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Divergent strategy in the synthesis of original dihydro benzo- and dihydronaphtho-acridines.

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A straightforward access to numerous novel substituted dihydrobenzo- and dihydronaphthoacridines is described using a unique molecular platform in two key steps. A large range of carbon-based substituents such as aromatic, vinyl, alkynyl fragments through Pd-catalysed couplings has been installed. The molecular diversity is extended to the introduction of aza-heterocycles and further authorizes the installation of alkylamino chains by mean of Cu-promoted C-N bonds formation. Possible access to quinolinium salts is also described. The methodology revealed convenient allowing the preparation of a wide panel of molecules that display various rigidity/flexibility and lipophilic/hydrophilic balances. Finally, the influence of structural modulations on the photophysical properties of these novel architectures is also studied. It is noteworthy that styryl and alkynyl derivatives are emissive in water ($\phi_F$ up to 12%).

Introduction

Acridine motif appears in a large range of natural products with biological activities and therefore attracts the scientific community attention.1 Indeed, its derivatives show pharmalogical activities such as anti-malarial,2 -microbial,3 -fungicidal,4 -inflammatory,5 -cancer6 or acetylcholinesterase inhibition7 activities. As their applications have been promising, their synthesis is well documented except for their parent dihydrobenzo- and dihydronaphtho-acridines respectively substituted on the 11th or 13th position. Indeed, to the best of our knowledge, only few syntheses of those types of acridine derivatives are reported.8 Most routes to acridines and derivatives proceed through the preparation of a linear chain incorporating functional groups which is then submitted to cyclization.9 Those steps require in general high temperature and/ or acidic medium.9a, 10 These conditions are not always compatible with sensitive functional groups. Moreover, even if some of the pathways leading to the construction of the lateral backbone of an acridine bearing functional groups look very attractive, they don’t give access to a wide range of acridines and stay limited and unadaptable. Futhermore, catalytic hydrogenation on substituted acridine backbones which could be an easy way to get access to partially hydrogenated ones, seems to be dependant of the position of the substituent11 and therefore lacks versatility. The need of developing new strategies that allow at the same time (i) the extension of the aromatic motif through additional benzo- or naphtho-fused rings, (ii) the introduction of partially hydrogenated cycles, (iii) the incorporation of additional nitrogen atoms is crucial and still challenging.

We have recently published our results describing the preparation and the influence of structural modulations on photo physical properties of fused acridino-fluorenone12 and the regiodefined construction of acridines, phenanthrolines and mixed higher homologues.13 The latter reported a new methodology allowing the direct access to acridines containing partially hydrogenated rings. We now wish to report a straightforward approach towards a new series of dihydrobenzo- and dihydro naphthoacridines.

The access to various polycyclic substituted acridines is envisioned through a two-step sequence involving the common chloro-vinylcarboxaldehyde precursor and iodoaniline to get the corresponding acridine-like platform. In the second step variously substituted aromatics, aza-heterocycles and further alkylamino chains were selectively installed by mean of Pd- and Cu-promoted C-C and C-N bond formations. Possible access to quinolinium salts is also described. Photophysical properties of these novel architectures are also studied (figure 1).
Results and discussion

Our first consideration was the preparation of iodo dihydro acridines 2a and 2b that have to be considered as starting molecular platforms. The latter were easily obtained in two steps involving (i) the preparation of chloro-vinylcarboxaldehydes 1a, 1b\textsuperscript{12,13} from the parent tetralone or phenanthrone respectively under Vilsmeier-Haack conditions.\textsuperscript{10,14} (ii) the construction of the condensed pyridine ring (scheme 1).

![Scheme 1. Synthesis of iodoacridines 2a and 2b.](image)

Reaction of equimolar amounts of ortho-iodoaniline and precursor 1a at 90°C in isoamyl alcohol cleanly afforded the expected iodo acridine 2a in 30% yield. The use of an excess of iodoaniline did increase conversions but concomitantly rendered purification tedious. Attempts to enhance the transformation through microwave activation were next studied. Results obtained at 90°C under various conditions are gathered in table 1.

![Table 1. Reaction conditions for the preparation of iodoacridines 2a and 2b.](image)

Although this reaction was faster under microwave irradiation (table 1, entries 2, 3, 4), decreasing the reaction times to 1.5h-2h, we were not able to significantly improve yields regardless of the conditions or the use of solvent. Similarly, iodoacridine 2b that display an extended conjugated system could be isolated in a fair 36% yield.

