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Graphical Abstract

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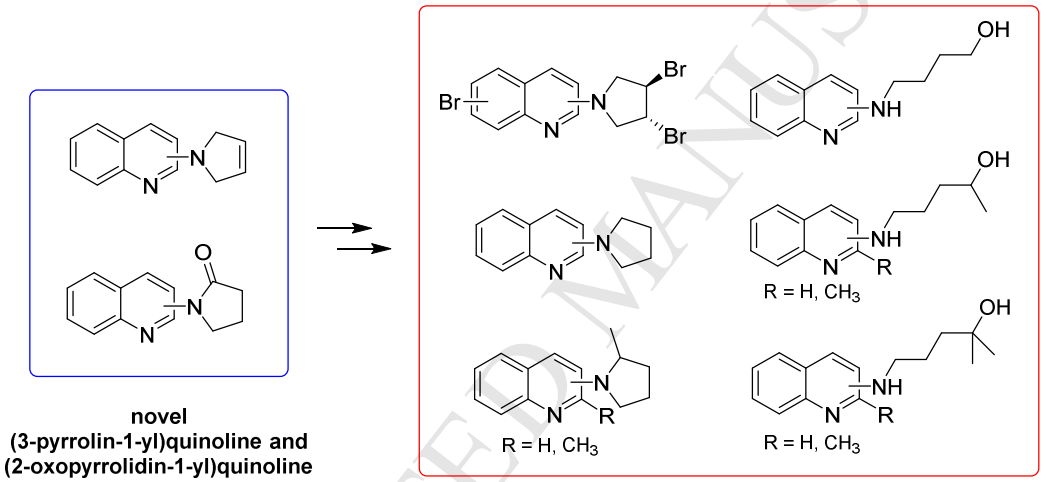

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Synthesis of functionalized 3-, 5-, 6- and 8-aminoquinolines via intermediate (3-pyrrolin-1-yl)- and (2-oxopyrrolidin-1-yl)quinolines and evaluation of their antiplasmodial and antifungal activity

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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 aluminium 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*.

Keywords: quinolines, pyrrolidine derivatives, antimalarial agents, antimicrobial agents

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

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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.

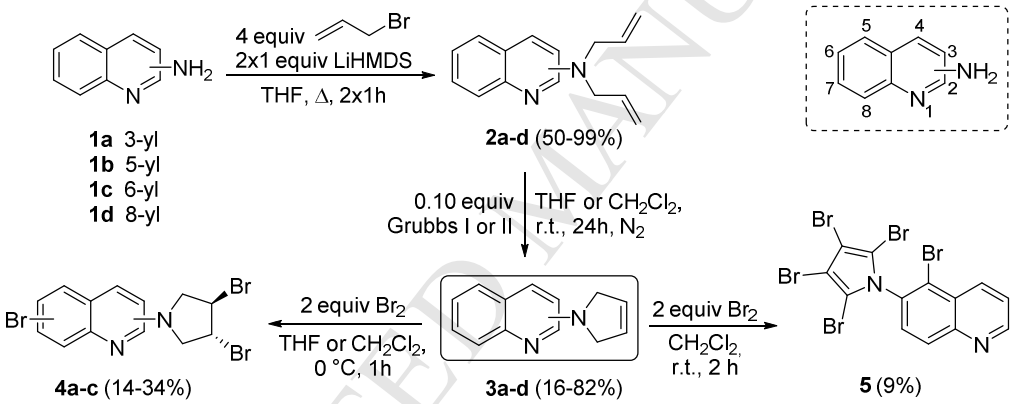
The majority of known quinoline drugs have a side chain on the 4- or 8-position of the quinoline building block. However, recently, it has been reported that moving a functionalized side chain around the quinoline core to the 3-, 5- or 6-position can result in retention of biological (*in casu* antiplasmodial) 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)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 quinolines **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).



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

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**.

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

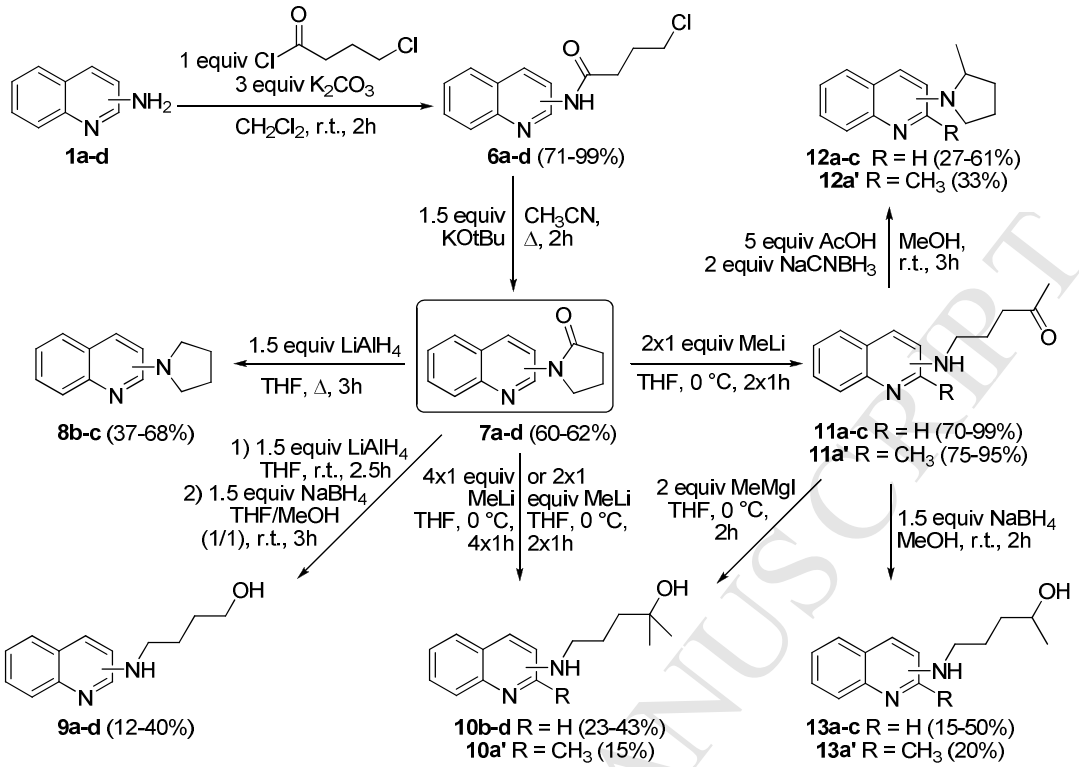
[a] Crude yields, purity >90% (NMR)

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 aluminium hydride was added to lactams **7b-c** and reaction at refluxing temperature mediated the reductive removal of the carbonyl group, furnishing (pyrrolidin-1-yl)quinolines **8b-c** in moderate to good yields (37-68%) (Scheme 2 and Table 2). However, when lactams **7a-d** were treated with lithium aluminium hydride at room temperature, the corresponding intermediate aldehydes were formed and addition of methanol and sodium borohydride to this reaction mixture afforded further reduction towards primary alcohols **9a-d**. Analytically pure samples of these 4-(quinolinylamino)butanols **9a-d** were obtained in low yields (12-40%) due to difficult purification steps (Scheme 2 and Table 2). Thirdly, lactams **7a-d** were sequentially treated with 4 equiv of a methyllithium solution, providing full conversion to 5-quinolinylamino-2-methylpentan-2-ols **10a-d**, but again the polar nature of these compounds accounted for a cumbersome purification, resulting in reduced yields (23-43%). It should be noted, however, that when this method was

applied to 3-(2-oxopyrrolidin-1-yl)quinoline **7a**, an additional methylation occurred at the 2-position of the quinoline scaffold affording methylketone **10a'** (R = Me) (Scheme 2 and Table 2). This reaction is expected to proceed *via* the 2-methyl-1,2-dihydroquinoline intermediate, followed by rearomatization mediated by light-induced oxidation. This type of nucleophilic alkyllithium addition onto a quinoline ring has been described in the literature [27]. Lastly, when lactams **7a-c** were sequentially treated with only 2 equiv of a methyllithium solution, 5-(quinolinylamino)pentan-2-ones **11a-c** were obtained in good to excellent yields (70-99%) and high purities (Scheme 2 and Table 2). Again methylation of the 2-position of the quinoline core took place when applying this method to 3-(2-oxopyrrolidin-1-yl)quinoline **7a**, yielding 5-(2-methylquinolin-3-ylamino)pentan-2-one **11a'** (R = Me). Temperature control appeared to be crucial in this reaction step, since the intermediate lithiate is only stable at temperatures below 0 °C. When the reaction was performed at higher temperatures, mixtures of methylketones **11a-c** and tertiary alcohols **10a-c** were obtained. However, this was not the case when 8-(2-oxopyrrolidin-1-yl)quinoline **7d** was used as substrate, as this reaction always resulted in the synthesis of 5-(quinolin-8-ylamino)-2-methylpentan-2-ol **10d**, even at reaction temperatures as low as -78 °C. This difference in reactivity has been explained by considering the formation of a coordination complex between the metal (lithium) and 8-aminoquinolines [28-29].

Furthermore, the newly synthesized methylketones **11a-c** were rather unstable and could not be purified over silica gel. Fortunately, these ketones were obtained in sufficiently high purities (>90%, NMR), allowing for direct further synthetic modification. The first modification strategy consisted of intramolecular ring closure by adding acetic acid and sodium cyanoborohydride to methylketones **11a-c**, affording full conversion to novel (2-methylpyrrolidin-1-yl)quinolines **12a-c** and analytically pure samples were obtained in low to good yields (27-61%) (Scheme 2 and Table 2). In order to get the full range of 4-aminobutanol side chains, 5-(quinolinylamino)pentan-2-ones **11a-c** were treated with sodium borohydride, affording 5-(quinolinylamino)pentan-2-ols **13a-c** in low to moderate yields (15-50%) (Scheme 2 and Table 2).



Scheme 2: Synthesis and functionalization of 1-(quinolinyl)pyrrolidin-2-ones **6**

It should be noted that 5-(quinolinylamino)pentan-2-ols **13a-c** could also be synthesized in a one-pot process by treating lactams **7a-c** with 2 equiv of a methyllithium solution for 2h, whereafter sodium borohydride and methanol were added to the mixture. 5-Quinolinylamino-2-methylpentan-2-ols **10a-b** could also be obtained through an alternative route where methylketones **11a-b** were treated with methylmagnesium iodide.

