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Synthesis of 7*H*-indolo[2,3-*c*]quinolines: study of the Pd-catalyzed intramolecular arylation of 3-(2-bromophenylamino)quinolines under microwave irradiation

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Abstract—D-ring substituted 5-methyl-5*H*-indolo[2,3-*c*]quinolines (**4**) have been synthesized in three steps starting from commercially available 3-bromoquinoline (**5**) and 2-bromoanilines (**6**). The methodology consists of two consecutive palladium-catalyzed reactions: a selective Buchwald–Hartwig amination followed by a regioselective intramolecular Heck-type reaction. The latter step has been investigated under microwave irradiation. Heating at 180 °C allows to seriously reduce the catalyst loading and get a full conversion to reaction product in 10 min. In addition, the former simplifies the purification.

1. Introduction

Every year between 300 and 500 million people worldwide are infected by the malaria parasite (*Plasmodium*). One to two million of them die as a direct consequence of this disease.[1] Besides the available synthetic drugs nature also has shown to be an interesting source for antiplasmodial compounds. For instance, in traditional medicine in West and Central Africa a decoction of the root of the plant *Cryptolepis sanguinolenta* is used to treat fevers caused by malaria. Cryptolepine (5-methyl-5*H*-indolo[3,2-*b*]quinoline) (**1**), neocryptolepine (cryptotackieine, 5-methyl-5*H*-indolo[2,3-*b*]quinoline) (**2**) and isocryptolepine (cryptosanguinolentine, 5-methyl-*5H*-indolo[3,2-*c*]quinoline) (**3**) are three of the thirteen characterized alkaloids of the root (Fig. 1).[2] These isomeric indoloquinolines show an interesting antiplasmodial activity. Interestingly, the 'missing' benzo-β-carboline isomer (5-methyl-5*H*-indolo[2,3-*c*]quinoline, for which we have adopted the name isoneocryptolepine (**4a**) (Fig. 1) has hitherto never been found in nature. Recently, we developed an efficient synthetic route for 5-methyl-5*H*-indolo[2,3-*c*]quinoline (**4a**) and its 7*H*-indolo[2,3-*c*]quinoline skeleton.[3] The methodology is based on the combination of a selective Buchwald–Hartwig amination with a regioselective Pd-catalyzed intramolecular arylation reaction starting from commercially available 3-bromoquinoline (**5**) and 2-bromoaniline (**6a**) (Scheme 1).[3,4] Although **4a** is about two times less active (K1 strain of *P. falciparum*, resistant to chloroquine and pyrimethamine) than **1**, the most active compound of the quartet isomeric indoloquinolines, it is four times less cytotoxic (L6 cells).[5] Therefore, **4a** has a much better selectivity index (cytotoxicity/antiplasmodial activity ratio) than **1**, which makes it a better lead compound for further validation of the indoloquinolines as a potential antiplasmodial drugs (Table 1). The mechanism of action of **4a** is similar to that of chloroquine inhibition of the haeme detoxification process.[6] The choice to study first the D-ring substitution of **4a** is based on the fact that the quinoline part in chloroquine and analogues is very important in the haeme complexation and only limited substitutions are tolerated. The commercial availability of several substituted 2-bromoanilines makes the 'selective Buchwald–Hartwig amination—regioselective Pd-catalyzed intramolecular arylation reaction' approach a preferred tool to easily get access to these D-ring functionalized 7*H*-indolo[2,3-*c*]quinolines and isoneocryptolepines.

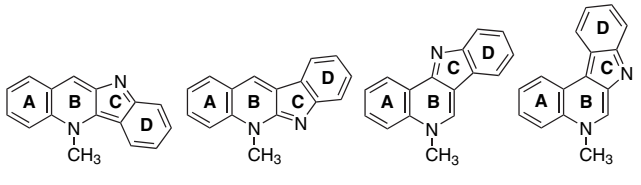

Figure 1. Cryptolepine (**1**), neocryptolepine (**2**), isocryptolepine (**3**) and isoneocryptolepine (**4a**).

Keywords: Palladium; Amination; Heck-type reaction; Microwave; Malaria.
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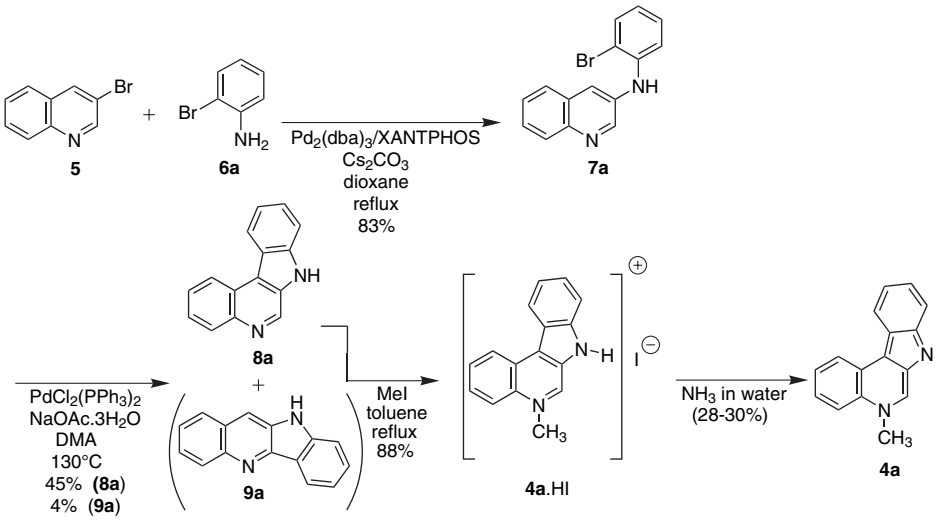


Scheme 1. Synthesis of isoneocryptolepine (**4**) based on a 'selective Buchwald–Hartwig amination—regioselective Pd-catalyzed intramolecular arylation reaction' approach.

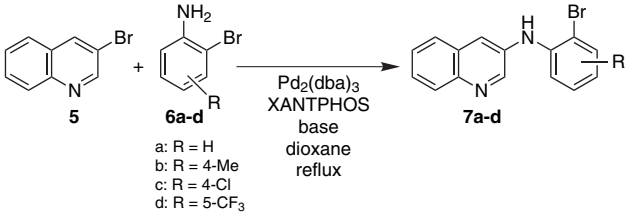
Table 1. Antiplasmodial activity (IC_{50}, μM), cytotoxicity (IC_{50}, μM) and selectivity index of compounds **1**–**4**

Compound	*Plasmodium falciparum* K1 IC_{50} (μM)	Cytotoxicity (L6 cells) IC_{50} (μM)	Selectivity index
1	0.12±0.02	1.12±0.07	9.3
2	2.61±0.67	3.24±0.04	1.2
3	0.78±0.30	1.19±0.26	1.5
4a	0.23±0.04	4.32±0.04	18.8

