DOI: 10.1002/ejoc.201001158

Palladium-Catalyzed Preparation of *N*-Alkylated Tacrine and Huprine Compounds

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Keywords: Amination / Palladium / Microwave chemistry / Nitrogen heterocycles / Cross-coupling

An efficient preparation of *N*-alkylated tacrine and huprine compounds using palladium-catalyzed amination was developed. Cross-coupling reactions with chloroquinolines and primary amines were achieved in good to excellent yields (50–95 %) following microwave irradiation. This method was found particularly useful for functionalized substrates which undergo degradation under S_NAr conditions and for the synthesis of tacrine- and huprine-based heterodimeric inhibitors, examples of which are described.

Introduction

Tacrine-[1] and huprine-like[2,3] aminoquinolines **3** and **4** have interesting pharmacological properties because they efficiently inhibit acetylcholinesterase (AChE) in a reversible fashion. Consequently they are promising candidates for use in the palliative treatment of Alzheimer's disease (AD). One strategy is to design dimeric inhibitors that take advantage of the structure of AChE with its two active sites; such compounds might be more potent and more selective than others lacking a dimeric structure. Prevention of AD by decreasing β-amyloid peptide deposition might therefore be viable.[4] These dimeric inhibitors are usually made up of at least one aminoquinoline core and can be homo- or heterodimers of tacrine or huprine, where the two active units are linked by a suitable spacer (Figure 1).

The preparation of such molecules is currently based on S_NAr reactions between chloroquinoline **1** or **2** and a primary amine. Alternatively, *N*-alkylation reactions of tacrine or huprine with appropriate halogenated linkers has also been employed to produce AChE inhibitors.[5] S_NAr reactions proceed with radically different efficiencies, whereas *N*-alkylation reactions often afford the desired products in only modest yields. Furthermore these reactions, which require high temperatures (refluxing phenol or 1-pentanol for S_NAr reactions) and long reaction times or harsh basic conditions (KOH in DMSO for multiple days for *N*-alkylation reactions), do not permit the use of substrates containing functional groups (e.g., esters).

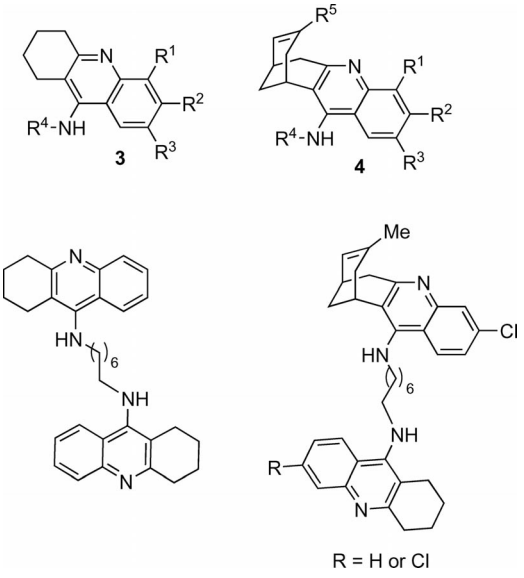

Figure 1. Structures of tacrine- and huprine-like aminoquinolines **3** and **4**, homo- and heterodimeric inhibitors.

Only one example of palladium-catalyzed amination[6] with 9-chlorotetrahydroacridine **1b** has been reported in the literature with low yield (40 %)[7] although many reactions of 2- or 4-chloroquinoline with aliphatic amines or anilines have been described previously.[8] The aim of the present study was to develop an efficient, general, and structurally tolerant reaction leading to *N*-alkylated aminoquinolines **3** and **4**.

Results and Discussion

Palladium-catalyzed amine couplings are highly substrate-dependent. To optimize conditions for the prepara-

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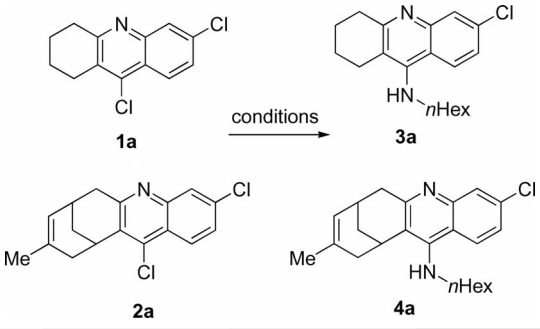
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001158.

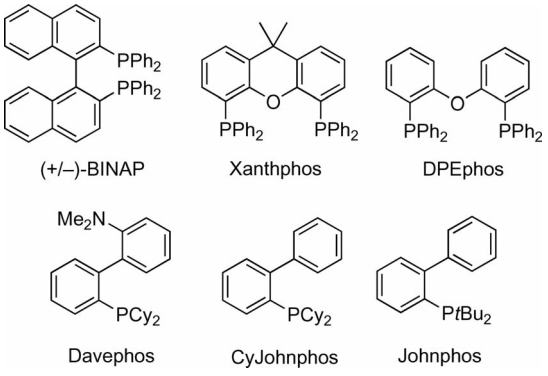
tion of *N*-alkylated tacrine and huprine compounds, the amination of chloroquinoline **1a/2a** or **1c/2c** with *n*-hexylamine was initially investigated to determine the effects of various ligands, palladium sources, solvents, and bases.

Catalyst effects, with a special emphasis on catalyst ligands, were the focus of initial efforts. In a preliminary study, the reaction conditions were arbitrarily set to chloroquinoline **1a/2a** (1 equiv.), *n*-hexylamine (1.5 equiv.), Cs_2CO_3 (2.5 equiv.), $Pd_2(dba)_3$ (4 mol-%), and mono- or diphosphane ligand (8 mol-%) heated at 100 °C for 24 h in 1,4-dioxane. Six different ligands were tested for the amination reaction (Table 1). The best result was obtained by using the diphosphane (±)-BINAP, which gave **3a** and **4a** in 45 and 57% yield, respectively. The use of other diphosphane ligands (Xantphos and DPEphos) gave lower yields. Although efficient in a large number of Pd-catalyzed amination reactions,[9] the use of biphenyl ligands for this application clearly impaired the production of **3a** and **4a** (only 22%) relative to other ligands.

Table 1. Ligand effect on Pd-catalyzed amination of chloroquinoline **1a/2a** with *n*-hexylamine.



Entry[a]	Substrate	Ligand[a]	Yield[b]
1	**1a**	(±)-BINAP	45
2	**2a**	(±)-BINAP	57
3	**1a**	Xantphos	31
4	**2a**	Xantphos	14
5	**1a**	Davephos	22
6	**2a**	Davephos	19
7	**1a**	Johnphos	21
8	**1a**	CyJohnphos	17
9	**1a**	DPEphos	16



[a] Reagents and conditions: **1a/2a** (1 equiv.), *n*-hexylamine (1.5 equiv.), $Pd_2(dba)_3$ (4 mol-%), ligand (8 mol-%), Cs_2CO_3 (2.5 equiv.), 1,4-dioxane, 100 °C, 24 h. [b] Isolated yield.

We next investigated the influence of solvent on the amination reaction. The three most commonly used solvents in Pd-catalyzed reactions (toluene, 1,4-dioxane, and 1,2-dimethoxyethane) were tested. Significant solvent effects were noted; the use of 1,4-dioxane correlated to the highest yields, whereas yields as low as 6% were observed for reactions run in toluene (Table 2).

Table 2. Solvent effects on the Pd-catalyzed reaction of chloroquinoline **1a/2a** with *n*-hexylamine.

Entry[a]	Substrate	Solvent	Yield [%][b]
1	**1a**	toluene	6
2	**2a**	toluene	14
3	**1a**	1,4-dioxane	45
4	**2a**	1,4-dioxane	57
5	**1a**	DME	12

[a] Reagents and conditions: **1a/2a** (1 equiv.), *n*-hexylamine (1.5 equiv.), $Pd_2(dba)_3$ (4 mol-%), (±)-BINAP (8 mol-%), Cs_2CO_3 (2.5 equiv.), 100 °C, 24 h. [b] Isolated yield.

The influence of base on the amination of chloroquinoline **1c/2c** with *n*-hexylamine was then evaluated, and the results are reported in Table 3. Among the bases evaluated, Cs_2CO_3 proved to be ideal. Using Cs_2CO_3, the amination was found to proceed efficiently, affording desired products **3c** and **4c** in 81 and 73% yield, respectively. A similar result was obtained by using K_3PO_4 as base, whereas *t*BuONa proved to be completely unsuitable leading to a yield of only 10% for **1c**.

