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Highly efficient one-pot synthesis of D-ring chloro-substituted neocryptolepines via a condensation—Pd-catalyzed intramolecular direct arylation strategy

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ABSTRACT

D-ring chloro-substituted neocryptolepines have been synthesized in excellent yield starting from 3-bromo-2-chloro-1-methylquinolinium triflate via a one-pot condensation—Pd-catalyzed intramolecular direct arylation strategy involving chloroanilines. The 3-bromo-2-chloro-1-methylquinolinium triflate was obtained via methylation of commercial 3-bromo-2-chloroquinoline with methyl triflate.

1. Introduction

Within the framework of our research toward the synthesis of new antiplasmodial indoloquinolines, we recently reported the synthesis and antiplasmodial activity of a set of aminoalkylamino-substituted derivatives of the natural product neocryptolepine (5-methyl-5*H*-indolo[2,3-*b*]quinoline) (**1**) (Fig. 1).[1] The most selective compound identified, the D-ring substituted N^1,N^1-diethyl-N^4-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-8-yl)pentane-1,4-diamine (**2**) (Fig. 1), showed an IC_{50} of 10 nM against the chloroquine-sensitive *P. falciparum* Ghana strain and a selectivity index of 1800, which is a 1500-fold increase in comparison to the natural product itself.[1] Although these aminoalkylamino-substituted neocryptolepines appear to be promising compounds, the synthesis of the required D-ring chloro-substituted neocryptolepine precursors (**3**) (Fig. 1) suffers from a low overall yield (8-chloroneocryptolepine (**3b**): 15.7%, 9-chloroneocryptolepine (**3a**): 7.9%) due to the inefficient Graebe–Ullmann reaction used for their preparation.[1] In order to be able to synthesize a broader set of aminoalkylamino-substituted neocryptolepines via Pd-catalyzed amination on **3**, a more efficient methodology to obtain these D-ring chloro-substituted neocryptolepines is desirable. When looking at literature procedures for the synthesis of neocryptolepine and its basic skeleton, generally three distinct strategies have been followed. The first strategy is based on the construction of the indoloquinoline skeleton via two consecutive cyclization steps in which both the indole and quinoline moieties are formed.[2–4] The second strategy starts from an indole compound and builds up the quinoline moiety.[5–8] Reversely, the third strategy starts from a quinoline compound and builds up the indole moiety.[9–11] As a large variety of substituted anilines is readily available, the third strategy that relies on anilines to construct the indole moiety has a clear advantage over the other strategies when D-ring substitution is aimed. We herein report a new and highly efficient synthesis of D-ring chloro-substituted neocryptolepines (**3a**–**d**) based on the third strategy.

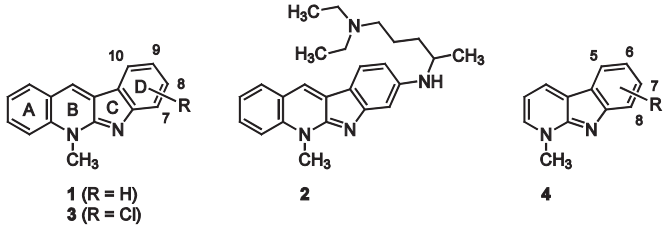

Fig. 1. Neocryptolepine (**1**), D-ring chloro-substituted neocryptolepines (**3**), N^1,N^1-diethyl-N^4-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-8-yl)pentane-1,4-diamine (**2**), and substituted 1-methyl-1*H*-α-carbolines (**4**).

2. Results and discussion

Based on previous research of our group for the synthesis of 1-methyl-1*H*-α-carbolines starting from 2,3-dichloropyridine, there are in principle two routes to prepare target compounds **3** (Fig. 2).[9] The first one involves Pd-catalyzed amination on a 2,3-dihaloquinoline with a chloroaniline (**A**), followed by Pd-catalyzed

