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Synthesis of *N*-substituted benzo[*c*][1,7]- and benzo[*c*][1,8] phenanthrolin-(5*H*)-6-ones through a Pd-mediated Suzuki–Miyaura heteroaryl-aryl coupling reaction

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ABSTRACT

In the course of the search for non-camptothecin topoisomerase I inhibitors we have undertaken the synthesis of *N*-substituted benzo[*c*][1,7]- and benzo[*c*][1,8]phenanthrolinone derivatives. An intermolecular Suzuki–Miyaura heteroaryl-aryl coupling reaction was planned as the key step. Then a nitro reduction followed by a concomitant lactamization achieved the construction of the tetracycle structures. This methodology permitted a rapid and efficient elaboration of biologically potent compounds.

1. Introduction

Benzo[*c*]phenanthridine alkaloids have a long history in medicinal use dating back to 1896 when extracts of *Chelidonium majus* were reported to treat cancer.[1] Among the different compounds isolated, sanguinarine **1** is currently used for its antibacterial properties, and nitidine **2** and fagaronine **3** are regarded as model compounds for the conception of DNA topoisomerase I inhibitors presenting a non-camptothecin skeleton (Fig. 1).[2] Herein, we wish to report our efforts towards the preparation of *N*-substituted benzo[*c*][1,7]- and benzo[*c*][1,8]phenanthrolinones (BZP) as functionalized aza-analogues of **2** and **3** via a concise synthetic approach (Fig. 2).

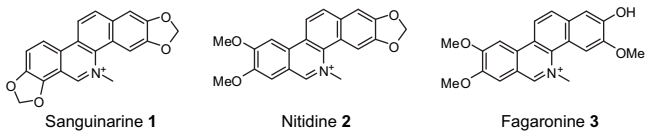


Figure 1. Examples of benzo[*c*]phenanthridine alkaloids.

In a preliminary work, the synthesis of benzo[*c*][1,8]phenanthrolinone backbone **4** was described in low yields through an intramolecular cyclization of a 2-bromo *N*-(isoquinol-5-yl)benzamide.[3] Further efforts in this way were unfruitful. We report in this paper a new synthetic approach based on an intermolecular Pd-mediated biaryl coupling reaction permitting the efficient elaboration of functionalized BZP.

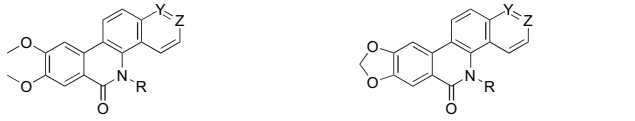
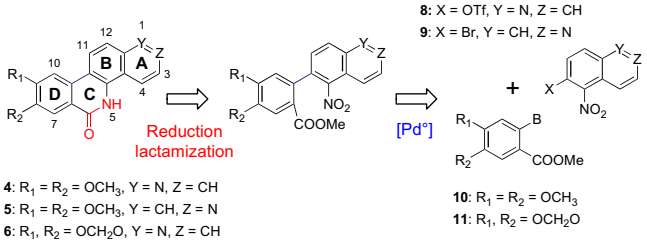


Figure 2. 1,7- and 1,8-benzo[*c*]phenanthrolinones.

Thus, ring C closure could be envisaged by a nitro reduction followed by an in situ lactamization from the corresponding heteroaryl-aryl compound (Scheme 1). An intermolecular Suzuki–Miyaura cross-coupling reaction between an aryl boronate ester corresponding to cycle D and a quinoline or an isoquinoline functionalized in position 6 representing AB motif was chosen as a very attractive methodology to construct the C10a–C10b bond.[4,5]



Scheme 1. Retrosynthesis.

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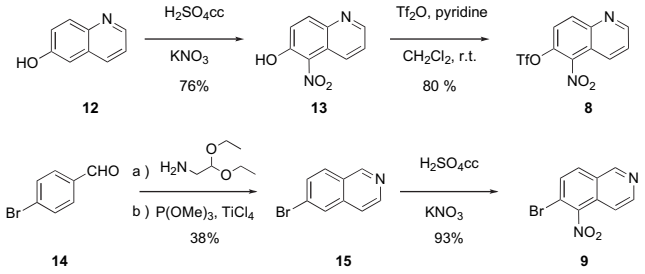
2. Results and discussion

Functionalized AB units correspond to quinoline **8** or to isoquinoline **9** substituted in position 5 by a nitro group and in position 6, respectively, by a halogen atom or a triflate. These two different compounds were easily prepared (Scheme 2). Concerning the quinoline series, nitration with KNO_3 in sulfuric acid of commercially available 6-hydroxyquinoline **12** provided exclusively the corresponding 5-nitro 6-hydroxyquinoline **13** in good yields. Then the hydroxy function was converted into the corresponding triflate, upon treatment with triflic anhydride in CH_2Cl_2 in the presence of pyridine.[6]

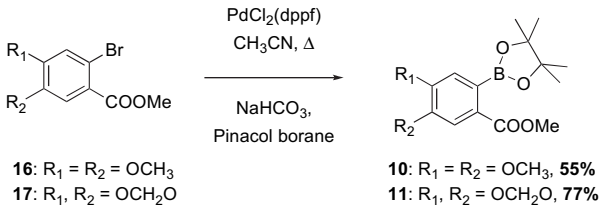


Scheme 2. AB Units.

Preparation of 6-bromo 5-nitro isoquinoline **9** started from 4-bromobenzaldehyde **14**.[7] Reaction with amino acetaldehyde diethylacetal furnished the corresponding imine, which was cyclized with trimethylphosphite and titanium chloride in 38% overall yields. Selective nitration at position 5 was realized as previously described (Scheme 2).

Finally quinoline **8** was prepared in two steps with 61% yield and isoquinoline **9** in 35% yield over three steps.

*Pinacol boronates **10** and **11*** were envisioned as partners for the biaryl coupling with unit AB (Scheme 1). Preparation of these compounds was envisaged via a Pd catalyzed coupling reaction (Scheme 3).[8] Several experimental conditions were screened and the $PdCl_2$(dppf)/$NaHCO_3$ system in acetonitrile, giving the more satisfying results, was retained. Thus methyl esters of 6-bromo veratric acid **16** and piperonic acid **17** were converted to the corresponding boronates in 77% yields and 55% yields, respectively.[9,10]



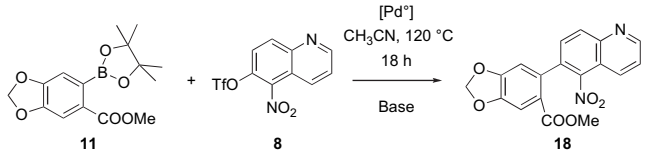
Scheme 3. Preparation of boronates **16** and **17**.