Table 3. Base effect on the Pd-catalyzed reaction of chloroquinoline **1c/2c** with *n*-hexylamine.

Entry[a]	Substrate	Base	Yield [%][b]
1	**1c**	*t*BuONa	10
2	**1c**	K_3PO_4	73
3	**1c**	Cs_2CO_3	81
4	**2c**	Cs_2CO_3	73

[a] Reagents and conditions: **1c/2c** (1 equiv.), *n*-hexylamine (1.5 equiv.), $Pd_2(dba)_3$ (4 mol-%), (±)-BINAP (8 mol-%), base (2.5 equiv.), 1,4-dioxane, 100 °C, 24 h. [b] Isolated yield.

Finally, to complete this reaction optimization process, we investigated palladium source effects. As reported in Table 4, two sources of palladium were tested and both afforded some amination product, although the highest yield was obtained by using $Pd_2(dba)_3$ (4 mol-%). We noticed that the use of a lower catalyst loading (2 mol-%) resulted in a noticeable decrease in coupling efficiency.

Table 4. Pd source effect on the Pd-catalyzed reaction of chloroquinoline **1c** with *n*-hexylamine.

Entry[a]	Pd Source	Yield [%][b]
1	$Pd_2(dba)_3$	81
2	$Pd(OAc)_2$	61

[a] Reagents and conditions: **1c** (1 equiv.), *n*-hexylamine (1.5 equiv.), Pd source (8 mol-%), (±)-BINAP (8 mol-%), Cs_2CO_3 (2.5 equiv.), 1,4-dioxane, 100 °C, 24 h. [b] Isolated yield.

From the screening of reaction parameters we concluded that the ideal reaction conditions involve chloroquinoline (1 equiv.), amine (1.5 equiv.), BINAP (8 mol-%), $Pd_2(dba)_3$

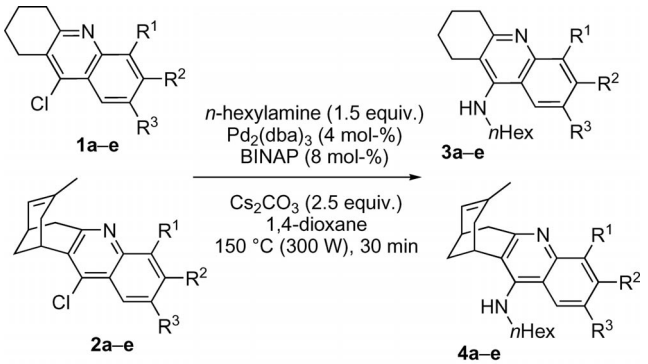
(4 mol-%), and Cs_2CO_3 (2.5 equiv.) in 1,4-dioxane heated to 100 °C for 24 h. However, the application of these conditions proved to be far from ideal and increasing the reaction time from 24 to 68 h for compound **3a** led only to a modest yield improvement (62% instead of 45%) with residual starting material remaining. To achieve total substrate conversion while also reducing reaction times, we investigated the use of microwave irradiation.[10]

In determining the correlation of temperature to irradiation time we again focused on the amination of **1a** with *n*-hexylamine. This reaction was carried out at three temperatures (100, 120, and 150 °C) using a CEM Discover apparatus (Figure 2) set to 300 W. At 100 °C (Figure 2, Graph A), the yield of **3a** was very low. After a 120 min irradiation, 60% of **1a** remained, and only 35% of desired product **3a** was obtained.

Notably, we observed the formation of compound **3b** arising from the reduction of the second chlorine atom and product **5** arising from the reaction with a second equivalent of *n*-hexylamine; the *N*,*N*-diarylated product was never observed. All products of this reaction were isolated and fully characterized by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. Increasing the reaction temperature (Figure 2, Graph B) improved the yield of **3a** to 60% after a 2 h reaction time although 18% of the starting material remained. Heating to 150 °C (Figure 2, Graph C) with a 30 min irradiation afforded complete conversion and **3a** was produced in 65% yield. However, the prolonged reaction time dramatically increased the amount of **3b** formed. In light of these results, the irradiation conditions were fixed at 150 °C for 30 min. Because some direct amination reactions using microwave activation without transition-metal catalyst have been reported in the literature,[11] the reaction with **1a** and *n*-hexylamine was carried out in the absence of a Pd catalyst. Importantly, the absence of Pd precluded production of **3a**, thus confirming the necessity of the catalyst.

We subsequently applied the established microwave conditions to differently substituted 9-chlorotetrahydroacridines **1a**–**e** and the corresponding 12-chlorotetrahydro-7,11-methanocycloocta[*b*]quinolines **2a**–**e** to explore the reaction scope in term of substrate (Table 5). Using the optimized conditions, most chloroquinolines could be coupled efficiently with *n*-hexylamine (Table 5 , Entries 1, 3, 4, 8, and 9). However, nonactivated 9-chlorotetrahydroacridine **1b** and 12-chlorotetrahydro-7,11-methanocycloocta[*b*]quinol-

Table 5. Cross-coupling of **1a**–**e** and **2a**–**e** with *n*-hexylamine under microwave irradiation.



a : R^1, R^3 = H, R^2 = Cl; **b** : R^1, R^2, R^3 = H; **c**: R^1, R^2 = H, R^3 = NO_2
d: R^1 = H, R^2, R^3 = F; **e**: R^1, R^3 = Cl, R^2 = H

Entry	ArX	Yield [%][a]
1	**1a**	60
2	**1b**	68[b]
3	**1c**	77
4	**1d**	83
5	**1e**	38
6	**2a**	50[c,d]
7	**2b**	95[b]
8	**2c**	94
9	**2d**	59
10	**2e**	31[e]

[a] Isolated yield after flash chromatography. [b] The reaction was carried out for 2 h. [c] The reaction was carried out for 5 h at 120 °C (300 W). [d] Product **2a** was obtained in 90% yield by using conventional heating (100 °C, 48 h). [e] Isolated along with **2e** (30%).

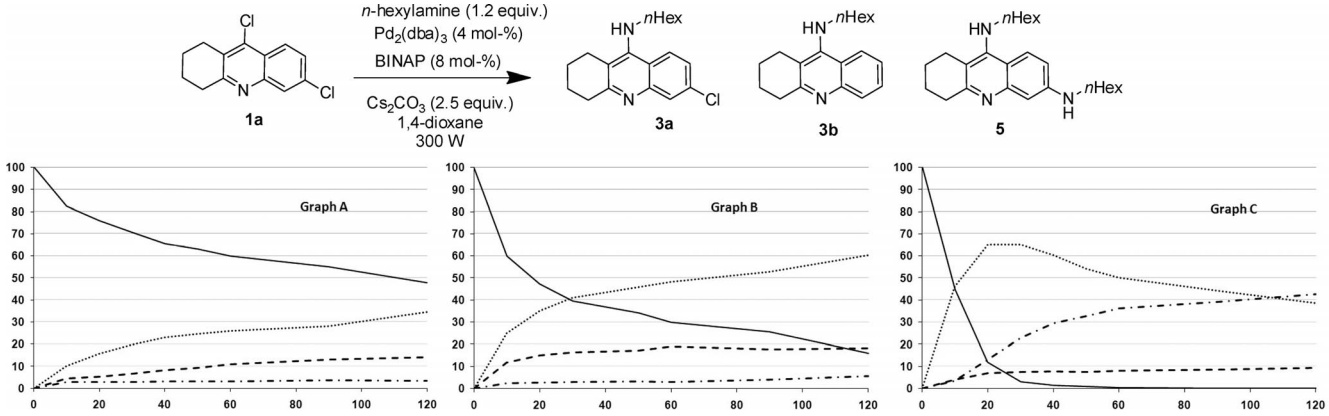


Figure 2. Time and temperature optimization of microwave irradiation for the amination of **1a** with *n*-hexylamine. Proportion of products in reaction mixture was determined by HPLC every 10 min for 1 h with additional measurements being made at 90n and 120 min: **1a** (——); **3a** (·····); **3b** (–·–·–) and **5** (-----). Reaction temperatures: Graph A: 100 °C, Graph B: 120 °C, Graph C: 150 °C.

ine **2b** required longer reaction times to furnish compounds **3b** and **4b** in 68 and 95% yield, respectively. Surprisingly, low selectivity of amination was observed for the coupling reactions of *n*-hexylamine with trihalogenated compounds **1e** and **2e**. Under the optimized reaction conditions, desired products **3e** and **4e** were obtained in 38 and 31% yield (along with 30% of **2e**), respectively, along with significant amounts of **6** (24%) or **7** (29%), whose structures were unambiguously confirmed by 1D and 2D NMR spectroscopic analysis (Figure 3). These results show that a large variety of *N*-alkylated tacrine and huprine compounds are attainable in good to excellent yields by using the reported coupling conditions.