2. Discussion

First, we focussed on the amination of 3-bromoquinoline (**5**) with 2-bromoanilines (**6**) and decided to restudy the selective coupling of **5** with 2-bromoaniline (**6a**) (Scheme 1), under the same reaction conditions as previously reported by us [standard conditions: 2.5 mol % $Pd_2(dba)_3$/5.5 mol % XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene) catalyst, 1.2 equiv **6a**, 3 equiv Cs_2CO_3, 12 mL dioxane and reflux], in order to determine whether there is a '*base effect*' for this C–N bond forming reaction.[7] Therefore, we carefully followed the reaction of **5** with **6a** by TLC and MS and found that the reaction is already completed after 16 h.[8] An isolated yield of 3-(2-bromophenylamino)-quinoline (**7a**) of 85% was obtained (Table 2, entry 1), which is essentially the same as we reported previously for a 30 h reflux (Scheme 1). When the same experiment was performed using only 2 equiv of caesium carbonate (instead of 3 equiv as used in the standard experiment) an incomplete conversion of starting material was observed in 16 h. Work up of the mixture yielded only 62% of **7a** and a recovery of 26% of substrate **5** (Table 2, entry 2). These data clearly indicate a rate-limiting deprotonation of the Pd(II)-amine complex intermediate formed in the catalytic cycle.[7] Gratifyingly, selective amination of **5** with 2-bromo-4-methylaniline (**6b**) using the optimized reaction conditions gave 85% of 3-(2-bromo-4-methylphenylamino)quinoline (**7b**) (Table 2, entry 3). Unfortunately, amination of **5** with 4-chloro-2-bromoaniline (**6c**) and 2-bromo-5-trifluoromethylaniline (**6d**) gave incomplete conversions and an isolated yield of 3-arylaminoquinoline of 63% (**7c**) and 59% (**7d**) respectively

Table 2. Selective Buchwald–Hartwig amination of 3-bromoquinoline (**5**) with 2-bromoanilines (**6**)



Entry	**6**	$Pd_2(dba)_3$ loading (mol %)	XANTPHOS loading (mol %)	Base	Time (h)	Yield[a] (%)
1	**6a**	2.5	5.5	Cs_2CO_3	16	85
2	**6a**	2.5	5.5	Cs_2CO_3	16	62[b]
3	**6b**	2.5	5.5	Cs_2CO_3	16	85
4	**6c**	2.5	5.5	Cs_2CO_3	16	63
5	**6d**	2.5	5.5	Cs_2CO_3	16	59
6	**6c**	2.5	5.5	Cs_2CO_3	24	55[c]
7	**6c**	2.5	10.0	Cs_2CO_3	24	62
8	**6c**	2.5	5.5	Cs_2CO_3	24	61[d]
9	**6c**	2.5	5.5	K_3PO_4	24	51[e]
10	**6c**	2.5	5.5	Cs_2CO_3	24	37[b]
11	**6c**	5.0	11.0	Cs_2CO_3	24	83

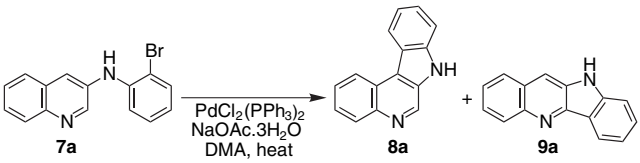
[a] $Pd_2(dba)_3$ (5 mol %), 5.5 mol % XANTPHOS, 3 mmol **5**, 3.6 mmol **6**, 9 mmol Cs_2CO_3, 12 mL dioxane, reflux.
[b] Cs_2CO_3 (6 mmol) was used.
[c] 5.4 mmol **6c** was used.
[d] 6 mL dioxane was used.
[e] 9 mmol K_3PO_4 was used.

(Table 2, entries 4 and 5). We decided to study the coupling of **5** with **6c** in more detail. Altering the excess of **6c** from 1.2 to 1.8 equiv (Table 2, entry 6), changing the palladium/ligand ratio from 1/1.1 to 1/2 (Table 2, entry 7) as well as doubling the concentration of the reaction (Table 2, entry 8) all gave similar isolated yield of **7c** and an incomplete conversion of starting material in a fixed reaction time of 24 h. Also the use of K_3PO_4 as base did not provide us with a better result (Table 2, entry 9). Interestingly, a test experiment with 2 equiv of Cs_2CO_3 gave only 37% **7c** and a recovery of 37% **5** (Table 2, entry 10), which also supports that the deprotonation of the Pd(II)-amine complex intermediate occurs in the

rate-limiting step for the studied type of amination reactions. Interestingly, when we doubled the catalyst loading for the coupling of **5** and **6c** within 24 h under otherwise standard conditions an almost complete conversion was observed with an isolated yield of 83% **7c** (Table 2, entry 11). The selective coupling reactions of **5** with **6a–d** (via chemoselective oxidative addition) can be explained by taking into account that the C–Br bond of **5** is more reactive than the C–Br bond of **6a–d** due to the amino substituent of the latter, which sterically and electronically deactivates the C2–Br bond for oxidative addition. Interestingly, the introduction of a chlorine atom or a trifluoromethyl group (electron withdrawing) on 2-bromoaniline does not seem to influence the selectivity (chemoselective oxidative addition) of the Buchwald–Hartwig amination reaction. Particularly, the successful use of **6c** is interesting since the C4–Cl of **6c** is a potential third position for oxidative addition in the reaction of **5** with **6c**.

Secondly, we turned our attention to the cyclodehydrobromination of **7a–d** via a regioselective intramolecular Heck-type reaction that involves C–H bond activation of an aryl group.[9] The already previously reported cyclization of **7a** required a very high loading of catalyst (23 mol %) and a long reaction time (48 h) to achieve a reasonable result (Scheme 1).[3] Therefore, we decided to study the Pd-catalyzed cyclodehydrobromination of **7a** in more detail with an HPLC–UV system under the same reaction conditions [standard conditions: 23 mol % $PdCl_2(PPh_3)_2$ catalyst, 2.45 equiv $NaOAc\cdot 3H_2O$, 10 mL dimethylacetamide and 130 °C (oil bath temperature)]. Surprisingly, we found that most of the conversion of starting material occurs in the first hour and subsequently an extremely slow further transformation to reaction product **8a** follows (Table 3, A).[10] Also with 5 mol % loading of $PdCl_2(PPh_3)_2$ a similar behaviour could be observed (Table 3, B). For both experiments complete conversion of substrate **7a** can not be achieved and the reaction mixture obtained a dark colour within the first hour of reaction. Importantly, increasing the oil bath temperature to 160 °C for the former experiment gave an almost complete reaction within 1 h (Table 3, C). This observation inspired us to study the cyclodehydrobromination of **7a** under microwave irradiation in a single-mode microwave unit (Discover, CEM).[11] We decided to perform the reactions on a same scale as the oil bath experiments but increased the concentration of the microwave reactions by a factor of ten (use of 1 mL instead of 10 mL DMA) since the standard disposable microwave vials (with crimp cap) have a volume of 10 mL. At 180 °C using a loading of 23 mol % a complete conversion of **7a** was observed within 10 min of irradiation. Astonishingly, a systematic reduction of the catalyst loading revealed that 0.2 mol % still gave a complete transformation of **7a** in 10 min heating under microwave irradiation. This is a reduction in reaction time by a factor of 288 and a 115-fold decrease of the catalyst loading. Working up the reaction mixture gave an isolated yield of 7*H*-indolo[2,3-*c*]quinoline (**8a**) of 66% (Table 4, entry 1). This is 21% higher than the previously reported yield under standard conditions (Scheme 1) and most probably a combination of two main factors.[12] First of all, in an oil bath at 130 °C using 23 mol % of catalyst the reaction can never be brought to complete conversion (even after 48 h of heating) (Table 3, A) and secondly the very high loading of catalyst generates