2.1. Suzuki–Miyaura cross-coupling: creation of the C10a–C10b bond

At this stage a Suzuki–Miyaura reaction was planned to realize the biaryl connection.[5] Several reaction conditions were examined with boronic esters **11** and quinoline **8** and results are summarized in Table 1.[11]

Different solvents were considered. Acetonitrile gave the best results and was consequently employed for further investigations. Three palladium complexes, $PdCl_2$(dppf), $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$, were selected. Also, the influence of the base was investigated. The same bases were used in these experiments, thus

Table 1
Systematic study in methylenedioxy 'series'



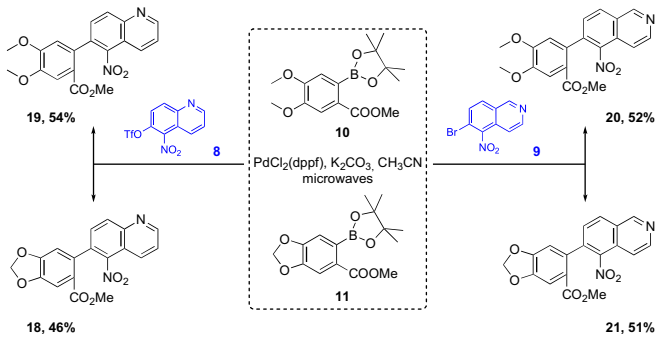
Entry	Base	Yield[a,b]		
		$PdCl_2$(dppf)	$PdCl_2(PPh_3)_2$	$Pd(PPh_3)_4$
1	KOAc	No reaction	Degradation	Degradation
2	Et_3N	No reaction	37%	No reaction
3	NaOH	49%	Degradation	Degradation
4	Cs_2CO_3	14%	Degradation	12%
5	K_2CO_3	**46**%	21%	38%
6	$NaHCO_3$	No reaction	**60**%	50%

[a] Isolated yields.
[b] Reaction conditions: Pd complex (10 mol %), base (3 equiv), **8** (1 equiv) **11** (1.5 equiv), CH_3CN, 120 °C for 18 h.

permitting a direct comparison of the Pd/base systems. Different reactivities were observed: the reaction proceeded, did not take place ($PdCl_2$(dppf) and $Pd(PPh_3)_4$), or degradation was observed ($PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$).[12] With all Pd complexes, KOAc was not appropriate, giving no reaction or degradation products (entry 1). In contrast, K_2CO_3 gave more satisfying results, providing the cross-coupled product **18** in all cases in moderate 46%, 21% and 38% yields, respectively (entry 5). Besides other carbonate bases, such as Cs_2CO_3 and $NaHCO_3$, are also tolerated since they provided the cross-coupled product **18** with two of the three Pd complexes (entries 4 and 6). The use of organic mild base Et_3N seemed limited to one Pd complex (entry 2). A stronger base, such as NaOH, gave an interesting good result with $PdCl_2$(dppf) (entry 3). Unfortunately whatever the conditions employed, the yield of the reaction is limited to 60% (entry 6), which is acceptable for this type of aryl-heterocycle cross-coupling reaction.

We examined the possibility of combining the two steps, that is introduction of the boron moiety and cross-coupling. The $PdCl_2$(dppf)/$NaHCO_3$ system retained for the boronate preparation proved to be unsuccessful for the biaryl connection (entry 6). Moreover, the efficient $PdCl_2(PPh_3)_2$/$NaHCO_3$ system of the study (entry 6) only furnished de-brominated benzoates when applied to methyl esters **16** and **17**.

The $PdCl_2(PPh_3)_2$/$NaHCO_3$ system giving the better results (entry 6), was retained for the elaboration of the other series. Unfortunately, extension to the three other series gave disappointing results. Pd complex/base system effects were re-evaluated with the other substrates and $PdCl_2$(dppf)/K_2CO_3 association showed the best compromise, leading to the different series of heteroaryl-aryl compounds in a range of 50% yields (Scheme 4).[13]



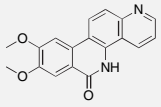
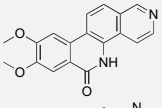
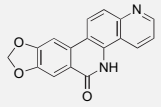
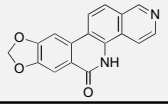
Scheme 4. Summary of the Suzuki–Miyaura reaction.

Moreover, microwave irradiation proved to be useful on the experimental aspect permitting to dramatically decrease the initial reaction time of 18 h to 1 h in the four series with the same yields.

2.2. Ring C closure

Access to the tetracycles was envisioned through nitro reduction followed by spontaneous cyclization. Reducing agents such as $SnCl_2$ and catalytic hydrogenation were envisaged.[14] Various reactivities were observed in the different series and results are summarized in Table 2.

Table 2
Ring C closure

Entry	Product		Yield[a]	
			H_2/Ni Raney[b]	$SnCl_2$[c]
1		**4**	**77**%	47%
2		**5**	**78**%	55%
3		**6**	33%	**90**%
4		**7**	36%	**83**%

[a] isolated yields.
[b] Reaction conditions: cat Ni Raney (5 equiv), H_2 (5 bar), EtOH, rt for 48 h.
[c] Reaction conditions: $SnCl_2.2H_2O$ (5 equiv), MeOH, reflux for 48 h.

Results can be divided into two groups according to the substitution pattern on cycle D, i.e., dimethoxy (entries 1 and 2) and methylenedioxy (entries 3 and 4). In the dimethoxy series (entries 1 and 2), good yields in tetracycle are obtained with catalytic hydrogenation, whereas moderate yields are attained with $SnCl_2$.

In the methylenedioxy series (entries 3 and 4) reverse outcomes are observed, $SnCl_2$ offering thus the best alternative. The main drawback in this step is the low solubility of the tetracycles, which severely hinders the purification process after the catalytic reduction.

2.3. Introduction of dialkylaminoalkyl side chains

Having now the different tetracycles in hand, introduction of an alkylaminoalkyl side chain can be envisaged. This structural modification is currently used in particular to increase DNA interactions.[15] At first, three dialkylaminoalkyl residues were selected for their biological effectiveness in related series, thus conducting to the preparation of 12 compounds (Table 3).[16] The objective here is to show the feasibility of our synthetic route for a medicinal chemistry approach.

Introduction of the desired aminoalkyl residues was performed by treating the BZP with NaI, NaH and the corresponding dialkylaminoalkylchloride in DMF (Table 3).[17] After careful chromatography, the corresponding substituted compounds were isolated in low to moderate yields.

3. Conclusion

We disclosed here a versatile synthetic route to access new and functionalized benzo[*c*]phenanthrolinones. The BZP skeleton was thus prepared in only three steps in 22% yields for the dimethoxy-substituted series and 32% for the methylenedioxy-substituted series. The envisaged intermolecular Suzuki–Miyaura reaction to construct the aryl-(*iso*)quinoline connections proved to be more reliable in these series than the intramolecular cyclization. This methodology permitted the access to a small library of 12 compounds for which the biological applicability, mainly the DNA Topoisomerase I inhibition and the cytotoxicity are currently under investigation.