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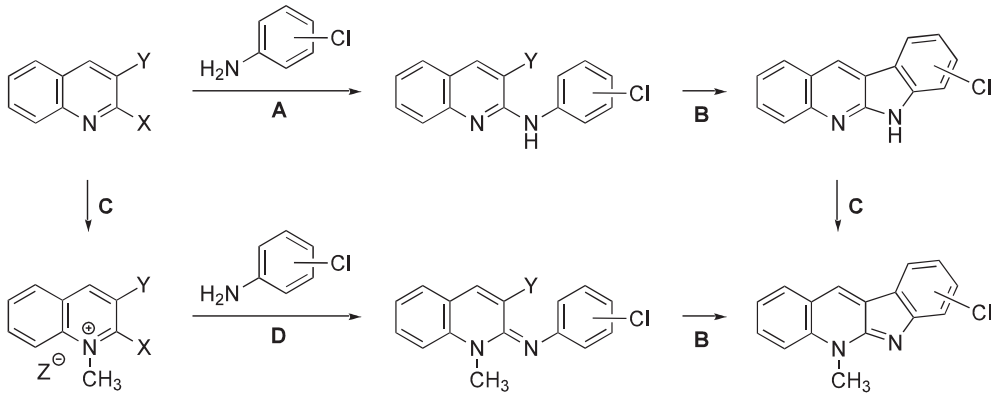
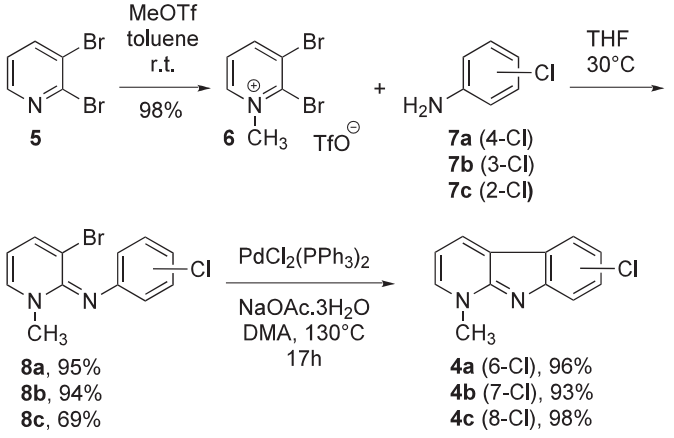


Fig. 2. Two proposed synthetic routes toward D-ring chloro-substituted neocryptolepines: **A**: Pd-catalyzed amination, **B**: Pd-catalyzed intramolecular direct arylation, **C**: (regioselective) methylation, **D**: condensation.

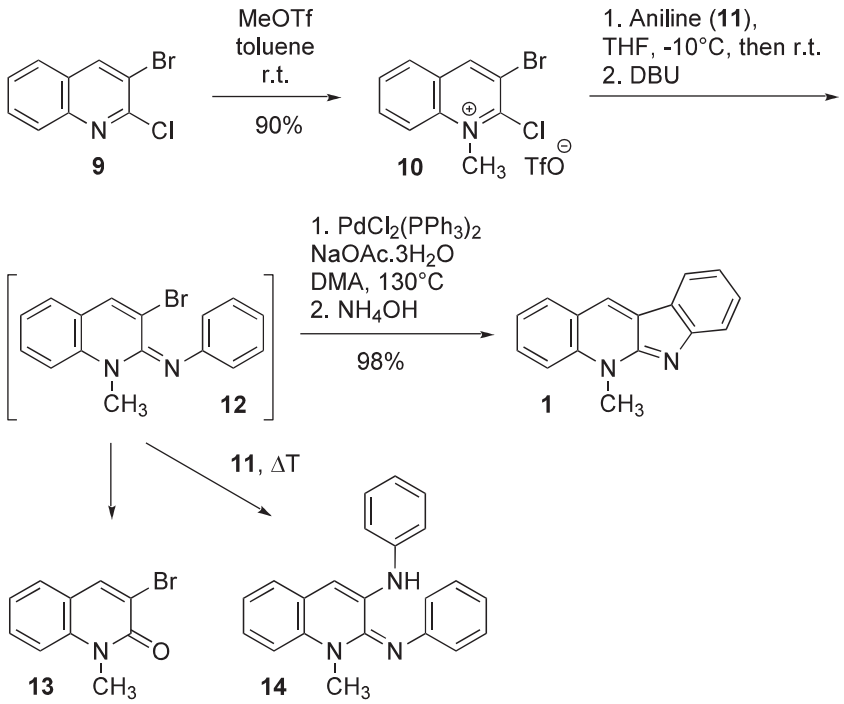
intramolecular direct arylation (**B**) and regioselective methylation (**C**). The second route has the methylation in the first step (**C**) followed by condensation of the methylquinolinium salt with a chloroaniline (**D**) and Pd-catalyzed intramolecular direct arylation (**B**). We opted for the latter approach as milder reaction conditions can be used. In addition no palladium is required for the C–N bond formation. In order to obtain the required chemoselectivity in the intramolecular direct arylation step we selected 3-bromo-2-chloroquinoline (**9**) instead of 2,3-dichloroquinoline as starting material,[9] since a carbon–bromine bond is more reactive for oxidative addition to a Pd-catalyst than a carbon–chlorine bond. Although this substrate is commercially available, it can be easily prepared from 3-bromoquinoline according to a literature procedure.[12,13] 2,3-Dibromoquinoline would also be a suitable substrate but a chlorine atom at C-2 is more reactive in the condensation step. As a model system, efforts were made to first synthesize the corresponding chloro-substituted 1-methyl-1*H*-α-carbolines (**4a**–**c**) from commercially available 2,3-dibromopyridine (**5**) (Scheme 1) as 3-bromo-2-chloropyridine was not yet commercially available at the start of this research.[14]