Table 2: Substitution pattern and isolated yields of quinolines **6**, **7**, **8**, **9**, **10**, **11**, **12** and **13**

Compound	Quinolin-	R	Yield (%)	Compound	Quinolin-	R	Yield (%)
6a	3-yl	-	84[a]	**10b**	5-yl	H	23
6b	5-yl	-	95[a]	**10c**	6-yl	H	43
6c	6-yl	-	93[a]	**10d**	8-yl	H	40
6d	8-yl	-	97[a]	**11a**	3-yl	H	83[a]
7a	3-yl	-	75	**11a'**	3-yl	CH_3	85[a]
7b	5-yl	-	62	**11b**	5-yl	H	88[a]
7c	6-yl	-	80	**11c**	6-yl	H	94[a]
7d	8-yl	-	72	**12a**	3-yl	H	61
8b	5-yl	-	37	**12a'**	3-yl	CH_3	33
8c	6-yl	-	68	**12b**	5-yl	H	31
9a	3-yl	-	40	**12c**	6-yl	H	27
9b	5-yl	-	15	**13a**	3-yl	H	20

9c	6-yl	-	40	**13a'**	3-yl	CH_3	20
9d	8-yl	-	25	**13b**	5-yl	H	17
10a'	3-yl	CH_3	15	**13c**	6-yl	H	50

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

2.2. Biological assay

With this small library of (pyrrolidin-1-yl)quinolines **3a-d**, **4a-c**, **5**, **7a-d**, **8c**, **12a-c** and their ring-opened derivatives **9a-d**, **10a-d**, **13a-c** in hand, biological screening was performed. All 30 quinoline derivatives were subjected to antiplasmodial testing. (Hydroxyalkylamino)quinoline derivatives **9a-d**, **10a-d** and **13a-c** were also selected for an antimicrobial assay since they are closely related to 4-(aminobutyloxy)quinolines which are known to display antimicrobial activity [19].

2.2.1. In vitro antiplasmodial activity

For the antiplasmodial assay, all samples were tested in triplicate against a chloroquine-sensitive (CQS) strain of *Plasmodium falciparum* (NF54). Subsequently, those samples showing promising antiplasmodial activity (*i.e.* compounds **9b** and **12a'**) 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 [30]. Quantitative assessment of antiplasmodial activity *in vitro* was determined *via* the parasite lactate dehydrogenase assay using a modified method described by Makler [31]. The test samples were tested in triplicate on one occasion. The MTT-assay was used to measure all growth and survival, and compares well with other available assays [32-33]. The tetrazolium salt MTT was used to measure growth and chemosensitivity. The test samples were tested in triplicate on one occasion. The results of the biological evaluation are summarized in Table 3 and 4.

Table 3: IC_{50} values of (pyrrolidin-1-yl)quinolines **3a-d**, **4a-c**, **5**, **7a-d**, **8c**, **12a-c** and their ring-opened derivatives **9a-d, 10a-d, 13a-c** tested for *in vitro* antimalarial activity against a CQS *P. falciparum* strain.

Compound	NF54: IC_{50} (µM)	Compound	NF54: IC_{50} (µM)	Compound	NF54: IC_{50} (µM)
3a	>50	**8a**	>50	**12a**	31.1 ± 8.5
3b	>50	**8b**	>50	**12a'**	13.3 ± 3.5
3c	>50	**8c**	>50	**12b**	>45
3d	>50	**9a**	>45	**12c**	41.9 ± 5.7
4a	>20	**9b**	19.9 ± 5.6	**13a**	>40
4b	>20	**9c**	>45	**13a'**	>40
5	>15	**9d**	>45	**13b**	32.6 ± 6.5
7a	>45	**10a'**	>35	**13c**	>40
7b	>45	**10b**	28.2 ± 4.5	CQ (n=14)	0.021 ± 0.005
7c	>45	**10c**	>40	Artesunate (n=8)	0.005
7d	>45	**10d**	>40		

CQ = chloroquine.

Table 4: IC_{50} values of quinolines **9b** and **12a'** tested for *in vitro* antimalarial activity (against a CQR *P. falciparum* strain) and cytotoxicity.

Compound	NF54: IC_{50} (µM)	Dd2: IC_{50} (µM)	CHO: IC_{50} (µM)	SI[a]	RI[b]
9b	19.9 ± 5.6	49.0 ± 10.2	>100	23	2.5
12a'	13.3 ± 3.5	38.0 ± 4.4	293.5 ± 50.4	22	2.9
CQ (n=14)	0.021	0.274	-	-	13.0
Artunesate (n=8)	0.005	0.011	-	-	2.2
Emetine	-	-	0.125	-	-

CQ = chloroquine; [a] SI (Selectivity Index) = IC_{50} CHO/IC_{50} NF54; [b] RI (Resistance Index) = IC_{50} Dd2/IC_{50} NF54.

It can be seen that some of the tested compounds exhibited micromolar potencies against a chloroquine-sensitive NF54 strain of *P. falciparum*, with six samples displaying IC_{50} values between 13 and 42 µM. Subsequently, the activity of the two most potent compounds **9b** and **12a'** (IC_{50} < 20 µM) was determined against a chloroquine-resistant strain of *P. falciparum* (Dd2), which resulted in micromolar activities with IC_{50} values ranging between 38 and 49 µM (Table 4). With regard to structure-activity relationships, this assay shows that (hydroxyalkylamino)quinolines **9**, **10** and **13** display the best activities when they are linked to the quinoline ring at position 5. Quinolines **12** on the other hand give better results when the 2-methylpyrrolidinyl side chain is present at the 3- or 6-position of the quinoline ring. Due to the diversity of this library (focusing on various substitution patterns across the quinoline core), these results cannot be generalized, but they can be seen as a valuable starting point for further research on 3-, 5-, 6- or 8-functionalized quinolines.

2.2.2. Antimicrobial activity

Finally, the antimicrobial activity of (hydroxyalkylamino)quinoline derivatives **9**, **10** and **13** was tested against two yeast strains (*Candida albicans* (IHEM 374) and *Rhodotorula bogoriensis* (MUCL11796)) and one mold strain (*Aspergillus flavus* (IHEM5785)) by the Disk Diffusion method to carry out a preliminary assessment of their antimicrobial potency [34]. This test revealed an interesting profile for six compounds (**9c**, **9d**, **10b**, **10d**, **13a** and **13c**), displaying antimicrobial activity against all 3 microorganisms. These compounds were subsequently subjected to a Minimum Inhibitory Concentration (MIC) determination test *via* microdilution [35]. The MIC values are reported in Table 5.

Table 5: MIC values

Compound	*Candida albicans*		*Rhodotorula bogoriensis*		*Aspergillus flavus*	
	(mg/L)	(mM)	(mg/L)	(mM)	(mg/L)	(mM)
9c	250.0	1.2	250.0	1.2	2.0	0.01
9d	250.0	1.2	7.8	0.04	31.6	0.1
10b	500.0	2.0	3.9	0.02	62.5	0.3
10d	250.0	1.0	7.8	0.03	15.6	0.06
13a	250.0	1.1	62.5	0.3	31.3	0.1
13c	250.0	1.1	250.0	1.1	62.5	0.3
Amphotericin B	<0.2	<0.0002	<0.2	<0.0002	3.1	0.03

The obtained MIC values confirm compounds **9d**, **10b** and **10d** to display promising activity against the *Rhodotorula bogoriensis* yeast strain (MIC values between 0.016 and 0.036 mM) and can be considered as promising hit compounds. Furthermore, all (hydroxyalkylamino)quinoline derivatives exhibit activity toward the *Aspergillus flavus* strain, but particularly interesting is the fact that compound **9c** displays antifungal activity toward *A. flavus* comparable to Amphotericin B, the best-known commercially available antifungal agent. Therefore, compound **9c** can be considered as a promising novel antifungal (anti-*Aspergillus flavus*) lead structure. When comparing these results to the antimicrobial activities of similar molecules such as 3-, 5-, 6- and 8-(4-aminobutyloxy)quinolines, previously described in the literature, it appears that (hydroxyalkylamino)quinolines **9**, **10** and **13** retain potency when the side chain is moved around the quinoline core, while only 8-substituted (4-aminobutyloxy)quinolines displayed antifungal activity [21]. Future research should verify whether changing the substitution pattern of other amino side chains also provides retention of antifungal activity. The presence of one or two methyl groups on the hydroxyalkylamino side chain however, does not seem to have a significant influence on the compounds' antifungal potency.

3. Conclusion

In summary, preparation of (3-pyrrolin-1-yl)- and (2-oxopyrrolidin-1-yl)quinoline intermediates was established by cyclization of diallylaminoquinolines and 4-chloro-*N*-quinolinylbutanamides, respectively. The reactivity of (3-pyrrolin-1-yl)quinolines was subsequently evaluated by bromination reactions and the susceptibility of (2-oxopyrrolidin-1-yl)quinolines toward lithium aluminium hydride and methyllithium was assessed. Furthermore, the antiplasmodial activity of the novel functionalized (pyrrolidin-1-yl)- and (hydroxyalkylamino)quinolines was evaluated. Some of the tested compounds displayed micromolar activity against a chloroquine-sensitive strain of *P. falciparum*, and two compounds exhibited micromolar activity against a chloroquine-resistant strain of *P. falciparum*. Finally, antifungal assessment of (hydroxyalkylamino)quinolines resulted in the identification of three compounds displaying considerable activity against *R. bogoriensis* and one compound showing significant potency against *A. flavus*.

4. Experimental methods

4.1. General information

All reagents were purchased from commercial suppliers (Sigma–Aldrich, Acros, TCI), and were used as received without any purification unless otherwise noted. Solvents were dried with sodium (THF) or calcium hydride (dichloromethane), and distilled before use. Other solvents were purchased from commercial suppliers and used as supplied. The petroleum ether used during product purification steps had a boiling range of 40–60 °C. Crude reaction mixtures were analyzed by LC/MS/UV. Thin-layer chromatography was carried out on silica gel 60F254 plates (Merck). Column chromatography was performed in a glass column with silica gel (particle size 70−200 μm, pore diameter 60 Å). Preparative TLC was executed with 2000 μm 20 × 20 cm TLC plates. High-resolution ^{1}H and ^{13}C magnetic resonance (NMR) spectra were recorded with Jeol Eclipse+ 300 or Bruker AVANCE III 400 FT NMR spectrometers in $CDCl_3$, unless otherwise noted. Chemical shifts were calibrated using tetramethylsilane, which was used as an internal reference, unless otherwise indicated. Peak assignments were obtained with the aid of APT and HSQC spectra. Attenuated total reflection (ATR) IR spectra were recorded with a Perkin–Elmer Spectrum BX spectrometer, equipped with a ZnSe crystal, at room temperature (neat). Low-resolution mass spectra were recorded with an Agilent Technologies 1100 series VL mass spectrometer (ESI, 70 eV). High-resolution mass were obtained with an HPLC coupled to an Agilent Technologies 6210 series time-of-flight mass spectrometer equipped with an ESI/APCI-multimode source. Melting points were measured with a Büchi B-540 apparatus.

*4.2. General procedure for the synthesis of diallylaminoquinolines **2a-d***

To a solution of aminoquinoline **1** (3.5 mmol) in dry tetrahydrofuran (50 mL), 5.3 mL lithium bis(trimethylsilyl)amide (1M in THF) (5.3 mmol; 1.5 equiv) and 1.2 mL allyl bromide (14.0 mmol, 4 equiv) were added at 0 °C. After stirring for 1 h at reflux conditions under inert atmosphere (N_2), the flask was cooled to 0 °C and again lithium bis(trimethylsilyl)amide (1M in THF) (5.3 mmol; 1.5 equiv) was slowly added to the solution. The mixture was again stirred for 1 h at reflux conditions. The reaction mixture was quenched with 10 mL of a saturated ammonium chloride solution, poured into water (30 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtration of the drying agent and removal of the solvent in vacuo afforded diallylaminoquinolines **2a-d** in high purities (>90%, ^{1}H NMR).