4. Experimental

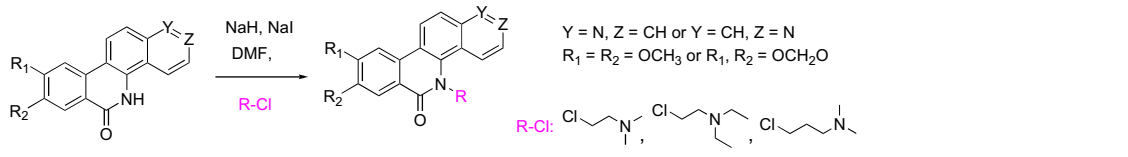
4.1. General informations

All reactions were carried out in a dried glassware under an argon atmosphere. All solvents were purchased with an analytical grade from SDS. $CH2Cl_2$ was distilled from CaH_2. Methanol, acetonitrile and DMF were dried over molecular sieves. $PdCl_2$(dppf) complex was purchased from Alfa Aesar. All other commercially available reagents were used as-received. Yield refers to chromatography and spectroscopically pure compounds, unless otherwise noted. ^1H NMR and ^{13}C NMR spectra were recorded on a BRUCKER AC 300 MHz spectrometer or a BRUCKER AVANCE 400 MHz spectrometer. Chemical shifts are reported in ppm and corrected to δ_H 7.26 and δ_C 77.16 for $CDCl_3$ as internal reference. Coupling constants (*J*) are given in Hertz. Mass spectra were measured with a ZQ 2000 Waters mass spectrometer (ESI). High resolution mass spectra were obtained on a Q-ToF ESI mass spectrometer (Waters). Infra-red spectra were recorded on a Nicolet FTIR spectrometer. Microwave reactions were carried out on a Biotage apparatus (Initiator™ 2.0).

4.2. Experimental details and spectroscopic data

*4.2.1. 5-Nitro-6-hydroxyquinoline (**13**).* To a solution of concentrated H_2SO_4 (40 mL) was slowly added 6-hydroxyquinoline **12** (6.0 g, 41.4 mmol). After 5 min, solid KNO_3 (4.38 g, 43.5 mmol, 1.05 equiv)

Table 3
N-substituted benzo[*c*]phenanthrolinones



Entry	Amino Chain	Yield[a,b]			
		R_1=R_2=OCH_3, Y=CH, Z=N	R_1=R_2=OCH_3, Y=N, Z=CH	R_1, R_2=OCH_2O, Y=CH, Z=N	R_1, R_2=OCH_2O, Y=N, Z=CH
1	$NCH_2CH_2N(CH_3)_2$	**22**, 49%	**25**, 23%	**28**, 14%	**31**, 17%
2	$NCH_2CH_2N(C_2H_5)_2$	**23**, 48%	**26**, 35%	**29**, 22%	**32**, 17%
3	$NCH_2CH_2CH_2N(CH_3)_2$	**24**, 5%	**27**, 13%	**30**, 13%	**33**, 6%

[a] Isolated yields.
[b] Reaction conditions: NaI (1.5 equiv), R–Cl (1.1 equiv), NaH (3 equiv), DMF 110 °C for 3 h.

was added and the reaction mixture was stirred at 0 °C for 2 h, then poured into 400 g of crushed ice. pH was brought to 8–9 value using a 33% NH_4OH solution. The precipitate was filtered to give the title compound as a green solid (6.24 g, 79% yield). IR (CH_2Cl_2, cm^{-1}) 3393, 2912, 2843, 2357, 2342, 1630, 1526, 1499, 1395, 1322, 1275, 1034, 977, 877, 804; ^1H NMR (300 MHz, $CDCl_3$) δ 12.14 (SE, 1H), 9.26 (dd, J=8.9, 1.4 Hz, 1H), 8.88 (dd, J=4.3, 1.4 Hz, 1H), 8.29 (d, J=9.4 Hz, 1H), 7.63 (dd, J=8.9, 4.3 Hz, 1H), 7.51 (d, J=9.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 149.0, 143.4, 140.6, 131.6, 127.0, 124.7, 123.1 (2C); MS (ES^+) m/z 191 $[M+H]^+$; HRMS (ES^+) m/z calcd for $C_9H_7N_2O_3$ $[M+H]^+$ 191.0457, found 191.0451; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (3.88), 229 (4.06), 320 (3.68), 373 (3.56).

*4.2.2. 5-Nitro-6-trifluoromethanesulfonic quinoline (**8**).* To a solution of 5-nitro-6-hydroxyquinoline **13** (1.0 g, 5.3 mmol) in CH_2Cl_2 (25 mL), were successively added dried pyridine (850 μL, 10.6 mmol, 2 equiv) and freshly distilled triflic anhydride (1.3 mL, 7.95 mmol, 1.5 equiv). After disappearance of the starting material (TLC monitoring), water (30 mL) was added to the reaction mixture. Aqueous and organic layers were separated and the aqueous layer was washed with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The crude was purified by flash chromatography on silica gel (30% v/v ethyl acetate/cyclohexane) to provide the desired compound **8** as a pale yellow solid (1.4 g, 80% yield). IR (CH_2Cl_2, cm^{-1}) 3090, 3032, 2873, 1625, 1600, 1540, 1497, 1434, 1349, 1327, 1221, 1192, 1135, 1043, 1022, 963, 879, 840, 825, 795, 768, 701; ^1H NMR (300 MHz, $CDCl_3$) δ 9.13 (dd, J=4.0, 1.3 Hz, 1H), 8.44 (d, J=9.4 Hz, 1H), 8.32 (dd, J=8.8, 1.3 Hz, 1H), 7.80 (d, J=9.4 Hz, 1H), 7.70 (dd, J=8.8, 4.0 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 146.2, 138.4, 135.5, 131.0, 124.5, 122.7, 121.0, 120.6, 116.3; MS (ES^+) m/z 323 $[M+H]^+$; HRMS (ES^+) m/z calcd for $C_{10}H_5F_3N_2O_5S$ $[M+H]^+$ 322.9950, found 322.9947; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 216 (3.85), 222 (3.87), 229 (4.23), 317 (3.52).

*4.2.3. 6-Bromoisoquinoline (**15**).* Aminoacetaldehyde diethylacetal (12.4 mL, 85.6 mmol, 1.02 equiv) was added to a solution of 4-bromobenzaldehyde **14** (15.54 g, 84 mmol) in toluene (100 mL). The mixture was refluxed in a Dean Stark apparatus to remove water. After 3 h, toluene was removed under reduced pressure. The residue was dissolved in chlorobenzene (200 mL) and the solution was cooled to −10 °C. After dropwise addition of ethyl chloroformate (8.17 mL, 85 mmol, 1.01 equiv), stirring was continued at −10 °C under N_2 for 10 min. Trimethylphosphite (11.9 mL, 101 mmol, 1.2 equiv) was added, and the resulting mixture was warmed to rt and stirred under N_2 for 40 h. Then, the solution was cooled to 0 °C and $TiCl_4$ (54 mL, 286 mmol, 3.4 equiv) was slowly added. The reaction mixture was stirred at 100 °C under N_2 for 24 h. After cooling to rt, the mixture was diluted with ethyl acetate and basified in an ice-water bath using a 5 M aqueous NaOH solution. The product was extracted with a mixture of ethyl acetate and hexanes (1:2, v/v). The organic layer was extracted with a 1 M aqueous HCl solution and after separation the aqueous layer was basified to pH>10 with a 5 M aqueous NaOH solution and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 filtered and concentrated under reduced pressure to give the expected compound **15** as a pale yellow solid (6.60 g, 38% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.55 (d, J=5.8 Hz, 1H), 8.01 (d, J=1.7 Hz, 1H), 7.84 (d, J=8.7 Hz, 1H), 7.68 (dd, J=8.7, 1.7 Hz, 1H), 7.57 (d, J=5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 144.0, 136.8, 130.9, 129.3, 128.8, 127.0, 125.2, 119.4; MS (ES^+) m/z 208 $[M+H]^+$. Spectroscopic data were identical to data collected from a commercial sample.