Scheme 1. Synthesis of chloro-substituted 1-methyl-1*H*-α-carbolines (**4a**–**c**) via consecutive condensation and Pd-catalyzed intramolecular direct arylation of **8a**–**c**.

Thus, 2,3-dibromo-1-methylpyridinium trifluoromethanesulfonate (**6**) was prepared in nearly quantitative yield via methylation of 2,3-dibromopyridine (**5**) with methyl trifluoromethanesulfonate in toluene (Scheme 1). Reaction of this substrate with 4-chloro- (**7a**), 3-chloro- (**7b**), and 2-chloroaniline (**7c**) in THF furnished the respective *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]anilines **8a**–**c** (Scheme 1). While *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]-4-chloroaniline (**8a**) and *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]-3-chloroaniline (**8b**) could be obtained in excellent yield, *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]-2-chloroaniline (**8c**) was obtained in low yield only under the same reaction conditions. When a longer reaction time was applied (48 h instead of 24 h), this compound could be isolated in an acceptable yield (50%). By using a larger excess of 2-chloroaniline (**7c**) (5 equiv instead of 3 equiv), the yield increased to 69%. For the Pd-catalyzed intramolecular direct arylation step we first applied reaction conditions, which we previously optimized for related brominated substrates [$PdCl_2(PPh_3)_2$, $NaOAc\cdot 3H_2O$, DMA, 130 °C].[15] A catalyst loading of 1 mol % and a reaction time of 17 h were found optimal for the intramolecular direct arylation reaction of *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]-4-chloroaniline (**8a**). When using only 0.5 mol % $PdCl_2(PPh_3)_2$, an incomplete reaction was observed. Under optimized reaction conditions, 6-chloro-1-methyl-1*H*-pyrido[2,3-*b*]indole (**4a**), 7-chloro-1-methyl-1*H*-pyrido[2,3-*b*]indole (**4b**), and 8-chloro-1-methyl-1*H*-pyrido[2,3-*b*]indole (**4c**) could be obtained in excellent yield (Scheme 1). When using *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]-3-chloroaniline (**8b**) as substrate for arylation, a 100:3 regioselectivity in favor of 7-chloro-1-methyl-1*H*-pyrido[2,3-*b*]indole (**4b**) over 5-chloro-1-methyl-1*H*-pyrido[2,3-*b*]indole was observed by ^{1}H NMR.

We implemented this methodology to the synthesis of neocryptolepine (**1**) and subsequently to the synthesis of our target compounds. Methylation of 3-bromo-2-chloroquinoline (**9**) with methyl trifluoromethanesulfonate in toluene at room temperature afforded 3-bromo-2-chloro-1-methylquinolinium trifluoromethanesulfonate (**10**) in 90% after a reaction time of 48 h (Scheme 2). Subsequent reaction with aniline (**11**) under the same reaction conditions as used for the synthesis of the *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene] chloroanilines (**8a**–**c**) proceeded very smoothly. However, the purification of *N*-[3-bromo-1-methylquinolin-2(1*H*)-ylidene]aniline (**12**) was very tricky since hydrolysis to 3-bromo-1-methylquinolin-2(1*H*)-one (**13**) during work-up occurred easily. Moreover, due to the exothermic condensation reaction a side product was formed, which is probably 1-methyl-*N*-phenyl-2-(phenylimino)-1,2-dihydroquinolin-3-amine (**14**) as indicated by mass spectrometry. This side product could not be separated via column chromatography. Its formation was inhibited by slow addition of 3-bromo-2-chloro-1-methylquinolinium trifluoromethanesulfonate (**10**) to aniline at −10 °C and subsequent addition of cold anhydrous THF. In a reaction time of 6 h, the reaction mixture was allowed to reach room temperature. DBU was then added to deprotonate the *N*-[3-bromo-1-methylquinolin-2(1*H*)-ylidene]anilinium salt, which is necessary to avoid hydrolysis of this compound in the next step. To the resulting mixture, $PdCl_2(PPh_3)_2$, $NaOAc\cdot 3H_2O$, and DMA were added and after 17 h heating at 130 °C, neocryptolepine (**1**) could be obtained. A catalyst loading of 2.5 mol % was required to obtain complete conversion of starting material in this timeframe. After optimization of the work-up procedure, neocryptolepine (**1**) could be isolated in 98% yield (Scheme 1). A careful literature investigation

