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To cite this version:

Sarah Zeghada, Ghenia Bentabed-Ababsa, Olivier Mongin, William Erb, Laurent Picot, et al.. 2-Aminobenzaldehyde, a common precursor to acridines and acridones endowed with bioactivities. Tetrahedron, 2020, 76 (38), pp.131435. 10.1016/j.tet.2020.131435 . hal-03302141

HAL Id: hal-03302141

https://univ-rennes.hal.science/hal-03302141v1

Submitted on 8 Sep 2021

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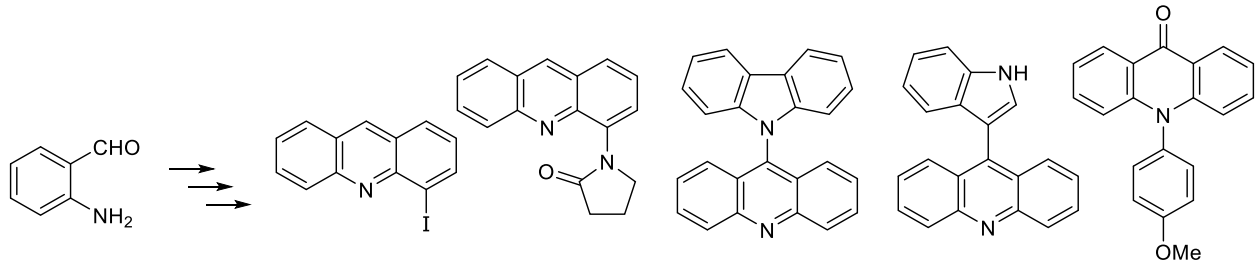
Graphical Abstract



2-Aminobenzaldehyde, a common precursor to acridines and acridones endowed with bioactivities

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Keywords: acridine; acridone; *N*-arylation; copper; antiproliferative activity; melanoma cells

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Abstract:

By starting from a common substrate, 2-aminobenzaldehyde, both acridines and acridones were prepared. The former were generated in high yields by copper-catalyzed *N*-arylation followed by acid-mediated cyclization while the latter were obtained by double copper-catalyzed *N*-arylation followed by cyclization under the same reaction conditions. Moreover, acridine was subjected to deprotometalation by recourse to a lithium-zinc base and converted to the corresponding 4-iodo derivative, which was involved in copper-catalyzed couplings with pyrrolidinone and pyrazole. Finally, addition of pyrazole, indole and carbazole onto the 9 position of bare acridine was improved. While moderate biological activity was noticed in melanoma cells growth inhibition, the newly prepared compounds feature interesting photophysical properties which were evaluated in a preliminary study.

1. Introduction

Heteroaromatic units such as acridines and acridones play an important role in various molecules exhibiting biological properties as well as in organic materials for a wide range of applications (e.g. related to fluorescence).[1] For example, *N*-(2-(dimethylamino)ethyl)acridine-4-carboxamide (**DACA**) and amsacrine (***m*-AMSA**) are topoisomerase II inhibitors and, while the former has been used in trials for the treatment of lung cancer or brain and CNS tumors, the latter is also a potent intercalating antineoplastic agent used for the treatment of acute myeloid leukemia (Figure 1, left).[1b]

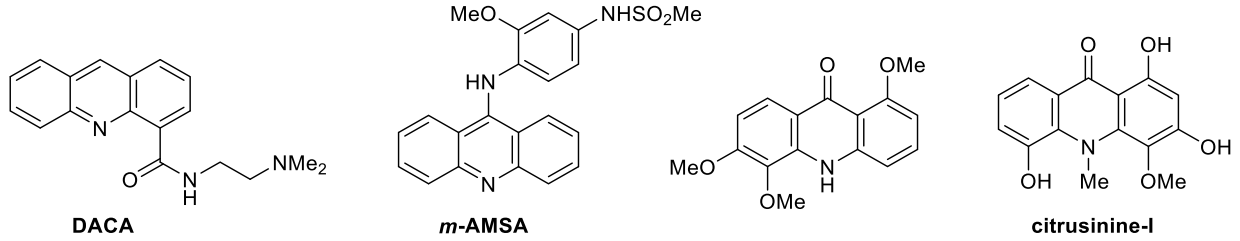

Figure 1. Structures of biologically active acridines (left) and acridones (right).