*4.2.4. 5-Nitro-6-bromoisoquinoline (**9**).* To a solution of concentrated H_2SO_4 (40 mL) was slowly added 6-bromoisoquinoline **15** (6.6 g, 31.5 mmol). After 5 min, solid KNO_3 (3.35 g, 33.1 mmol, 1.05 equiv) was added and the reaction mixture was stirred at 0 °C for 2 h, then poured into 400 g of crushed ice. pH was brought to 8–9 value using a 33% NH_4OH solution. The precipitate was filtered to give the title compound **9** as a yellow solid (7.95 g, 95% yield). IR (CH_2Cl_2, cm^{-1}) 3054, 2863, 1618, 1560, 1479, 1452, 1400, 1362, 1343, 1269, 1217, 1201, 1121, 1017, 932, 879, 824; ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, J=0.9 Hz, 1H), 8.73 (d, J=6.1 Hz, 1H), 8.02 (dd, J=8.8, 0.8 Hz, 1H), 7.85 (d, J=8.8 Hz, 1H), 7.54 (td, J=6.1, 0.9, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 146.3 (2C), 131.3, 131.1, 128.6, 127.1, 116.8, 113.8; MS (ES^+) m/z 253, 255 $[M+H]^+$; HRMS (ES^+) m/z calcd for $C_9H_6BrN_2O_2$ $[M+H]^+$ 252.9613, found 252.9609; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (4.22), 232 (4.45).

*4.2.5. 2-Bromo-4,5-dimethoxybenzoic acid methyl ester (**16**).* A solution of 2-bromoveratric acid (10.0 g, 38.3 mmol) in methanol (150 mL) was refluxed for 24 h in the presence of a catalytic amount of concentrated sulfuric acid (1.5 mL). After disappearance of the starting material, the solution was cooled to rt and concentrated under reduced pressure. The residue was poured into water and extracted by CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to afford the title ester **16** as a solid (7.48 g, 71% yield). IR (CH_2Cl_2, cm^{-1}) 3579, 3385, 3003, 2936, 2833, 1725, 1596, 1509, 1431, 1370, 1344, 1261, 1206, 1172, 1115, 1023, 986, 920, 866, 831, 810, 771; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.11 (s, 1H) 3.93 (s, 3H), 3.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 152.0, 147.8, 122.9, 116.9, 114.2, 114.0, 56.3, 56.2, 52.3; MS (ES^+) m/z 297 $[M+Na]^+$; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 214 (3.55), 222 (4.15), 231 (4.35), 296 (3.59). Spectroscopic data were identical to reported data.[8]

*4.2.6. 2-bromo-4,5-methylenedioxybenzoic acid methyl ester (**17**).* A solution of 6-bromopiperonic acid (10.0 g, 40.8 mmol) in methanol (150 mL) was refluxed for 24 h in presence of a catalytic amount of concentrated sulfuric acid (1.5 mL). After disappearance of the starting material, the solution was cooled to rt and concentrated under reduced pressure. The residue was poured into water and extracted by CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum to afford the title ester **17** as a solid (7.61 g, 72% yield). IR (CH_2Cl_2, cm^{-1}) 3003, 2960, 2914, 1728, 1614, 1505, 1496, 1437, 1383, 1354, 1248, 1184, 1140, 1087, 1033, 990, 935, 914, 867, 844, 773; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.14 (s, 1H), 6.10 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 150.9, 147.1, 124.3, 114.9, 114.3, 110.9, 102.6, 52.3; MS (ES^+) m/z 281 $[M+Na]^+$; U.V. λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (3.88), 232 (4.07), 266 (3.74), 301 (3.61). Spectroscopic data were identical to reported data: Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875.

*4.2.7. 2-pinacolborane-4,5-dimethoxybenzoic acid methyl ester (**10**).* 2-bromo-4,5-dimethoxybenzoic acid methyl ester **16** (330 mg, 1.2 mmol), $NaHCO_3$ (312 mg, 3.36 mmol, 3 equiv) and $PdCl_2$(dppf) (101 mg, 10% mol) were added in a round-bottom flask and purged with a cycle vacuum-Argon flushing (3 x). Dried and degazed CH_3CN (5 mL) was added and the resulting mixture was stirred for one min. Pinacolborane (540 μL, 3.6 mmol, 3 equiv) was then slowly added and the deep-red solution was stirred at 120 °C (oil bath) for 1 h. The mixture was then cooled to rt, diluted with CH_2Cl_2 (5 mL) and washed with H_2O (1×10 mL). The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting dark-brown residue was purified by column chromatography on silica gel (10% v/v ethyl acetate/cyclohexane) to give the desired boronate **10** (212 mg, 55% yield) and the de-halogenated 4,5-methylenedioxybenzoic acid methyl ester (102 mg, 43% yield). IR (CH_2Cl_2, cm^{-1}) 3395, 2916, 2851, 1653, 1560, 1440, 1271, 1075, 1042, 879; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.90 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 1.42 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 167.9, 151.9, 149.0, 126.2 (2C), 113.7, 111.5, 83.8 (2C), 55.8 (2C), 52.0, 24.8 (4C); MS (ES^+) *m/z* 345 $[M+Na]^+$; HRMS (ES^+) *m/z* calcd for $C_{16}H_{23}O_6Na$ $[M+Na]^+$ 345.1485, found 345.1469; U.V. λ_{max} (nm) (log ε) (CH_2Cl_2) 229 (4.3), 267 (4.1), 288 (3.9).

*4.2.8. 2-pinacolborane-4,5-methylenedioxybenzoic acid methyl ester (**11**).* 6-bromo-2,3-methylenedioxybenzoic acid methyl ester **17** (500 mg, 1.93 mmol), $NaHCO_3$ (487 mg, 5.8 mmol, 3 equiv) and $PdCl_2$(dppf) (155 mg, 10% mol) were added in a round-bottom flask and purged with a cycle vacuum-Argon flushing (3 x). Dried and degazed CH_3CN (5 mL) was added and the resulting mixture was stirred for one min. Pinacolborane (850 μL, 5.8 mmol, 3 equiv) was then slowly added and the deep-red solution was stirred at 120 °C (oil-bath) for 1 h. The mixture was then cooled to rt, diluted with CH_2Cl_2 (5 mL) and washed with H_2O (1×10 mL). The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting dark-brown residue was purified by column chromatography on silica gel (10% v/v ethyl acetate/cyclohexane) to give the desired boronate **11** (456 mg, 77% yield) and the de-halogenated 4,5-methylenedioxybenzoic acid methyl ester (59 mg, 17% yield). IR (CH_2Cl_2, cm^{-1}) 2977, 2953, 1713, 1610, 1507, 1489, 1427, 1376, 1314, 1268, 1214, 1130, 1094, 1038, 964, 858, 786, 709, 669, 611; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.87 (s, 1H), 6.00 (s, 2H), 3.87 (s, 3H), 1.40 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 151.0, 148.3, 127.5 (2C), 111.3, 109.1, 101.7, 83.9 (2C), 52.3, 24.8 (4C); MS (ES^+) *m/z* 329 $[M+Na]^+$; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (3.56), 230 (3.99), 269 (3.77), 298 (3.71). Spectroscopic data were identical to reported data.[8]