We then focused on the installation of various carbon-based substituents at iodoacridine platforms 2a and 2b. In this context, we first explored the Suzuki-Miyaura coupling reaction taking advantage of the presence of the iodide atom. Gratifyingly, the coupling reaction between acridine derivative 2a and ortho-tolylboronic acid using Pd(PPh\textsubscript{3})\textsubscript{4}Cl\textsubscript{2}, K\textsubscript{2}CO\textsubscript{3} as the catalytic system and the base respectively afforded dihydroacridine 3a in 95% yield (scheme 2).

![Scheme 2. Synthesis of arylicridine motives 3a and 3c.](image)

Careful analysis of \textsuperscript{1}H NMR spectra showed the presence of two distinct signals resonating at 2.17 and 2.09 ppm in a 95/5 ratio that account for two different methyl groups.\textsuperscript{15} In fact, 3a was obtained as a mixture of two conformers that arise from a restricted rotation around the new formed aryl-aryl carbon bond. This behaviour might plausibly be attributed to the presence of the nitrogen lone pair located in the crowded bay region of the platform. In light of these results, we also tried to introduce a benzyl alcohol group. Thus, acridine 2a was reacted with 2-(hydroxymethyl)phenylboronic acid cyclic monoester, employing Cs\textsubscript{2}CO\textsubscript{3} and PdCl\textsubscript{2}dpdf\textsubscript{17} as the catalytic system in degassed toluene. After heating the reaction medium overnight, at 90°C, the formation of the expected benzyl alcohol derivative was not detected. Instead, we isolated the corresponding carboxaldehyde 3c (scheme 2). \textsuperscript{1}H NMR spectrum of 3c revealed the presence of a...
singlet at δ 9.71 ppm which undoubtedly accounts for an aldehyde proton. Mass analysis confirmed the molecular structure of 3c. In fact, we assumed that the expected benzyl alcohol was firstly formed rapidly evolve towards the carboxaldehyde through a controlled oxidation due to the presence of palladium (II) salts in the medium. Under those conditions, compound 3c was isolated in a 67 % yield.

We next extended our methodology to the preparation of various dihydroacridine-based architectures starting from platform 2a and 2b. As shown in scheme 3, 1,3-bis(5,6-dihydrobenzo[c]acridin-11-yl)benzene 3d, could be obtained in a fair 42% yield through bis Suzuki-Miyaura coupling using CsF and Pd(PPh3)4 as catalytic system in degassed dioxane (scheme 3).

Scheme 3. Synthesis of 1,3-bis acridinylbenzene 3d.

Application of our strategy to the naphthoacridine 2b was further examined (scheme 4). In this case, the enhanced crowding within the bay region caused by the presence of both the nitrogen lone pair and the additional condensed benzene ring might render the installation of aryl substituents synthetically more challenging. Gratifyingly, 3b was obtained in a 72 % yield showing that it is possible to extend the π-conjugation at both sides of the central dihydroacridine core.

Scheme 4. Arylation in the naphthylacridine series: access to 3b.

The presence of an additional cycle impacted the chemical shift of H(1) proton from 8.15 ppm for 3a to 9.63 ppm for 3b as previously observed in related series. This observation was undoubtedly correlated with a move towards helical three dimensional shape of such molecular architectures. The scope of our methodology was then to further extended to the installation of sp²- and sp-C based substituents. Therefore, acridines 2a and 2b were submitted to Heck coupling reaction conditions by using K2CO3, nBu4NBr, Pd(OAc)2 and PPh3 as the catalytic system.

Again, both starting reactants behave similarly affording styrene derivatives 4a and 4b in almost equal efficiencies (scheme 5).

Scheme 5. Heck coupling reaction conditions.

We next submitted acridines 2a and 2b to Sonogashira-type coupling reaction involving phenylacetylene and Pd(PPh3)2Cl2 as the catalytic system (scheme 6, table 2). Copper free methodology developed by Leadbeater et al. was tested first. Under such conditions at 70°C for 1h, 5a was obtained in 52% yield from starting 2a. This yield was switched to 75% using more classical Cu/Pd combination, triethylamine, and DMF as the solvent.

