Organic & Biomolecular Chemistry

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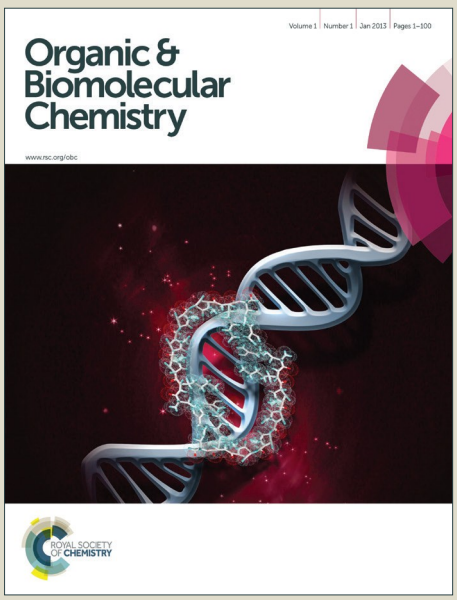

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ARTICLE

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 (ϕ_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] -cancer[6] or acetylcholinesterase inhibition[7] 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 substituent[11] 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-fluorenones[12] 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 iodo-aniline 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).

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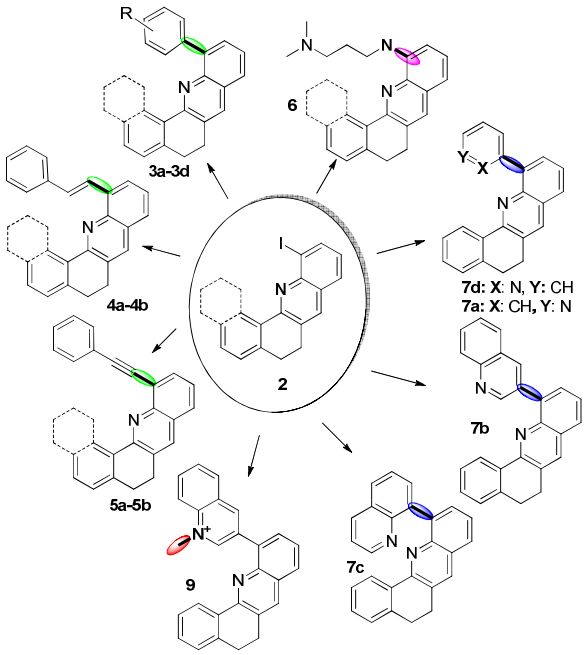
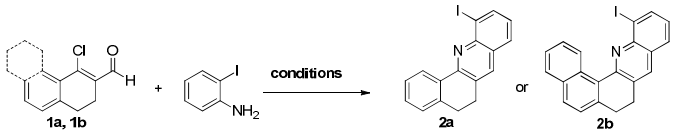


Figure 1. Divergent strategy in the synthesis of substituted dihydroacridines.

Results and discussion

Our first consideration was the preparation of iododihydro 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**[12, 13] from the parent tetralone or phenanthrone respectively under Vilsmeier-Haack conditions.[10,14] (ii) the construction of the condensed pyridine ring (scheme 1).



Scheme 1. Synthesis of iodoacridines **2a** and **2b**.

Reaction of equimolar amounts of *ortho*-iodoaniline and precursor **1a** at 90°C in *iso*propanol 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.

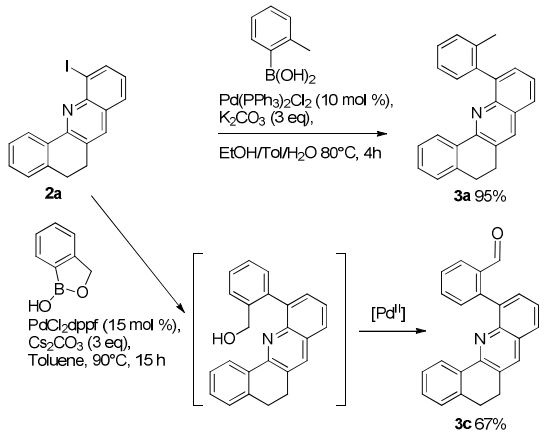
Entry	Reactant	Conditions	Acridine (yield)
1	1a	^{i}PrOH, 90°C, 5h	**2a** (30 %)
2	1a	^{i}PrOH, 90°C MW[a], 1.5h	**2a** (35 %)
3	1a	Neat, 90°C MW[a], 2h	**2a** (37 %)
4	1b	Neat, 120°C MW[a], 2h	**2b** (36 %)

[a]: see MW profile in ESI

Table 1. Reaction conditions for the preparation of iodoacridines **2a** and **2b**.