Table 3. Pd-catalyzed intramolecular arylation of **7a** under conventional heating

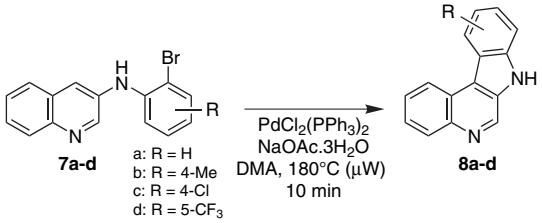


	Time (min)	Conversion (%)[a]	**8a**[b,c] (%)
A[d]			
1	10	48	85
2	20	61	84
3	30	66	81
4	60	71	80
5	120	74	81
6	360	75	79
B[d]			
1	10	26	87
2	20	32	87
3	30	34	85
4	60	36	87
5	120	37	86
6	360	39	86
C[d]			
1	10	71	85
2	20	82	84
3	30	86	85
4	60	90	84
5	120	92	84
6	360	94	83

[a] Conversion based on HPLC–UV: (**8a+9a**)/(**7a+8a+9a**)×100.
[b] X mol % $PdCl_2(PPh_3)_2$, 0.6 mmol **7a**, 1.47 mmol $NaOAc\cdot 3H_2O$, 10 mL DMA.
[c] Percentage of **8a** based on HPLC–UV: **8a**/(**8a+9a**)×100.
[d] A: 23 mol % $PdCl_2(PPh_3)_2$ catalyst at 130 °C, B: 5 mol % $PdCl_2(PPh_3)_2$ catalyst at 130 °C and C: 23 mol % $PdCl_2(PPh_3)_2$ catalyst at 160 °C.

a large amount of triphenylphoshine and triphenylphosphine oxide, which makes the work up very difficult involving a lot of purification steps with reaction product loss as an obvious consequence. An attempt to further reduce the catalyst loading to 0.1 mol % was unsuccessful since starting material **7a** remained and only 30% of **8a** could be obtained in a reaction time of 10 min at 180 °C. We decided to study the Pd-catalyzed cyclodehydrobromination of **7b–d** with a higher catalyst loading (1 mol %) than 0.2 mol % in order to have

Table 4. Pd-catalyzed intramolecular arylation of **7a–d** under microwave irradiation[10]



Entry	**7**	$PdCl_2(PPh_3)_2$ loading (mol %)	Yield[a] (%)
1	**7a**	0.2	66
2	**7b**	1	58
3	**7c**	1	69
4	**7d**	1	76

[a] X mol % $PdCl_2(PPh_3)_2$, 0.6 mmol **7a–d**, 1.47 mmol $NaOAc\cdot 3H_2O$, 1 mL DMA and 180 °C (microwave).

a general applicable protocol for the synthesis of the indoloquinoline skeleton of the substituted 5-methyl-5*H*-indolo[2,3-*c*]quinolines. Upon the use of a 1 mol % catalyst loading, **7b–d** could be smoothly transformed to **8b–d** in only 10 min (Table 4, entries 2, 3 and 4). Complete conversion of the substrates (**7b–d**) as well as the good isolated yields of **8b–d** support the generality of the developed protocol. Interestingly, to the best of our knowledge microwave-assisted Pd-catalyzed intramolecular arylation reactions using dedicated microwave equipment are unprecedented in the literature.[13] The studied intramolecular Heck-type reactions on **7a–d** are regioselective since only a small fraction of quindolines **9a–d** could be isolated during column chromatography.[14] When one accepts the mechanism of the Pd-catalyzed cyclodehydrohalogenation of **7a–d** to occur via the intramolecular electrophilic attack of the oxidative addition complex on a π system,[9,15] the preferential C4–H activation of **7a–d** can be explained by taking into account that in this case three resonance contributors, which do not break the aromatic character of the benzene ring in the carbocationic intermediate, can be drawn versus only one in the case of C2–H activation. In addition, the electron density is larger on C-4 than on C-2.

To investigate a possible existence of non-thermal microwave effects[11b] in the Pd-catalyzed intramolecular arylation reactions, we searched for a method which allows to mimic the heating profile of an oil bath experiment with that of a microwave reaction. This setup choice is inspired by the fact that it should be easier to control microwave heating by altering the power output of the machine (programming of stages with a different set power) than controlling the heating gradient of an oil bath. Comparisons between oil bath and microwave experiments can be best executed with the same vessel and therefore, we constructed a homemade 'attenuator' which allows sealing of the 10 mL microwave vessel, with internal fiber optic temperature measurement, without placing it in the microwave cavity (Figs. 2 and 3). Our system can be easily used to perform on-line pressure and temperature monitoring of the oil bath experiment by programming a hypothetical experiment with a set power of 0 W and a set temperature higher than the desired value. The heating profile we obtained by performing an intramolecular Heck-type reaction on **7a** with 5 mol % of $PdCl_2(PPh_3)_2$ in a preheated oil bath at 155 °C is shown in Figure 4. An oil bath temperature of 155 °C gave an internal temperature of 150 °C. This figure also shows the mimicked profile of exactly the same experiment performed under microwave heating. As can be seen in the figure the two heating profiles are not exactly the same but very similar. Differences are due to the software of the microwave system. A power moderation algorithm is used which automatically