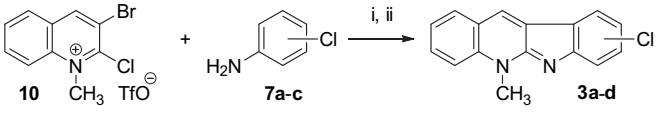


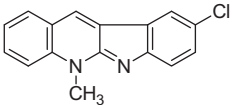
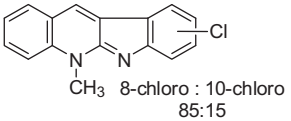
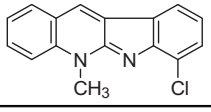
Scheme 2. Synthesis of neocryptolepine (**1**) via a one-pot condensation – Pd-catalyzed intramolecular direct arylation.

shows that this three-reactions-two-step synthesis of neocryptolepine (**1**) is the most efficient route hitherto reported in terms of overall yield (88%). Our previously reported procedure in which the methyl group is introduced in the last step rather than in the first step, requiring three work-ups instead of two, gave **1** in 77% overall yield.

Finally, we successfully applied our optimized reaction conditions to the synthesis of 7-, 8-, 9- ,and 10-chloroneocryptolepine (**3a**–**d**) from 3-bromo-2-chloro-1-methylquinolinium trifluoromethanesulfonate (**10**) and 4-chloro- (**7a**), 3-chloro- (**7b**), and 2-chloroaniline (**7c**) (Table 1). For the solid 4-chloroaniline (**7a**), a concentrated solution in THF was used for the addition of 3-bromo-2-chloro-1-methylquinolinium trifluoromethanesulfonate (**10**). The Pd-catalyzed intramolecular direct arylation reaction step required, in the three cases, a catalyst loading of only 1 mol % $PdCl_2(PPh_3)_2$. 7-Chloro- (**3c**) and 9-chloroneocryptolepine (**3a**) could be obtained in excellent yield (Table 1). With 3-chloroaniline (**7b**) as starting material, a mixture of 8-chloro (**3b**) and 10-chloroneocryptolepine (**10d**) was obtained in excellent yield in an 85:15 ratio in favor of the 8-chloro isomer as confirmed by ^{1}H NMR. These isomers could be separated using an automated chromatography system.

Table 1
Synthesis of D-ring chloro-substituted neocryptolepines (**3a**–**d**) via one-pot condensation and Pd-catalyzed intramolecular direct arylation



Entry		Product	Yield[a]
1	**3a**		98%
2	**3b**, **3d**	 8-chloro : 10-chloro 85:15	98%
4	**3c**		87%

[a] Reaction conditions: (i) 1. **10**, 5 equiv **7a**–**c**, THF, −10 °C to rt 2. 2 equiv DBU. (ii) 1 mol % $PdCl_2(PPh_3)_2$, $NaOAc{\cdot}3H_2O$, DMA, 130 °C, 17 h.

3. Conclusion

In conclusion, we succeeded in developing a simple but efficient protocol that is suitable for the synthesis of D-ring chloro-substituted neocryptolepines (**3**). This protocol consists of a methylation and a one-pot condensation—Pd-catalyzed intramolecular direct arylation reaction. For the latter step, a catalyst loading of only 1 mol % Pd was sufficient. The new protocol has clear advantages in terms of efficiency over the Graebe–Ullmann method for the synthesis of chloroneocryptolepines **3**.

4. Experimental

4.1. General

All melting points were determined on a Büchi apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer Avance II 400 in the solvent indicated with TMS as the internal standard. All coupling constants are given in hertz and chemical shifts are given in parts per million. 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 (Waters-Micromass). Accurate mass data were acquired on a Q-TOF 2 mass spectrometer (Waters-Micromass) 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 internal calibrant (lock mass). $PdCl_2(PPh_3)_2$ (Aldrich), 2,3-dibromopyridine (ABCR), $NaOAc\cdot 3H_2O$ (Acros), anhydrous THF (Acros), DMA (Acros), toluene (Acros), DBU (Aldrich), methyl trifluoromethanesulfonate (Aldrich) as well as the anilines (Acros) were obtained from commercial sources and used without further purification. Flash column chromatography was performed on Kieselgel 60 (ROCC SI 1721, 40–60 μm) or using an automated chromatography system with Silica Flash Cartridges.