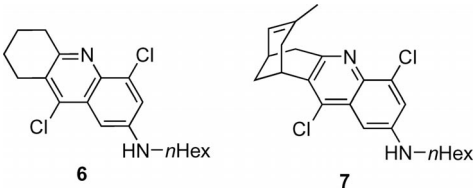
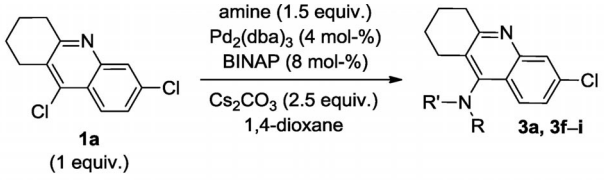


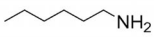
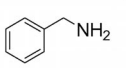
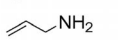
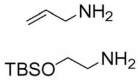
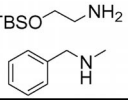
Figure 3. Side products arising from the nonselective reaction with **1e** and **2e**.

With the goal to efficiently prepare heterodimeric AChE inhibitors and their precursors, we were interested in exploring the scope of the amination reaction with various amines, specifically with functionalizable primary amines (Table 6). Towards this end, amination reactions were carried out by using either microwave irradiation or conventional heating, and the best results are shown below. For any single combination of **1a** and amine, one of the two reaction conditions was found to lead selectively to the *N*-alkylated tacrine in yields ranging from 55 to 71%.

Table 6. Substrate scope for the coupling with **1a** under microwave activation or conventional heating.

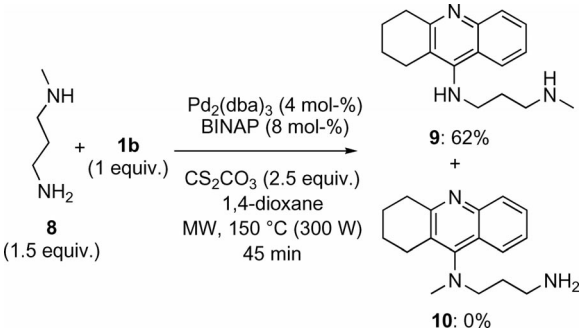


Conditions A (conventionnal heating): 100 °C, 24 h
Conditions B (MW): 150 °C (300 W), 30 min

Entry	Amine	Product	Conditions	Yield [%][a]
1		**3a**	B	60
2		**3f**	B	55
3		**3g**	A	71[b]
4		**3h**	B	60
5		**3i**	A	60[c]

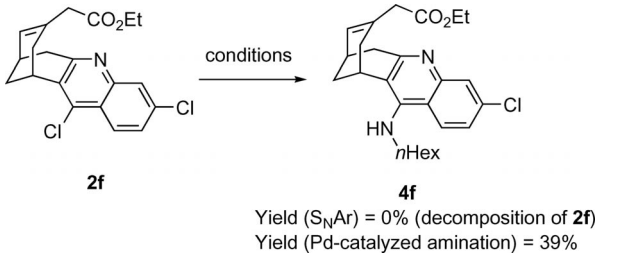
[a] Isolated yield after flash chromatography. [b] Product **3g** was obtained in 56% yield under conditions B. [c] Product **3i** was obtained in 39% yield under conditions B.

Finally, we explored the selectivity of arylation between primary and secondary amines by using diamine **8** as the substrate. It is known that Pd-catalyzed amination of diamines[12] or acyclic polyamines[8a,13] takes place preferentially on the primary amino group. Accordingly, we found amination of **1b** to proceed with the primary amino group of **8** but not the secondary amine. Coupled product **9** resulting from primary amine arylation was obtained in 62% yield (Scheme 1); no trace of **10** was evident.



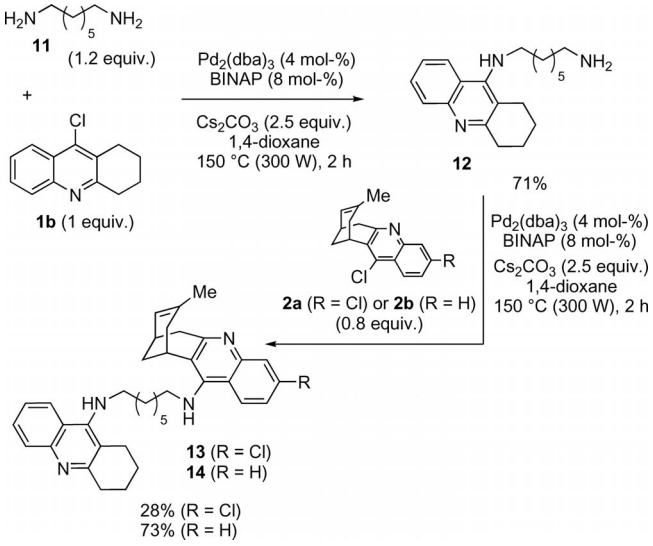
Scheme 1. Amination of **1b** with *N*-methylpropanediamine **8**.

As a validation example, the coupling reaction between *n*-hexylamine and 12-chloroquinoline **2f** – an interesting compound for which we recently reported the synthesis[3b,14] – was performed by using both S_NAr and Pd-catalyzed amination reactions (Scheme 2). Although the S_NAr reaction led, as expected, to only substrate degradation, our microwave-assisted Pd-catalyzed amination conditions afforded **4f** in 39% yield (not optimized).



Scheme 2. Conditions and reagents for the S_NAr reaction: **2f** (1 equiv.), *n*-hexylamine (1.2 equiv.), phenol, NaI (0.25 equiv.), 160 °C, 3 h. Conditions and reagents for the Pd-catalyzed amination reaction: **2f** (1 equiv.), *n*-hexylamine (1.5 equiv.), Cs_2CO_3 (2.5 equiv.), $Pd_2(dba)_3$ (4 mol-%), (±)-BINAP (8 mol-%), 1,4-dioxane, 150 °C (300 W), 30 min.

Finally, in order to illustrate the efficiency of this new method, two heterodimeric AChE inhibitors **13** [IC_{50} (*human* AChE) = 0.34 nM][5c] and **14** were prepared in two steps as depicted in Scheme 3. Pd-catalyzed arylations of 1,7-diaminoheptane (**11**) were realized consecutively with **1b** and **2a**/**2b** to afford desired inhibitors **13** and **14** in an overall yield of 20 (after preparative HPLC) and 52%, respectively.



Scheme 3. Synthesis of heterodimeric AChE inhibitors **13** and **14**.

Conclusions

In conclusion, we have developed an efficient method of preparing *N*-alkylated tacrine and huprine compounds by using palladium-catalyzed amination of chloroquinolines **1** and **2**. A large variety of 9-chlorotetrahydroacridines **1a**–**e** and 12-chlorotetrahydro-7,11-methanocycloocta[*b*]quinolines **2a**–**f** can be coupled with primary amines in good to excellent yields. Finally, this reaction represents an excellent alternative method to rapidly access quinoline-based dual–site binding AChE inhibitors.