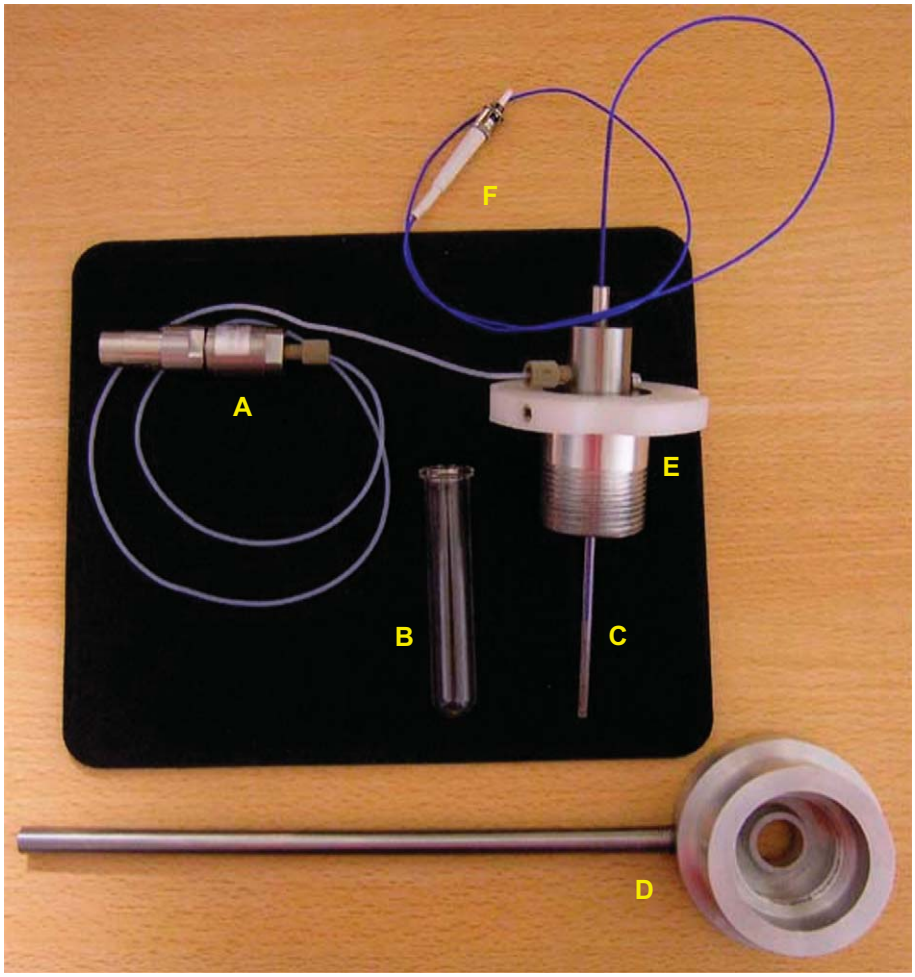
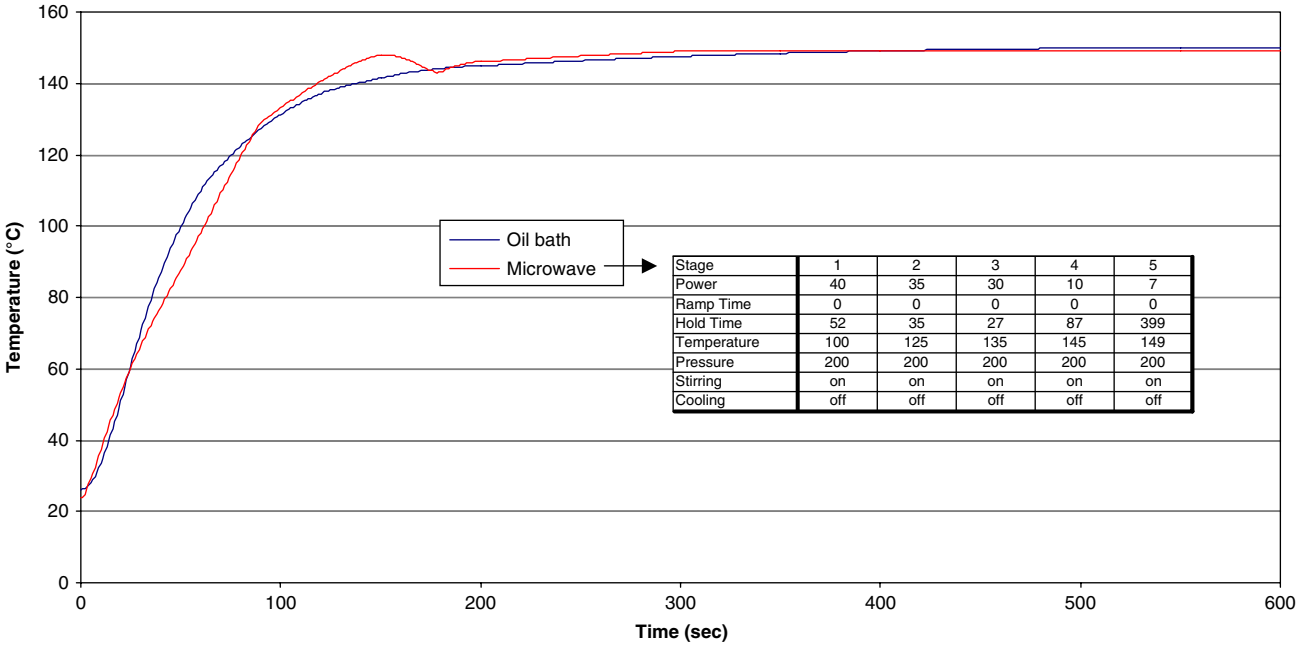


Figure 2. Pressure sensor (A), 10 mL microwave vial (B), thermowell (C), homemade 'attenuator' (D), locking cover assembly (E) and fiber optic temperature sensor (F).

Figure 3. Experimental setup for the determination of a heating profile (via the microwave software) of an experiment executed in an oil bath.

alters the power to a lower value, even though it has not been programmed by the user. This algorithm has been incorporated as a safety feature to prevent explosions due to too rapid heating of a reaction mixture. Although a reasonably good comparison has been obtained between oil bath and microwave heating profile, this algorithm prevented us to exactly mimic the profiles. The two reactions shown in Figure 4 have been analyzed by an HPLC–UV system. Interestingly, both gave exactly the same conversion to reaction products (**8a** and **9a**) in a reaction time of 10 min [microwave: % reaction products = 41.8 (this percentage consists of 85% **8a**), oil bath: % reaction products = 41.4 (this percentage consists of 86% **8a**)] and therefore, non-thermal effects can be excluded. The studied microwave-assisted reactions are governed only by thermal effects (Arrhenius). Nevertheless, from a practical point of view,



Stage	1	2	3	4	5
Power	40	35	30	10	7
Ramp Time	0	0	0	0	0
Hold Time	52	35	27	87	399
Temperature	100	125	135	145	149
Pressure	200	200	200	200	200
Stirring	on	on	on	on	on
Cooling	off	off	off	off	off

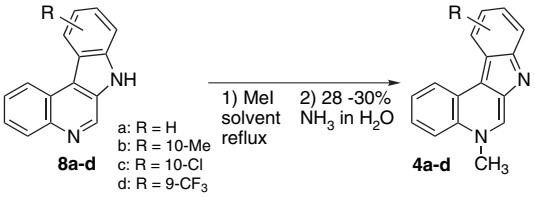
Figure 4. Attempt to mimic the heating profile of an oil bath experiment with that of a microwave experiment.

the microwave-assisted procedure is still more convenient than classical heating since it is easier to reach high temperatures.