4.2. Methylation of 2,3-dibromopyridine (5) and 3-bromo-2-chloroquinoline (9)

A flame dried round-bottomed flask was charged with the respective dihalo compound (10 mmol), methyl trifluoromethanesulfonate (1.2 mL, 10.6 mmol) (*CAUTION*: Causes burns by all exposure routes.) and dry toluene (15 mL). The resulting solution was stirred under Ar atmosphere for the time indicated at room temperature. A white precipitate was formed, which was collected on a fritted filter, rinsed well with dry toluene (50 mL), and dried under reduced pressure.

According to this procedure, the following compounds were prepared:

*4.2.1. 2,3-Dibromo-1-methylpyridinium trifluoromethanesulfonate (**6**).* 2,3-Dibromopyridine (2.369 g, 10 mmol); Reaction time: 2 h; yield: 96%. As this compound is very hydrolysis sensitive it was immediately used in subsequent condensation reactions.

*4.2.2. 3-Bromo-2-chloro-1-methylquinolinium trifluoromethanesulfonate (**10**).* 3-Bromo-2-chloroquinoline (2.425 g, 10 mmol); Reaction time: 48 h; yield: 90%. As this compound is very hydrolysis sensitive it was immediately used in subsequent condensation reactions.

4.3. Synthesis of *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene] chloroanilines (8a–c)

A flame dried round-bottomed flask was charged with 2,3-dibromo-1-methylpyridinium trifluoromethanesulfonate (**6**) (0.802 g, 2.0 mmol), chloroaniline (**7**) (0.765 g, 6 mmol), and anhydrous THF (5 mL). The resulting suspension was stirred for 24 h at 30 °C. After cooling down, the solvent was removed under reduced pressure. Next, the residue was extracted with 28–30% NH_4OH (30 mL) and dichloromethane (3×30 mL). The combined organic phase was dried using $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified via flash column chromatography on silica gel using a dichloromethane/(7 N) ammonia in methanol gradient (from dichloromethane to dichloromethane/(7 N) NH_3 in MeOH 98:2).

According to this procedure, the following compounds were prepared:

*4.3.1. N-[3-Bromo-1-methylpyridin-2(1H)-ylidene]-4-chloroaniline (**8a**).* Reagent: 4-chloroaniline (**7a**); yield: 95%; yellow solid; mp 97 °C; δ_H ($CDCl_3$): 7.32 (dd, *J*=7.1, 1.7 Hz, 1H, H-4′), 7.17 (dd, *J*=6.8, 1.7 Hz, 1H, H-6′), 7.12 (d, *J*=8.8 Hz, 2H, H-3, and H-5), 6.68 (d, *J*=8.8 Hz, 2H, H-2, and H-6), 5.73 (dd, *J*=7.1, 6.8 Hz, 1H, H-5′), 3.49 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 148.9, 145.4, 142.0, 138.8, 127.8, 125.5, 122.7, 109.1, 102.8, 41.7; HRMS (ESI) for $C_{12}H_{11}BrClN_2$ $[M+H]^+$: calcd: 296.9789, found: 296.9788.

*4.3.2. N-[3-Bromo-1-methylpyridin-2(1H)-ylidene]-3-chloroaniline (**8b**).* Reagent: 3-chloroaniline (**7b**); yield: 94%; yellow solid; mp 92 °C; δ_H ($CDCl_3$): 7.34 (dd, *J*=7.1, 1.7 Hz, 1H, H-6′), 7.18 (dd, *J*=6.8, 1.7 Hz, 1H, H-4′), 7.08 (dd, *J*=7.9, 7.9 Hz, 1H, H-5), 6.85 (ddd, *J*=7.9, 2.1, 1.0 Hz, 1H, H-4), 6.75 (dd, *J*=2.1, 2.0 Hz, 1H, H-2), 6.64 (ddd, *J*=7.9, 2.0, 1.0 Hz, 1H, H-6), 5.75 (dd, *J*=7.1, 6.8 Hz, 1H, H-5′), 3.49 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 151.6, 145.6, 142.1, 138.8, 133.5, 128.7, 121.6, 120.5, 119.9, 109.2, 103.1, 41.8; HRMS (ESI) for $C_{12}H_{11}BrClN_2$ $[M+H]^+$: calcd: 296.9789, found: 296.9782.