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 $Pd(PPh_3)_2Cl_2$,[15] K_2CO_3 as the catalytic system and the base respectively afforded dihydroacridine **3a** in 95% yield (scheme 2).



Scheme 2. Synthesis of arylacridine motives **3a** and **3c**.

Careful analysis of ^{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.[16] In fact, **3a** was obtained as a mixture of two conformers that arise from a restricted rotation around the neo 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_2CO_3 and $PdCl_2dppf$[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). ^{1}H NMR spectrum of **3c** revealed the presence of a

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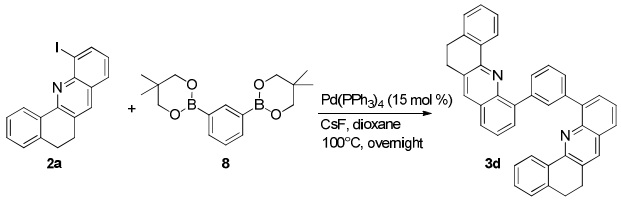
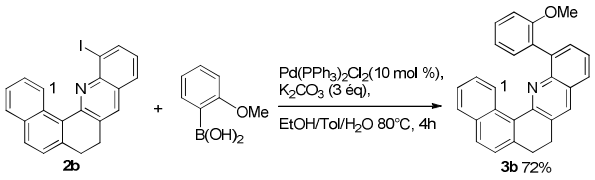
singlet at δ 9.71 ppm which undoubtedly accounts for an aldehyde proton. Mass analysis confirmed the molecular structure of **3c**.[18]
In fact, we assumed that the expected benzyl alcohol was firstly formed rapidly evolve towards the carboxaldehyde through a controlled oxidation due to the presence 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 $Pd(PPh_3)_4$ as catalytic system in degassed dioxane (scheme 3).



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

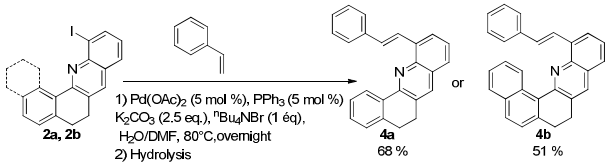
Application of our strategy to the naphthoacridine **2b** was further examined (scheme 4). In this case, the enhanced crowding within the bay region caused by the presence of both the nitrogen lone pair and the additional condensed benzene ring might render the installation of aryl substituents synthetically 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**.

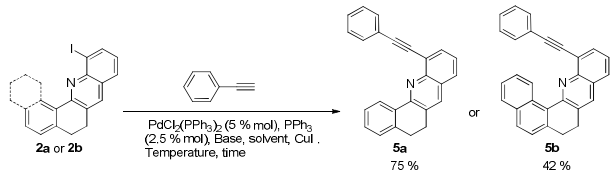
The presence of an additional cycle impacted the chemical shift of H(1) proton from 8.15 ppm for **3a** to 9.63 ppm for **3b** as previously observed in related series.[10] This observation was undoubtedly correlated with a move towards helical three dimensional shape of such molecular architectures.
The scope of our methodology was then to further extended to the installation of sp^2- and sp-C based substituents. Therefore, acridines **2a** and **2b** were submitted to Heck coupling reaction conditions by using K_2CO_3, *n*Bu_4NBr, $Pd(OAc)_2$ and PPh_3 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 $Pd(PPh_3)_2Cl_2$ as the catalytic system (scheme 6, table 2). Copper free methodology developed by Leadbeater *et al*[19] 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.[20]



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

Entry	Conditions	CuI (eq.)	Temp. Time	Product (Yield)
1	Piperidine	-	70°C, 1h	**5a** (52 %)
2	Et_3N, DMF	0.25	rt, 18h	**5a** (75 %)
3	Et_3N, DMF	0.25	rt, 18h	**5b** (42 %)

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 CuI catalyzed coupling reaction promoted by *L*-Proline (scheme 7) under the catalytic conditions recently described by *Ma et al*.[21]