4.2.1. 3-Diallylaminoquinoline **2a** (90-99%)

Spectral data of 3-diallylaminoquinoline **2a** corresponded with data described in the literature [23].

4.2.2. 5-Diallylaminoquinoline **2b** (79-95%)

Orange-brown oil. R_f (SiO_2) = 0.27 (Petroleumether/EtOAc 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): 3.78 (4H, d, *J* = 6.1 Hz); 5.16 (2H, d, *J* = 10.5 Hz); 5.24 (2H, d, *J* = 17.1 Hz); 5.78-5.91 (2H, m); 7.13 (1H, d, *J* = 8.3 Hz); 7.38 (1H, dd, *J* = 8.3, 4.4 Hz); 7.60 (1H, t, *J* = 8.3 Hz); 7.80 (1H, d, *J* = 8.3 Hz); 8.60 (1H, d, *J* = 8.3 Hz); 8.89 (1H, d, *J* = 4.4 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 56.4, 117.6, 118.0, 120.3, 124.4, 125.2, 129.0, 132.6, 134.5, 147.9, 149.5, 150.0. IR (cm^{-1}): ν_{max} = 3074, 2818, 1588, 1572, 1397, 986, 918, 799. MS (70 eV): m/z (%): 225 (M^++1,100). HRMS (ESI) calcd for $C_{15}H_{17}N_2$ 225.1386 $[M+H]^+$, found 225.1392.

4.2.3. 6-Diallylaminoquinoline **2c** (50-70%)

Brown-yellow oil. R_f (SiO_2) = 0.3 (Petroleumeter/EtOAc 9/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (4H, d, *J* = 4.7 Hz); 5.03-5.09 (4H, m); 5.71-5.80 (2H, m); 6.65 (1H, d, *J* = 2.9 Hz); 7.08 (1H, dd, *J* = 8.2, 4.2 Hz); 7.13 (1H, dd, *J* = 9.3, 2.9 Hz); 7.75 (1H, dd, *J* = 8.2, 1.6 Hz); 7.76 (1H, d, *J* = 9.3); 8.44 (1H, dd, *J* = 4.2, 1.6 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 52.9, 104.8, 116.4, 119.2, 121.3, 129.8, 130.0, 133.4, 134.0, 142.3, 146.2, 146.8. IR (cm^{-1}): ν_{max} = 3078, 1618, 1589, 1507, 1388, 1356, 1227, 920, 822. MS (70 eV): m/z (%): 225 (M^++1, 100) HRMS (ESI) calcd for $C_{15}H_{17}N_2$ 225.1386 $[M+H]^+$, found 225.1396.

4.2.4. 8-Diallylaminoquinoline **2d** (71%)

Orange-brown oil. R_f (SiO_2) = 0.28 (Petroleumether/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): 4.07 (4H, d, *J* = 6.1 Hz); 5.04 (2H, d, *J* = 10.5 Hz); 5.09 (2H, d, *J* = 17.6 Hz); 5.78-5.92 (2H, m); 7.00 (1H, dd, *J* = 7.2, 1.7 Hz); 7.21 (1H, dd, *J* = 8.3, 3.9 Hz); 7.25 (1H, dd, *J* = 7.2, 1.7 Hz); 7.29 (1H, t, *J* = 7.2 Hz); 7.94 (1H, dd, *J* = 8.3, 1.7 Hz); 8.80 (1H, dd, *J* = 3.9, 1.7 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 55.6, 117.5, 118.5, 120.8, 120.9, 126.4, 129.8, 135.2, 136.5, 143.1, 147.4, 147.9. IR (cm^{-1}): ν_{max} = 2976, 1565, 1498, 1469, 1389, 1241, 1098, 915, 822, 805, 788, 749. MS (70 eV): m/z (%): 225 (M^++1,100). HRMS (ESI) calcd for $C_{15}H_{17}N_2$ 225.1386 $[M+H]^+$, found 225.1386.

*4.3. General procedure for the synthesis of (3-pyrrolin-1-yl)quinolines **3a-d***

To a solution of diallylaminoquinoline **2** (1.6 mmol) in dry dichloromethane or tetrahydrofuran (25 mL), 1st generation Grubbs catalyst (0.2 mmol, 10 mol%) was added (for 8-diallylaminoquinoline **2d**

2nd generation Grubbs catalyst was necessary). After stirring for 24 h at room temperature under nitrogen atmosphere, the solvent was removed in vacuo and the crude reaction mixture was purified by means of preparative thin layer chromatoghraphy (pTLC) or column chromatography on silica gel, affording (3-pyrrolin-1-yl)quinolines **3a-d**.

4.3.1. 3-(3-pyrrolin-1-yl)quinoline **3a** (20-53%)

Brown crystals. R_f (SiO_2) = 0.39 (Petroleumether/EtOAc 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29 (4H, s); 6.03 (2H, s); 6.96 (1H, d, *J* = 2.8 Hz); 7.36-7.45 (2H, m); 7.64 (1H, dd, *J* = 7.2, 2.8 Hz); 7.96 (1H, dd); 8.54 (1H, d, *J* = 2.8 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 54.5, 110.6, 124.5, 125.9, 126.2, 126.9, 129.1, 129.7, 140.1, 140.5, 141.3. IR (cm^{-1}): ν_{max} = 3028, 2922, 2834, 1597, 1437, 1402, 834, 740, 674, 673. MS (70 eV): m/z (%): 197 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{13}N_2$ 197.1073 $[M+H]^+$, found 197.1073. T_m = 134 °C.

4.3.2. 5-(3-pyrrolin-1-yl)quinoline **3b** (48-82%)

Orange-brown oil. R_f (SiO_2) = 0.13-0.31 (Petroleumether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 (4H, s); 5.98 (2H, s); 6.98 (1H, dd, *J* = 7.6, 0.9 Hz); 7.31 (1H, dd, *J* = 8.7, 4.1 Hz); 7.59 (1H, dd, *J* = 8.3, 7.6 Hz); 7.65 (1H, dd, *J* = 8.3, 0.9 Hz); 8.64 (1H, dd, *J* = 8.7, 1.7 Hz); 8.85 (1H, dd, *J* = 4.1, 1.7 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$) δ 59.0, 111.5, 118.8, 121.4, 122.4, 126.5, 129.6, 133.4, 147.0, 149.7, 149.9. IR (cm^{-1}): ν_{max} = 2848, 1570, 1461, 1410, 1307, 907, 784, 727, 674. MS (70 eV): m/z (%): 197 (M^++1,100). HRMS (ESI) calcd for $C_{13}H_{13}N_2$ 197.10732 $[M+H]^+$, found 197.1076.

4.3.3. 6-(3-pyrrolin-1-yl)quinoline **3c** (50-80%)

Brown-yellow oil. R_f (SiO_2) = 0.15 (Petroleumether/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.22 (4H, s); 5.99 (2H, s); 6.59 (1H, d, *J* = 2,7 Hz); 7.15 (1H, dd, *J* = 9.2, 2.7 Hz); 7.25 (1H, dd, *J* = 8.4, 4.1 Hz); 7.93 (1H, dd, *J* = 8.4, 1.5 Hz); 7.97 (1H, d, *J* = 9.2 Hz); 8.59 (1H, dd, *J* = 4.1, 1.5 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 54.6, 103.1, 118.5, 121.4, 126.3, 130.1, 130.2, 133.9, 141.8, 145.1, 145.5. IR (cm^{-1}): ν_{max} = 3030, 1629, 1615, 1588, 1508, 1467, 1438, 1375, 1346, 1173, 1124, 672. MS (70 eV): m/z (%): 197 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{13}N_2$ 197.1073 $[M+H]^+$, found 197.1077.

4.3.4. 8-(3-pyrrolin-1-yl)quinoline **3d** (16-53%)

Orange viscous oil. R_f (SiO_2) = 0.59-0.67 (Petroleumether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (4H, s); 5.99 (2H, s); 6.68 (1H, dd, *J* = 7.9, 0.9 Hz); 7.09 (1H, dd, *J* = 7.9, 0.9 Hz); 7.29 (1H, dd, *J* = 8.3, 4.1 Hz); 7.38 (1H, t, *J* = 7.9 Hz); 8.02 (1H, dd, *J* = 8.3, 1.9 Hz); 8.72 (1H, dd, *J* = 4.1, 1.9 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$) δ 58.3, 109.4, 115.2, 120.6, 126.2, 127.3, 130.1, 135.6, 140.6, 145.4, 145.5. IR (cm^{-1}): ν_{max} = 2853, 1561, 1503, 1476, 1461, 1426, 1398, 1363, 1336, 1166, 1121, 810, 784, 747, 733, 674. MS (70 eV): m/z (%): 197 (M^++1,100). HRMS (ESI) calcd for $C_{13}H_{13}N_2$ 197.1073 $[M+H]^+$, found 197.1075.

*4.4. General procedure for the synthesis of 1-bromoquinolinyl-3,4-dibromopyrrolidines **4a-c***

To a solution of (3-pyrrolin-1-yl)quinolines **3** (0.5 mmol) in dry dichloromethane or tetrahydrofuran (25 mL) at 0 °C, bromine (1.0 mmol, 2 equiv) was slowly added. After stirring for 1 h at 0 °C under inert atmosphere (N_2), the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with a saturated sodium bicarbonate

solution (20 mL) and subsequently dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude products **4a-c**, which were purified by means of column chromatography on silica gel followed by purification by means of pTLC.

4.4.1. 1-(4-Bromoquinolin-3-yl)-*trans*-3,4-dibromopyrrolidine **4a** (28%)

Light-yellow powder. R_f (SiO_2) = 0.51 (Petroleumether/EtOAc 3/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (2H, d, *J* = 11.6 Hz); 4.73 (2H, d, *J* = 3.9 Hz); 4.93 (2H, dd, *J* = 11.6, 3.9 Hz); 7.59-7.61 (2H, m); 8.02 (1H, dd, *J* = 6.1, 3.3 Hz); 8.19 (1H, dd, *J* = 6.1, 3.3 Hz); 8.70 (1H, s). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 51.2, 58.0, 120.3, 126.0, 127.6, 128.4, 129.0, 129.5, 140.6, 143.1, 144.4. IR (cm^{-1}): ν_{NH} = 3330, ν_{max} = 2924, 1552, 1368, 1343, 1316, 759, 732. MS (70 eV): m/z (%): 433/435/437/439 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{12}Br_3N_2$ 432.8545 $[M+H]^+$, found 432.8543. T_m = 118.5 °C.