*4.3.3. N-[3-Bromo-1-methylpyridin-2(1H)-ylidene]-2-chloroaniline (**8c**).* Reagent: 2-chloroaniline (**7c**) (1.276 g, 10 mmol); reaction time: 48 h; yield: 69%; yellow solid; mp 77 °C; δ_H ($CDCl_3$): 7.32 (dd, *J*=7.1, 1.7 Hz, 1H, H-6′), 7.25 (ddd, *J*=7.9, 1.5, 0.3 Hz, 1H, H-3), 7.19 (dd, *J*=6.8, 1.7 Hz, 1H, H-4′), 7.08 (ddd, *J*=8.0, 7.3, 1.5 Hz, 1H, H-5), 6.84 (ddd, *J*=8.0, 1.5, 0.3 Hz, 1H, H-6), 6.81 (ddd, *J*=7.9, 7.3, 1.5 Hz, 1H, H-4), 5.75 (dd, *J*=7.1, 6.8 Hz, 1H, H-5′), 3.55 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 147.5, 145.9, 141.4, 138.5, 128.5, 126.3, 126.2, 123.3, 121.3, 109.5, 103.0, 41.9; HRMS (ESI) for $C_{12}H_{11}BrClN_2$ $[M+H]^+$: calcd: 296.9789, found: 296.9790.

4.4. Synthesis of chloro-substituted 1-methyl-1*H*-α-carbolines (4a–c)

A round-bottomed flask was charged with $PdCl_2(PPh_3)_2$ (0.0070 g, 0.01 mmol, 1 mol %), *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]chloroaniline (**8a–c**) (0.298 g, 1 mmol), $NaOAc\cdot 3H_2O$ (0.204 g, 1.5 mmol) followed by dimethylacetamide (DMA) (10 mL). The mixture was flushed with Ar for 2 min and then stirred at 130 °C under Ar atmosphere for 17 h. After cooling down, the mixture was evaporated to dryness under reduced pressure. Finally, the crude product was purified via column chromatography on silica gel (the residue was brought on column mixed with silica).

According to this procedure, the following compounds were synthesized:

*4.4.1. 6-Chloro-1-methyl-1H-pyrido[2,3-b]indole (**4a**).* Substrate: *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]-4-chloroaniline (**8a**); eluent: dichloromethane/(7 N) ammonia in methanol (98:2); yield: 96%; yellow solid; mp 151 °C; δ_H (DMSO-d_6): 8.67 (dd, *J*=7.2, 1.0 Hz, 1H, H-4), 8.28 (dd, *J*=6.4, 1.0 Hz, 1H, H-2), 8.24 (d, *J*=2.2 Hz, 1H, H-5), 7.63 (d, *J*=8.6 Hz, 1H, H-8), 7.43 (dd, *J*=8.6, 2.2 Hz, 1H, H-7), 6.99 (dd, *J*=7.2, 6.4 Hz, 1H, H-3), 4.23 (s, 3H, N–CH_3); δ_C (DMSO-d_6): 153.7, 152.0, 136.9, 131.7, 127.3, 124.7, 124.5, 122.6, 121.2, 119.3, 107.7, 40.1; HRMS (ESI) for $C_{12}H_{10}ClN_2$ $[M+H]^+$: calcd: 217.0527, found: 217.0527.

*4.4.2. 7-Chloro-1-methyl-1H-pyrido[2,3-b]indole (**4b**).* Substrate: *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]-3-chloroaniline (**8b**); eluent: dichloromethane/(7 N) ammonia in methanol (99:1); yield: 93%; yellow solid; mp 146 °C; δ_H (DMSO-d_6): 8.64 (dd, *J*=7.2, 1.2 Hz, 1H, H-4), 8.27 (dd, *J*=6.4, 1.2 Hz, 1H, H-2), 8.15 (dd, *J*=8.2, 0.5 Hz, 1H, H-5), 7.63 (dd, *J*=1.9, 0.5 Hz, 1H, H-8), 7.14 (dd, *J*=8.2, 1.9 Hz, 1H, H-6), 7.02 (dd, *J*=7.2, 6.4 Hz, 1H, H-3), 4.22 (s, 3H, N–CH_3); δ_C (DMSO-d_6): 154.4, 154.2, 136.5, 131.9, 131.1, 124.8, 122.9, 122.1, 118.6, 117.3, 108.1, 40.1; HRMS (ESI) for $C_{12}H_{10}ClN_2$ $[M+H]^+$: calcd: 217.0527, found: 217.0526.