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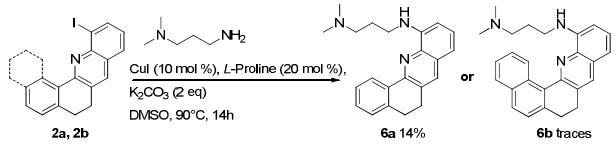
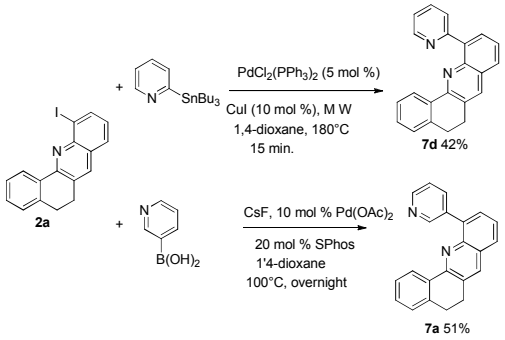


Scheme 7. Syntheses of acridinyl propanediamines **6a** and **6b**.

The coupling reaction between iodoacridines **2a** or **2b** and 3-dimethylaminopropylamine in the presence of *L*-Proline and K_2CO_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 conduced to traces of **6b**.

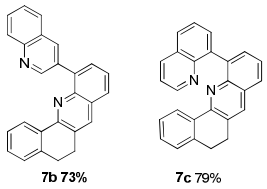
We then examined the introduction of aza heterocycles such as pyridine and quinoline (schemes 8 and 9). Coupling reactions involving pyridine boronic acids may suffer from severe drawbacks depending on the substitution pattern. Indeed, 2-pyridyl derivatives undergo prevalent protodeborylation, dimerization and relative low transmetallation steps, during Suzuki-Miyaura coupling sequence.[22] Thus in order to avoid the formation of such side-products, installation of 2-pyridylmotif 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[23] and pyridin-3-ylboronic acid,[24] using CuI, $PdPPh_3Cl_2$ 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.



Scheme 8. Syntheses of pyridinylacridines **7a** and **7d**.

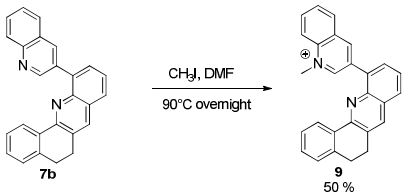
Quinolin-3-ylboronic acid and quinolin-8-ylboronic acid could be efficiently coupled to the dihydroacridine platform **2a**. Indeed, we were able to isolate extended dihydroacridines **7b** and **7c** in high yields ranging from 73 to 79% (scheme 9).



Scheme 9. Synthesis of quinolylacridines **7b** and **7c**.

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.



Scheme 10. Regioselective methylation.

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).

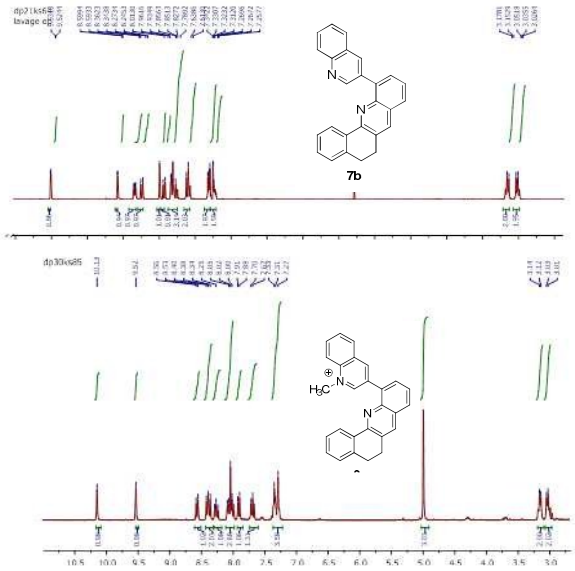


Figure 2. Comparison of ^1H NMR spectra of acridine **7b** and acridinium **9**.

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Comparison of **7b** and **9** ^{1}H 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).

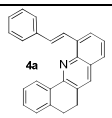
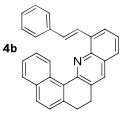
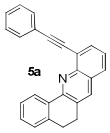
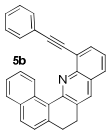
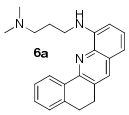
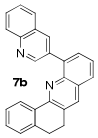
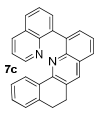
Entry	Analogs	λ_{max} nm (ε $M^{-1}.cm^{-1}$)	λ_{max} ém (nm)	δ_{Stokes} nm	Φ_Φ
1		349 (25350)	437	88	0.43
2		368 (19100)	443	75	0.36
3		354 (24750)	401	47	0.36
4		376 (9950)	417	41	0.09
5		394 (5500)	502	108	<0.001
7		350 (16450)	405	55	0.013
8		348 (13550)	402	54	0.008

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**.