For the selective N-5 methylation of the 7*H*-indolo[2,3-*c*]quinolines (**8b–d**) we first tried to use the conditions (CH_3I, toluene, reflux, 2 h; then 28–30% NH_3 in H_2O) we previously reported for the selective methylation of 7*H*-indolo[2,3-*c*]quinoline (**8a**).[3] The use of toluene allowed selective methylation of **8a** since the formed isoneocryptolepinium hydroiodide (**4a**·HI) immediately precipitated and the formation of 7-methylisoneocryptolepinium iodide could therefore be avoided. For 10-methyl-7*H*-indolo[2,3-*c*]quinoline (**8b**) this procedure worked smoothly giving access to the desired 5,10-dimethyl-5*H*-indolo[2,3-*c*]quinoline (**4b**) in 95% yield (Table 5). However, under these reaction conditions methylation of 10-chloro-7*H*-indolo[2,3-*c*]quinoline (**8c**) and 9-trifluoromethyl-7*H*-indolo[2,3-*c*]quinoline (**8d**) yielded the respective 5-methyl-5*H*-indolo[2,3-*c*]quinolines **4c** and **4d** in lower yields (75 and 60%). Interestingly, based on a report for the selective methylation of quindoline, we found that methylation of **8c** and **8d** with MeI in refluxing tetrahydrofuran gave superior results (Table 5).[16] Also in this case a precipitate (**4c**·HI and **4d**·HI) forms during the reaction.

In conclusion, we smoothly synthesized D-ring substituted 5-methyl-5*H*-indolo[2,3-*c*]quinolines (**4b–d**) via our earlier developed three-step approach for the construction of unsubstituted isoneocryptolepine. The procedure consists of the combination of a selective Buchwald–Hartwig amination and a regioselective intramolecular Heck-type reaction. The latter step [Pd-catalyzed intramolecular arylation of 3-(2-bromophenylamino)quinolines] was studied under microwave irradiation. Superior reaction conditions have clearly been identified since the catalyst loading and reaction time can be seriously reduced by performing the ring closure reaction at a higher temperature. In addition the new conditions allow an easier work up. The biological evaluation (antiplasmodial activity and cytotoxicity) of **4b–d** is currently in progress and the screening results will be reported in due course.

Table 5. Methylation of **8a–d**



Entry	8	Solvent	Yield (%)
1	**8a**	Toluene	88[a]
2	**8b**	Toluene	95[a]
3	**8c**	THF	94[b]
4	**8d**	THF	95[b]

[a] 0.5 mmol **8a–b**, 3 mL MeI, 7.5 mL toluene, reflux, 2 h and then 28–30% NH_3 in H_2O.

[b] 0.5 mmol **8c–d**, 0.25 mL MeI, 2.5 mL THF, reflux, overnight and then 28–30% NH_3 in H_2O.

3. Experimental

3.1. General

All melting points were determined on a Büchi apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Brücker spectrometer Avance 400 in the solvent indicated with TMS (**7** and **8**) or CD_3COOD (**4**) as an internal standard. All coupling constants are given in Hertz and chemical shifts are given in parts per million. The assignment of the ^1H NMR signals of **4** is based on 2D NMR techniques (NOESY and COSY). The chemical shifts of the signals in the ^1H NMR spectra of **4** are concentration dependant. For mass spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. Injections (1 μL) were directed to the mass spectrometer at a flow rate of 5 μL/min (CH_3OH and 0.1% formic acid), using a CapLC HPLC system. Accurate mass data were acquired on a Qq-TOF 2 (Micromass) mass spectrometer equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (approx. 35 V) and capillary voltage (approx. 3.3 kV) were optimized on one compound and used for all others. For the determination of the accurate mass of the molecular ion $[M+H]^+$, a solution of polyethylene glycol 300 in CH_3OH/H_2O with 1 mmol ammonium acetate, was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated masses of PEG $[M+H]^+$ and $[M+NH_4]^+$ ions were used as lock mass. For the product ion experiments (MS) the mass of the $[M+H]^+$ was used as lock mass for the fragments. Fragmentation was induced by low energy collisional activation using different collision energies between 20 and 30 eV. All signals with a signal to noise ratio ≥5/1 were reported. 3-Bromoquinoline (Acros), 2-bromanilines (Acros and Aldrich), XANTPHOS (Aldrich), $PdCl_2(PPh_3)_2$ (Aldrich) and $Pd_2(dba)_3$ (Acros) were obtained from commercial sources and used as such. For the Buchwald–Hartwig amination Cs_2CO_3 (99%) (Aldrich) and freshly distilled dioxane (dried over sodium benzophenone) were used. Flash column chromatography was performed on Kieselgel 60 (ROCC, 0.040–0.063 mm).

3.2. Pd-catalyzed amination of 3-bromoquinoline (5) with 2-bromoanilines (6)

3.2.1. 3-(2-Bromo-4-methylphenylamino)quinoline (7b). A round-bottomed flask was charged with $Pd_2(dba)_3$ (0.069 g, 0.075 mmol, 2.5 mol %) and XANTPHOS [9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene] (0.096 g, 0.165 mmol, 5.5 mol %) followed by dry dioxane (12 mL) (freshly distilled). The mixture was flushed with N_2 for 10 min. Meanwhile, in another round-bottomed flask 3-bromoquinoline (**5**) (0.624 g, 3 mmol), 2-bromo-4-methylaniline (**6b**) (0.670 g, 3.6 mmol) and caesium carbonate (2.932 g, 9 mmol) (Aldrich, 99%) were weighed. To this mixture, the Pd-catalyst was added and the flask was flushed with N_2 for 5 min. The resulting mixture was heated at reflux (oil bath temperature: 110 °C) for 16 h under magnetic stirring. After cooling down to room temperature dichloromethane (25 mL) was added and the suspension was filtered over a path of Celite and rinsed with dichloromethane (125 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography on

silica gel using dichloromethane as the eluent yielding the title compound in 85%.

White solid; mp 107 °C; δ_H ($CDCl_3$): 8.74 (d, J=2.7 Hz, 1H, H-2), 8.03 (dd, J=8.4, 0.9 Hz, 1H, H-8), 7.67 (d, J=2.7 Hz, 1H, H-4), 7.63 (dd, J=8.1, 1.4 Hz, 1H, H-5), 7.53 (ddd, J=8.4, 6.9, 1.4 Hz, 1H, H-7), 7.46 (ddd, J=8.1, 6.9, 0.9 Hz, 1H, H-6), 7.42 (d, J=1.5 Hz, 1H, H-3′), 7.26 (d, J=8.3 Hz, 1H, H-6′), 7.05 (dd, J=8.3, 1.5 Hz, 1H, H-5′), 6.15 (br s, 1H, NH), 2.30 (s, 3H, CH_3); MS (ESI): 313, 233, 218, 184; HRMS (ESI) for $C_{16}H_{14}N_2Br$ $[M+H]^+$: calcd 313.0340, found 313.0352.

3.2.2. 3-(2-Bromo-4-chlorophenylamino)quinoline (7c). 2-Bromo-4-choroaniline (0.743 g, 3.6 mmol); eluent: CH_2Cl_2/heptane (9/1); yield: 63%; white solid; mp 139 °C; δ_H ($CDCl_3$): 8.76 (d, J=2.7 Hz, 1H, H-2), 8.06 (dd, J=8.4, 0.9 Hz, 1H, H-8), 7.76 (d, J=2.7 Hz, 1H, H-4), 7.68 (dd, J=8.1, 1.5 Hz, 1H, H-5), 7.60 (ddd, J=8.4, 6.9, 1.5 Hz, 1H, H-7), 7.58 (dd, J=1.8, 0.9 Hz, 1H, H-3′), 7.51 (ddd, J=8.1, 6.9, 0.9 Hz, 1H, H-6), 7.20 (m, 2H, H-5′ and H-6′), 6.25 (br s, 1H, NH); MS (ESI): 333, 253, 218, 204; HRMS (ESI) for $C_{15}H_{11}N_2ClBr$ $[M+H]^+$: calcd 332.9794, found 332.9809.