4.4.2. 1-(6-Bromoquinolin-5-yl)-*trans*-3,4-dibromopyrrolidine **4b** (28-34%)

Orange-red powder. R_f (SiO_2) = 0.24-0.38 (Petroleumether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (2H, dt, *J* = 11.7, 1.1 Hz); 4.58 (2H, dd, *J* = 11.7, 4.1 Hz); 4.71 (2H, dt, *J* = 4.1, 1.1 Hz); 6.95 (1H, d, *J* = 8.3 Hz); 7.44 (1H, dd, *J* = 8.6, 4.2 Hz); 7.92 (1H, d, *J* = 8.3 Hz); 8.48 (1H, dd, *J* = 8.6, 1.6 Hz); 9.03 (1H, dd, *J* = 4.2, 1.6 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$) δ 50.8, 59.5, 113.3, 120.0, 124.2, 128.2, 134.8, 136.7, 143.1, 146.3, 149.6. IR (cm^{-1}): ν_{max} = 2922, 1577, 1558, 1453, 1407, 1389, 1361, 1312, 1269, 1219, 1212, 1148, 786, 764. MS (70 eV): m/z (%): 433/435/437/439 (M^++1,100). HRMS (ESI) calcd for $C_{13}H_{12}Br_3N_2$ 432.8545 $[M+H]^+$, found 432.8530. T_m = 145.5 °C

4.4.3. 1-(5-Bromoquinolin-6-yl)-*trans*-3,4-dibromopyrrolidine **4c** (14%)

Brown-yellow oil. R_f (SiO_2) = 0.32 (Petroleumether/EtOAc 3/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (2H, d, *J* = 12.0 Hz); 4.69 (2H, dt, *J* = 3.9, 1.0 Hz); 4.84 (2H, dd, *J* = 12.0, 3.9 Hz); 7.43 (1H, dd, *J* = 8.6, 4.2 Hz); 7.52 (1H, d, *J* = 9.2 Hz); 8.01 (1H, d, *J* = 9.2 Hz); 8.55 (1H, dd, *J* = 8.6, 1.5 Hz); 8.76 (1H, dd, *J* = 4.2, 1.5 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 51.3, 58.2, 109.7, 122.0, 122.4, 129.5, 129.6, 134.7, 144.8, 145.4, 148.4. IR (cm^{-1}): ν_{max} = 2850, 1610, 1498, 1356, 800. MS (70 eV): m/z (%): 433/435/437/439 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{12}Br_3N_2$ 432.8545 $[M+H]^+$, found 432.8545.

*4.5. Procedure for the synthesis of 1-(5-bromoquinolin-6-yl)-2,3,4,5-tetrabromopyrrole **5***

To an ice-cooled solution of 6-(3-pyrrolin-1-yl)quinoline **3c** (0.5 mmol) in dry dichloromethane (25 mL), bromine (2.0 mmol, 2 equiv) was slowly added. After stirring for 2 h at room temperature, the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with a saturated sodium bicarbonate solution (20 mL) and subsequently dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude mixture, and 1-(5-bromoquinolin-6-yl)-2,3,4,5-tetrabromopyrrole **5** was isolated after column chromatography on silica gel followed by purification by means of pTLC.

4.5.1. 1-(5-Bromoquinolin-6-yl)-2,3,4,5-tetrabromopyrrolidine **5** (9%)

Yellow oil. R_f (SiO_2) = 0.4 (Petroleumether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, d, *J* = 8.9 Hz); 7.64 (1H, dd, *J* = 8.6, 4.2 Hz); 8.24 (1H, dd, *J* = 8.9, 0.7 Hz); 8.68 (1H, ddd, *J* = 8.6, 1.6, 0.7 Hz); 9.07 (1H, dd, *J* = 4.2, 1.6 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 103.1, 104.2, 123.2, 124.8, 128.2, 130.0,

130.6, 135.8, 136.5, 148.7, 152.6. IR (cm^{-1}): ν_{max} = 2922, 1490, 1458, 1367, 1318, 1297, 1284, 955, 833, 808, 770. MS (70 eV): m/z (%): 585/587/589/591/593/595 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_6Br_5N_2$ 584.6442 $[M+H]^+$, found 584.6452.

*4.6. General procedure for the synthesis of 4-chloro-N-(quinolinyl)butanamides **6a-d***

To a solution of aminoquinoline **1** (3.5 mmol) in dry dichloromethane (40 mL) under nitrogen atmosphere were added potassium carbonate (10.5 mmol, 3 equiv) and butyryl chloride (3.5 mmol, 1 equiv). After stirring for 2 h at room temperature, the reaction mixture was poured into water (30 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were subsequently dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude 4-chloro-*N*-(quinolinyl)butanamides **6a-d** (purity > 90%, NMR), which were used as such for the next reaction.

4.6.1. 4-Chloro-*N*-(quinolin-3-yl)butanamide **6a** (71-97%)

Light-yellow crystals. R_f (SiO_2) = 0.27 (Petroleumether/EtOAc 1/2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (2H, p, *J* = 6.6 Hz); 2.69 (2H, t, *J* = 6.6 Hz); 3.71 (2H, t, *J* = 6.6 Hz); 7.55 (1H, t, *J* = 7.2 Hz); 7.55 (1H, s (broad); 7.65 (1H, t, *J* = 7.2 Hz); 7.81 (1H, d, *J* = 7.2 Hz); 8.05 (1H, d, *J* = 7.2 Hz); 8.75 (1H, d, *J* = 2.2 Hz); 8.78 (1H, d, *J* = 2.2 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 27.9, 34.0, 44.5, 124.8, 127.6, 127.9, 128.2, 128.4, 128.8, 131.9, 143.6, 144.4, 171.3. IR (cm^{-1}): ν_{NH} = 3324, $\nu_{C=O}$ = 1549, ν_{max} = 2964, 1695, 1676, 1581, 1532, 1384, 746. MS (70 eV): m/z (%): 249/251 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{14}ClN_2O$ 249.0789 $[M+H]^+$, found 249.0792. T_m = 138 °C.

4.6.2. 4-Chloro-*N*-(quinolin-5-yl)butanamide **6b** (44-98%)

Light yellow powder. R_f (SiO_2) = 0.25 (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (2H, p, *J* = 6.6 Hz); 2.71 (2H, t, *J* = 6.6 Hz); 3.71 (2H, t, *J* = 6.6 Hz); 7.40 (1H, dd, *J* = 8.3, 4.4 Hz); 7.67 (1H, t, *J* = 8.3 Hz); 7.78 (1H, d, *J* = 8.3 Hz); 7.80 (1H, d, *J* = 4.4 Hz); 7.97 (1H, d, *J* = 8.3 Hz); 8.18 (1H, d, *J* = 8.2 Hz); 8.91 (1H, s (broad)). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$) δ 28.0, 33.8, 44.6, 121.2, 122.4, 123.2, 127.8, 129.3, 130.2, 132.2, 148.5, 150.5, 171.1. IR (cm^{-1}): ν_{NH} = 3283, $\nu_{C=O}$ = 1660, ν_{max} = 1524, 1492, 796, 698, 644. MS (70 eV): m/z (%): 249/251 (M^++1,100). HRMS (ESI) calcd for $C_{13}H_{14}ClN_2O$ 249.0789 $[M+H]^+$, found 249.0797. T_m = 115 °C.

4.6.3. 4-Chloro-*N*-(quinolin-6-yl)butanamide **6c** (65-99%)

Light-yellow crystals. R_f (SiO_2) = 0.19 (Petroleumether/EtOAc 1/2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (2H, p, *J* = 6.6 Hz); 2.65 (2H, t, *J* = 6.6 Hz); 3.69 (2H, t, *J* = 6.6 Hz); 7.40 (1H, dd, *J* = 8.8, 4.4 Hz); 7.57 (1H, dd, *J* = 8.8, 2.8 Hz); 7.98 (1H, s (broad)); 8.04 (1H, d, *J* = 8.8 Hz); 8.12 (1H, d, *J* = 8.8 Hz); 8.41 (1H, s); 8.84 (1H, d, *J* = 4.4 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 27.9, 34.2, 44.5, 116.3, 121.8, 123.3, 128.9, 130.1, 135.9, 136.2, 145.4, 149.4, 170.6. IR (cm^{-1}): ν_{NH} = 3259, $\nu_{C=O}$ = 1684, ν_{max} = 2922, 1581, 1561, 1382, 1239, 1233, 828, 802. MS (70 eV): m/z (%): 249/251 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{14}ClN_2O$ 249.0789 $[M+H]^+$, found 249.0794. T_m = 144 °C.

4.6.4. 4-Chloro-*N*-(quinolin-8-yl)butanamide **6d** (37-99%)

Beige powder. R_f (SiO_2) = 0.25 (Petroleumether/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (2H, p, *J* = 6.6 Hz); 2.78 (2H, t, *J* = 6.6 Hz); 3.72 (2H, t, *J* = 6.6 Hz); 7.47 (1H, dd, *J* = 8.3, 4.4 Hz); 7.52 (1H, t, *J* = 6.6 Hz); 7.53 (1H, d, *J* = 6.6 Hz); 8.18 (1H, d, *J* = 8.3 Hz); 8.76 (1H, d, *J* = 6.6 Hz); 8.82 (1H, d, *J* = 4.4 Hz); 9.87 (1H, s (broad)). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$) δ 28.1, 34.7, 44.6, 116.7, 121.70, 121.74, 127.5,

128.1, 134.4, 136.6, 138.2, 148.2, 170.5. IR (cm^{-1}): $\nu_{C=O}$ = 1695, ν_{NH} = 3355, ν_{max} = 1519, 1483, 1322, 1144, 826, 790, 661. MS (70 eV): m/z (%): 249 /251 (M^++1,100). HRMS (ESI) calcd for $C_{13}H_{14}ClN_2O$ 249.0789 $[M+H]^+$, found 249.0790. T_m = 64 °C.

*4.7. General procedure for the synthesis of (2-oxopyrrolidin-1-yl)quinolines **7a-d***

To a solution of 1-quinolinyl-4-chlorobutyramides **6** (2.7 mmol) in acetonitrile (40 mL) was added potassium *tert*-butoxide (4.1 mmol, 1.5 equiv). After stirring for 2 h at reflux conditions the reaction mixture was poured into brine (30 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were subsequently dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded (2-oxopyrrolidin-1-yl)quinolines **7a-d**, which were purified by means of column chromatography on silica gel.

4.7.1. 3-(2-oxopyrrolidin-1-yl)quinoline **7a** (60-90%)

Spectral data of 3-(2-oxopyrrolidin-1-yl)quinoline **7a** corresponded with data described in the literature [36].

4.7.2. 5-(2-oxopyrrolidin-1-yl)quinoline **7b** (62%)

Yellow oil. R_f (SiO_2) = 0.03 (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (2H, p, *J* = 7.7 Hz); 2.72 (2H, t, *J* = 7.7 Hz); 3.89 (2H, t, *J* = 7.7 Hz); 7.44 (1H, dd, *J* = 8.3, 2.9 Hz); 7.45 (1H, d, *J* = 8.3 Hz); 7.73 (1H, t, *J* = 8.3 Hz); 8.10 (2H, d, *J* = 8.3 Hz); 8.94 (1H, d, *J* = 2.8 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$) δ 19.4, 31.6, 52.0, 121.6, 124.4, 125.0, 129.1, 129.7, 131.8, 135.7, 149.0, 150.9, 175.5. IR (cm^{-1}): $\nu_{C=O}$ = 1678, ν_{max} = 1595, 1416, 1402, 1297, 1246, 802, 726, 668. MS (70 eV): m/z (%): 213 (M^++1,100). HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ 213.1022 $[M+H]^+$, found 213.1032.