*4.4.3. 8-Chloro-1-methyl-1H-pyrido[2,3-b]indole (**4c**).* Substrate: *N*-[3-bromo-1-methylpyridin-2(1*H*)-ylidene]-2-chloroaniline (**8c**); eluent: dichloromethane/(7 N) ammonia in methanol (99:1); yield: 98%; yellow solid; mp 210 °C; δ_H (DMSO-d_6): 8.69 (dd, *J*=7.2, 0.9 Hz, 1H, H-4), 8.33 (dd, *J*=6.3, 0.9 Hz, 1H, H-2), 8.12 (dd, *J*=7.7, 0.9 Hz, 1H, H-5), 7.51 (dd, *J*=7.6, 0.9 Hz, 1H, H-7), 7.12 (dd, *J*=7.7, 7.6 Hz, 1H, H-6), 7.04 (dd, *J*=7.2, 6.3 Hz, 1H, H-3), 4.28 (s, 3H, N–CH_3); δ_C (DMSO-d_6): 153.4, 149.8, 137.0, 132.0, 127.0, 125.5, 125.1, 121.9, 120.5, 119.2,

108.3, 40.3; HRMS (ESI) for $C_{12}H_{10}ClN_2$ $[M+H]^+$: calcd: 217.0527, found: 217.0543.

4.5. Synthesis of 5-methyl-5*H*-indolo[2,3-*b*]quinolines (1 and 3a–c)

A flame dried round-bottomed flask was charged with cold aniline (**11** or **7a–c**) (5.0 mmol) under Ar atmosphere. The flask was placed in an acetone/ice bath at −10 °C and magnetically stirred for 15 min. Then, 3-bromo-2-chloro-1-methylquinolinium trifluoromethanesulfonate (**10**) (1.0 mmol, 0.407 g) was added in small portions (an exothermic reaction occurred and an orange-red precipitate was formed) to the vigorously stirred aniline. When addition was completed, cold anhydrous THF (2.5 mL) was added, the acetone/ice bath was removed and the resulting mixture was stirred for 6 h at room temperature under Ar atmosphere. Subsequently, DBU (2 mmol, 0.3 mL) was added and the reaction mixture was stirred for another 30 min. In another round-bottomed flask, $PdCl_2(PPh_3)_2$ (0.0175 g, 2.5 mol % or 0.0070 g, 1 mol %) and $NaOAc\cdot 3H_2O$ (0.204 g, 1.5 mmol) were weighed. Then, DMA (5 mL) was added and the mixture was stirred for 5 min under Ar atmosphere. The catalyst solution was added to the amidine solution and the flask was rinsed with DMA (5 mL). The resulting mixture was magnetically stirred at 130 °C for 17 h under Ar atmosphere. After cooling down, the solvent was removed under reduced pressure and the residue was dried under vacuum. Subsequently, the crude reaction mixture was extracted with 28–30% NH_4OH (30 mL) and dichloromethane (3×30 mL). The combined organic phase was dried over $MgSO_4$ and evaporated to dryness. The crude product was further purified via flash column chromatography on silica gel.

According to this procedure, the following compounds were prepared:

*4.5.1. 5-Methyl-5H-indolo[2,3-b]quinoline (**1**).* Reagent: aniline (**11**) (0.46 mL, 5 mmol). 2.5 mol % $PdCl_2(PPh_3)_2$ was used. Eluent: dichloromethane/(7 N) ammonia in methanol (98:2); yield: 98%; orange solid; the characterization data are identical to those reported in literature.[4]

*4.5.2. 9-Chloro-5-methyl-5H-indolo[2,3-b]quinoline (**3a**).* Reagent: 4-chloroaniline (**7a**) (0.638 g, 5 mmol); solid 4-chloroaniline was dissolved in anhydrous THF (0.5 mL); additional THF (2 mL instead of 2.5 mL) was added; 1 mol % $PdCl_2(PPh_3)_2$ was used. Eluent: dichloromethane/(7 N) ammonia in methanol (99:1); yield: 98%; orange solid; mp 227 °C; δ_H ($CDCl_3$): 8.37 (s, 1H, H-11), 7.91 (dd, *J*=8.0, 1.5 Hz, 1H, H-1), 7.87 (d, *J*=2.2 Hz, 1H, H-10), 7.75 (ddd, *J*=8.6, 7.0, 1.5 Hz, 1H, H-3), 7.67 (d, *J*=8.6 Hz, 1H, H-4), 7.58 (d, *J*=8.5 Hz, 1H, H-7), 7.42 (dd, *J*=8.0, 7.0 Hz, 1H, H-2), 7.41 (dd, *J*=8.5, 2.2 Hz, 1H, H-8), 4.27 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 156.0, 153.4, 137.0, 130.8, 130.1, 129.1, 129.0, 126.9, 124.9, 124.9, 122.1, 120.7, 120.6, 118.4, 114.1, 33.0; HRMS (ESI) for $C_{16}H_{12}ClN_2$ $[M+H]^+$: calcd: 267.0684, found: 267.0685.