Experimental Section

General: Column chromatography was performed on silica gel (40–63 μm) from SdS. Thin-layer chromatography (TLC) was carried out on Merck DC Kieselgel 60 F-254 aluminum sheets. Compounds were visualized by one of the two following methods: (1) illumination with a short-wavelength UV lamp (λ = 254 nm) or (2) staining with a 3.5% (w/v) phosphomolybdic acid solution in absolute ethanol. All solvents were dried following standard procedures (CH_2Cl_2, 1,2-dichloroethane, and CH_3CN: distillation over P_2O_5; DMF and DMSO: distillation over BaO under reduced pressure; THF, toluene, and Et_2O: distillation over Na/benzophenone). Triethylamine (TEA) and pyridine were distilled from CaH_2 and stored over BaO or KOH. Melting points were recorded with a LEICA VMHB Kofler system at atmospheric pressure. Microanalyses were carried out with a Carlo–Erba 1106. Infrared spectra were recorded as KBr pellets using a Perkin–Elmer FTIR Paragon 500 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DPX 300 spectrometer (Bruker, Wissembourg, France). Chemical shifts are expressed in parts per million (ppm) using $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm), [D_6]DMSO (δ_H = 2.50 ppm, δ_C = 39.52 ppm), or CD_3OD (δ_H = 3.31 ppm, δ_C = 49.00 ppm) as internal standards. ^{1}H and ^{13}C NMR spectra of all compounds were assigned through 2D-NMR experiments (COSY, HSQC, HMBC). Mass spectra were obtained with a Finnigan LCQ Advantage MAX (ion trap) apparatus equipped with an electrospray source. All analyses were performed in the positive mode. Microwave reactions were performed using a CEM Focused Microwave™ Synthesis System apparatus, Model Discover. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. All the reactions were performed in special glass vessels under an atmosphere of argon. Reaction mixture temperatures were measured during microwave heating with an IR surface sensor located in the base of the Discover. The chromatographic system used for the preparative HPLC purification step involved reverse-phase HPLC (C18, Thermo Hypersil GOLD, 5μ, 21.2 × 250 mm) with CH_3CN and 0.1% trifluoroacetic acid (TFA 0.1%, pH 2.0) as the eluents [100% H_2O (TFA 0.1%) (5 min), then linear gradient from 0 to 100% (50 min) of CH_3CN] at a flow rate of 20.0 mL/min. UV/Vis detection was achieved at 264 nm.

General Procedure for the Palladium-Catalyzed Amination Reaction under Conventional Heating: A Schlenk tube containing a stir bar was charged with chloroquinoline (125 μmol, 1 equiv.), $Pd_2(dba)_3$ (4.6 mg, 4 mol-%), (±)-BINAP (6.2 mg, 8 mol-%), and Cs_2CO_3 (102 mg, 313 μmol, 2.5 equiv.). The vessel was sealed with a septum and purged with argon. Degassed 1,4-dioxane (0.5 mL) and distilled amine (188 μmol, 1.5 equiv.) were then introduced through the septum and the resulting mixture was heated to 100 °C for 24 h unless otherwise stated. After cooling, the reaction mixture was concentrated and purified by flash chromatography.

General Procedure for the Palladium-Catalyzed Amination Reaction under Microwave Irradiation: A 10-mL microwave tube containing a stir bar was charged with chloroquinoline (125 μmol, 1 equiv.), $Pd_2(dba)_3$ (4.6 mg, 4 mol-%), (±)-BINAP (6.2 mg, 8 mol-%), and Cs_2CO_3 (102 mg, 313 μmol, 2.5 equiv.). The vessel was sealed with a microwave septum and purged with argon. Degassed 1,4-dioxane (0.5 mL) and distilled amine (188 μmol, 1.5 equiv.) were introduced through the septum, and the resulting mixture was heated by using a CEM Discover apparatus to 150 °C (300 W) for 30 min unless otherwise stated. After cooling, the reaction mixture was concentrated and purified by flash chromatography.

6-Chloro-*N*-hexyl-1,2,3,4-tetrahydroacridin-9-amine (3a): The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1a** (63 mg, 0.25 mmol) and hexylamine (50 μL, 375 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 8:2:0.1) afforded **3a** as a white solid (47.0 mg, 60%). R_f (EtOAc) = 0.33. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H, 16-H), 1.24–1.38 (m, 6 H, 13-H, 14-H, 15-H), 1.59–1.69 (m, 2 H, 12-H), 1.87–1.93 (m, 4 H, 7-H, 8-H), 2.62–2.67 (m, 2 H, 9-H), 2.98–3.03 (m, 2 H, 6-H), 3.45 (t, J = 7.0 Hz, 2 H, 11-H), 3.80 (br. s, 1 H, NH), 7.25 (dd, J = 8.9, 2.1 Hz, 1 H, 2-H), 7.88 (d, J = 2.1 Hz, 1 H, 1-H), 7.89 (d, J = 8.9 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.7 (2 C, C-7, C-8), 23.0 (C-15), 24.6 (C-9), 26.7 (C-13), 31.6 (C-14), 31.9 (C-12), 34.0 (C-6), 49.7 (C-11), 115.6 (C-10a), 118.4 (C-9a), 124.3 (C-2), 124.8 (C-4), 127.4 (C-1), 134.2 (C-3), 148.0 (C-4a), 151.1 (C-10), 159.4 (C-5a) ppm. MS (ESI+): *m*/*z* (%) = 319 (31), 317 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{19}H_{26}N_2Cl$ 317.1802; found 317.1795.

***N*-Hexyl-1,2,3,4-tetrahydroacridin-9-amine (3b):** The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1b** (63 mg, 0.25 mmol) and hexylamine (50 μL, 375 μmol). The reaction mixture was heated to 150 °C (300 W) for 2 h. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 8:2:0.2) afforded **3b** as a yellow solid (48 mg, 68%). R_f (EtOAc/MeOH, 9:1) = 0.17. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.4 Hz, 3 H, 16-H), 1.24–1.42 (m, 6 H, 13-H, 14-H, 15-H), 1.59–1.69 (m, 2 H, 12-H), 1.87–1.93

(m, 4 H, 7-H, 8-H), 2.65–2.71 (m, 2 H, 9-H), 3.05–3.11 (m, 2 H, 6-H), 3.52 (t, J = 7.4 Hz, 2 H, 11-H), 4.49 (br. s, 1 H, NH), 7.34 (t, J = 8.1 Hz, 1 H, 2-H), 7.55 (t, J = 8.1 Hz, 1 H, 3-H), 7.96 (d, J = 8.1 Hz, 2 H, 1-H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.7 (2 C, C-7, C-8), 23.1 (C-15), 24.8 (C-9), 26.7 (C-13), 31.7 (C-14), 31.9 (C-12), 33.4 (C-6), 49.6 (C-11), 115.3 (C-10a), 119.8 (C-9a), 123.1 (C-1), 123.8 (C-2), 127.9 (C-4), 128.8 (C-3), 146.6 (C-4a), 151.5 (C-10), 157.8 (C-5a) ppm. MS (ESI+): m/z (%) = 284 (25), 283 (100) $[M + H]^+$. HRMS (ESI+):calcd. for $C_{19}H_{27}N_2$ 283.2174; found 283.2183.

***N*-Hexyl-7-nitro-1,2,3,4-tetrahydroacridin-9-amine (3c):** The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1c** (65.7 mg, 0.25 mmol) and hexylamine (50 μL, 375 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 5:5:0.2) afforded **3c** as a yellow solid (63 mg, 77%). R_f (EtOAc) = 0.53. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.0 Hz, 3 H, 16-H), 1.26–1.32 (m, 4 H, 13-H, 14-H), 1.38–1.44 (m, 2 H, 15-H), 1.70–1.74 (m, 2 H, 12-H), 1.89–1.92 (m, 4 H, 7-H, 8-H), 2.58–2.61 (m, 2 H, 9-H), 2.98–3.03 (m, 2 H, 6-H), 3.63 (dt, J = 7.0, 5.8 Hz, 2 H, 11-H), 4.28 (br. s, 1 H, NH), 7.83 (d, J = 9.3 Hz, 1 H, 4-H), 8.21 (dd, J = 9.3, 2.5 Hz, 1 H, 3-H), 8.99 (d, J = 2.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (C-16), 22.5 (C-7 or C-8 or C-13), 22.6 (C-7 or C-8 or C-13), 22.7 (C-7 or C-8 or C-13), 24.4 (C-9), 26.5 (C-15), 31.5 (C-14), 31.8 (C-12), 34.4 (C-6), 49.7 (C-11), 115.4 (C-9a), 117.5 (C-10a), 121.7 (2 C, C-1, C-3), 130.1 (C-4), 142.4 (C-4a), 150.3 (C-2), 152.2 (C-10), 161.9 (C-5a) ppm. MS (ESI+): m/z (%) = 328 (100) $[M + H]^+$. HRMS (ESI+):calcd. for $C_{19}H_{-26}N_3O_2$ 328.2028; found 328.2025.