4.7.3. 6-(2-oxopyrrolidin-1-yl)quinoline **7c** (70-90%)

Brown-red crystals. R_f (SiO_2) = 0.10 (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (2H, p, *J* = 7.7 Hz); 2.66 (2H, t, *J* = 7.7 Hz); 3.96 (2H, t, *J* = 7.7 Hz); 7.73 (1H, dd, *J* = 7.7, 3.9 Hz); 7.96 (1H, s); 8.07-8.15 (3H, m); 8.84 (1H, d, *J* = 3.9 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 17.9, 32.8, 48.8, 116.2, 121.6, 122.9, 128.4, 129.9, 135.8, 137.6, 145.4, 149.7, 174.6. IR (cm^{-1}): $\nu_{C=O}$ = 1689, ν_{max} = 2924, 1505, 1402, 1370, 1332, 1295, 1242, 1219, 879, 838. MS (70 eV): m/z (%): 213 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{13}N_2O$ 213.1022 $[M+H]^+$, found 213.1029. T_m = 125 °C.

4.7.4. 8-(2-oxopyrrolidin-1-yl)quinoline **7d** (72%)

Spectral data of 8-(2-oxopyrrolidin-1-yl)quinoline **7d** corresponded with data described in the literature.[37]

*4.8. General procedure for the synthesis of 6-(pyrrolidin-1-yl)quinolines **8a-c***

To a solution of (2-oxopyrrolidin-1-yl)quinolines **7** (0.5 mmol) in dry tetrahydrofuran (25 mL), a lithium aluminium hydride solution (1M in THF) (0.8 mmol, 1.5 equiv) was added slowly under inert atmosphere (N_2) at 0 °C. After stirring for 3 h at reflux conditions, the reaction mixture was quenched with 10 mL of saturated ammonium chloride solution, poured into water (20 mL) and extracted with

ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded (pyrrolidin-1-yl)quinoline **8a-c**, which was purified by means of column chromatography on silica gel.

4.8.1. 3-(Pyrrolidin-1-yl)quinoline **8a** (40%)

Spectral data of 3-(pyrrolidin-1-yl)quinoline **8a** corresponded with data described in the literature [38].

4.8.2. 5-(Pyrrolidin-1-yl)quinoline **8b** (37%)

Spectral data of 5-(pyrrolidin-1-yl)quinoline **8b** corresponded with data described in the literature [39].

4.8.3. 6-(Pyrrolidin-1-yl)quinoline **8c** (68%)

Spectral data of 6-(pyrrolidin-1-yl)quinoline **8c** corresponded with data described in the literature [40].

*4.9. General procedure for the synthesis of 4-(quinolinylamino)butanols **9a-d***

To a solution of (2-oxopyrrolidin-1-yl)quinolines **7** (0.5 mmol) in dry tetrahydrofuran (25 mL) lithium aluminium hydride solution (1M in THF) (0.8 mmol, 1.5 equiv) was added slowly under inert atmosphere at 0 °C. After stirring for 2.5 h at room temperature, methanol (25 mL) and sodium borohydride (0.8 mmol, 1.5 equiv) were added to the mixture. The solution was stirred for three additional hours at room temperature. Finally the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded 4-(quinolinylamino)butanols **9a-d**, which were purified by means of pTLC.

4.9.1. 4-(Quinolin-3-ylamino)butanol **9a** (40%)

Yellow oil. R_f (SiO_2) = 0.11 (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70-1.87 (4H, m); 3.27 (2H, t, *J* = 6.6 Hz); 3.75 (2H, t, *J* = 6.6 Hz); 7.03 (1H, d, *J* = 2.2 Hz); 7.38-7.45 (2H, m); 7.62 (1H, d, *J* = 7.7 Hz); 7.94 (1H, d, *J* = 7.7 Hz); 8.84 (1H, d, *J* = 2.2 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 25.7, 30.3, 43.6, 62.5, 110.1, 125.0, 126.0, 127.1, 128.9, 129.7, 141.8, 141.9, 143.4. IR (cm^{-1}): $\nu_{OH,NH}$ = 3328, 3162, ν_{max} = 2941, 2859, 1612, 1537, 1060, 1017, 778, 753. MS (70 eV): m/z (%): 217 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{17}N_2O$ 217.1335 $[M+H]^+$, found 217.1343. T_m = 122 °C.

4.9.2. 4-(Quinolin-5-ylamino)butanol **9b** (12-17%)

Yellow crystals. R_f (SiO_2) = 0.11-0.30 (100% EtOAc). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 1.58 (2H, p, *J* = 6.7 Hz); 1.74 (2H, p, *J* = 6.7 Hz); 2.78 (2H, s (broad)); 3.20 (2H, t, *J* = 6.7 Hz); 3.51 (2H, t, *J* = 6.7 Hz); 6.50 (1H, d, *J* = 8.1 Hz); 7.18 (1H, d, *J* = 8.1 Hz); 7.21 (1H, dd, *J* = 8.6, 4.2 Hz); 7.39 (1H, t, *J* = 8.1 Hz); 8.56 (1H, dd, *J* = 8.6, 1.7 Hz); 8.66 (1H, dd, *J* = 4.2, 1.7 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$) δ 23.9, 28.5, 42.2, 60.6, 102.6, 116.2, 116.6, 117.3, 127.0, 128.6, 141.9, 147.2, 147.9. IR (cm^{-1}): $\nu_{NH,\ OH}$ = 3353, ν_{max} = 2925, 15.86, 1418, 1351, 1329, 1050, 1025, 793. MS (70 eV): m/z (%): 217 (M^++1,100). HRMS (ESI) calcd for $C_{13}H_{17}N_2O$ 217.1335 $[M+H]^+$, found 217.1338. T_m = 124 °C.

4.9.3. 4-(Quinolin-6-ylamino)butanol **9c** (40%)

Yellow oil. R_f (SiO_2) = 0.17 (CH_3CN/CH_2Cl_2 1/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69-1.83 (4H, m); 3.23 (2H, t, *J* = 6.7 Hz); 3.73 (2H, t, *J* = 6.1 Hz); 6.66 (1H, d, *J* = 2.6 Hz); 7.05 (1H, dd, *J* = 9.1, 2.6 Hz); 7.25 (1H, dd, *J* = 8.2, 4.3 Hz); 7.85 (1H, d, *J* = 9.1 Hz); 7.91 (1H, dd, *J* = 8.2, 1.6 Hz); 8.57 (1H, dd, *J* = 4.3, 1.6 Hz). ^{13}C NMR (100.6 MHz, Ref = $CDCl_3$): δ 25.8, 30.3, 43.7, 62.4, 102.7, 121.3, 121.7, 129.8, 130.3, 134.1, 142.7, 145.6, 146.4. IR (cm^{-1}): $\nu_{OH,\ NH}$ = 3313, ν_{max} = 2935, 2864, 1624, 1523, 1383, 1247, 828. MS (70 eV) m/z (%): 217 (M^++1, 100). HRMS (ESI) calcd for $C_{13}H_{17}N_2O$: 217.1335 $[M+H]^+$, found: 217.1337.

4.9.4. 4-(Quinolin-8-ylamino)butanol **9d** (25%)

Light yellow-green oil. R_f (SiO_2) = 0.23-0.32 (Petroleumether/EtOAc 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71-1.78 (2H, m); 1.81-1.88 (2H, m); 1.96 (1H, s (broad)); 3.32 (2H, t, *J* = 6.2 Hz); 3.70 (2H, t, *J* = 6.2 Hz); 6.13 (1H, s (broad)); 6.66 (1H, dd, *J* = 7.9, 0.9 Hz); 7.03 (1H, dd, *J* = 7.9, 0.9 Hz); 7.34 (1H, dd, *J* = 8.3, 4.2 Hz); 7.37 (1H, t, *J* = 7.9 Hz); 8.03 (1H, dd, *J* = 8.3, 1.7 Hz); 8.69 (1H, dd, *J* = 4.4, 1.7 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$) δ 25.7, 30.5, 43.2, 62.6, 104.7, 113.7, 121.4, 127.8, 128.7, 136.1, 138.2, 144.8, 146.8. IR (cm^{-1}): $\nu_{NH,\ OH}$ = 3400, ν_{max} = 2936, 1575, 1519, 1476, 1379, 1337, 907, 817, 789, 728. MS (70 eV): m/z (%): 217 (M^++1,100). HRMS (ESI) calcd for $C_{13}H_{17}N_2O$ 217.1335 $[M+H]^+$, found 217.1333.

*4.10. Procedures for the synthesis of 5-quinolinylamino-2-methylpentan-2-ols **10a'-d***

1st method: To a solution of 6-(2-oxopyrrolidin-1-yl)quinoline **7c** (0.5 mmol) in dry tetrahydrofuran (25 mL), a methyllithium solution (1.6M in Et_2O) (0.5 mmol, 1 equiv) was added slowly under inert atmosphere (N_2) at 0 °C. After stirring for 1 h at 0 °C, again methyllithium solution (1.6M in Et_2O) (0.5 mmol, 1 equiv) was added slowly to the mixture, which was stirred for one additional hour at 0 °C. This step was repeated two more times until a total of 4 equiv of methyllithium was added. Finally the reaction mixture was quenched with 20 mL of saturated ammonium chloride solution, poured into water (30 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with a saturated sodium bicarbonate solution (20 mL) and subsequently dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded 5-quinolin-6-ylamino-2-methylpentan-2-ol **10c**, which was purified by means of pTLC.

2nd method: To a solution of 5-(quinolinylamino)pentan-2-ones **11a-b** (0.5 mmol) in dry tetrahydrofuran (25 mL), methylmagnesium iodide (3M in THF) (1.0 mmol, 2 equiv) was added under inert atmosphere (N_2) at 0 °C. After stirring for 2 h at 0 °C the reaction mixture was quenched with a solution of saturated ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded 5-quinolinylamino-2-methylpentan-2-ols **10a-b**, which were purified by means of pTLC.

3rd method: To a solution of 8-(2-oxopyrrolidin-1-yl)quinoline **7d** (0.5 mmol) in dry tetrahydrofuran (25 mL), a methyllithium solution (1.6M in Et_2O) (0.5 mmol, 1 equiv) was added slowly under inert

atmosphere (N_2) at 0 °C. After stirring for 1 h at 0 °C, again a methyllithium solution (1.6M in Et_2O) (0.5 mmol, 1 equiv) was added slowly to the mixture. Afterward, the solution was stirred for one additional hour at 0 °C. Finally the reaction mixture was quenched with 10 mL of saturated ammonium chloride solution, poured into water (30 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with a saturated sodium bicarbonate solution (15 mL) and subsequently dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded 5-(quinolin-8-ylamino)-2-methylpentan-2-ol **10d**, which was purified by means of pTLC.