*4.5.3. 8-Chloro-5-methyl-5H-indolo[2,3-b]quinoline (**3b**) and 10-chloro-5-methyl-5H-indolo[2,3-b]quinoline (**3d**).* Reagent: 3-chloroaniline (**7b**) (0.53 mL, 5 mmol). 1 mol % $PdCl_2(PPh_3)_2$ was used. Eluent: dichloromethane/(7 N) ammonia in methanol (99:1); yield: 98%. The isomers were separated with an automated chromatography system using Silica Flash Cartridges applying a heptane/ethyl acetate gradient (from heptane to heptane/ethyl acetate (1:1) in 35 min, 35 mL/min).

Data for **3b**: yellow-orange solid; mp 187 °C; δ_H ($CDCl_3$): 8.35 (s, 1H, H-11), 7.90 (d, *J*=7.8 Hz, 1H, H-1), 7.82 (d, *J*=8.1 Hz, 1H, H-10), 7.74 (dd, *J*=8.5, 7.1 Hz, 1H, H-3), 7.67 (d, *J*=8.5 Hz, 1H, H-4), 7.64 (d, *J*=1.7 Hz, 1H, H-7), 7.42 (dd, *J*=7.8, 7.1 Hz, 1H, H-2), 7.13 (dd, *J*=8.1, 1.7 Hz, 1H, H-9), 4.26 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 156.8, 156.4, 136.8, 134.7, 130.6, 130.0, 128.3, 127.1, 122.4, 122.2, 121.5, 120.8, 119.9, 117.8, 114.2, 33.0; HRMS (ESI) for $C_{16}H_{12}ClN_2$ $[M+H]^+$: calcd: 267.0684, found: 267.0681.

Data for **3d**: yellow solid; mp 178 °C; δ_H ($CDCl_3$): 8.92 (s, 1H, H-11), 7.99 (dd, *J*=8.0, 1.1 Hz, 1H, H-1), 7.79–7.69 (m, 2H, H-3, and H-4), 7.62 (dd, *J*=7.9, 0.5 Hz, 1H, H-7), 7.46–7.41 (m, 2H, H-2, and H-8), 7.17 (dd, *J*=7.9, 0.5 Hz, 1H, H-9), 4.33 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 156.4, 156.0, 136.8, 131.7, 130.9, 130.5, 129.4, 129.0, 126.7, 122.1, 121.4, 121.0, 120.4, 116.1, 114.1, 33.1; HRMS (ESI) for $C_{16}H_{12}ClN_2$ $[M+H]^+$: calcd: 267.0684, found: 267.0681.

*4.5.4. 7-Chloro-5-methyl-5H-indolo[2,3-b]quinoline (**3c**).* Reagent: 2-chloroaniline (**7c**) (0.53 mL, 5 mmol). 1 mol % $PdCl_2(PPh_3)_2$ was used. Eluent: dichloromethane/(7 N) ammonia in methanol (99:1); yield: 87%; orange solid; mp 234 °C; δ_H ($CDCl_3$): 9.10 (s, 1H, H-11), 8.20 (d, *J*=7.9 Hz, 1H, H-1), 8.13 (d, *J*=7.5 Hz, 1H, H-10), 8.06 (d, *J*=8.6 Hz, 1H, H-4), 7.91 (dd, *J*=8.6, 7.1 Hz, 1H, H-3), 7.58–7.53 (m, 2H, H-2, and H-8), 7.18 (dd, *J*=7.8, 7.5 Hz, 1H, H-9), 4.38 (s, 3H, N–CH_3); δ_C ($CDCl_3$): 156.2, 151.9, 137.1, 130.8, 130.1, 129.3, 128.9, 127.9, 125.6, 122.3, 122.2, 120.8, 120.2, 119.3, 114.4, 33.3; HRMS (ESI) for $C_{16}H_{12}ClN_2$ $[M+H]^+$: calcd: 267.0684, found: 267.0679.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.10.077.

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