		Toluene E_T^N=0.10	CH_2Cl_2 E_T^N=0.31	EtOH E_T^N=0.65	H_2O E_T^N=1.00
4a	λem	432	436	457	468
	Φ_F	nd	0.43	nd	0.12
4b	λem	438	445	454	503
	Φ_F	nd	0.36	nd	0.016
5a	λem	404	401	415	424
	Φ_F	nd	0.36	nd	0.018
5b	λem	415	423	454	467
	Φ_F	nd	0.09	nd	0.005

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

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Conclusions

In summary, numerous novel substituted dihydrobenzo- and dihydronaphthoacridines 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 emission band with increasing solvent polarity that should be in accordance with a strong charge transfer interaction in the lowest excited stated. Finally, those molecules are also emissive in water with moderate to good fluorescence quantum yields up to 12 %.

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 F254 TLC plates (0.5 mm tickness). The crude products were purified by column chromatography using Merck Kieselgel 60 silica gel. ^{1}H and ^{13}C were recorded with Bruker Advance-300 spectrometers and referenced to $CDCl_3$or CD_2Cl_2. 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 UVevisible 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 H_2SO_4 (FF = 0.54) as reference.

11-Iodo-5, 6-dihydrobenzo[*c*]acridine 2a:

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 : 6/4) to give **2a** (133 mg, 37 %) as a brown solid.

Mp: 119.3 °C

^{1}H NMR (300 MHz, $CDCl_3$): 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.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 145.9, 139.5, 139.1, 134.4, 134.1, 131.5, 130.2, 130.1, 128.2, 128.0, 127.9, 127.5, 127.2, 126.8, 103.9, 28.3, 28.2 ppm.

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

^{1}H NMR (300 MHz, $CDCl_3$): 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.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 146.2, 140.6, 139.1, 134.0, 133.9, 133.7, 131.1, 131.0, 129.3, 128.9, 128.3, 127.6, 127.5, 127.4, 126.4, 125.5, 103.7, 30.2, 28.9 ppm.

HRMS (ESI : calcd for $C_{21}H_{15}IN$ $[M+H]^+$: 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.), K_2CO_3 (58 mg, 0.42 mmol, 3 eq.), in degassed EtOH/toluene/H_2O : 0.028 mL/0.140 mL/0.028 mL was added $Pd(PPh_3)_2Cl_2$ (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.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17-8.14 (m, 1H), 7.97 (s, 1H), 7.79 (m, 1H), 7.60-7.52 (m, 2H), 7.41-7.30 (m, 6H), 7.28-7.22 (m, 1H), 3.16-3.14 (m, 2H), 3.04-2.99 (m, 2H), 2.17 (s, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 145.4, 141.4, 140.3, 139.1, 137.3, 135.0, 133.8, 130.6, 130.1, 129.6, 129.4, 129.3 127.8, 127.7, 127.2, 127.1, 126.5, 126.0, 125.7, 125.1, 28.6, 28.3, 20.8 ppm.

HRMS (ESI): calcd for $C_{24}H_{20}N$ $[M+H]^+$: 322.1596 found: 322.1596.

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13-(2-methoxyphenyl)-7,8-dihydronaphtho[2,1-*c*]acridine 3b:

Using the same procedure as for **7** starting from acridine 2**b** (35 mg, 0.086 mmol), 2-methoxyphenylboronic acid (26.14 mg, 0.17 mmol, 2 equiv), K_2CO_3 (35.6 mg, 0.26 mmol, 3 eq.), $PdCl_2(PPh_3)_2$ (6 mg, 0.009 mmol, 0.1 equiv) in degassed EtOH/toluene/H_2O : 0.017 mL/0.086 mL/0.017 mL. The crude product was purified by flash chromatography on silica gel (EP/DCM: 7/3) to give **7** (24 mg, 72 %) as a yellow solid.

Mp: 147°C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (d, *J*= 9 Hz, 1H), 8.03 (s, 1H), 7.83-7.76 (m, 3H), 7.66 (dd, *J*= 9 and 6 Hz, 1H), 7.61-7.56 (m, 1H), 7.51-7.41 (m, 2H), 7.40-7.34 (m, 2H), 7.25-7.20 (m, 1H), 7.15-7.10 (m, 2H), 3.68 (s, 3H), 3.10 (s, 4H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 154.4, 145.8, 140.2, 138.7, 133.8, 133.2, 132.5, 131.8, 131.3, 130.5, 130.2, 129.6, 128.6, 128.2, 127.9, 126.9, 126.8, 126.5, 126.4, 125.9, 125.0, 120.3, 110.8, 55.6, 30.5, 29.3 ppm.