4.10.1. 5-(2-Methylquinolin-3-ylamino)-2-methylpentan-2-ol **10a'** (15%)

Yellow oil. Rf (SiO_2)= 0.21; (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (6H, s); 1.63-1.68 (2H, m); 1.82-1.92 (2H, m); 2.59 (3H, s); 3.25 (2H, t, *J* = 7.0 Hz); 7.00 (1H, s); 7.35-7.41 (2H, m); 7.59-7.63 (1H, m); 7.87-7.90 (1H, m). ^{13}C NMR (100.6 MHz, Ref = $CDCl_3$): δ 19.5, 22.1, 27.6, 39.2, 42.3, 58.5, 107.3, 122.8, 123.7, 124.1, 126.2, 127.2, 138.6, 139.1, 147.4. IR (cm^{-1}): $\nu_{OH,\ NH}$ = 3346, ν_{max} = 2965, 2929, 1608, 1515, 1487, 1467, 1486, 1438, 1386, 1360, 1331, 1243, 1183, 749. MS (70 eV) m/z (%): 259 (M^++1, 100). HRMS (ESI) calcd for $C_{16}H_{23}N_2O$ 259.1805 $[M+H]^+$, found 259.1810.

4.10.2. 5-(Quinolin-5-ylamino)-2-methylpentan-2-ol **10b** (23%)

Green oil. R_f (SiO_2) = 0.09-0.15 (Petroleumether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, s); 1.63-1.68 (2H, m); 1.83-1.90 (2H, m); 3.33 (2H, t, *J* = 6.9 Hz); 6.15 (1H, s (broad)); 6.67 (1H, dd, *J* = 7.9, 0.9 Hz); 7.03 (1H, dd, *J* = 7.9, 0.9 Hz); 7.35 (1H, dd, *J* = 8.2, 4.3 Hz); 7.37 (1H, t, *J* = 7.9 Hz); 8.04 (1H, dd, *J* = 8.2, 1.7 Hz); 8.70 (1H, dd, *J* = 4.3, 1.7 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$) δ 24.3, 29.3, 41.4, 43.9, 70.8, 104.6, 113.7, 121.4, 127.8, 128.7, 136.0, 138.2, 144.9, 146.8. IR (cm^{-1}): $\nu_{NH,\ OH}$ = 3401, ν_{max} = 2967, 1575, 1520, 1378, 13.36, 817, 789, 731. MS (70 eV): m/z (%): 245 (M^++1,100). HRMS (ESI) calcd for $C_{15}H_{21}N_2O$ 245.1648 $[M+H]^+$, found 245.1650.

4.10.3. 5-(Quinolin-6-ylamino)-2-methylpentan-2-ol **10c** (43%)

Yellow oil. R_f (SiO_2) = 0.21 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (6H, s); 1.59-1.65 (2H, m); 1.76-1.83 (2H, m); 3.23 (2H, t, *J* = 7.0 Hz); 6.68 (1H, d, *J* = 2.6 Hz); 7.07 (1H, dd, *J* = 9.1, 2.6 Hz); 7.25 (1H, dd, *J* = 8.4, 4.2 Hz); 7.86 (1H, d, *J* = 9.1 Hz); 7.91 (1H, dd, *J* = 8.4, 1.6 Hz); 8.59 (1H, dd, *J* = 4.2, 1.6 Hz). ^{13}C NMR (100.6 MHz, Ref = $CDCl_3$): δ 24.1, 29.5, 41.1, 44.4, 70.7, 102.7, 121.4, 121.5, 130.0, 130.2, 133.9, 143.0, 145.9, 146.3. IR (cm^{-1}): $\nu_{OH,\ NH}$ = 3314, ν_{max} = 2966, 1624, 1523, 1469, 1381, 1243, 828. MS (70 eV) m/z (%): 245 (M^++1, 100). HRMS (ESI) calcd for $C_{15}H_{21}N_2O$ 245.1648 $[M+H]^+$, found 245.1657.

4.10.4. 5-(Quinolin-8-ylamino)-2-methylpentan-2-ol **10d** (26-43%)

Yellow oil. R_f (SiO_2) = 0.29 (Petroleumether/EtOAc 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (6H, s); 1.64 (2H, t, *J* = 7.7 Hz); 1.86 (2H, p, *J* = 7.7 Hz); 3.32 (2H, t, *J* = 7.7 Hz); 6.15 (1H, s (broad)); 6.66 (1H, d, *J* = 7.7 Hz); 7.03 (1H, d, *J* = 7.7 Hz); 7.34 (1H, dd, *J* = 8.3, 4.4 Hz); 7.38 (1H, t, *J* = 7.7 Hz); 8.04 (1H, d, *J* = 8.3 Hz); 8.70 (1H, d, *J* = 4.4 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$) δ 24.4, 29.4, 41.5, 44.0, 70.9, 104.7, 113.7, 121.5, 127.9, 128.8, 136.1, 138.2, 144.9, 146.9. IR (cm^{-1}): $\nu_{NH/OH}$ = 3400, ν_{max} = 2965, 1574, 1519, 1378, 1336, 817, 789, 739. MS (70 eV): m/z (%): 245 (M^++1,100). HRMS (ESI) calcd for $C_{15}H_{21}N_2O$ 245.1648 $[M+H]^+$, found 245.1654.

*4.11. General procedure for the synthesis of 5-(quinolinylamino)pentan-2-ones **11a-c***

To a solution of 1-quinolinylpyrrolidin-2-one **7** (0.5 mmol) in dry tetrahydrofuran (25 mL), a methyllithium solution (1.6M in Et_2O) (0.5 mmol, 1 equiv) was added slowly under inert atmosphere (N_2) at 0 °C. After stirring for 1 h at 0 °C, again a methyllithium solution (1.6M in Et_2O) (0.5 mmol, 1 equiv) was added slowly to the mixture. Afterward, the solution was stirred for one additional hour at 0 °C. Finally the reaction mixture was quenched with 10 mL of saturated ammonium chloride solution and poured into water (30 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with a saturated sodium bicarbonate solution (15 mL) and subsequently dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded 5-(quinolinylamino)pentan-2-ones **11a-c**. These methylketones were not stable enough to purify over silica gel and were thus used as such for further reactions (purity > 90%, NMR). For the synthesis of 5-(2-methylquinolin-3-yl)pentan-2-one **11a'**, the reaction was performed at room temperature instead of at 0 °C.

4.11.1. 5-(Quinolin-3-ylamino)pentan-2-one **11a** (70-97%)

Yellow-orange oil. R_f (SiO_2) = 0.51 (CH_3CN/CH_2Cl_2 3/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97 (2H, p, *J* = 6.6 Hz); 2.18 (3H, s); 2.62 (2H, t, *J* = 6.6 Hz); 3.21 (2H, t, *J* = 6.6 Hz); 4.19 (1H, s (broad)); 7.01 (1H, d, *J* = 2.2 Hz); 7.37-7.44 (2H, m); 7.61 (1H, d, *J* = 7.7 Hz); 7.93 (1H, d, *J* = 7.7 Hz); 8.41 (1H, d, *J* = 2.2 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$): δ 22.8, 30.1, 41.1, 43.0, 109.7, 124.8, 126.0, 127.0, 127.7, 128.6, 128.8, 129.7, 143.5, 208.7. IR (cm^{-1}): ν_{NH} = 3362, $\nu_{C=O}$ = 1709, ν_{max} = 2949, 1608, 1389, 1368, 1350, 780, 748. MS (70 eV): m/z (%): 229 (M^++1, 100). HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ 229.1335 $[M+H]^+$, found 229.1340.

4.11.2. 5-(Quinolin-3-ylamino)pentan-2-one **11a'** (75-95%)

Due to the instability of this compound complete characterization was not possible, and only the ^{1}H NMR data are depicted below.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (2H, t, *J* = 6.6 Hz, $C\underline{H}_2CH_2CO$); 2.05 (1H, s (broad), NH); 2.21 (3H, s); 2.63-2.70 (5H, m); 3.25 (2H, t, *J* = 6.6 Hz); 7.04 (1H, s); 7.39-7.42(2H, m); 7.61-7.64 (1H, m); 7.94-7.99 (1H, m).

4.11.3. 5-(Quinolin-5-ylamino)pentan-2-one **11b** (84-92%)

Yellow oil. R_f (SiO_2) = 0.30 (100% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03 (2H, p, *J* = 6.6 Hz); 2.16 (3H, s); 2.65 (2H, t, *J* = 6.6 Hz); 3.23 (2H, t, *J* = 6.6 Hz); 4.85 (1H, s (broad)); 6.55 (1H, d, *J* = 8.3 Hz); 7.30 (1H, dd, *J* = 8.3, 4.4 Hz); 7.45 (1H, d, *J* = 8.3 Hz); 7.54 (1H, t, *J* = 8.3 Hz); 8.18 (1H, d, *J* = 8.3 Hz); 8.84 (1H, d, *J* = 4.4 Hz). ^{13}C NMR (75.6 MHz, ref = $CDCl_3$) δ 22.5, 30.2, 41.9, 44.1, 104.0, 117.9, 118.5, 119.4, 129.2, 130.6, 144.0, 149.2, 149.9, 209.7. IR (cm^{-1}): $\nu_{C=O}$ = 1707, ν_{NH} = 3368, ν_{max} = 2360, 1586, 1576, 1415, 1327, 788, 731. MS (70 eV): m/z (%): 229 (M^++1,100). HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ 229.1335 $[M+H]^+$, found 229.1340.

4.11.4. 5-(Quinolin-6-ylamino)pentan-2-one **11c** (90-99%)

Brown-yellow oil. Rf (SiO_2) = 0.15 (Petroleumether/EtOAc 1/2).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (2H, p, *J* = 6.8 Hz); 2.18 (3H, s); 2.63 (2H, t, *J* = 6.8 Hz); 3.24 (2H, t, *J* = 6.8 Hz); 6.69 (1H, d, *J* = 2.6 Hz); 7.07

(1H, dd, *J* = 9.1, 2.6 Hz); 7.26 (1H, dd, *J* = 8.0, 4.2 Hz); 7.86 (1H, d, *J* = 9.1 Hz); 7.91 (1H, dd, *J* = 8,0, 1.6 Hz); 8.61 (1H, dd, *J* = 4.2, 1.6 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 22.9, 30.0, 41.1, 43.3, 102.6, 121.3, 121.5, 130.0, 130.2, 133.8, 143.0, 145.9, 146.2, 208.5. IR (cm^{-1}): ν_{NH} = 3342, $\nu_{C=O}$ = 1708, ν_{max} = 2928, 1608, 1504, 1378, 1292, 1244, 828, 208,5. MS (70 eV): m/z (%): 229 (M^++1, 100). HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ 229.1335 $[M+H]^+$, found 229.1343.

*4.12. General procedure for the synthesis of (2-methylpyrrolidin-1-yl)quinolines **12a-c***

To a solution of 5-(quinolinylamino)pentan-2-ones **11** (0.5 mmol) in methanol (25 mL), acetic acid (2.5 mmol, 5 equiv) and sodium cyanoborohydride (1.0 mmol, 2 equiv) were added. After stirring for 3 h at room temperature, the reaction mixture was poured into water (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtration of the drying agent and removal of the solvent in vacuo afforded the crude products **12a-c**, which were purified by means of column chromatography on silica gel or pTLC.