6,7-Difluoro-*N*-hexyl-1,2,3,4-tetrahydroacridin-9-amine (3d): The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1d** (63.4 mg, 0.25 mmol) and hexylamine (50 μL, 375 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (cyclohexane/EtOAc, 10:0 to 8:2) afforded **3d** as a yellow solid (66 mg, 83%). R_f (EtOAc) = 0.59. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.6 Hz, 3 H, 16-H), 1.24–1.30 (m, 4 H, 14-H, 15-H), 1.31–1.41 (m, 2 H, 13-H), 1.57–1.68 (m, 2 H, 12-H), 1.85–1.91 (m, 4 H, 7-H, 8-H), 2.61–2.66 (m, 2 H, 9-H), 2.95–3.01 (m, 2 H, 6-H), 3.40 (t, J = 7.2 Hz, 2 H, 11-H), 3.75 (br. s, 1 H, NH), 7.58 (dd, J = 11.9, 8.1 Hz, 1 H, 4-H), 7.65 (dd, J = 11.9, 8.1 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.6 (C-7), 22.7 (C-8), 23.0 (C-15), 24.5 (C-9), 26.7 (C-13), 31.6 (C-14), 31.8 (C-12), 34.0 (C-6), 49.6 (C-11), 109.3 (dd, J = 18.5, 1.6 Hz, C-1), 114.6 (d, J = 15.8 Hz, C-4), 116.1 (C-9a), 116.8 (d, J = 5.5 Hz, C-10a), 145.7 (dd, J = 97.6, 10.4 Hz, C-2), 149.8 (d, J = 5.5 Hz, C-10), 150.5 (d, J = 3.3 Hz, C-4a), 151.4 (dd, J = 97.6, 10.4 Hz, C-3), 159.1 (C-5a) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –139.3 (d, J = 21.7 Hz, 2-F), –134.7 (d, J = 21.7 Hz, 3-F) ppm. MS (ESI+): m/z (%) = 320 (20), 319 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{19}H_{25}N_2F_2$ 319.1974; found 319.1986.

5,7-Dichloro-*N*-hexyl-1,2,3,4-tetrahydroacridin-9-amine (3e): The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1e** (72 mg, 0.25 mmol) and hexylamine (50 μL, 375 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (cyclohexane/EtOAc, 100:0 to 94:6) afforded **3e** as a yellow solid (33 mg, 38%). R_f (cyclohexane/EtOAc, 9:1) = 0.36. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3 H, 16-H), 1.24–1.34 (m, 4 H, 14-H, 15-H), 1.35–1.44 (m, 2 H, 13-H), 1.59–1.70 (m, 2 H, 12-H), 1.89–1.93 (m, 4 H, 7-H, 8-H), 2.65–2.71 (m, 2 H, 9-H), 3.08–3.13 (m, 2 H, 6-H), 3.43 (t, J = 7.4 Hz, 2 H, 11-H), 3.88 (br. s, 1 H, NH), 7.65 (d, J = 2.3 Hz, 1 H, 3-H), 7.87 (d, J = 2.3 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.7 (2 C, C-7, C-8), 23.0 (C-15), 24.8 (C-9), 26.7 (C-13), 31.7 (C-14), 31.9 (C-12), 34.6 (C-6), 50.0 (C-11), 117.9 (C-10a), 121.7 (C-1), 121.9 (C-9a), 128.0 (C-4), 128.9 (C-3), 134.0 (C-2), 142.7 (C-4a), 150.6 (C-10), 160.0 (C-5a) ppm. MS (ESI+): m/z (%) = 353 (66), 351 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{19}H_{25}Cl_2N_2$ 351.1395; found 351.1387.

***N*-Benzyl-6-chloro-1,2,3,4-tetrahydroacridin-9-amine (3f):** The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1a** (32 mg, 125 μmol) and benzylamine (20.5 μL, 188 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 8:2:0.2) afforded **3f** as pale-yellow solid (22 mg, 55%). R_f (EtOAc) = 0.37. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84–1.90 (m, 4 H, 7-H, 8-H), 2.58 (t, J = 6.2 Hz, 2 H, 9-H), 3.03 (t, J = 6.2 Hz, 2 H, 6-H), 4.06 (br. s, 1 H, NH), 4.61 (s, 2 H, 11-H), 7.26 (dd, J = 8.9, 2.1 Hz, 1 H, 2-H), 7.28–7.37 (m, 5 H, 13-H, 14-H, 15-H, 16-H, 17-H), 7.90 (d, J = 8.9 Hz, 1 H, 1-H), 7.92 (d, J = 2.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7 (C-7 or C-8), 22.9 (C-7 or C-8), 24.7 (C-9), 34.0 (C-6), 53.7 (C-11), 116.8 (C-10a), 118.6 (C-9a), 124.6 (C-1), 124.8 (C-2), 127.7 (3 C, C-13, C-15, C-17), 128.0 (C-4), 129.1 (2 C, C-14, C-16), 134.3 (C-3), 139.5 (C-12), 148.1 (C-10), 150.7 (C-4a), 159.8 (C-5a) ppm. MS (ESI+): m/z (%) = 325 (31), 323 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{20}H_{20}N_2Cl$ 323.1318; found 323.1315.

***N*-Allyl-6-chloro-1,2,3,4-tetrahydroacridin-9-amine (3g)**

Procedure 1: The general procedure for the palladium-catalyzed amination reaction with conventional heating was followed using **1a** (31 mg, 125 μmol) and allylamine (14 μL, 188 μmol). The reaction mixture was heated to 100 °C for 24 h. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 8:2:0.2%) afforded **3g** as a pale-yellow solid (22 mg, 71%).

Procedure 2: The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1a** (31 mg, 125 μmol) and allylamine (14 μL, 188 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 8:2:0.1) afforded **3g** as a pale-yellow solid (19 mg, 56%). R_f (EtOAc) = 0.29. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87–1.92 (m, 4 H, 7-H, 8-H), 2.65–2.70 (m, 2 H, 9-H), 3.00–3.05 (m, 2 H, 6-H), 4.00 (br. s, 1 H, NH), 4.07 (d, J = 5.5 Hz, 2 H, 11-H), 5.29 (dd, J = 45.9, 10.2 Hz, 2 H, 13-H), 5.92–6.05 (m, 1 H, 12-H), 7.26 (dd, J = 9.1, 2.1 Hz, 1 H, 2-H), 7.85 (d, J = 9.1 Hz, 1 H, 1-H), 7.88 (d, J = 2.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (C-7 or C-8), 22.9 (C-7 or C-8), 24.7 (C-9), 33.8 (C-6), 51.8 (C-11), 116.4 (C-10a), 117.3 (C-13), 118.4 (C-9a), 124.6 (C-1 or C-2), 124.7 (C-1 or C-2), 127.2 (C-4), 134.4 (C-3), 135.5 (C-12), 147.7 (C-10), 150.9 (C-4a), 159.4 (C-5a) ppm. MS (ESI+): m/z (%) = 275 (37), 273 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{16}H_{18}N_2Cl$ 273.1167; found 273.1159.

***N*-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-6-chloro-1,2,3,4-tetrahydroacridin-9-amine (3h)**

Procedure 1: The general procedure for the palladium-catalyzed amination reaction with conventional heating was followed using **1a** (31.5 mg, 125 μmol) and 2-(*tert*-butyldimethylsilyloxy)ethanamine (33 mg, 188 μmol). The reaction mixture was heated to 100 °C for 24 h. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 8:2:0.2%) afforded **3h** as a yellow solid (26 mg, 53%).