4.3. Heteroaryl-aryl formation: typical procedure

In a microwave vial were successively added boronate ester **10** or **11** (0.65 mmol or 0.62 mmol, 1.5 equiv), 5-nitro-6-trifluoromethanesulfonic quinoline **8** or 5-nitro-6-bromoisoquinoline **9** (0.43 or 0.41 mmol), K_2CO_3 (1.29 or 1.23 mmol, 3 equiv) and $PdCl_2$(dppf) complex (0.043 or 0.041 mmol, 10% mol). The vial was closed and subjected to a vacuum/Argon flushing cycle (3×). Then degazed acetonitrile (5 mL) was added and the reaction mixture was stirred for 1 h at 120 °C under microwave irradiation. The mixture was cooled to rt, diluted with water and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. The remaining dark-brown oil was purified by flash chromatography on silica gel (40% v/v ethyl acetate/cyclohexane) to afford the corresponding biaryl.

*4.3.1. 2-(5-Nitroquinolin-6-yl)-4,5-methylenedioxybenzoic acid methyl ester (**18**).* (70 mg, 46% yield) IR (CH_2Cl_2, cm^{-1}) 2949, 2922, 2844, 1722, 1614, 1526, 1504, 1486, 1436, 1376, 1254, 1131, 1084, 1037, 925, 839, 812, 796; ^1H NMR (300 MHz, $CDCl_3$) δ 9.02 (dd, *J*=4.2, 1.6 Hz, 1H), 8.26 (dd, *J*=8.7, 0.8 Hz, 1H), 8.18 (ddd, *J*=8.7, 1.6, 0.8 Hz, 1H), 7.59 (d, *J*=8.7 Hz, 1H), 7.56 (dd, *J*=8.7, 4.2 Hz, 1H), 7.55 (s, 1H), 6.75 (s, 1H), 6.10 (dd, *J*=4.5, 1.2 Hz, 2H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 151.6, 150.8, 148.2, 147.1, 145.3, 133.7, 132.9, 131.9, 130.9, 130.7, 123.4, 123.2, 120.1, 110.6, 110.4, 102.5, 52.1; MS (ES^+) *m/z* 376 $[M+Na]^+$; HRMS (ES^+) *m/z* calcd for $C_{18}H_{12}N_20_6Na$ $[M+Na]^+$ 375.0593, found 375.0610; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (4.48), 231 (4.68).

*4.3.2. 2-(5-Nitroquinolin-6-yl)-4,5-dimethoxybenzoic acid methyl ester (**19**).* (81 mg, 54% yield) IR (CH_2Cl_2, cm^{-1}) 3371, 2951, 2919, 2851, 1717, 1600, 1526, 1493, 1434, 1355, 1277, 1207, 1174, 1111, 1057, 881, 775; ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (dd, *J*=4.2, 1.5 Hz, 1H), 8.25 (dd, *J*=8.6, 1.5 Hz, 1H), 8.15 (d, *J*=8.6 Hz, 1H), 7.64 (s, 1H), 7.61 (d, *J*=8.6 Hz, 1H), 7.54 (dd, *J*=8.6, 4.2 Hz, 1H), 6.76 (s, 1H), 3.97 (s, 3H), 3.88 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 151.8, 151.5, 148.8, 147.0, 145.5, 133.8, 131.6, 131.2, 131.1, 130.7, 123.3, 121.5, 120.1, 113.2, 112.9, 56.2 (2C), 52.1; MS (ES^+) *m/z* 369 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{19}H_{16}N_2O_6Na$ $[M+Na]^+$ 391.0906, found 391.0921; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 241 (4.1).

*4.3.3. 2-(5-Nitroisoquinolin-6-yl)-4,5-dimethoxybenzoic acid methyl ester (**20**).* (78 mg, 52% yield) IR (CH_2Cl_2, cm^{-1}) 3584, 3405, 2949, 2843, 1718, 1630, 1524, 1434, 1400, 1354, 1270, 1208, 1169, 1112, 1065, 1043, 995, 836, 773; ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.68 (d, *J*=6.1 Hz, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 7.65 (d, *J*=6.1 Hz, 1H), 7.62 (s, 1H), 7.53 (d, *J*=8.4 Hz, 1H), 6.75 (s, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 152.4, 151.9, 148.9, 145.6, 144.8, 137.8, 130.9, 129.6, 129.4, 127.5 (2C), 121.3, 114.7, 113.2, 112.5, 56.2 (2C), 52.1; MS (ES^+) *m/z* 369 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{19}H_{16}N_2O_6Na$ $[M+Na]^+$ 391.0906, found 391.0889; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (4.58), 232 (4.67).

*4.3.4. 2-(5-Nitroisoquinolin-6-yl)-4,5-methylenedioxybenzoic acid methyl ester (**21**).* (90 mg, 51% yield) IR (CH_2Cl_2, cm^{-1}) 3390, 2911, 2850, 1713, 1625, 1527, 1500, 1430, 1369, 1261, 1130, 1086, 1032, 923, 782; ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.71 (d, *J*=5.9 Hz, 1H), 8.15 (d, *J*=8.5 Hz, 1H), 7.70 (d, *J*=5.9 Hz, 1H), 7.55 (d, *J*=8.5 Hz, 1H), 7.53 (s, 1H), 6.74 (s, 1H), 6.13 (dd, *J*=4.1, 1.1 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 152.1, 150.9, 148.4, 145.1, 144.7, 138.0, 132.7, 129.9, 129.4, 127.7 (2C), 123.0, 115.1, 110.7, 110.1, 102.6, 52.2; MS (ES^+) *m/z* 353 $[M+H]^+$, 416 $[M+CH_3CN+Na]^+$; HRMS (ES^+) *m/z* calcd for $C_{18}H_{12}N_2O_6Na$ $[M+Na]^+$ 375.0593, found 375.0587; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 235 (4.8), 272 (4.3), 297 (4.1), 304 (3.7).

4.4. Nitro reduction and cyclization: typical procedures

4.4.1. Method 1: Reducing agent $SnCl_2$. To a solution of biaryl (200 mg, 0.54 mmol or 0.57 mmol) in methanol (150 mL) was added $SnCl_2$ (5 equiv) and the reaction mixture was refluxed under argon for 48 h. Then the solvent was removed under reduced pressure and the residue was poured into a 28% ammonia solution. The precipitate formed was filtered, washed with CH_2Cl_2 and dried. This material was then used without any further purification.