4.12.1. 3-(2-Methylpyrrolidin-1-yl)quinoline **12a** (61%)

Yellow oil. R_f (SiO_2) = 0.55 (Petroleumether/EtOAc 1/2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, d, *J* = 6.6 Hz); 1.75-1.85 (1H, m); 2.05-2.21 (3H, m); 3.27-3.35 (1H, m); 3.56-3.61 (1H, m); 4.08 (1H, p, *J* = 6.6 Hz); 6.98 (1H, d, *J* = 2.2 Hz); 7.34-7.42 (2H, m); 7.61 (1H, d, *J* = 7.7 Hz); 7.94 (1H, d, *J* = 7.7 Hz); 8.57 (1H, d, *J* = 2.2 Hz). ^{13}C NMR (75.6 MHz, ref = C_6D_6): δ 18.8, 22.8, 32.7, 47.5, 53.2, 110.6, 124.2, 125.8, 126.7, 129.8, 130.1, 140.6, 141.1, 141.9. IR (cm^{-1}): ν_{max} = 2963, 1594, 1432, 1393, 1379, 1370, 745. MS (70 eV): m/z (%): 213 (M^++1, 100). HRMS (ESI) calcd for $C_{14}H_{17}N_2$ 213.1386 $[M+H]^+$, found 213.1393.

4.12.2. 2-Methyl-3-(2-methylpyrrolidin-1-yl)quinoline **12a'** (33%)

Brown-yellow oil. Rf (SiO_2) = 0.5 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 6.0 Hz); 1.61-1.71 (1H, m); 1.80-1.91 (1H, m); 1.95-2.04 (1H, m); 2.19-2.29 (1H, m); 2.71 (3H, s); 2.89 (1H, td, *J* = 8.7, 3.8 Hz); 3.66-3.73 (1H, m); 3.79-3.87 (1H, m); 7.39-7.43 (1H, m); 7.43 (1H, s); 7.47-7.51 (1H, m); 7.66 (1H, dd, *J* = 8.0, 1.2 Hz); 7.95 (1H, d, *J* = 8.3 Hz). ^{13}C NMR (100.6 MHz, ref=$CDCl_3$): δ 18.7, 23.7, 23.8, 33.9, 53.1, 55.0, 120.6, 125.8, 126.2, 126.6, 127.9, 142.71, 142.72, 143.0, 156.5. IR (cm^{-1}): ν_{max} = 2964, 1594, 1424, 1375, 1362, 1347, 1325, 749. MS (70 eV): m/z (%): 227 (M^++1, 100). HRMS (ESI) calcd for $C_{15}H_{19}N_2$ 227.1543 $[M+H]^+$, found 227.1541.

4.12.3. 5-(2-methylpyrrolidin-1-yl)quinoline **12b** (31%)

Yellow oil. R_f (SiO_2) = 0.13 (Petroleumether/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$): 1.08 (3H, d, *J* = 6.0 Hz); 1.65-1.74 (1H, m); 1.79-1.90 (1H, m); 1.96-2.04 (1H, m); 2.20-2.27 (1H, m); 2.99 (2H, td, *J* = 8.8, 4.7 Hz); 3.74 (1H, m); 7.03 (1H, d, *J* = 7.5 Hz); 7.32 (1H, dd, *J* = 8.6, 4.2 Hz); 7.59 (1H, dd, *J* = 8.4, 7.6 Hz); 7.72 (1H, d, *J* = 8.4 Hz); 8.54 (1H, dd, *J* = 8.5, 1.6 Hz); 8.85 (1H, dd, *J* = 4.2, 1.6 Hz). ^{13}C NMR (100.6 MHz, ref = 100.6 MHz): δ 18.7, 23.8, 33.8, 55.7, 56.0, 114.0, 119.3, 122.8, 124.9, 129.4, 133.4, 147.2, 149.6, 149.9. IR (cm^{-1}): ν_{max} = 2963, 1587, 1570, 1464, 1398, 1315, 1286, 1089, 794. MS (70 eV): m/z (%): 213 (M^++1,100). HRMS (ESI) calcd for $C_{14}H_{17}N_2$ 213.1386 $[M+H]^+$, found 213.1389.

4.12.4. 6-(2-methylpyrrolidin-1-yl)quinoline **12c** (27%)

Brown-yellow oil. Rf (SiO_2) = 0.3 (Petroleumether/EtOAc 1/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, d, *J* = 6.2 Hz); 1.76-1.79 (1H, m); 2.03-2.18 (3H, m); 3.26-3.33 (1H, m); 3.51-3.56 (1H, m); 4.01-4.07 (1H, m); 6.63 (1H, d, *J* = 2.7 Hz); 7.21-7.25 (2H, m); 7.91 (1H, dd, *J* = 8.1, 1.4 Hz); 7.93 (1H, d, *J* = 9.4 Hz); 8.57 (1H, dd, *J* = 4.2, 1.4 Hz). ^{13}C NMR (100.6 MHz, ref=$CDCl_3$): δ 19.3, 23.3, 33.1, 48.3, 53.8,

103.6, 119.4, 121.2, 129.7, 130.3, 133.9, 141.5, 145.1, 145.3. IR (cm^{-1}): ν_{max} = 2962, 1618, 1589, 1380, 1364, 1124, 1076, 823. MS (70 eV): m/z (%): 213 (M^++1, 100). HRMS (ESI) calcd for $C_{14}H_{17}N_2$ 213.1386 $[M+H]^+$, found 213.1394.

*4.13. General procedure for the synthesis of 5-(quinolinylamino)pentan-2-ols **13a-c***

To a solution of 5-(quinolinylamino)pentan-2-ones **11** (0.5 mmol) in methanol (25 mL), sodium borohydride (0.8 mmol, 1.5 equiv) was added. After stirring for 2 h at room temperature, the reaction mixture was poured into water (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and filtration of the drying agent and removal of the solvent in vacuo afforded the crude 5-(quinolinylamino)pentan-2-ols **13a-c**, which were purified by means of pTLC.

4.13.1. 5-(Quinolin-3-ylamino)pentan-2-ol **13a** (32%)

Yellow oil. Rf (SiO_2) = 0.13 (100% EtOAc).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, d, *J* = 6.2 Hz); 1.57-1.62 (2H, m); 1.70-1.88 (2H, m); 3.20 (2H, t, *J* = 7.1 Hz); 3.88 (1H, sext, *J* = 6.2 Hz); 6.98 (1H, d, *J* = 2.8 Hz); 7.36-7.43 (2H, m); 7.59 (1H, dd, *J* = 7.3, 2.3 Hz); 7.93 (1H, dd, *J* = 7.3, 2.3 Hz); 8.40 (1H, d, *J* = 2.8 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 23.8, 25.4, 36.6, 43.6, 67.6, 109.9, 124.8, 125.9, 126.9, 128.8, 129.6, 141.77, 141.81, 143.3. IR (cm^{-1}): $\nu_{OH,\ NH}$ = 3306, ν_{max} = 2962, 2930, 1611, 1535, 1488, 1473, 1392, 1372, 1350, 1223, 779, 748. MS (70 eV): m/z (%): 231 (M^++1, 100). HRMS (ESI): calcd for $C_{14}H_{19}N_2O$ 231.1492 $[M+H]^+$, found 231.1491.

4.13.2. 5-(2-Methylquinolin-3-ylamino)pentan-2-ol **13a'** (20%)

Yellow oil. Rf (SiO_2) = 0.18 (100% EtOAc).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, d, *J* = 6.2 Hz); 1.59-1.66 (2H, m); 1.77-1.91 (2H, m); 2.57 (3H, s); 3.24 (2H, t, *J* = 7.0 Hz); 3.91 (1H, sext, *J* = 6.2 Hz); 6.99 (1H, s); 7.35-7.40 (2H, m); 7.58-7.62 (1H, m); 7.87-7.91 (1H, m). ^{13}C NMR (100.6 MHz, ref=$CDCl_3$): δ 21.3, 23.9, 25.3, 36.7, 43.8, 67.7, 109.3, 124.7, 125.5, 126.0, 128.0, 129.1, 140.5, 140.9, 149.3. IR (cm^{-1}): $\nu_{OH,\ NH}$ = 3337, ν_{max} = 2962, 2929, 1608, 1517, 1488, 1436, 1418, 1387, 1372, 1359, 1245, 749. MS (70 eV): m/z (%): 245 (M^++1, 100). HRMS (ESI): calcd for $C_{15}H_{21}N_2O$ 245.1648 $[M+H]^+$, found 245.1655.

4.13.3. 5-(Quinolin-5-ylamino)pentan-2-ol **13b** (15-18%)

Yellow oil. R_f (SiO_2) = 0.19-0.36 (100% EtOAc).^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (3H, d, *J* = 6.2 Hz); 1.63-1.68 (2H, m); 1.83-1.95 (2H, m); 3.30 (2H, t, *J* = 6.8 Hz); 3.92 (1H, sext, *J* = 6.2 Hz); 6.62 (1H, dd, *J* = 7.8, 0.7 Hz); 7.30 (1H, dd, *J* = 8.5, 4.2 Hz); 7.47 (1H, dd, *J* = 8.4, 0.7 Hz); 7.56 (1H, dd, *J* = 8.4, 7.8 Hz); 8.17 (1H, dd, *J* = 8.5, 1.6 Hz); 8.85 (1H, dd, *J* = 4.2, 1.6 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 23.9, 25.5, 36.8, 44.3, 67.9, 104.5, 118.1, 118.4, 119.2, 128.8, 130.5, 143.8, 149.1, 149.9. IR (cm^{-1}): $\nu_{NH,\ OH}$ = 3344, ν_{max} = 2925, 1610, 1585, 1579, 1535, 1484, 1463, 1417, 1371, 1350, 1328, 1284, 1118, 789. MS (70 eV): m/z (%): 231 (M^++1,100). HRMS (ESI) calcd for $C_{14}H_{19}N_2O$ 231.1492 $[M+H]^+$, found 231.1499.

4.13.4. 5-(Quinolin-6-ylamino)pentan-2-ol **13c** (50%)

Yellow oil. Rf (SiO_2) = 0.13 (100% EtOAc).^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, d, *J* = 6.2 Hz); 1.55-1.62 (2H, m); 1.67-1.85 (2H, m); 3.17 (2H, t, *J* = 6.9 Hz); 3.87 (1H, sext, *J* = 6.2 Hz); 6.62 (1H, d, *J* = 2.6 Hz); 7.01 (1H, dd, *J* = 9.1, 2.6 Hz); 7.21 (1H, dd, *J* = 8.3, 4.2 Hz); 7.83 (1H, d, *J* = 9.1 Hz); 7.87 (1H, dd, *J* = 8.3, 1.4 Hz); 8.55 (1H, dd, *J* = 4.2, 1.4 Hz). ^{13}C NMR (100.6 MHz, ref = $CDCl_3$): δ 23.8, 25.5, 36.7, 43.9, 67.4, 102.6, 121.3, 121.6, 129.8, 130.3, 133.9, 142.8, 145.6, 146.4. IR (cm^{-1}): $\nu_{OH,\ NH}$ = 3318, ν_{max} =

2926, 1623, 1521, 1468, 1381, 1247, 1124, 826. MS (70 eV): m/z (%): 231 (M^++1, 100). HRMS (ESI): calcd for $C_{14}H_{19}N_2O$ 231.1492 $[M+H]^+$, found 231.1503.