Procedure 2: The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1a** (31 mg, 125 μmol) and 2-(*tert*-butyldimethylsilyloxy)ethanamine (33 mg, 188 μmol). The reaction mixture was heated to 150 °C (300 W) for 50 min. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 8:2:0.2) afforded **3h** as a yellow solid (37 mg, 60%). R_f (EtOAc) = 0.68. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 6 H, 13-H, 14-H), 0.93 (s, 9 H, 16-H, 17-H, 18-H), 1.87–1.94 (m, 4 H, 7-H, 8-H), 2.71–2.77 (m, 2 H, 9-H), 3.00–3.06 (m, 2 H, 6-H), 3.55 (t, J = 4.8 Hz, 2 H, 11-H), 3.72 (t, J = 4.8 Hz, 2 H, 12-H), 4.64 (br. s, 1 H, NH), 7.18 (dd, J = 9.0, 2.1 Hz, 1 H, 2-H), 7.80 (d, J = 2.1 Hz, 1 H, 4-H), 7.83 (d, J = 9.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$):: δ = –5.4 (2 C, C-13, C-14), 18.2 (C-5), 22.7 (C-7 or C-8), 22.9 (C-7 or C-8), 24.5 (C-9), 25.9 (3 C, C-16, C-17, C-18), 34.1 (C-6), 51.3 (C-11), 62.4 (C-12), 117.2 (C-9a), 119.0 (C-10a), 124.4 (C-2), 124.6 (C-1), 127.7 (C-4), 133.9 (C-3), 148.09 (C-10), 150.8 (C-4a), 159.8 (C-5a) ppm. MS (ESI+): *m*/*z* (%) = 393 (45), 391 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{21}H_{32}N_2OSiCl$ 391.1957; found 391.1972.

***N*-Benzyl-6-chloro-*N*-methyl-1,2,3,4-tetrahydroacridin-9-amine (3i)**

Procedure 1: The general procedure for the palladium-catalyzed amination reaction with conventional heating was followed using **1a** (31 mg, 125 μmol) and *N*-methylbenzylamine (24 μL, 188 μmol). The reaction mixture was heated to 100 °C for 24 h. Purification by flash chromatography (cyclohexane/EtOAc/Et_3N, 10:0:0 to 8:2:0.2%) afforded **3i** as a pale-yellow solid (24 mg, 60%).

Procedure 2: The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1a** (63 mg, 0.25 mmol) and *N*-methylbenzylamine (24 μL, 188 μmol). The reaction mixture was heated to 120 °C (300 W) for 2 h. Purification by flash chromatography (petroleum ether/EtOAc, 10:0 to 8:2) afforded **3i** as a pale-yellow solid (16 mg, 39%). R_f (EtOAc) = 0.92. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.76–1.85 (m, 2 H, 8-H), 1.89–1.98 (m, 2 H, 7-H), 2.81 (t, J = 6.2 Hz, 2 H, 9-H), 2.90 (s, 3 H, 18-H), 3.11 (t, J = 6.6 Hz, 2 H, 6-H), 4.36 (s, 2 H, 11-H), 7.26–7.38 (m, 6 H, 2-H, 13-H, 14-H, 15-H, 16-H, 17-H), 7.96 (d, J = 2.3 Hz, 1 H, 4-H), 7.98 (d, J = 8.9 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9 (C-8), 23.0 (C-7), 27.0 (C-9), 34.1 (C-6), 40.4 (C-18), 60.4 (C-11), 124.5 (C-10a), 125.9 (C-2), 126.0 (C-4), 127.5 (C-15), 127.8 (C-1), 128.2 (C-9a), 128.6 (2 C, C-13, C-17), 128.7 (2 C, C-14, C-16), 134.1 (C-3), 139.1 (C-12), 148.5 (C-10), 154.6 (C-4a), 161.9 (C-5a) ppm. MS (ESI+): *m*/*z* (%) = 339 (37), 337 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{21}H_{22}N_2Cl$ 337.1455; found 337.1472.

***N*-Hexyl-9-methyl-3-chloro-6,7,10,11-tetrahydro-7,11-ethanocycloocta[*b*]quinolin-12-amine (4a)**

Procedure 1: The general procedure for the palladium-catalyzed amination reaction with conventional heating was followed using **2a** (38.0 mg, 125 μmol) and hexylamine (25 μL, 188 μmol). The reaction mixture was heated to 100 °C for 48 h. Purification by flash chromatography (petroleum ether/EtOAc, 10:0 to 7.5:2.5) afforded **4a** as a pale-yellow solid (41 mg, 90%).

Procedure 2: The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **2a** (38.0 mg, 125 μmol) and hexylamine (25 μL, 188 μmol). The reaction mixture was heated to 120 °C (300 W) for 5 h. Purification by flash chromatography (petroleum ether/EtOAc, 10:0 to 7.5:2.5) afforded **4a** as a pale-yellow solid (22 mg, 50%). R_f (EtOAc/MeOH, 9:1) = 0.70. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.0 Hz, 3 H, 20-H), 1.21–1.38 (m, 6 H, 18-H, 19-H, 17-H), 1.44 (s, 3 H, 14-H), 1.58–1.68 (m, 2 H, 16-H), 1.74 (d, J = 17.2 Hz, 1 H, 13-H), 1.84 (d, J = 12.4 Hz, 1 H, 10-H), 1.93–2.00 (m, 1 H, 10-H), 2.45 (dd, J = 17.9, 5.6 Hz, 1 H, 13-H), 2.62–2.68 (m, 1 H, 7-H), 2.92 (dt, J = 17.7, 1.9 Hz, 1 H, 6-H), 3.07 (dd, J = 17.7, 5.5 Hz, 1 H, 6-H), 3.18–3.24 (m, 1 H, 11-H), 3.33–3.49 (m, 2 H, 15-H), 3.99 (br. s, 1 H, NH), 5.46 (d, J = 4.5 Hz, 1 H, 8-H), 7.19 (dd, J = 6.6, 2.1 Hz, 1 H, 2-H), 7.85 (d, J = 2.1 Hz, 1 H, 4-H), 7.88 (d, J = 2.1 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-20), 22.7 (C-19), 23.5 (C-14), 26.8 (C-17), 27.7 (C-11), 28.3 (C-7), 29.3 (C-10), 31.7 (C-18), 31.9 (C-16), 37.0 (C-13), 39.8 (C-6), 50.8 (C-15), 119.0 (C-11a or C-12a), 121.0 (C-11a or C-12a), 124.3 (C-2), 125.6 (2 C, C-1, C-8), 127.5 (C-4), 131.8 (C-3), 134.2 (C-9), 148.5 (C-4a or C-12), 150.7 (C-4a or C-12), 158.5 (C-5a) ppm. MS (ESI+): *m*/*z* (%) = 371 (42), 369 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{23}H_{30}N_2Cl$ 369.2089; found 369.2098.

***N*-Hexyl-9-methyl-6,7,10,11-tetrahydro-7,11-methanocycloocta[*b*]-quinolin-12-amine (4b):** The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using chloroquinoline **2b** (34 mg, 125 μmol) and hexylamine (25 μL, 188 μmol). The reaction mixture was heated to 150 °C (300 W) for 2 h. Purification by flash chromatography (petroleum ether/EtOAc, 10:0 to 7.5:2.5) afforded **4b** as a pale-yellow solid (40 mg, 95%). R_f (EtOAc/MeOH, 9:1) = 0.29. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.6 Hz, 3 H, 20-H), 1.29–1.36 (m, 4 H, 18-H, 19-H), 1.39–1.44 (m, 2 H, 17-H), 1.50 (s, 3 H, 14-H), 1.66–1.76 (m, 2 H, 16-H, 13-H), 1.82 (d, J = 16.7 Hz, 1 H, 13-H), 1.93 (dd, J = 12.2, 1.5 Hz, 1 H, 10-H), 2.01–2.07 (m, 1 H, 10-H), 2.53 (dd, J = 16.7, 4.4 Hz, 1 H, 13-H), 2.71–2.75 (m, 1 H, 7-H), 3.03 (d, J = 17.3 Hz, 1 H, 6-H), 3.17 (dd, J = 17.3, 5.5 Hz, 1 H, 6-H), 3.30–3.34 (m, 1 H, 11-H), 3.40–3.56 (m, 2 H, 15-H), 4.04 (br. s, 1 H, NH), 5.53 (d, J = 4.5 Hz, 1 H, 8-H), 7.33 (t, J = 7.1 Hz, 1 H, 2-H), 7.53 (t, J = 7.1 Hz, 1 H, 3-H), 7.90 (d, J = 8.5 Hz, 1 H, 4-H), 8.00 (d, J = 8.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-20), 22.7 (C-19), 23.5 (C-14), 26.8 (C-17), 27.7 (C-11), 28.4 (C-7), 29.3 (C-10), 31.7 (C-18), 31.9 (C-16), 37.2 (C-13), 40.0 (C-6), 50.6 (C-15), 120.9 (C-11a or C-12a), 121.1 (C-11a or C-12a), 123.6 (C-2), 124.0 (C-1), 125.6 (C-8), 128.4 (C-3), 128.7 (C-4), 131.8 (C-9), 147.9 (C-4a or C-12), 150.5 (C-4a or C-12), 157.4 (C-5a) ppm. MS (ESI+): *m*/*z* (%) = 335 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{23}H_{31}N_2$ 335.2477; found 335.2487.