3.2.3. 3-(2-Bromo-5-trifluoromethylphenylamino)quinoline (7d). 2-Bromo-5-trifluoromethylaniline (0.864 g, 3.6 mmol); eluent: CH_2Cl_2/heptane (9/1); yield: 59%; white solid; mp 109 °C; δ_H ($CDCl_3$): 8.83 (d, J=2.6 Hz, 1H, H-2), 8.10 (dd, J=8.5, 1.1 Hz, 1H, H-8), 7.88 (d, J=2.6 Hz, 1H, H-4), 7.75 (dd, J=8.1, 1.5 Hz, 1H, H-5), 7.70 (br dq, J=8.3 Hz, $^5J_{H-F}$=0.8 Hz, 1H, H-3′), 7.66 (ddd, J=8.5, 6.9, 1.5 Hz, 1H, H-7), 7.56 (ddd, J=8.1, 6.9, 1.1 Hz, 1H, H-6), 7.44 (br d, J=1.9 Hz, 1H, H-6′), 7.06 (br ddq, J=8.3, 1.9 Hz, $^4J_{H-F}$=0.6 Hz, 1H, H-4′), 6.44 (br s, 1H, NH); MS (ESI): 367, 287; HRMS (ESI) for $C_{16}H_{11}N_2BrF_3$ $[M+H]^+$: calcd 367.0058, found 367.0069.

3.3. Microwave-assisted intramolecular arylation of 3-(2-bromophenylamino)quinolines (7)

3.3.1. 7*H*-Indolo[2,3-*c*]quinoline (8a). A microwave vial of 10 mL was charged with 3-(2-bromophenylamino)quinoline (**7a**) (0.180 g, 0.6 mmol) and $NaOAc \cdot 3H_2O$ (0.200 g, 1.47 mmol). Subsequently, the vial was flushed with Ar for 1 min. Then, 0.2 mL of a stock solution[†] of the catalyst in DMA (0.2 mol %) and DMA (0.8 mL) was added via a syringe and the resulting mixture was stirred and flushed with Ar for an additional 2 min. Next, the vial was sealed with an Al crimp cap with a septum and heated at 180 °C in a CEM Discover microwave apparatus. The set power was 100 W and the total heating time was 10 min. After the reaction vial was cooled down to room temperature using a propelled air flow, it was opened and poured in a round-bottomed flask. The vial was rinsed with methanol (50 mL) and the combined organic phase was evaporated to dryness. Finally, the crude product was purified via column chromatography on silica gel (the residue was brought on column mixed with silica) using dichloromethane/methanol (98/2) as the eluent yielding the title compound in 66%.[3]

3.3.2. 10-Methyl-7*H*-indolo[2,3-*c*]quinoline (8b). 3-(2-Bromo-4-methylphenylamino)quinoline (**7b**) (0.188 g, 0.6 mmol) and 1 mL of stock solution of catalyst (1 mol %); eluent: dichloromethane/methanol (98/2); yield: 58%; beige solid; mp >270 °C (decomp.); δ_H (DMSO-d_6): 12.06 (br s, 1H, NH), 9.28 (s, 1H, H-6), 8.81 (dd, J=8.2, 1.2 Hz, 1H, H-4), 8.49 (s, 1H, H-11), 8.19 (dd, J=8.3, 1.2 Hz, 1H, H-1), 7.76 (ddd, J=8.2, 6.9, 1.2 Hz, 1H, H-3), 7.66 (ddd, J=8.3, 6.9, 1.2 Hz, 1H, H-2), 7.66 (d, J=8.4 Hz, 1H, H-8), 7.43 (d, J=8.4 Hz, 1H, H-9), 2.59 (s, 3H, CH_3); MS (ESI): 233, 218; HRMS (ESI) for $C_{16}H_{13}N_2$ $[M+H]^+$: calcd 233.1079, found 233.1069.

3.3.3. 10-Chloro-7*H*-indolo[2,3-*c*]quinoline (8c). 3-(2-Bromo-4-chlorophenylamino)quinoline (**7c**) (0.200 g, 0.6 mmol) and 1 mL of stock solution of catalyst (1 mol %); eluent: dichloromethane/methanol (98/2); yield: 69%; light yellow solid; mp >250 °C (decomp.); δ_H (DMSO-d_6): 12.38 (br s, 1H, NH), 9.33 (s, 1H, H-6), 8.82 (dd, J=8.1, 1.1 Hz, 1H, H-4), 8.74 (d, J=1.9 Hz, 1H, H-11), 8.21 (dd, J=8.3, 1.1 Hz, 1H, H-1), 7.81 (d, J=8.8 Hz, 1H, H-8), 7.78 (ddd, J=8.1, 6.9, 1.1 Hz, 1H, H-3), 7.70 (ddd, J=8.3, 6.9, 1.1 Hz, 1H, H-2), 7.62 (dd, J=8.8, 1.9 Hz, 1H, H-9); MS (ESI): 253, 218, 190; HRMS (ESI) for $C_{15}H_{10}N_2Cl$ $[M+H]^+$: calcd 253.0533, found 253.0534.

3.3.4. 9-Trifluoromethyl-7*H*-indolo[2,3-*c*]quinoline (8d). 3-(2-Bromo-5-trifluoromethylphenylamino)quinoline (**7d**) (0.220 g, 0.6 mmol) and 1 mL of stock solution of catalyst (1 mol %); eluent: dichloromethane/methanol (98/2); yield: 76%; light yellow solid; mp 240 °C; δ_H (DMSO-d_6): 12.52 (br s, 1H, NH), 9.41 (s, 1H, H-6), 8.89 (d, J=8.6 Hz, 1H, H-11), 8.82 (dd, J=8.2, 1.2 Hz, 1H, H-4), 8.24 (dd, J=8.3, 1.1 Hz, 1H, H-1), 8.13 (s, 1H, H-8), 7.81 (ddd, J=8.2, 7.0, 1.1 Hz, 1H, H-3), 7.73 (ddd, J=8.3, 7.0, 1.2 Hz, 1H, H-2), 7.67 (d, J=8.6 Hz, 1H, H-10); MS (ESI): 287, 267, 233, 218; HRMS (ESI) for $C_{16}H_{10}N_2F_3$ $[M+H]^+$: calcd 287.0796, found 287.0791.