4.14. Bioactivity evaluation methods

4.14.1. *In vitro* antimalarial assay

The test samples were prepared to a 20 mg/mL stock solution in 100% DMSO. Stock solutions were stored at -20 °C. Further dilutions were prepared on the day of the experiment. Chloroquine andartenusate were used as the reference drugs in all experiments. A full dose-response was performed for all compounds with a starting concentration of 10 µg/mL, which was then serially diluted twofold in complete medium to give 10 concentrations; with the lowest concentration being 0.02 µg/mL. The same dilution technique was used for all samples. Reference drugs were tested at a starting concentration of 1000 ng/mL against a CQS strain. The highest concentration of solvent to which the parasites were exposed to had no measurable effect on the parasite viability (data not shown).

4.14.2. *In vitro* assay for the evaluation of cytotoxic activity

The same stock solution which was prepared for antiplasmodial assays were used for this assay. Dilutions were prepared on the day of the experiment. Emetine was used as the reference drug in all experiments. The initial concentration of emetine was 100 µg/mL, which was serially diluted in complete medium with 10-fold dilutions to give 6 concentrations, the lowest being 0.001 µg/mL. The same dilution technique was applied to all test samples. The highest concentration of solvent to which the cells were exposed to had no measurable effect on the cell viability. The 50% inhibitory concentration (IC_{50}) were obtained using a non-linear dose-response curve fitting analysis *via* Graph Pad Prism v.4.0 software.

4.14.3. Antimicrobial evaluation - Disk diffusion method

The fungal strains were subcultured onto Sabouraud dextrose agar at 37 °C (*C. albicans* and *A. flavus*) or 20 °C (*R. bogoriensis*). Inoculum was prepared by suspending distinct colonies (yeasts) or mycelium and spores (*A. flavus*) into sterile saline, until a transmittance equivalent to a 0.5 McFarland standard was obtained. The fungal inocula were streaked evenly over the dried surface of Mueller-Hinton + GMB plates (20% glucose, 0.5 µg/mL Methylene Blue dye) by using a sterile cotton swab. The disks were then dispensed over the surface of the inoculated agar, nystatin and DMSO disks were used as positive and negative control respectively. The compounds (dissolved in DMSO) were applied to sterile antibiotic assay paper (Whattman, 6mm) and the disks were freeze-dried

before being dispensed over the surface of the inoculated agar surface. The plates were incubated at 37 °C for 1 day (*C. albicans* and *A. flavus*) or 20 °C for 4 days (*R. bogoriensis*). In the experimental setup, a compound dose of 600 µg/dish was tested in triplicate.

4.14.4. Antimicrobial evaluation – MIC determination test via microdilution

For each compound, a $\log_2$ dilution series was prepared in a 96-well microtiter plate starting from stock solutions of the 6 compounds in 10% DMSO, which were then 1:5 diluted with RPMI 1640 medium, supplemented with glutamine and without bicarbonate (Sigma). A 1:1000 dilution with RPMI 1640 medium was used as working suspension (1 × 103 CFU/mL) for *C. albicans* and *A. flavus* and a 1:10 dilution with RPMI 1640 medium was used as working suspension (1 × 105 CFU/mL) for *R. bogoriensis*; 100 µL of the working suspension was added to 100 µL of the $\log_2$ dilution series. The plates were incubated at 37 °C (*C. albicans* and *A. flavus*) or 20 °C (*R. bogoriensis*), and the results were read with a microtiter plate spectrophotometer (Bio-rad) at 530 nm. The MIC was decided to be the concentration giving rise to an inhibition of growth of 50% of that of the negative control (1% DMSO in medium), Amphotericin B was used as positive control.

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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)

Compound	Quinolin-	R	Yield (%)	Compound	Quinolin-	R	Yield (%)
6a	3-yl	-	84[a]	**10b**	5-yl	H	23
6b	5-yl	-	95[a]	**10c**	6-yl	H	43
6c	6-yl	-	93[a]	**10d**	8-yl	H	40
6d	8-yl	-	97[a]	**11a**	3-yl	H	83[a]
7a	3-yl	-	75	**11a'**	3-yl	CH_3	85[a]
7b	5-yl	-	62	**11b**	5-yl	H	88[a]
7c	6-yl	-	80	**11c**	6-yl	H	94[a]
7d	8-yl	-	72	**12a**	3-yl	H	61
8b	5-yl	-	37	**12a'**	3-yl	CH_3	33
8c	6-yl	-	68	**12b**	5-yl	H	31
9a	3-yl	-	40	**12c**	6-yl	H	27
9b	5-yl	-	15	**13a**	3-yl	H	20
9c	6-yl	-	40	**13a'**	3-yl	CH_3	20
9d	8-yl	-	25	**13b**	5-yl	H	17
10a'	3-yl	CH_3	15	**13c**	6-yl	H	50

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

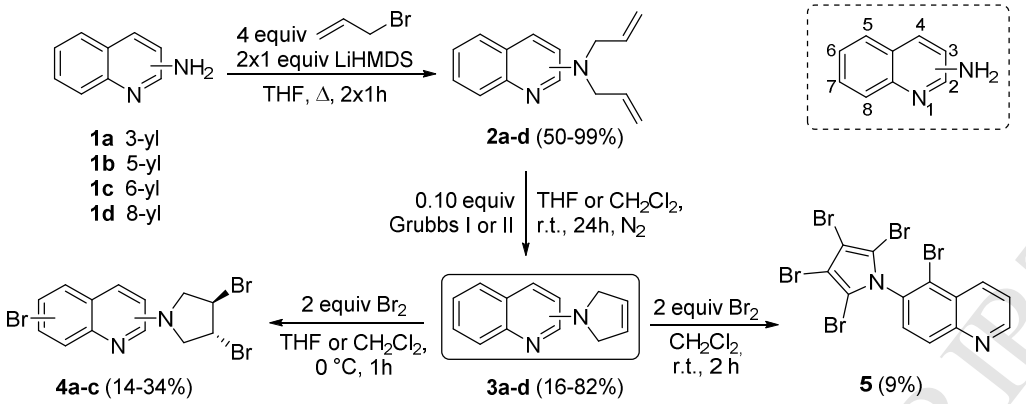
Compound	NF54: IC_{50} (μM)	Compound	NF54: IC_{50} (μM)	Compound	NF54: IC_{50} (μM)
3a	>50	**8a**	>50	**12a**	31.1 ± 8.5
3b	>50	**8b**	>50	**12a'**	13.3 ± 3.5
3c	>50	**8c**	>50	**12b**	>45
3d	>50	**9a**	>45	**12c**	41.9 ± 5.7
4a	>20	**9b**	19.9 ± 5.6	**13a**	>40
4b	>20	**9c**	>45	**13a'**	>40
5	>15	**9d**	>45	**13b**	32.6 ± 6.5
7a	>45	**10a'**	>35	**13c**	>40
7b	>45	**10b**	28.2 ± 4.5	CQ (n=14)	0.021 ± 0.005
7c	>45	**10c**	>40	Artesunate (n=8)	0.005
7d	>45	**10d**	>40		

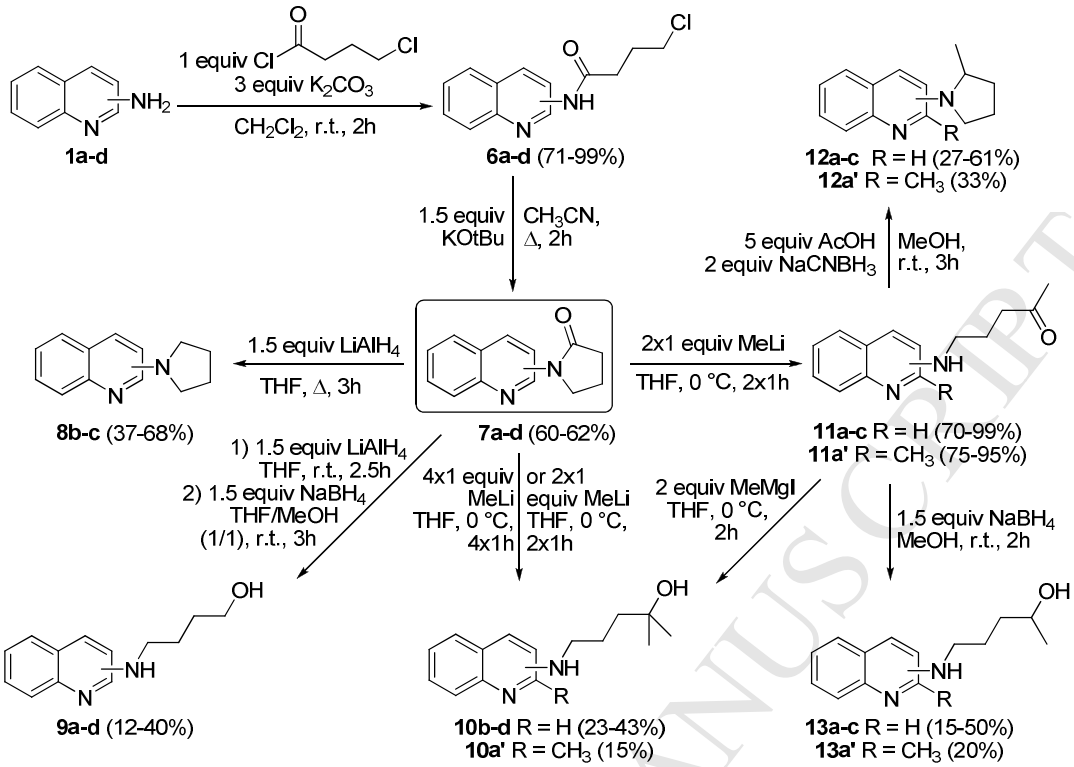
CQ = chloroquine.

Compound	NF54: IC_{50} (µM)	Dd2: IC_{50} (µM)	CHO: IC_{50} (µM)	SI[a]	RI[b]
9b	19.9 ± 5.6	49.0 ± 10.2	>100	23	2.5
12a'	13.3 ± 3.5	38.0 ± 4.4	293.5 ± 50.4	22	2.9
CQ (n=14)	0.021	0.274	-	-	13.0
Artunesate (n=8)	0.005	0.011	-	-	2.2
Emetine	-	-	0.125	-	-

CQ = chloroquine; [a] SI (Selectivity Index) = IC_{50} CHO/IC_{50} NF54; [b] RI (Resistance Index) = IC_{50} Dd2/IC_{50} NF54.

Compound	*Candida albicans*		*Rhodotorula bogoriensis*		*Aspergillus flavus*	
	(mg/L)	(mM)	(mg/L)	(mM)	(mg/L)	(mM)
9c	250.0	1.2	250.0	1.2	2.0	0.01
9d	250.0	1.2	7.8	0.04	31.6	0.1
10b	500.0	2.0	3.9	0.02	62.5	0.3
10d	250.0	1.0	7.8	0.03	15.6	0.06
13a	250.0	1.1	62.5	0.3	31.3	0.1
13c	250.0	1.1	250.0	1.1	62.5	0.3
Amphotericin B	<0.2	<0.0002	<0.2	<0.0002	3.1	0.03





Highlights

- Synthetic exploration of 3-, 5-, 6- and 8-aminoquinolines
- Novel (3-pyrrolin-1-yl)- and (2-oxopyrrolidin-1-yl)quinoline building blocks
- Moderate antiplasmodial but significant antifungal activities