Scheme 6. Synthesis of styrylacridines 5a and 5b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Cul (eq.)</th>
<th>Temp.</th>
<th>Product (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Piperidine</td>
<td>-</td>
<td>70°C, 1h</td>
<td>5a (52 %)</td>
</tr>
<tr>
<td>2</td>
<td>Et3N, DMF</td>
<td>0.25</td>
<td>rt, 18h</td>
<td>5a (75 %)</td>
</tr>
<tr>
<td>3</td>
<td>Et3N, DMF</td>
<td>0.25</td>
<td>rt, 18h</td>
<td>5b (42 %)</td>
</tr>
</tbody>
</table>

Table 2. Reaction conditions for the preparation of alkynylacridines 5a and 5b.

Installation of phenylethynyl fragment at position 13 of the dihydronaphthoacridine core was successfully achieved under the aforementioned catalytic conditions leading to acridine 5b in 42 % yield starting from precursor 2b. Finally, we envisioned to enhance the structural diversity by (i) introducing additional nitrogen atoms (ii) modifying the aromatic/aliphatic balance of our targets (iii) trying to alkylate nitrogen atom of azaheterocycles in order to potentially modulate the hydrophilic/lipophylic balance of our molecules. Taking into account those criteria, we tried first an amination reaction using a Cul catalyzed coupling reaction promoted by L-Proline (scheme 7) under the catalytic conditions recently described by Ma et al.
The coupling reaction between iodoacridines 2a or 2b and 3-dimethylaminopropylamine in the presence of L-Proline and K$_2$CO$_3$ occurred in DMSO at 90°C. Although, reactions were carefully carried out under argon atmosphere, acridine 6a could only be obtained in a modest 14% yield. Unfortunately, using iodoacridine 2b under the same conditions conducted to traces of 6b.

We then examined the introduction of aza heterocycles such as pyridine and quinoline (schemes 8 and 9). Coupling reactions involving pyridine boronic acids may suffer from severe drawbacks depending on the substitution pattern. Indeed, 2-pyridyl derivatives undergo prevalent protodeborylation, dimerization and relative low transmetalation steps, during Suzuki-Miyaura coupling sequence. Thus in order to avoid the formation of such side-products, installation of 2-pyridyl motif was envisioned through Stille-type coupling and 3-pyridyl motif through Suzuki-Miyaura reaction as shown below. Thus iodoacridine 2a was coupled to 2-tributylstannyl-pyridine and pyridin-3-ylboronic acid, using CuI, PdPPh$_3$Cl$_2$ and MW activation as well as CsF, Pd(OAc)$_2$ and SPhos as catalytic systems respectively. Both coupling reactions proceeded smoothly affording acridines 7a and 7d in 42 and 51% yields respectively.

Finally, with the aim of raising the hydrophilicity of the acridine-derivatives, we also envisioned the preparation of the corresponding ammonium salts. The methylation of the quinoline ring-nitrogen was performed with a large excess of iodomethane in DMF at 90°C (scheme 10).
Surprisingly, this methylation proceeded selectively. Only one of the two nitrogen atoms of 7b was methylated as evidenced by HRMS analysis.

A careful examination of the NMR spectra and comparison with quinoline 7b, allowed us to accomplish complete assignment of the signals and determine on which nitrogen atom, methylation occurred (figure 2).

Quinolin-3-ylboronic acid and quinolin-8-ylboronic acid could be efficiently coupled to the dihydroacridine platform 2a. Indeed, we were able to isolate extended dihydroacridines 7b and 7c in high yields ranging from 73 to 79% (scheme 9).
Comparison of 7b and 9 1H NMR spectra revealed the presence of a singlet at δ= 5 ppm, integrating for three protons that account for the methylquinolinium salt. A further evidence for the obtention of a monomethylated product arose from the analysis of the aromatic region. Indeed, only chemical shifts of the quinoline protons were impacted by this methylation.

Photophysical properties

The absorption and emission properties of compounds 4-7 were studied by recording the UV-Vis and fluorescence spectra in dichloromethane at 25°C (table 3). These compounds showed maximum absorption wavelengths in the UV or visible region (349-394 nm).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Analogs</th>
<th>λ_{max} nm (ε M^{-1}.cm^{-1})</th>
<th>λ_{max} nm</th>
<th>ΔStokes nm</th>
<th>Φ_F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>349 (25350)</td>
<td>437</td>
<td>88</td>
<td>0.43</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>368 (19100)</td>
<td>443</td>
<td>75</td>
<td>0.36</td>
</tr>
<tr>
<td>3</td>
<td>5a</td>
<td>354 (24750)</td>
<td>401</td>
<td>47</td>
<td>0.36</td>
</tr>
<tr>
<td>4</td>
<td>4b</td>
<td>376 (9950)</td>
<td>417</td>
<td>41</td>
<td>0.09</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>394 (5500)</td>
<td>502</td>
<td>108</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7</td>
<td>7b</td>
<td>350 (16450)</td>
<td>405</td>
<td>55</td>
<td>0.013</td>
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<tr>
<td>8</td>
<td>5b</td>
<td>348 (13550)</td>
<td>402</td>
<td>54</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 3. Photophysical properties of compounds 4a-7c in DCM at 25°C.