HRMS (ESI): calcd for $C_{28}H_{22}NO$ $[M+H]^+$: 388.1701 found: 388.1701.

2-(5,6-Dihydrobenzo[c]acridin-11-yl)benzaldehyde 3c:

To a stirred suspension of acridine **2a** (50 mg, 0.14 mmol), 2-(hydroxymethyl)phenylboronic acid cyclic monoester (18.7 mg, 1 eq.), Cs_2CO_3 (136.84 mg, 0.42 mmol, 3 eq.), in degassed toluene (1 mL) was added $PddppfCl_2$ (15.4 mg, 0.021 mmol, 0.15 eq.). The reaction mixture was stirred at 90 °C for 2 hours. Then, 2-(hydroxymethyl)phenylboronic acid cyclic monoester (9.4 mg, 0.5 eq.) was added. The reaction mixture was stirred at 90°C overnight and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EP/DCM: 8/2) to give **3c** (31.6 mg, 67.4 %) as a brown solid.

Mp: 120°C

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.71 (s, 1H), 8.19 (d, *J*= 6 Hz, 1H), 8.03-8.00 (m, 1H), 7.98 (s, 1H), 7.86 (d, *J*= 6 Hz, 1H), 7.75-7.70 (m, 2H), 7.63-7.58 (m, 2H), 7.55 (d, *J*= 6 Hz, 1H), 7.30-7.28 (m, 2H), 7.22-7.20 (m,1H), 3.01-2.96 (s, 4H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 145.5, 142.8, 139.3, 137.1, 135.4, 134.4, 133.9, 133.3, 131.9, 131.0, 130.4, 129.9, 127.9, 127.8, 127.7, 127.6, 127.4, 126.3, 126.2, 125.8, 28.6, 28.3 ppm.

HRMS (ESI): calcd for $C_{24}H_{18}N$ $[M+H]^+$: 336.1388 found: 336.1394.

1,3-bis(5,6-dihydrobenzo[*c*]acridin-11-yl)benzene 3d:

To a stirred suspension of acridine **2a** (100 mg, 0.28 mmol, 2 eq.), boronic acid (42 mg, 0.14 mmol.), CsF (127 mg, 0.84 mmol, 6 eq.), in degassed 1,4-dioxane (2 mL), was added $Pd(PPh_3)_4$ (24 mg, 0.021 mmol, 0.15 eq.). The reaction mixture was stirred at 100 °C overnight and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EP/DCM: 8/2) to give **3d** (31.6 mg, 42 %) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46-8.43 (m, 2H), 8.28 (m, 1H), 8.00 (d, *J*= 6 Hz, 2H), 7.94 (s, 2H), 7.90 (d, *J*= 6 Hz, 2H), 7.74-7.70 (m, 3H), 7.54-7.49 (m, 2H), 7.32-7.20 (m, 6H), 3.13-3.11 (m, 4H), 3.02-3.00 (m, 4H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 145.0, 140.7, 139.2, 138.9, 135.1, 133.9, 133.5, 130.2, 130.1, 129.5, 129.4, 128.3, 127.8, 127.1, 126.6, 126.5, 126.4, 125.9, 28.6, 28.4 ppm.

HRMS (ESI): calcd for $C_{40}H_{29}N_2$ $[M+H]^+$: 537.2339 found: 537.2331.

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

To a stirred suspension of acridine **2a** (50 mg, 0.14 mmol), pyridin-3-ylboronic acid (34.4 mg, 0.28 mmol, 2 eq.), CsF (85 mg, 0.56 mmol, 4 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 (EtOAc) to give **7a** (22.2 mg, 95 %) as a yellow solid.

Mp: 172 °C.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.11 (s, 1H), 8.69 (m, 1H), 8.35-8.32 (m, 1H), 8.24 (d, *J*= 9 Hz, 1H), 8.00 (s, 1H), 7.82 (d, *J*= 9 Hz, 1H), 7.73 (d, *J*=6 Hz, 1H), 7.60-7.55 (m, 1H), 7.52-7.48 (m, 1H), 7.37-7.32 (m, 2H), 7.25 (d, *J*= 6 Hz, 1H), 3.19-3.15 (m, 2H), 3.05-3.01 (m, 2H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 151.1, 147.8, 144.6, 139.3, 138.7, 136.7, 135.4, 134.7, 134.0, 130.7, 129.8, 129.4, 128.3, 127.9, 127.6, 127.4, 126.2, 125.9, 122.7, 28.6, 28.3 ppm.