4.4.2. Method 2: hydrogenation. A stainless steel autoclave was charged with a solution of biaryl (200 mg, 0.54 mmol or 0.57 mmol) in methanol (150 mL). After addition of Raney Ni (5 equiv), the autoclave was pressurized with H_2 (5 bar) for 48 h. The autoclave was then ventiled and the resulting mixture was filtered, washed with DMF and concentrated in vacuo. The residue was washed with CH_2Cl_2. The product was used without any further purification.

*4.4.3. 8,9-Dimethoxybenzo[c][1,7]phenanthrolin-6-one (**4**).* Method 1: 78 mg, 47% yield Method 2: 127 mg, 77% yield IR (KBr, cm^{-1}) 2360, 1648, 1494, 1373, 1272, 1125, 865; (ES^+) *m/z* 307 $[M+H]^+$.

*4.4.4. 8,9-Dimethoxybenzo[c][1,8]phenanthrolin-6-one (**5**).* Method 1: 91 mg, 55% yield Method 2: 129 mg, 78% yield IR (KBr, cm^{-1}) 1664; 1652; 1645; 1610; 1524; 1385; 1285; 1090; (ES^+) *m/z* 307 $[M+H]^+$.

*4.4.5. 8,9-Methylenedioxybenzo[c][1,7]phenanthrolin-6-one (**6**).* Method 1: 149 mg, 90% yield Method 2: 55 mg, 33% yield IR (KBr, cm^{-1}) 3393, 3124, 3031, 2906, 1653, 1626, 1605, 1529, 1499, 1402, 1351, 1262, 1199, 1035; (ES^+) *m/z* 291 $[M+H]^+$.

*4.4.6. 8,9-Methylenedioxybenzo[c][1,8]phenanthrolin-6-one (**7**).* Method 1: 130 mg, 83% yield Method 2: 60 mg, 36% yield IR (KBr,

cm^{-1}) 3419, 3185, 3030, 2917, 1655, 1615, 1495, 1444, 1410, 1271, 1252, 1025; (ES^+) *m/z* 291 $[M+H]^+$.

4.5. Introduction of dialkylaminoalkyl side chains: general procedure

At 0 °C, to a solution of a benzo[*c*]phenanthrolin-6-one (80 mg), NaI (1.5 equiv) and the appropriate dialkylaminoalkylchloride hydrochloride (1.1 equiv) in DMF (20 mL) was added NaH (60% mineral oil suspension, 3 equiv) in small portions over 5 min. The mixture was allowed to warm to rt with stirring for 45 min. Then the flask was transferred into a preheated oil bath (65 °C), and heated at 110 °C for 3 h. After disappearance of the starting material (TLC monitoring), the mixture was cooled to rt and quenched by addition of a few drops of water. The solvent was removed under vacuum and the crude product was dissolved in 1 M aqueous HCl solution (50 mL). The aqueous layer was washed with CH_2Cl_2 (3×50 mL), basified with a 30% aqueous NaOH solution and extracted with CH_2Cl_2 (6×75 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by chromatography on silica gel (20/45 μ, CH_2Cl_2/MeOH/NH_4OH 95/4.35/0.65 v/v/v).

*4.5.1. 5-[2′-(Dimethylamino)ethyl]-8,9-dimethoxybenzo[c][1,8]-phenanthrolin-6(5H)-one (**22**).* (48 mg, 49% yield) IR (CH_2Cl_2, cm^{-1}) 3403, 2934, 2854, 2778, 2356, 2343, 1731, 1645, 1615, 1591, 1523, 1486, 1455, 1417, 1329, 1274, 1209, 1035, 835, 789, 757, 723; ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.84 (d, *J*=5.6 Hz, 1H), 8.72 (d, *J*=5.6 Hz, 1H), 8.32 (d, *J*=8.9 Hz, 1H), 7.85 (d, *J*=8.9 Hz, 1H), 7.77 (s, 1H), 7.72 (s, 1H), 4.91 (t, *J*=5.9 Hz, 2H), 4.14 (s, 3H), 4.10 (s, 3H), 3.01 (t, *J*=5.9 Hz, 2H), 2.50 (s, 2×3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 153.0, 151.3, 150.3, 144.2, 137.7, 135.0, 130.4, 128.0, 122.9, 121.4, 120.9, 117.4, 115.1, 104.6, 102.4, 63.7, 57.8, 56.3, 56.2, 45.8 (2C); MS (ES^+) *m/z* 378 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{22}H_{24}N_3O_3$ $[M+H]^+$ 378.1818, found 378.1807; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 212 (3.89), 222 (4.26), 229 (4.33), 281 (4.68), 342 (3.65), 359 (3.59).

*4.5.2. 5-[2′-(Diethylamino)ethyl]-8,9-dimethoxybenzo[c][1,8]-phenanthrolin-6(5H)-one (**23**).* (50 mg, 48% yield) IR (CH_2Cl_2, cm^{-1}) 3379, 2957, 2921, 2851, 1731, 1714, 1592, 1523, 1455, 1423, 1329, 1273, 1209, 1162, 1121, 1092, 1037, 789; ^1H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.83 (d, *J*=5.8 Hz, 1H), 8.66 (d, *J*=5.8 Hz, 1H), 8.33 (d, *J*=9.1 Hz, 1H), 7.85 (d, *J*=9.1 Hz, 1H), 7.77 (s, 1H), 7.71 (s, 1H), 4.93 (t, *J*=6.0 Hz, 2H), 4.13 (s, 3H), 4.07 (s, 3H), 3.22 (t, *J*=6.0 Hz, 2H), 2.86 (q, *J*=7.2 Hz, 2×2H), 1.21 (t, *J*=7.2 Hz, 2×3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 152.9, 151.0, 150.3, 143.7, 137.5, 135.0, 130.3, 128.0, 122.7, 121.5, 121.0, 117.6, 115.0, 104.4, 102.4, 63.5, 56.2, 56.1, 50.9, 47.9 (2C), 11.2 (2C); MS (ES^+) *m/z* 405 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{24}H_{28}N_3O_3$ $[M+H]^+$ 406.2131, found 406.2112; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 214 (3.8), 222 (4.3), 229 (4.3), 281 (4.6), 342 (3.6), 359 (3.5).

*4.5.3. 5-[3′-(Dimethylamino)propyl]-8,9-dimethoxybenzo[c][1,8]-phenanthrolin-6(5H)-one (**24**).* (5 mg, 5% yield) IR (CH_2Cl_2, cm^{-1}) 3400, 2915, 1646, 1615, 1591, 1523, 1485, 1448, 1426, 1275, 1093, 1034; ^1H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.83 (d, *J*=5.8 Hz, 1H), 8.66 (d, *J*=5.8 Hz, 1H), 8.36 (d, *J*=9.0 Hz, 1H), 7.90 (d, *J*=9.0 Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 4.84 (t, *J*=6.2 Hz, 2H), 4.14 (s, 3H), 4.11 (s, 3H), 3.02 (t, *J*=7.5 Hz, 2H), 2.63 (s, 2×3H), 2.48–2.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 153.1, 151.0, 150.4, 143.6, 137.4, 135.1, 130.3, 128.0, 122.8, 121.6, 121.1, 117.6, 115.0, 104.3, 102.4, 63.6, 56.6, 56.2 (2C), 44.2 (2C), 25.7; MS (ES^+) *m/z* 392 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{23}H_{26}N_3O_3$ $[M+H]^+$ 392.1974, found 392.1983; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 196 (3.7), 222 (4.1), 229 (4.1), 281 (4.4), 361 (3.4).