They are not strong absorbers and exhibit modest molar extinction coefficients ranging from 5500 to 25350 M^{-1}.cm^{-1}. Compounds b bearing an extra fused ring display a red-shift both in absorption and emission compared to their analogs a (entries 1 versus 2, 3 versus 4, 5 versus 6). This is due to the extension of the conjugation by the benzene ring (table 3). They all emit around 400 nm except compound 6a which displays a red-shift in both absorption and emission. Interestingly, compound 6a displays large Stokes shift (108 nm). The method used to determine the fluorescence quantum yields is not sensitive enough to determine the low quantum yield of 6a. Nonetheless, the conjugated compounds 4 and 5 exhibit high fluorescence quantum yields (9 to 43%).

The dihydronaphtho-acridines 4b and 5b display lower quantum yield than their corresponding dihydrobenzo-acridines 4a and 5a (43% for 4a vs 36% for 4b and 36% for 5a compared to 9% for 5b). The increase of steric congestion within the bay region and the helical shape of the ortho-condensed pattern in 4b and 5b by comparison with 4a and 5a might explain the observed quantum yield trend.

A fluorosolvatochromic study has been carried out on compounds 4 and 5 (table 4). A bathochromic shift of the emission band can be observed with increasing solvent polarity. Such a fluorosolvatochromic behaviour evidences a strong interaction charge transfer in the lowest excited state.23 Interestingly, these compounds are emissive in water with moderate to good fluorescence quantum yields (0.5% to 12%). As observed for the fluorescence quantum yield in dichloromethane, the largest aromatic compounds 4b and 5b exhibit lower quantum yield in water than their analogs 4a and 5a.

<table>
<thead>
<tr>
<th></th>
<th>Toluene</th>
<th>CHCl₃</th>
<th>EtOH</th>
<th>H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E_{T^N}^{N=0.10}</td>
<td>E_{T^N}^{N=0.31}</td>
<td>E_{T^N}^{N=0.65}</td>
<td>E_{T^N}^{N=1.00}</td>
</tr>
<tr>
<td>4a</td>
<td>λ_em</td>
<td>432</td>
<td>436</td>
<td>457</td>
</tr>
<tr>
<td></td>
<td>Φ_F</td>
<td>nd</td>
<td>0.43</td>
<td>nd</td>
</tr>
<tr>
<td>4b</td>
<td>λ_em</td>
<td>438</td>
<td>445</td>
<td>454</td>
</tr>
<tr>
<td></td>
<td>Φ_F</td>
<td>nd</td>
<td>0.36</td>
<td>nd</td>
</tr>
<tr>
<td>5a</td>
<td>λ_em</td>
<td>404</td>
<td>401</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td>Φ_F</td>
<td>nd</td>
<td>0.36</td>
<td>nd</td>
</tr>
<tr>
<td>5b</td>
<td>λ_em</td>
<td>415</td>
<td>423</td>
<td>454</td>
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<tr>
<td></td>
<td>Φ_F</td>
<td>nd</td>
<td>0.09</td>
<td>nd</td>
</tr>
</tbody>
</table>

Table 4. Photophysical properties of compounds 4a-5b in various solvents at 25°C.
Conclusions

In summary, numerous novel substituted dihydrobenzo- and dihydronapthoacridines have been synthesized from a unique acridine-based backbone. This versatile methodology allowed the access of a large panel of molecules presenting rigidity/flexibility and lipophilic/hydrophilic balances properties. Photophysical studies highlighted that conjugated compounds 4 and 5 exhibit high fluorescence quantum yield. In these series, a fluorosolvatochromic study revealed a batochromic shift of the high fluorescence quantum yield. In these series, a measured according to Williams comparative method using with the emitted wavelength. Fluorescence quantum yield were corrected with a blank and from the variations of the detector.

Measurements were performed at room temperature with solutions.