3.4. Methylation of 7*H*-indolo[2,3-*c*]quinolines (8)

3.4.1. 5,10-Dimethyl-5*H*-indolo[2,3-*c*]quinoline (4b). In a round-bottomed flask 10-methyl-7*H*-indolo[2,3-*c*]quinoline (**8b**) (0.116 g, 0.5 mmol), toluene (7.5 mL) and CH_3I (3 mL) were heated at reflux under N_2 atmosphere (oil bath temperature: 120 °C) for 2 h under magnetic stirring. Then the precipitated material was filtered off and rinsed well with toluene (100 mL). The residue was dissolved in methanol (300 mL) to remove it from the filter and the solution was subsequently evaporated to dryness under reduced pressure. The crude product was purified via column chromatography on silica gel [eluent: dichloromethane/methanol (8/2)]. The residue was brought on column mixed with silica giving 10-methylisoneocryptolepine hydroiodide (**4b**·HI) as a yellow solid. To obtain the free base, **4b**·HI was brought in a mixture of dichloromethane (100 mL) and 28–30% ammonia in water (100 mL). The organic phase was separated and the aqueous phase was subsequently extracted with dichloromethane (2×100 mL). The combined organic phase was

[†] Preparation of the stock solution of catalyst: $PdCl_2(PPh_3)_2$ (0.211 g, 0.03 mmol) was dissolved in 5 mL of DMA. Next, the mixture was flushed with Ar for 5 min and subsequently stirred until the catalyst was completely dissolved.

dried over $MgSO_4$, filtered and evaporated to dryness to quantitatively yield **4b** as a red solid in 75%.

Red solid; mp >180 °C (decomp.); δ_H (CD_3COOD):[17] 9.48 (s, 1H, H-6), 8.62 (d, J=7.2 Hz, 1H, H-1), 8.24 (d, J=8.7 Hz, 1H, H-4), 8.03 (s, 1H, H-11), 7.94 (m, 2H, H-2 and H-3), 7.60 (d, J=8.5 Hz, 1H, H-8), 7.48 (d, J=8.5 Hz, 1H, H-9), 4.60 (s, 3H, NCH_3), 2.50 (s, 3H, CCH_3); δ_C (CD_3COOD): 143.0, 137.7, 134.2, 133.8, 133.4, 130.8, 130.6, 130.3, 127.0, 126.0, 125.0, 123.6, 120.9, 119.6, 114.1, 46.3, 21.6; MS (ESI): 247, 232; HRMS (ESI) for $C_{17}H_{15}N_2$ $[M+H]^+$: calcd 247.1235, found 247.1239.

3.4.2. 10-Chloro-5-methyl-5*H*-indolo[2,3-*c*]quinoline (4c). A round-bottomed flask was charged with 10-chloro-7*H*-indolo[2,3-*c*]quinoline (**8c**) (0.126 g, 0.5 mmol), dry THF (2.5 mL) and MeI (0.25 mL). After overnight heating at reflux (oil bath temperature: 75 °C) under Ar atmosphere and magnetic stirring, the solvent was evaporated under reduced pressure. The crude product was purified via column chromatography on silica gel [eluent: dichloromethane/methanol (9/1)]. The residue was brought on column mixed with silica giving 10-chloroisoneocryptolepine hydroiodide (**4c**·HI) as a yellow solid. To obtain the free base, **4c**·HI was brought in a mixture of dichloromethane (100 mL) and 28–30% ammonia in water (100 mL). The organic phase was separated and the aqueous phase was subsequently extracted with dichloromethane (2×100 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated to dryness to yield **4c** as a red solid in 94%.

Red solid; mp >200 °C (decomp.); δ_H (CD_3COOD):[17] 9.80 (s, 1H, H-6), 8.73 (dd, J=7.2, 2.5 Hz, 1H, H-1), 8.37 (m, 2H, H-4 and H-11), 8.02 (m, 2H, H-2 and H-3), 7.78 (d, J=8.9 Hz, 1H, H-8), 7.62 (dd, J=8.9, 1.7 Hz, 1H, H-9), 4.73 (s, 3H, NCH_3); δ_C (CD_3COOD): 142.4, 138.6, 133.8, 132.0, 131.1, 131.0, 130.7, 128.6, 126.1, 125.6, 124.6, 123.2, 121.0, 119.8, 115.9, 46.5; MS (ESI): 267, 252, 232; HRMS (ESI) for $C_{16}H_{12}N_2Cl$ $[M+H]^+$: calcd 267.0689, found 267.0685.

3.4.3. 9-Trifluoromethyl-5-methyl-5*H*-indolo[2,3-*c*]quinoline (4d). Yield: 95%; orange solid; mp >250 °C (decomp.); δ_H (CD_3COOD):[17] 9.90 (s, 1H, H-6), 8.80 (dd, J=7.3, 2.3 Hz, 1H, H-1), 8.64 (d, J=8.6 Hz, 1H, H-11), 8.40 (dd, J=7.7, 2.2 Hz, 1H, H-4), 8.13 (s, 1H, H-8), 8.03 (m, 2H, H-2 and H-3), 7.67 (dd, J=8.6, 0.8 Hz, 1H, H-10), 4.75 (s, 3H, NCH_3); δ_C (CD_3COOD): 143.4, 139.7, 134.3, 132.8 (q, $^2J_{C-F}$=32.4 Hz), 132.3, 131.3, 131.2, 126.9, 126.0, 125.9 (br d, J_{C-F}=2.8 Hz), 125.4, 125.2 (q, $^1J_{C-F}$=272.2 Hz), 122.9, 120.2, 119.3 (q, J_{C-F}=3.1 Hz), 112.5 (q, J_{C-F}= 4.5 Hz), 46.9; MS (ESI): 301, 286, 281, 233, 183; HRMS (ESI) for $C_{17}H_{12}N_2F_3$ $[M+H]^+$: calcd 301.0953, found 301.0954.

3.5. General procedure for the kinetic experiments

A two-necked round-bottom flask was charged with $PdCl_2(PPh_3)_2$ (0.097 g, 0.138 mmol, 23 mol % or 0.021 g, 0.030 mmol, 5 mol %), 3-(2-bromophenylamino)quinoline (**7a**) (0.180 g, 0.6 mmol), $NaOAc \cdot 3H_2O$ (0.200 g, 1.47 mmol) followed by dimethylacetamide (DMA) (10 mL). The mixture was flushed with Ar for 5 min and then stirred at 130 or 160 °C under Ar atmosphere in a preheated oil bath. At 10, 20, 30, 60, 120 and 360 min 50 μL of fluid was taken from the flask via a septum and diluted with MeOH to a concentration of 1.5×10^{-3} M. The obtained solutions were filtered (0.2 μm; Nylon) and diluted with MeOH to a concentration of 1.5×10^{-4} M. Subsequently, the samples were analyzed with LC–UV–MS. The conversion is determined by dividing the sum of the UV peak areas of 7*H*-indolo[2,3-*c*]quinoline (**8a**) and 10*H*-indolo[3,2-*b*]quinoline (**9a**) by the sum of the peak areas of the starting material (**7a**), 7*H*-indolo[2,3-*c*]quinoline (**8a**) and 10*H*-indolo[3,2-*b*]quinoline (**9a**) after a correction factor on the peak areas, based on the difference in extinction coefficient of the starting material and reaction products at the used wavelength (260 nm), has been taken into account.