HRMS (ESI): calcd for $C_{22}H_{17}N_2$ $[M+H]^+$: 309.1392found: 309.1392.

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

Using the same procedure as for **7a** starting from acridine **2a** (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.), SPhos (11.5 mg, 0.028 mmol, 0.2 equiv) and $PdOAc_2$ (3.1 mg, 0.014 mmol, 0.1 eq.) in degassed 1,4-dioxane. 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.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.52 (d, *J*=1.9 Hz, 1H), 8.59 (d, *J*=1.9 Hz, 1H), 8.37-8.34 (m, 1H), 8.23 (d, *J*=5.5 Hz, 1H), 8.01 (s, 1H), 7.95 (d, *J*=5.5 Hz, 1H), 7.87-8.85 (m, 2H), 7.83-7.79 (m, 1H), 7.63-7.61 (m, 2H), 7.34-7.31 (m, 2H), 7.27-7.26 (m, 1H), 3.18-3.15 (m, 2H), 3.00-3.02 (m, 2H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4, 153.1, 146.7, 144.8, 139.2, 137.1, 136.8, 134.6, 134.0, 133.0, 130.9, 129.8, 129.3, 129.0, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 126.6, 126.3, 126.0, 28.6, 28.3 ppm.

HRMS (ESI): calcd for $C_{26}H_{19}N_2$ $[M+H]^+$: 359.1548 found: 359.1551.

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11-(quinolin-8-yl)-5,6-dihydrobenzo[*c*]acridine 7c:

Using the same procedure as for **7b** starting from acridine **2a** (50 mg, 0.14 mmol), quinolin-8-ylboronic acid (48.4 mg, 0.28 mmol, 2 eq.), CsF (85 mg, 0.56 mmol, 4 eq.), SPhos (11.5 mg, 0.028 mmol, 0.2 equiv) and $PdOAc_2$ (3.1 mg, 0.014 mmol, 0.1 equiv) in degassed 1,4-dioxane (1 mL). 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 (EtOAc) to give **7c** (39.6 mg, 79 %) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (dd, *J*=1.8, 4.2 Hz, *1H*), 8.28 (dd, *J*=1.8, 8.3 Hz, 1H), 7.98 (s, 1H), 7.97-7.94 (m, 2H), 7.88-7.84 (m, 2H), 7.74-7.69 (m, 1H), 7.66-7.59 (m, 2H), 7.40 (dd, *J*=4.2, 8.3 Hz, 1H), 7.2-7.16 (m, 2H), 7.09-7.05 (m, 1H), 3.13-3.10 (m, 2H), 2.98-2.94 (m, 2H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 149.7, 147.3, 146.0, 139.3, 139.1, 138.9, 136.2, 135.1, 133.7, 132.2, 130.7, 130.1, 129.1, 128.3, 128.0, 127.6, 127.5, 127.0, 126.9, 125.9, 125.8, 125.6, 120.5, 28.56, 28.33 ppm.

HRMS (ESI): calcd for $C_{26}H_{19}N_2$ $[M+H]^+$: 359.1548 found: 359.1548.

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 K_2CO_3 (2.5 eq.), $^nBu_4NBr$ (1 eq.), PPh_3 (0.05 eq.), $Pd(OAc)_2$ (0.05 eq.) and H_2O (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 ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel.

(*E*)-11-styryl-5,6-dihydrobenzo[*c*]acridine 4a:

The reaction mixture was stirred overnight at 80 °C. After hydrolysis, the aqueous layer was extracted with EtOAc (3 x 10 mL). The crude product was purified by flash chromatography on silica gel (EP/DCM : 6/4) to give **4a** (31.7 mg, 68 %) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): 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), 3.18-3.15 (m, 2H), 3.08-3.06 (m, 2H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 145.0, 139.4, 138.2, 135.7, 135.0, 134, 130.5, 130.1, 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.

HRMS (ESI): calcd for $C_{25}H_{20}N$ $[M+H]^+$: 334.1596 found: 334.1596.