Spectra were recorded using Cary Eclipse apparatus. A mixture of 1-chloro-3,4-dihydronaphthalene-2-carbaldehyde 1a (192 mg, 1 mmol) and 2-iodoaniline (240.9 mg, 1.1 mmol, 1.1 eq.) were placed in a sealed vessel and exposed to microwave irradiation conditions (90 °C, 2 hours). The reaction mixture was then poured in a flask and the vessel washed with DCM (3 x 10 mL). The crude product was concentrated under reduced pressure and purified by flash chromatography on silica gel (EP/DCM: 8/2) to give 2a (133 mg, 37 %) as a brown solid.

HRMS (ESI): calcd for C_{17}H_{13}IN [M+H]^+ : 358.0093 found: 358.0097.

13-Iodo7,8-dihydronaphtho[2,1,c]acridine 2b:

Using the same procedure as for iodoacridine 2a starting from 4-chloro-1,2-dihydrophenanthrene-3-carbaldehyde 1b (100 mg, 0.41 mmol) and 2-iodoaniline (98.8 mg, 0.45 mmol, 1.1 eq.) and exposed to microwave irradiation conditions (120 °C, 2 hours). The crude product was concentrated under reduced pressure and purified by flash chromatography on silica gel (EP/DCM: 8/2) to give 2b (59.4 mg, 36 %) as a reddish solid.

Mp: 174.5 °C

1H NMR (300 MHz, CDCl₃): δ = 10.38 (d, J = 9 Hz, 1H), 8.36 (d, J = 6 Hz, 1H), 7.97-7.95 (m, 2H), 7.92 (s, 1H), 7.81-7.76 (m, 2H), 7.63-7.58 (m, 1H), 7.44 (d, J = 9 Hz, 1H), 7.22-7.17 (m, 2H), 3.18-3.14 (m, 2H), 3.05-3.00 (m, 2H) ppm.

HRMS (ESI) : calcd for C_{17}H_{13}IN [M+H]^+: 408.0249 found: 408.0244.

Suzuki coupling:

11-(o-Tolyl)-5,6-dihydrobenzo[c]acridine 3a:

To a stirred suspension of acridine 2a (50 mg, 0.14 mmol), 2-methylphenylboronic acid (38 mg, 0.28 mmol, 2 eq.), K₂CO₃ (58 mg, 0.42 mmol, 3 eq.), in degassed EtOH/toluene/H₂O : 0.028 mL/0.140 mL/0.028 mL was added Pd(PPh₃)₄Cl₂ (10 mg, 0.014 mmol, 0.1 equiv). The reaction mixture was stirred at 80 °C for 4 hours and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EP/DCM: 8/2) to give 3a (49.2 mg, 95 %) as a brown oil.

Mp: 119.3 °C

1H NMR (300 MHz, CDCl₃): δ = 8.73 (d, J = 9 Hz, 1H), 8.27 (d, J = 6 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 9 Hz, 1H), 7.47-7.27 (m, 2H), 7.28 (d, J = 6 Hz, 1H), 7.22-7.17 (m, 2H), 3.18-3.14 (m, 2H), 3.05-3.00 (m, 2H) ppm.

HRMS (ESI): calcd for C_{17}H_{13}IN [M+H]^+: 322.1596 found: 322.1596.

Acknowledgements

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Experimental Section

General considerations: Reactions were carried out in round-bottomed flasks equipped with a magnetic stirring bar and capped with a septum. Solvents were used without further purification. TLC analyses were performed on Merck Silica gel 60 F 254 TLC plates (0.5 mm thickness). The crude products were purified by column chromatography using Merck Kieselgel 60 silica gel. 1H and 13C were recorded with Bruker Advance-300 spectrometers and referenced to CDCl₃ or CD₃COCD₂Cl₂. High-resolution mass spectra were measured with a Perkin-Elmer Finnigan MAT 95 S spectrometer. Microwave irradiations were realized using an Anton Paar Monowave 300 apparatus. Quantitative UV/visible spectra were recorded with a Cary 300 spectrometer. Fluorescence spectra were recorded using Cary Eclipse apparatus. Measurements were performed at room temperature with solutions of OD < 0.1 to avoid re-absorption of the emitted light, and data were corrected with a blank and from the variations of the detector with the emitted wavelength. Fluorescence quantum yield were measured according to Williams comparative method using quinine bisulfate in 1 M H₂SO₄ (FF = 0.54) as a reference.
To a stirred suspension of acridine (35 mg, 0.14 mmol), in degassed 1,4-dioxane (2 mL), was added Pd(PPh₃)₄ (6 mg, 0.009 mmol, 0.1 equiv) in degassed EtOH/toluene/H₂O: [0.017 mL/0.086 mL/0.017 mL]. The crude product was purified by flash chromatography on silica gel (EP/DCM: 8/2) to give 3c (31.6 mg, 67%) as a brown solid.