*4.5.4. 5-[2′-(Dimethylamino)ethyl]-8,9-dimethoxybenzo[c][1,7]-phenanthrolin-6(5H)-one (**25**).* (23 mg, 23% yield) IR (CH_2Cl_2, cm^{-1}) 3370, 2943, 1614, 1592, 1525, 1496, 1463, 1426, 1416, 1328, 1272, 1208, 1179, 1116, 1059, 1031, 1001, 820, 758; ^1H NMR (300 MHz, $CDCl_3$) δ 9.45 (dd, *J*=8.1, 1.8 Hz, 1H), 8.99 (dd, *J*=4.1, 1.8 Hz, 1H), 8.53 (dd, *J*=9.2, 1.8 Hz, 1H), 8.08 (d, *J*=9.2 Hz, 1H), 7.85 (s, 1H), 7.74 (s, 1H), 7.56 (dd, *J*=8.1, 4.1 Hz, 1H), 4.91 (t, *J*=6.0 Hz, 2H), 4.14 (s, 3H), 4.10 (s, 3H), 2.99 (t, *J*=6.0 Hz, 2H), 2.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 152.9, 150.3, 149.7, 148.6, 138.8, 133.0, 130.6, 126.6, 125.4, 123.5, 121.2, 118.2, 114.4, 104.5, 102.2, 64.4, 58.2, 56.1 (2C), 46.2 (2C); MS (ES^+) *m/z* 378 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{22}H_{24}N_3O_3$ $[M+H]^+$ 378.1818, found 378.1818; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (4.68), 282 (4.98), 338 (3.98), 353 (3.65).

*4.5.5. 5-[2′-(Diethylamino)ethyl]-8,9-dimethoxybenzo[c][1,7]-phenanthrolin-6(5H)-one (**26**).* (37 mg, 35% yield) IR (CH_2Cl_2, cm^{-1}) 3381, 2966, 2925, 1659, 1592, 1524, 1428, 1272, 1116, 1087, 1060, 1037, 786; ^1H NMR (300 MHz, $CDCl_3$) δ 9.47 (dd, *J*=8.4, 1.5 Hz, 1H), 9.00 (dd, *J*=4.3, 1.5 Hz, 1H), 8.55 (d, *J*=9.3 Hz, 1H), 8.09 (d, *J*=9.3 Hz, 1H), 7.86 (s, 1H), 7.74 (s, 1H), 7.59 (dd, *J*=8.4, 4.3 Hz, 1H), 4.95 (t, *J*=6.1 Hz, 2H), 4.17 (s, 3H), 4.10 (s, 3H), 3.21 (t, *J*=6.1 Hz, 2H), 2.86 (q, *J*=7.2 Hz, 2×2H), 1.23 (t, *J*=7.2 Hz, 2×3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 153.0, 150.3, 149.8, 148.6, 138.8, 133.0, 130.6, 126.6, 125.5, 123.6, 121.2, 118.2, 114.4, 104.4, 102.2, 64.4, 56.1 (2C), 51.2, 48.1 (2C), 11.9 (2C); MS (ES^+) *m/z* 405 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{24}H_{28}N_3O_3$ $[M+H]^+$ 406.2131, found 406.2126; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (4.4), 282 (4.6).

*4.5.6. 5-[3′-(Dimethylamino)propyl]-8,9-dimethoxybenzo[c][1,7]-phenanthrolin-6(5H)-one (**27**).* (13 mg, 13% yield) IR (CH_2Cl_2, cm^{-1}) 3369, 2944, 1660, 1614, 1592, 1525, 1496, 1428, 1415, 1332, 1272, 1208, 1178, 1059, 1037, 820, 788; ^1H NMR (300 MHz, $CDCl_3$) δ 9.47 (ddd, *J*=8.3, 1.8, 0.7 Hz, 1H), 8.99 (d, *J*=4.3, 1.8 Hz, 1H), 8.53 (d, *J*=9.2 Hz, 1H), 8.08 (dd, *J*=9.2, 0.7 Hz, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.58 (d, *J*=8.3, 4.3 Hz, 1H), 4.84 (t, *J*=6.5 Hz, 2H), 4.16 (s, 3H), 4.10 (s, 3H), 2.63 (t, *J*=7.4 Hz, 2H), 2.35 (s, 2×3H), 2.27–2.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 152.9, 150.3, 149.8, 148.6, 138.9, 133.1, 130.6, 126.6, 125.3, 123.6, 121.1, 118.1, 114.5, 104.3, 102.2, 64.6, 56.9, 56.1 (2C), 45.6 (2C), 27.4; MS (ES^+) *m/z* 392 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{23}H_{26}N_3O_3$ $[M+H]^+$ 392.1974, found 392.1978; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (4.5), 282 (4.7).

*4.5.7. 5-[2′-(Dimethylamino)ethyl]-8,9-methylenedioxybenzo[c][1,8]-phenanthrolin-6(5H)-one (**28**).* (14 mg, 14% yield) IR (CH_2Cl_2, cm^{-1}) 3363, 2911, 2845, 2763, 1620, 1576, 1489, 1467, 1260, 1195, 1032, 939, 836, 759; ^1H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.87 (d, *J*=5.7 Hz, 1H), 8.74 (d, *J*=5.7 Hz, 1H), 8.31 (d, *J*=9.0 Hz, 1H), 7.87 (d, *J*=9.0 Hz, 1H), 7.86 (s, 1H), 7.76 (s, 1H), 6.18 (s, 2H), 4.91 (t, *J*=5.8 Hz, 2H), 2.99 (t, *J*=5.8 Hz, 2H), 2.48 (s, 2×3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 151.6, 151.3, 148.6, 144.2, 137.9, 135.0, 132.2, 128.1, 122.8, 121.5, 121.2, 117.5, 116.5, 102.7, 102.0, 100.4, 64.5, 58.2, 46.1 (2C); MS (ES^+) *m/z* 362 $[M+H]^+$; HRMS (ES^+) *m/z* calcd for $C_{21}H_{20}N_3O_3$ $[M+H]^+$ 362.1505, found 362.1487; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 281 (4.6), 342 (3.4), 360 (3.4).