(*E*)-13-styryl-7,8-dihydronaphtho[2,1-*c*]acridine 4b:

The reaction mixture was stirred overnight at 105 °C. After hydrolysis, the aqueous layer was extracted with DCM (3 x 20 mL). The crude product was purified by flash chromatography on silica gel (EP/DCM: 7/3) to give **4b** (46.7 mg, 51 %) as a yellow solid.

Mp: 75 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.04 (d, *J*=9 Hz, 1H), 8.80 (d, *J*=15 Hz, 1H), 8.08 (d, *J*=9 Hz, 1H), 8.00 (s, 1H), 7.95-7.88 (m, 2H), 7.73-7.70 (m, 3H), 7.66-7.63 (m, 1H), 7.60-7.52 (m, 2H), 7.46-7.39 (m, 4H), 7.33-7.31 (m, 1H), 3.13 (s, 4H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 144.5, 140.3, 138.0, 135.7, 134.0, 133.2, 131.2, 130.5, 130.0, 129.6, 128.6, 128.4, 128.0, 127.5, 127.2, 127.0, 126.8, 126.5, 126.3, 126.2, 125.4, 125.1, 123.9, 30.3, 27.0 ppm.

HRMS (ESI): calcd for $C_{29}H_{22}N$ $[M+H]^+$: 384.1752 found: 384.1752.

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 (0.7 mg, 0.0035 mmol, 0.025 eq.), Et_3N (28 µL, 0.21 mmol, 1.5 eq.), PPh_3 (1 mg, 0.0035 mmol, 0.025 eq.) in degassed DMF (0.35 mL) was added $Pd(PPh_3)_2Cl_2$ (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.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (d, *J*= 6 Hz, 1H), 7.95-7.93 (m, 2H), 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.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 147.3, 139.4, 134.7, 134.1, 132.8, 131.8, 131.1, 95.3, 87.8, 28.7, 28.3 ppm.

HRMS (ESI): calcd for $C_{25}H_{18}N$ $[M+H]^+$: 332.1439 found: 332.1430.

13-(Phenylethynyl)-7,8-dihydronaphtho[2,1-*c*]acridine 5b:

Using the same procedure as for **13** starting from acridine **2b** (50 mg, 0.12 mmol), phenylacetylene (17 µL, 0.156 mmol, 1.3 eq.), CuI (0.57 mg, 0.003 mmol, 0.025 eq.), Et_3N (25.1 µL, 0.18 mmol, 1.5 eq.), PPh_3 (0.8 mg, 0.003 mmol, 0.025 eq.) in degassed DMF (0.300 mL) was added $Pd(PPh_3)_2Cl_2$ (4.2 mg, 0.006 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: 8/2) to give **5b** (19.3 mg, 42 %) as a brown solid.

Mp: 200°C.

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^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.35 (d, *J*= 9 Hz, 1H), 8.03 (s, 1H), 7.98 (d, *J*= 6 Hz, 1H), 7.91-7.87 (m, 2H), 7.77 (d, *J*= 6 Hz, 1H), 7.67-7.63 (m, 2H), 7.53 (d, *J*= 6 Hz, 1H), 7.49-7.47(m, 1H), 7.45-7.41 (m, 2H), 7.38-7.36 (m, 3H), 3.12 (m, 4H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 147.1, 140.5, 134.0, 133.5, 133.3, 132.7(2), 132.1, 131.4, 130.9, 129.6, 128.3, 128.2(2), 128.1, 128.0, 127.7, 127.1, 126.9, 126.3, 125.8, 125.2, 123.7, 123.2, 95.0, 88.1, 30.3, 29.1 ppm.

HRMS (ESI): calcd for $C_{29}H_{20}N$ $[M+H]^+$: 382.1596 found: 382.1596.

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 K_2CO_3 (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 ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (EtOH/DCM: 0/100, then 10/90).

***N*^{1}-(5,6-dihydrobenzo[c]acridin-11-y)-*N*^{3},*N*^{3}-dimethylpropane-1,3-diamine 6a:**

Obtained as a brown oil (9 mg, 14% yield).

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.46 (d, *J* = 7.4 Hz, 1H), 7.75 (s, 1H), 7.37 – 7.15 (m, 4H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 3.34 (t, *J* = 6.5 Hz, 2H), 3.02 (dd, *J* = 8.9, 5.2 Hz, 2H), 2.92 (dd, *J* = 8.5, 5.5 Hz, 2H), 2.50 (s, 2H), 2.27 (s, 6H), 1.91 (p, *J* = 6.5, 5.9 Hz, 2H) ppm.

