*-(2-methyl)allylation of 4-hydroxyquinolines has not been reported in the literature so far. Having introduced this (2-methyl)allyl group on the

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1-position of the quinolone ring, functionalization of the exocyclic double bond provides an opportunity to move away from the *N*-substituents already described in the literature for 4-quinolones (ethyl, cyclopropyl, aryl groups, etc). In addition, also direct functionalization of the 4-quinolone nucleus can give acces to novel derivatives.

In a first approach, selective bromination at the 3-position of the quinolone ring was achieved in an efficient way by treating 4-quinolones **2** with 1.5 equiv of *N*-bromosuccinimide (NBS) in CH_2Cl_2 for 24 h at room temperature, thereby affording *N*-[(2-methyl)allyl]-3-bromo-4-quinolones **3a**–**d** in good to high yields (89–99%) and high purities (>95%, NMR) (Scheme 1 and Table 1). The position of the bromine insertion (3-position of the quinolone ring) in bromination reactions of 4-quinolones was confirmed by comparing the NMR spectra with literature data.[23,24]

The latter 3-bromo-4-quinolones **3** appeared to be excellent substrates for molecular hybridization reactions, which is an emerging strategy used in drug discovery programs.[25–30] In accordance with a recently described procedure, a copper-catalyzed C–N coupling of 3-bromo-4-quinolones **3** with (5-chloro)indole was performed.[23] Thus, quinolones **3b**, **d** were treated with 10 mol % of a Cu(0)-catalyst and 20 mol % of *N*,*N*′-dimethylethylenediamine (DMEDA) as a ligand in toluene in the presence of 1.5 equiv of K_2CO_3 and 1.2 equiv of (5-chloro)indole for 48 h at 135 °C under an inert atmosphere (N_2). This resulted in the formation of 3-[(5-chloro)indol-1-yl]-4-quinolones **4a**–**d** in good yields (61–84%) (Scheme 1 and Table 1).[31] The decision to utilize an indole ring in this coupling reaction was based upon literature data confirming the antiplasmodial activity of various indole alkaloids and indoloquinolines.[32–35]

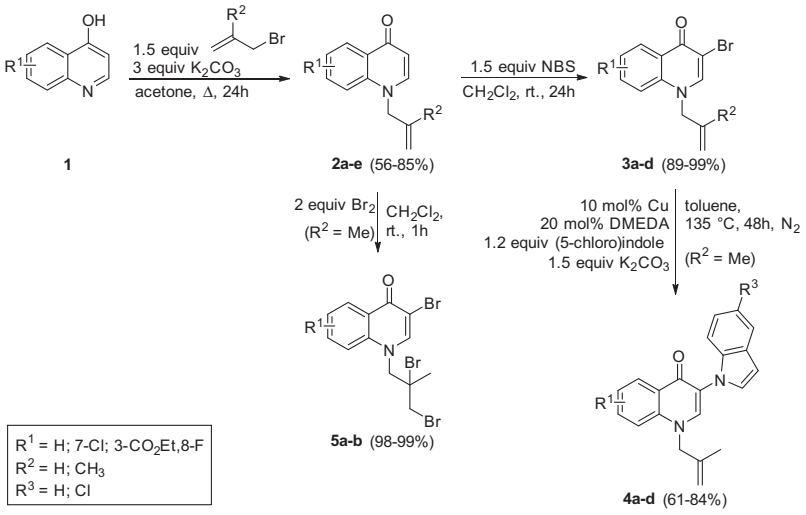
A second approach was based on a halogenation reaction with molecular bromine. In contrast to the bromination with NBS, both the exocyclic double bond and the 3-position of the quinolone ring were brominated, thus resulting in the simultaneous introduction of three bromo atoms in one step. Optimal results were achieved by dissolving *N*-(2-methylallyl)-4-quinolones **2b**, **d** in dry CH_2Cl_2 followed by treatment with 2 equiv of Br_2 for 1 h at room temperature. This procedure afforded halo-substituted 3-bromo-1-(2,3-dibromo-2-methylpropyl)-4-quinolones **5a**–**b** in high yields (98–99%) and purities (>95%, NMR) (Scheme 1 and Table 1).[36] It should thus be noted that selective mono- or tribromination of *N*-(2-methylallyl)-4-quinolones can be achieved upon proper selection of the halogenating agent (NBS vs Br_2). The purity of all compounds was assessed by means of HRMS analyses.

Table 1
Substitution pattern and yield of 4-quinolones **2**, **3**, **4** and **5**

Compound	R^1	R^2	R^3	Yield (%)
2a	H	H	–	75
2b	H	CH_3	–	79
2c	7-Cl	H	–	70
2d	7-Cl	CH_3	–	56
2e	3-COOEt,8-F	H	–	85
3a	H	H	–	89
3b	H	CH_3	–	98
3c	7-Cl	H	–	89
3d	7-Cl	CH_3	–	99
4a	H	–	H	84
4b	H	–	Cl	61
4c	7-Cl	–	H	84
4d	7-Cl	–	Cl	71
5a	H	–	–	98
5b	7-Cl	–	–	99

With these novel halogenated 4-quinolones **2**, **3**, **5** and 4-quinolone–indole hybrids **4** in hand, in vitro antiplasmodial screening was performed. All samples were screened against a chloroquine-sensitive (CQS) strain of *Plasmodium falciparum* (NF54). Subsequently, those samples showing promising antiplasmodial activity were tested against a chloroquine-resistant (CQR) strain of *P. falciparum* (Dd2) and screened for in vitro cytotoxicity against a mammalian cell-line, Chinese Hamster Ovarian (CHO), using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Continuous in vitro cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.[37] Quantitative assessment of in vitro antiplasmodial activity was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler et al.[38] The test samples were evaluated in triplicate on one occasion.[39] The MTT-assay was used as a colorimetric assay for cellular growth and survival, and compares well with other available assays.[40,41] The tetrazolium salt MTT was used to measure all growth and chemosensitivity. The samples were tested in triplicate on one occasion.[42] The results of the antiplasmodial evaluation are summarized in Table 2.

This study shows that all tested compounds exhibit micromolar potencies against a CQS strain of *P. falciparum* (NF54), with 8 of the 15 samples having IC_{50}-values between 3 and 50 μM. Subsequently, the activity of the five most potent compounds was determined against a CQR strain of *P. falciparum* (Dd2), again resulting in



Scheme 1. Synthesis of halogenated 4-quinolones **3** and **5** and 4-quinolone–indole hybrid molecules **4**.