11-(pyridin-3-yl)-5,6-dihydrobenzo[c]acridine 7b:

Using the same procedure as for 7a starting from acridine (50 mg, 0.14 mmol), quinolin-3-ylboronic acid (48.4 mg, 0.28 mmol, 2 eq.), CsF (85 mg, 0.56 mmol, 4 eq.), Pd(OAc)₂ (2.1 mg, 0.014 mmol, 0.1 eq.) in degassed 1,4-dioxane (1 mL), was added SPhos (11.5 mg, 0.028 mmol, 0.2 eq.) and Pd(OAc)₂ (3.1 mg, 0.014 mmol, 0.1 eq.). The reaction mixture was stirred at 80 °C overnight and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 2/8) to give 7b (36.4 mg, 73%) as a brown oil.

**General procedure for Heck coupling:**

To a suspension of iodo acridine 2a or 2b (1 equiv.) and styrene (1 eq.) in degassed DMF (0.7 mL/mmol), were successively added K₂CO₃ (2.5 eq.), Bu₃NBr (1 eq.), PPh₃ (0.05 eq.), Pd(OAc)₂ (0.05 eq.) and H₂O (0.7 mL/mmol). The reaction mixture was then degassed another time and heated overnight. Water was then added and the aqueous layer was extracted. The combined organic layers were dried (MgSO₄) and the aqueous layer was extracted. The combined organic layers were concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc:PE/DCM:7/3) to give 4a (31.7 mg, 68 %) as a yellow oil.

**3H NMR (300 MHz, CDCl₃):** δ = 8.72-8.66 (m, 2H), 8.02 (d, J=6 Hz, 1H), 7.94 (s, 1H), 7.76-7.69 (m, 3H), 7.53-7.28 (m, 8H), 3.17-3.15 (m, 2H), 3.08-3.06 (m, 2H) ppm.

**13C NMR (75 MHz, CDCl₃):** δ = 152.3, 145.0, 139.4, 138.2, 135.7, 135.0, 134.0, 130.5, 129.7, 128.7, 128.2, 128.0, 127.5, 127.4, 126.9, 126.5, 126.2, 126.0, 125.2, 124.7, 28.7, 28.4 ppm.


**Sonogashira coupling:**

**11-(phenylethynyl)-5,6-dihydrobenzo[c]acridine 5a:**

To a stirred suspension of acridine 2a (50 mg, 0.14 mmol), phenylacetylene (20 µL, 0.182 mmol, 1.3 eq.), CuI (0.57 mg, 0.003 mmol, 0.025 eq.), Et₃N (28 µL, 0.21 mmol, 1.5 eq.), PPh₃ (1 mg, 0.0035 mmol, 0.025 eq.) in degassed DMF (0.35 mL) was added Pd(PPh₃)₂Cl₂ (4.9 mg, 0.007 mmol, 0.05 eq.). The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EP/DCM: 7/3) to give 5a (35 mg, 75.5 %) as a yellow solid. 

**Mp: 80°C.**

**3H NMR (300 MHz, CDCl₃):** δ = 7.87 (d, J=6 Hz, 1H), 7.77-7.73 (m, 3H), 7.49-7.40 (m, 6H), 7.29 (m, 1H), 3.19-3.15 (m, 2H), 3.06-3.02 (m, 2H) ppm.

**13C NMR (75 MHz, CDCl₃):** δ = 153.7, 147.3, 139.4, 134.7, 134.1, 132.8, 131.1, 95.3, 87.8, 28.7, 28.3 ppm.

General procedure for CuI catalyzed coupling reaction:

To a solution of acridine (1 eq.), 3-dimethylaminopropylamine (1.5 eq.), CuI (0.1 eq.), in degassed DMSO (5 mL/mmol), was added, L-proline (2 eq.) and K2CO3 (2 eq.). The reaction mixture was stirred overnight at 90 °C. EtOAc (20 mL) was then added and the organic layer was washed with water (3 x 5 mL). The organic layer was dried (MgSO4), filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (EtOAc/DCM: 0/100, then 10/90).