***N*-Hexyl-9-methyl-2-nitro-6,7,10,11-tetrahydro-7,11-methanocycloocta[*b*]quinolin-12-amine (4c):** The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using chloroquinoline **2c** (79 mg, 0.25 mmol) and hexylamine (25 μL, 188 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (cyclohexane/EtOAc, 10:0 to 7.5:2.5) afforded **4c** as an orange solid (90 mg, 94%). R_f (EtOAc) = 0.79. M.p. 63–65 °C (decomp.). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.8 Hz, 3 H, 20-H), 1.31–1.37 (m, 4 H, 18-H, 19-H), 1.43–1.49 (m, 2 H, 17-H), 1.52 (s, 3 H, 14-H), 1.72–1.87 (m, 3 H, 16-H, 13-H), 1.92 (dd, J = 12.2, 1.7 Hz, 1 H, 10-H), 2.02–2.10 (m, 1 H, 10-H), 2.54 (dd, J = 16.9, 4.4 Hz, 1 H, 13-H), 2.72–2.77 (m, 1 H, 7-H), 2.96–3.05 (m, 1 H, 6-H), 3.16 (dd, J = 17.7, 5.5 Hz, 1 H, 6-H), 3.72–3.77 (m, 1 H, 11-H), 3.58–3.72 (m, 2 H, 15-H), 4.33 (br. s, 1 H, NH), 5.54 (d, J = 4.7 Hz, 1 H, 8-H), 7.88 (d, J = 9.2 Hz, 1 H, 4-H), 8.26 (dd, J = 9.2, 2.5 Hz, 1 H, 3-H), 9.08 (d, J = 2.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-20), 22.7 (C-19), 23.5 (C-14), 26.7 (C-17), 27.6 (C-11), 28.2 (C-7), 29.1 (C-10), 31.6 (C-18), 31.9 (C-16), 36.5 (C-13), 40.4 (C-6), 50.6 (C-15), 118.4 (C-11a or C-12a), 120.9 (C-11a or C-12a), 121.9 (C-3), 122.5 (C-1), 125.5 (C-8), 130.2 (C-4), 131.9 (C-3), 142.6 (C-2), 133.1 (C-9), 150.6 (C-4a or C-12), 151.9 (C-4a or C-12), 161.1 (C-5a) ppm. MS (ESI+): *m*/*z* (%) =

380 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{23}H_{30}N_3O_2$ 380.2354; found 380.2338.

2,3-Difluoro-*N*-hexyl-9-methyl-6,7,10,11-tetrahydro-7,11-methanocycloocta[*b*]quinolin-12-amine (4d): The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **2d** (76 mg, 0.25 mmol) and hexylamine (25 μL, 188 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (petroleum ether/EtOAc, 10:0 to 8:2) afforded **4d** as an orange solid (55 mg, 59%). R_f (cyclohexane/EtOAc, 5:5) = 0.64. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.0 Hz, 3 H, 20-H), 1.24–1.31 (m, 4 H, 18-H, 19-H), 1.32–1.38 (m, 2 H, 17-H), 1.45 (s, 3 H, 14-H), 1.58–1.67 (m, 2 H, 16-H), 1.73 (d, J = 17.3 Hz, 2 H, 13-H), 1.85 (d, J = 12.2 Hz, 1 H, 10-H), 1.94–2.02 (m, 1 H, 10-H), 2.47 (dd, J = 16.9, 4.3 Hz, 1 H, 13-H), 2.63–2.71 (m, 1 H, 7-H), 2.90 (d, J = 17.5 Hz, 1 H, 6-H), 3.06 (dd, J = 17.5, 5.5 Hz, 1 H, 6-H), 3.19–3.25 (m, 1 H, 11-H), 3.28–3.90 (m, 2 H, 15-H), 3.89 (br. s, 1 H, NH), 5.53 (d, J = 4.5 Hz, 1 H, 8-H), 7.60 (dd, J = 11.7, 7.9 Hz, 1 H, 4-H), 7.72 (dd, J = 11.7, 7.9 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-20), 22.7 (C-19), 23.5 (C-14), 26.7 (C-17), 27.6 (C-11), 28.3 (C-7), 29.2 (C-10), 31.7 (C-18), 31.8 (C-16), 37.2 (C-13), 39.9 (C-6), 50.5 (C-15), 110.1 (d, J = 19.1 Hz, C-1), 114.7 (d, J = 19.1 Hz, C-4), 117.6 (d, J = 6.0 Hz, C-12a), 121.6 (C-11a), 125.6 (C-8), 131.8 (C-9), 145.9 (dd, J = 75.8, 15.8 Hz, C-2), 149.7 (C-12), 150.1 (C-4a), 150.8 (d, J = 75.8 Hz, C-3), 158.1 (C-5a) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –139.1 (d, J = 21.6 Hz, 2-F), –134.5 (d, J = 21.6 Hz, 3-F) ppm. MS (ESI+): m/z (%) = 372 (25), 371 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{23}H_{29}N_2F_2$ 371.2305; found 371.2299.

Ethyl (3-Chloro-*N*-hexyl-6,7,10,11-tetrahydro-7,11-methanocycloocta[*b*]quinolin-9-yl)acetate (4f): The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **2f**[14] (47 mg, 125 μmol) and hexylamine (25 μL, 188 μmol). The reaction mixture was heated to 150 °C (300 W) for 30 min. Purification by flash chromatography (cyclohexane/EtOAc, 8:2 to 6:4) afforded **4f** as a yellow solid (21 mg, 39%). R_f (EtOAc) = 0.42. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87–0.92 (m, 3 H, 23-H), 1.01 (t, J = 7.2 Hz, 3 H, 17-H), 1.24–1.42 (m, 6 H, 21-H, 22-H, 20-H), 1.64–1.76 (m, 2 H, 19-H), 1.90–2.13 (m, 3 H, 10-H, 10-H, 13-H), 2.69 (d, J = 20.5 Hz, 1 H, 13-H), 2.75–2.80 (m, 1 H, 7-H), 2.84–2.89 (m, 2 H, 14-H), 3.03 (d, J = 17.9 Hz, 1 H, 6-H), 3.18 (dd, J = 17.9, 5.5 Hz, 1 H, 6-H), 3.29–3.33 (m, 1 H, 11-H), 3.43–3.57 (m, 2 H, 18-H), 3.94 (q, J = 7.2 Hz, 2 H, 16-H), 5.71 (d, J = 4.3 Hz, 1 H, 8-H), 7.27 (d, J = 9.0, 2.0 Hz, 1 H, 2-H), 7.89 (d, J = 2.0 Hz, 1 H, 4-H), 7.93 (d, J = 9.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-23), 14.2 (C-17), 22.7 (C-22), 26.7 (C-20), 27.3 (C-11), 28.2 (C-7), 28.9 (C-10), 29.8 (C-21), 31.6 (C-19), 35.1 (C-13), 39.2 (C-6), 43.3 (C-14), 50.5 (C-18), 60.6 (C-16), 105.5 (C-11a), 118.3 (C-12a), 123.6 (C-1), 124.7 (C-2), 125.7 (C-4), 129.4 (C-8), 131.5 (C-3), 138.9 (C-9), 149.6 (C-4a or C-12), 149.7 (C-4a or C-12), 164.9 (C-5a), 171.4 (C-15) ppm. MS (ESI+): m/z (%) = 429 (37), 427 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{26}H_{34}N_2O_2Cl$ 441.2337; found 441.2319.