3.6. Chromatographic conditions

The analytical column [XBridge C18 (4.6×50) mm, d_p=2.5 μm] was purchased from Waters. The LC analysis was executed with a gradient elution at 1 mL/min starting at 70/30 (v/v) H_2O/MeOH containing 0.1% formic acid. The composition of the mobile phase was altered to 45/55 (v/v) H_2O/MeOH containing 0.1% formic acid in 3 min and subsequently to 20/80 (v/v) H_2O/MeOH containing 0.1% formic acid in 7 min thus giving a total elution time of 10 min. For peak detection a UV-detector (SP8450) from Spectra-physics was used at a fixed wavelength (260 nm). Peak identification was performed with an AQA LC/MS (Quadrupole mass analyzer, $APCI^+$ mode, V_{inj}=25 μL) apparatus from Thermo Finnigan.

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References and notes

1. (a) Website of the World Health Organization: http://www.who.int/en/; (b) Egan, T. J. *Drug. Des. Rev.—Online* **2004**, *1*, 93–110.
2. (a) Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703–1706; (b)

Sharaf, M. H. M.; Schiff, P. L.; Tackie, A. N.; Phoebe, C. H.; Martin, G. E. *J. Heterocycl. Chem.* **1996**, *33*, 239–243; (c) Pousset, J.-L.; Martin, M.-T.; Jossang, A.; Bodo, B. *Phytochemistry* **1995**, *39*, 735–736.

3. Hostyn, S.; Maes, B. U. W.; Pieters, L.; Lemière, G. L. F.; Mátyus, P.; Hajós, G.; Dommisse, R. *Tetrahedron* **2005**, *61*, 1571–1577.
4. For synthetic procedures based on the combination of a selective Buchwald–Hartwig amination with an intramolecular Heck or Heck-type reaction see: (a) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505–1510; (b) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109–1112; (c) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310–2311; (d) Jonckers, T. H. M.; Maes, B. U. W.; Lemière, G. L. F.; Rombouts, G.; Pieters, L.; Haemers, A.; Dommisse, R. A. *Synlett* **2003**, 615–618; (e) Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2003**, *59*, 3737–3743; (f) Dajka-Halász, B.; Monsieurs, K.; Éliás, O.; Károlyházy, L.; Tapolcsányi, P.; Maes, B. U. W.; Riedl, Z.; Hajós, G.; Dommisse, R. A.; Lemière, G. L. F.; Košmrlj, J.; Mátyus, P. *Tetrahedron* **2004**, *60*, 2283–2291; (g) Mátyus, P.; Maes, B. U. W.; Riedl, Z.; Hajós, G.; Lemière, G. L. F.; Tapolcsányi, P.; Monsieurs, K.; Éliás, O.; Dommisse, R. A.; Krajsovszky, G. *Synlett* **2004**, 1123–1139.
5. Van Miert, S.; Hostyn, S.; Maes, B. U. W.; Cimanga, K.; Brun, R.; Kaiser, M.; Mátyus, P.; Dommisse, R.; Lemière, G.; Vlietinck, A.; Pieters, L. *J. Nat. Prod.* **2005**, *68*, 674–677.
6. The antiplasmodial activity of **1–4** is due to a combination of at least two mechanisms of action; haeme detoxification and DNA-intercalation. Haeme detoxification is a selective whereas DNA-intercalation is a nonselective mechanism. The latter process is responsible for the cytotoxicity of the compounds (see Ref. 5).
7. For examples on the '*base effect*' in Buchwald–Hartwig aminations see: (a) Maes, B. U. W.; Loones, K. T. J.; Jonckers, T. H. M.; Lemière, G. L. F.; Dommisse, R. A.; Haemers, A. *Synlett* **2002**, 1995–1998; (b) Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F.; Dommisse, R. A. *J. Org. Chem.* **2004**, *69*, 6010–6017.
8. In the previously reported procedure we did not follow the progress of the amination reaction (see Ref. 3). After a 30 h reflux, we checked the reaction by TLC and MS and found that all 3-bromoquinoline was converted and subsequently worked up the crude reaction mixture.
9. For a recent review dealing with direct arylation via cleavage of activated and unactivated C–H bonds see: Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241.
10. Hydrodebrominated **7a–d** and homocoupled **7a–d** are identified side products.
11. For recent reviews and books on microwave-assisted organic synthesis: (a) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM: Matthews, NC, 2002; (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (c) Hayes, B. L. *Aldrichimica Acta* **2004**, *37*, 66–77; (d) *Microwave-Assisted Organic Synthesis*; Lindström, P., Tierney, J. P., Eds.; Blackwell: Oxford, 2004; (e) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
12. The overall yield for the synthesis of 7*H*-indolo[2,3-*c*]quinoline (**8a**) via the combination of a selective Buchwald–Hartwig amination (yield **7a**: 85%) with a regioselective Pd-catalyzed intramolecular arylation reaction (yield **8a**: 66%), starting from commercially available 3-bromoquinoline (**5**) and 2-bromoaniline (**6a**), could be improved to 56%. This is 19% higher than previously reported by us (see Ref. 3). Following our optimized procedure a slightly higher overall yield can be obtained than with the two-step procedure developed by Fan and Ablordeppey (overall yield: 47%). Fan, P.; Ablordeppey, S. Y. *J. Heterocycl. Chem.* **1997**, *34*, 1789–1794; For other reported procedures to synthesize the 7*H*-indolo[2,3-*c*]quinoline skeleton see: (a) Kermack, W. O.; Slater, R. H. *J. Chem. Soc.* **1928**, 32–45; (b) Clemo, G. R.; Felton, D. G. I. *J. Chem. Soc.* **1951**, 671–677; (c) Kannadasan, S.; Srinivasan, P. C. *Synth. Commun.* **2004**, *34*, 1325–1335; (d) Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. *Org. Lett.* **2004**, *6*, 2741–2744; (e) Zhang, X.; Campo, A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763–766.
13. Fluorenones have been synthesized via an intramolecular Pd-catalyzed arylation in a kitchen microwave oven: (a) Qabaja, G.; Jones, G. B. *Tetrahedron Lett.* **2000**, *41*, 5317–5320; (b) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187–7194.
14. The column chromatography fractions that contained the quindolines **9a–d** were impure and contained hydrodebrominated **7a–d**. No attempts were made to further purify the minor isomers **9a–d**.
15. Echavarren, A. M.; Gómez-Lor, B.; González, J. J.; de Frutos, Ó. *Synlett* **2003**, 585–597.
16. Ho, T. L.; Jou, D. G. *Helv. Chim. Acta* **2002**, *85*, 3823–3827.
17. Selective N-5 methylation of **8b–d** could be determined by 2D-NMR (NOESY experiment). Observation of a NOE enhancement between the hydrogens of the methyl group and H-4 proved their neighbourhood. Moreover another NOE enhancement, between H-1 and H-11, further supported that in the intramolecular Heck-type reaction 7*H*-indolo[2,3-*c*]quinolines (**8b–d**) were formed as the major isomers.