^{13}C NMR (75 MHz, CD_2Cl_2): δ = 150.3, 145.7, 139.8, 137.6, 135.4, 134.3, 131.2, 129.1, 128.8, 128.5, 128.0, 127.4, 126.0, 113.3, 104.3, 58.3, 54.7, 54.6, 54.4, 54.2, 54.0, 53.9, 53.6, 53.3, 45.5, 42.5, 30.2, 29.1, 28.9, 26.9 ppm.

HRMS (ESI): calcd for $C_{22}H_{26}N_3$ $[M+H]^+$: 332.2127 found: 332.2131.

***N*^{1}-(7,8-dihydronaphtho[2,1,c]acridin-13-yl)-*N*^{3},*N*^{3}-dimethylpropane-1,3-diamine 6b:**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.71 (d, *J* = 8.2 Hz, 1H), 7.92 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.64 – 7.54 (m, 1H), 7.53 – 7.45 (m, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.30 (s, 1H), 3.41 (s, 2H), 3.06 (s, 4H), 2.59 (s, 2H), 2.32 (s, 6H), 2.01 (d, *J* = 6.9 Hz, 2H) ppm.

11-(pyridin-2-yl)-5,6-dihydrobenzo[*c*]acridine 7d:

A mixture of acridine **2a** (50 mg, 0.14 mmol), 2-tributylstannyl-pyridine (49.3 µL, 0.154 mmol, 1.1 eq.), CuI (2.7 mg, 0.014 mmol, 0.1 eq.), $PdCl_2(PPh_3)_2$ (4.9 mg, 0.007 mmol, 0.05 eq.) in degassed 1,4-dioxane (1 mL) were placed in a sealed vessel and exposed to microwave irradiation conditions (180 °C, 15 min). 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 (EtOAc) to give **7a** (20.7 mg, 42 %) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.85 (d, *J*=3 Hz, 1H), 8.45 (d, *J*=6 Hz, 1H), 8.36-8.33 (m, 1H), 8.23 (d, *J*=6, 1H), 8.02 (s, 1H), 7.96 (t, *J*= 15 Hz, 1H), 7.86 (d, *J*=6 Hz, 1H), 7.67-7.61 (m, 1H), 7.43-7.35 (m, 3H), 7.30-7.27 (m, 1H), 3.20-3.16 (m, 2H), 3.07-3.02 (m, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 153.1, 148.2, 144.5, 139.5, 137.3, 136.1, 134.8, 134.3, 130.7, 130.5, 129.8, 129.6, 128.2, 128.1, 128.0, 127.3, 126.2, 122.3, 28.6, 28.3 ppm.

HRMS (ESI): calcd for $C_{22}H_{17}N_2$ $[M+H]^+$: 309.1392 found: 309.1386.

3-(5,6-dihydrobenzo[c]acridin-11-yl)-1-methylquinolin-1-ium 9:

To a solution of acridine **7b** (25 mg, 0.07mmol) in DMF (0.5 mL) is added CH_3I (43,6 µL, 0.7 mmol, 10 eq.). The reaction mixture was stirred at 40 °C for 6 h and then at 90 °C overnight. The solvent was removed under reduced pressure and **9** (17.6 mg, 50.2 %) was obtained as a brown solid. No further purification was necessary.

Mp: 178°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.13 (s, 1H), 9.52 (s, 1H), 8.54 (d, *J = 9 Hz*, 1H), 8.37 (m, 2H), 8.25 (m, 1H), 8.00 (m, 3H), 7.89 (d, *J = 9 Hz*, 1H), 7.69 (m, 1H), 7.30 (m, 3H), 4.99 (s,3H), 3.13 (d, *J = 6 Hz*, 2H), 3.02 (d, *J = 6 Hz*, 2H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.7, 151.3, 147.5, 143.1, 139.7, 137.1, 135.9, 134.6, 134.0, 133.3, 131.5, 131.0, 130.8, 130.6, 130.5, 130.3, 129.8, 129.3, 128.4, 128.2, 127.4, 126.7, 125.3, 118.9, 47.4, 28.4, 28.0 ppm.

HRMS (ESI): calcd for $C_{27}H_{21}N_2$ $[M+H]^+$: 373.1705 found: 373.1704.

Notes and references

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Electronic Supplementary Information (ESI) available: copies of NMR spectra and MW profiles are given. See DOI: 10.1039/b000000x/

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