***N*-1-Methyl-*N*-3-(5,6,7,8-tetrahydroacridin-9-yl)propane-1,3-diamine (9):** The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1b** (63.0 mg, 0.28 mmol) and *N*-methyl-1,3-propanediamine (39 μL, 188 μmol). The reaction mixture was heated to 150 °C (300 W) for 45 min. Purification by flash chromatography (EtOAc then acetone/Et_3N, 100:0 to 93:7) afforded **9** as a yellow solid (46 mg, 62%). R_f (DCM/MeOH/Et_3N, 9:1:1) = 0.61. ^{1}H NMR (300 MHz, MeOD): δ = 1.78–1.91 (m, 6 H, 7-H, 8-H, 12-H), 2.35 (s, 3 H, 16-H), 2.61–2.70 (m, 4 H, 9-H, 13-H), 2.90–2.94 (m, 2 H, 6-H), 3.57 (t, J = 7.0 Hz, 2 H, 11-H), 7.34 (t, J = 7.1 Hz, 1 H, 2-H), 7.53 (t, J = 7.1 Hz, 1 H, 3-H), 7.74 (d, J = 8.3 Hz, 1 H, 4-H), 8.08 (d, J = 8.3 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1 (C-7 or C-8), 23.4 (C-7 or C-8), 25.4 (C-9), 30.9 (C-12), 34.2 (C-6), 36.8 (C-14), 48.9 (C-11), 50.8 (C-13), 115.9 (C-10a), 120.4 (C-9a), 123.2 (C-1), 123.6 (C-2), 128.4 (C-4), 128.8 (C-3), 147.7 (C-4a), 151.3 (C-10), 158.6 (C-5a) ppm. MS (ESI+): m/z (%) = 271 (26), 270 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{17}H_{24}N_3$ 270.1969; found 270.1970.

9-(7-Aminoheptyl)-1,2,3,4-tetrahydroacridine (12): The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using **1b** (63 mg, 0.29 mmol) and 1,7-diaminoheptane **15** (45 mg, 0.34 mmol). The reaction mixture was heated to 150 °C (300 W) for 2 h. Purification by flash chromatography (CH_2Cl_2/MeOH/Et_3N, 9:1:1) afforded **12** as a brown oil (64 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28–1.35 (m, 6 H, 13-H, 14-H, 15-H), 1.50–1.57 (m, 2 H, 16-H), 1.58–1.64 (m, 2 H, 12-H), 1.85–1.92 (m, 4 H, 7-H, 8-H), 2.62–2.68 (m, 2 H, 9-H), 2.73 (t, J = 7.2 Hz, 2 H, 17-H), 3.00–3.06 (m, 2 H, 6-H), 3.48 (t, J = 7.2 Hz, 2 H, 11-H), 5.60 (br. s, 3 H, NH, NH_2), 7.31 (t, J = 8.1 Hz, 1 H, 2-H), 7.51 (t, J = 8.1 Hz, 1 H, 3-H), 7.87–7.98 (m, 2 H, 1-H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (C-16), 22.5 (C-7 or C-8), 22.6 (C-7 or C-8), 24.79 (C-9), 26.6 (C-13 or C-15), 26.7 (C-13 or C-15), 28.9 (C-14), 30.9 (C-16), 31.4 (C-12), 33.1 (C-6), 41.1 (C-17), 49.2 (C-11), 115.1 (C-10a), 119.5 (C-9a), 123.1 (C-1), 123.8 (C-2), 127.4 (C-4), 128.8 (C-3), 146.1 (C-4a), 151.5 (C-10), 157.3 (C-5a) ppm. MS (ESI+): m/z (%) = 313 (29), 312 (100) $[M + H]^+$. HRMS (ESI+): calcd. for $C_{20}H_{30}N_3$ 312.2453; found 312.2440.

3-Chloro-6,7,10,11-tetrahydro-9-methyl-12-({7-[(1,2,3,4-tetrahydroacridin-9-yl)amino]heptyl}amino)-7,11-methanocycloocta[*b*]quinoline Ditrifluoroacetic Acid (13): The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using chloroquinoline **2a** (27 mg, 0.09 mmol) and amine **12** (33 mg, 0.105 mmol). The reaction mixture was heated to 150 °C (300 W) for 2 h. Purification by preparative HPLC afforded **13** as a yellow solid (20 mg, 28%). ^{1}H and ^{13}C NMR spectroscopic data are in agreement with those given in the literature.[5c] MS (ESI+): m/z (%) = 579 (50) $[M + H]^+$, 290 (100) $[M + 2H]^{2+}$. HRMS (ESI+): calcd. for $C_{37}H_{44}N_4Cl$ 579.3255; found 579.3244.

9-Methyl-6,7,10,11-tetrahydro-12-({8-[(1,2,3,4-tetrahydroacridin-9-yl)amino]heptyl}amino)-7,11-methanocycloocta[*b*]quinoline (14): The general procedure for the palladium-catalyzed amination reaction under microwave irradiation was followed using chloroquinoline **2b** (16 mg, 0.06 mmol) and amine **12** (28 mg, 0.09 mmol). The reaction mixture was heated to 150 °C (300 W) for 2 h. Purification by flash chromatography (CH_2Cl_2/MeOH/Et_3N, 9:1:1) afforded **14** as a brown oil (24 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.45 (m, 6 H, 17-H, 18-H, 19-H), 1.49 (s, 3 H, 14-H), 1.50–1.75 (m, 4 H, 16-H, 20-H), 1.75–1.85 (m, 1 H, 13-H), 1.85–1.95 (m, 5 H, 10-H, 29-H, 30-H), 2.02 (br. d, $J \approx$ 11 Hz, 1 H, 10-H), 2.51 (dd, J = 17.3, 4.7 Hz, 1 H, 13-H), 2.60–2.80 (m, 3 H, 7-H, 31-H), 2.95–3.10 (m, 3 H, 6-H, 28-H), 3.16 (dd, J = 17.5, 5.4 Hz, 1 H, 6-H), 3.25–3.35 (m, 1 H, 11-H), 3.40–3.60 (m, 4 H, 15-H, 21-H), 4.00 (br. s, 2 H, NH), 5.52 (d, J = 4.5 Hz, 1 H, 8-H), 7.32 (br. t, 2 H, 2-H, 24-H), 7.53 (br. t, 2 H, 3-H, 25-H), 7.85–8.05 (m, 4 H, 1-H, 4-H, 23-H, 26-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 (C-29 or C-30), 23.1 (C-29 or C-30), 23.5 (C-14), 24.8 (C-31), 26.9 (CH_2), 27.0 (CH_2), 27.7 (C-11), 28.3 (C-7), 29.2 (CH_2), 29.3 (CH_2), 31.8 (C-16 and C-20), 33.8 (C-28), 37.2 (C-13), 39.9 (C-6), 49.5 (C-15 or C-21), 50.5 (C-15 or C-21), 115.7 (C-22a), 120.0 (C-31a),

120.7 (C-11a or C-12a), 121.1 (C-11a or C-12a), 123.0 (C-23), 123.7 (C-2), 123.8 (C-24), 124.0 (C-1), 125.6 (C-8), 128.4 (C-3 or C-4 or C-25 or C-26), 128.5 (C-3 or C-4 or C-25 or C-26), 128.6 (C-3 or C-4 or C-25 or C-26), 128.7 (C-3 or C-4 or C-25 or C-26), 131.8 (C-9), 147.0 (C-26a), 147.6 (C-4a or C-12), 150.5 (C-4a or C-12), 151.1 (C-10), 157.2 (C-5a or C-25a), 158.1 (C-5a or C-25a) ppm. MS (ESI+): *m/z* (%) = 545 (10) $[M + H]^+$, 273 (100) $[M + 2H]^{2+}$. HRMS (ESI+): calcd. for $C_{37}H_{45}N_4$ 545.3652; found 545.3644.

Supporting Information (see footnote on the first page of this article): General experimental procedures, preparation and characterization of compounds **1a**–**e**, **2a**–**e**, and **5**–**7**, and ^1H and ^{13}C NMR spectra of all compounds.

Acknowledgments

The French MRES ("Ministère de l'Enseignement Supérieur et de la Recherche") is acknowledged for a PhD Fellowship to C. R.; FRM ("Fondation pour la Recherche Médicale") through INE20040300375, IUF ("Institut Universitaire de France"), ANR ("Agence Nationale pour la Recherche") through ANR_06_BLAN_0163 DETOXNEURO program, and the Région Haute Normandie (Crunch program) are gratefully acknowledged for their financial support. We thank Dr. Geoffroy Sorin for preparation of selected chloroquinolines, Pr. Thierry Besson (Université de Rouen) for helpful discussions on microwave technology, Dr. Anthony Romieu (Université de Rouen) for HPLC analyses, Elisabeth Roger (INSA de Rouen) for IR measurements, and Annick Leboisselier (INSA de Rouen) for the determination of elemental analyses.

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Received: August 17, 2010
Published Online: November 12, 2010