*4.5.8. 5-[2′-(Diethylamino)ethyl]-8,9-methylenedioxybenzo[c][1,8]-phenanthrolin-6(5H)-one (**29**).* (24 mg, 22% yield) IR (CH_2Cl_2, cm^{-1}) 3385, 2917, 2840, 1620, 1587, 1470, 1328, 1263, 1195, 1129, 1035; ^1H NMR (300 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.89 (d, *J*=5.7 Hz, 1H), 8.74 (d, *J*=5.7 Hz, 1H), 8.32 (d, *J*=9.0 Hz, 1H), 7.90 (d, *J*=9.0 Hz, 1H), 7.89 (s, 1H), 7.75 (s, 1H), 6.20 (s, 2H), 4.89 (t, *J*=6.3 Hz, 2H), 3.13 (t, *J*=6.3 Hz, 2H), 2.79 (q, *J*=7.1 Hz, 2×2H), 1.18 (t, *J*=7.1 Hz, 2×3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 151.7, 151.3, 148.7, 144.3, 138.0, 135.0, 132.4, 128.1, 123.0, 121.6, 121.2, 117.5, 116.6, 102.6, 102.1, 100.6, 64.7, 51.2, 48.0 (2C), 11.8 (2C); MS (ES^+) *m/z* 390 $[M+H]^+$; HRMS (ES^+) *m/z*

calcd for $C_{23}H_{24}N_3O_3$ $[M+H]^+$ 390.1818, found 390.1815; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 219 (4.3), 222 (4.3), 228 (4.0), 281 (4.3).

*4.5.9. 5-[3′-(Dimethylamino)propyl]-8,9-methylenedioxybenzo[c][1,8]-phenanthrolin-6(5H)-one (**30**).* (14 mg, 13% yield) IR (CH_2Cl_2, cm^{-1}) 3386, 2946, 2911, 2816, 2764, 1625, 1585, 1493, 1470, 1455, 1332, 1261, 1233, 1197, 1036, 838, 763; ^1H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.88 (d, J=5.7 Hz, 1H), 8.74 (d, J=5.7 Hz, 1H), 8.31 (d, J=9.0 Hz, 1H), 7.88 (d, J=9.0 Hz, 1H), 7.86 (s, 1H), 7.74 (s, 1H), 6.19 (s, 2H), 4.82 (t, J=6.4 Hz, 2H), 2.62 (t, J=7.1 Hz, 2H), 2.35 (s, 6H), 2.19 (td, J=7.1, 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 151.5, 151.3, 148.6, 144.2, 138.0, 135.0, 132.2, 128.1, 122.7, 121.5, 121.1, 117.5, 116.6, 102.5, 102.0, 100.5, 64.8, 56.8, 45.6 (2C), 27.4; MS (ES^+) m/z 376 $[M+H]^+$; HRMS (ES^+) m/z calcd for $C_{22}H_{22}N_3O_3$ $[M+H]^+$ 376.1661, found 376.1659; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 215 (4.0), 222 (4.6), 230 (4.3), 281 (4.7), 343 (3.6), 362 (3.5).

*4.5.10. 5-[2′-(Dimethylamino)ethyl]-8,9-methylenedioxybenzo[c][1,7]-phenanthrolin-6(5H)-one (**31**).* (17 mg, 17% yield) IR (CH_2Cl_2, cm^{-1}) 3371, 2915, 2854, 2357, 2342, 1658, 1478, 1457, 1257, 1031; ^1H NMR (300 MHz, $CDCl_3$) δ 9.46 (dd, J=8.4, 1.4 Hz, 1H), 9.00 (dd, J=4.3, 1.4 Hz, 1H), 8.48 (d, J=9.3 Hz, 1H), 8.07 (d, J=9.3 Hz, 1H), 7.90 (s, 1H), 7.77 (s, 1H), 7.57 (dd, J=8.4, 4.3 Hz, 1H), 6.19 (s, 2H), 4.92 (t, J=5.9 Hz, 2H), 3.00 (t, J=5.9 Hz, 2H), 2.48 (s, 2×3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 151.6, 150.5, 148.7, 148.2, 139.0, 133.0, 132.6, 126.5, 125.6, 123.7, 121.2, 118.6, 115.8, 102.6, 102.0, 100.3, 64.3, 58.1, 46.0 (2C); MS (ES^+) m/z 362 $[M+H]^+$; HRMS (ES^+) m/z calcd for $C_{21}H_{20}N_3O_3$ $[M+H]^+$ 362.1505, found 362.1492; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 222 (4.2), 239 (4.2), 281 (4.6).

*4.5.11. 5-[2′-(Diethylamino)ethyl]-8,9-methylenedioxybenzo[c][1,7]-phenanthrolin-6(5H)-one (**32**).* (19 mg, 17% yield) IR (CH_2Cl_2, cm^{-1}) 3379, 2959, 2910, 2845, 2355, 2333, 1603, 1527, 1467, 1440, 1325, 1293, 1255, 1184, 1124, 1032, 934, 825; ^1H NMR (300 MHz, $CDCl_3$) δ 9.44 (dd, J=8.3, 1.5 Hz, 1H), 9.00 (dd, J=4.3, 1.5 Hz, 1H), 8.43 (d, J=9.2 Hz, 1H), 8.05 (d, J=9.2 Hz, 1H), 7.85 (s, 1H), 7.70 (s, 1H), 7.57 (dd, J=8.3, 4.3 Hz, 1H), 6.18 (s, 2H), 4.88 (t, J=6.2 Hz, 2H), 3.14 (t, J=6.2 Hz 2H), 2.80 (q, J=7.1 Hz, 2×2H), 1.18 (t, J=7.1 Hz, 2×3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 151.5, 150.4, 148.7, 148.1, 138.9, 133.0, 132.5, 126.5, 125.6, 123.6, 121.1, 118.5, 115.7, 102.4, 101.9, 100.2, 64.4, 51.3, 48.0 (2C), 11.9 (2C); MS (ES^+) m/z 390 $[M+H]^+$; HRMS (ES^+) m/z calcd for $C_{23}H_{23}N_3O_3Na$ $[M+Na]^+$ 412.1637, found 412.1656; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 239 (4.5), 282 (4.7).

*4.5.12. 5-[3′-(Dimethylamino)propyl]-8,9-methylenedioxybenzo[c][1,7]-phenanthrolin-6(5H)-one (**33**).* (6 mg, 6% yield) IR (CH_2Cl_2, cm^{-1}) 3374, 2916, 2845, 1606, 1470, 1447, 1250, 1135, 1035; ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (dd, J=8.3, 1.4 Hz, 1H), 9.01 (dd, J=4.3, 1.4 Hz, 1H), 8.48 (d, J=9.2 Hz, 1H), 8.08 (d, J=9.2 Hz, 1H), 7.91 (s, 1H), 7.75 (s, 1H), 7.59 (dd, J=8.3, 4.3 Hz, 1H), 6.20 (s, 2H), 4.84 (t, J=6.3 Hz, 2H), 2.74 (t, J=7.6 Hz, 2H), 2.43 (s, 2×3H), 2.28 (qu, J=2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 151.6, 150.5, 148.7, 148.2, 139.0, 133.1, 132.6, 126.5, 125.6, 123.7, 121.2, 118.6, 115.7, 102.4, 102.0, 100.3, 64.3, 56.7, 45.1, 26.8 (2C); MS (ES^+) m/z 376 $[M+H]^+$; HRMS (ES^+) m/z calcd for $C_{22}H_{22}N_3O_3$ $[M+H]^+$ 376.1661, found 376.1657; UV λ_{max} (nm) (log ε) (CH_2Cl_2) 214 (3.9), 222 (4.3), 232 (4.2), 282 (4.5).

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2009.09.110.

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