Other biological activities can be found in acridone-based compounds. For example, 1,5,6-trimethoxyacridone is known for its ability to inhibit aromatase and glycosyltransferase, and its

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moderate cytotoxic activity against liver cancer cell line WRL-68 (IC_{50} = 86 μM). Finally, citrusinine-I is a natural acridone reported as herbicide model due to its ability to inhibit photosynthesis (Figure 1, right).[1b]

Acridines and acridones are traditionally prepared by using as key step copper-catalyzed C-N bond formation reactions between 2-halogenobenzoic acids and anilines.[1a,b] Among other methods reported to access acridines,[2] we can cite (i) the Bernthsen synthesis in which diphenylamine and carboxylic acids are heated in the presence of zinc chloride as catalyst to furnish 9-substituted acridines,[3] (ii) palladium-catalyzed *N*-arylation/intramolecular Heck reaction of 2-bromostyrenes with 2-chloroanilines developed by Buchwald and co-workers,[4] (iii) [4+2] annulation of 2-aminoaryl ketones with *in situ* formed arynes (by treating 2-(trimethylsilyl)aryl triflates with cesium fluoride) documented by Larock and co-workers to afford unsymmetrical acridines,[5] (iv) palladium-catalyzed consecutive C=C bond and C-N bond formations between 1,2-dibromobenzenes and *N*-tosyl hydrazones of 2-aminophenyl ketones reported by Wang and co-workers,[6] (v) the appoach of Ellman and co-workers who employed aromatic azides with aromatic imines in a [3+3] annulation reaction (Rh(III)-catalyzed amination followed by intramolecular electrophilic aromatic substitution and aromatization),[7] (vi) palladium-catalyzed *N*-arylation/Friedel-Crafts reactions of anilines reported by Guo, Wang and co-workers from 2-formylphenyl triflates and anilines,[8] and by Xu and co-workers from 2-bromobenzaldehydes,[9] both in the presence of copper salts, (vii) tandem *N*-arylation/Friedel-Crafts reactions of 2-aminophenones with diaryliodonium salts[10] and arylboronic acids,[11] (viii) Wang's[12] and Wu's[13] annulation-aerobic oxidative dehydrogenation and Deng's palladium-catalyzed reaction[14] of 2-aminophenones with cyclohexanones, and (ix) Jiang's nitrogen/iodine exchange of diaryliodonium salts with sodium azide[15] (Scheme 1).

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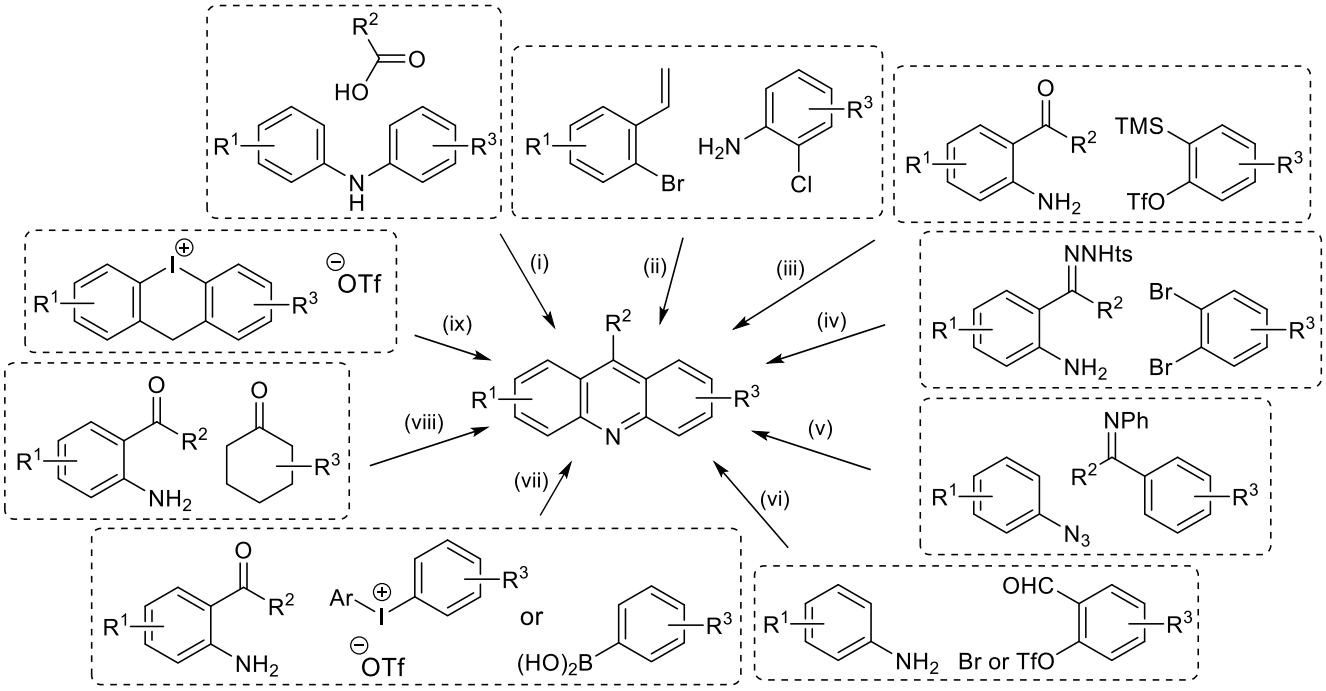

Scheme 1. General ways reported in the literature to access acridines.

Among a few other specific syntheses,[16] the general ways to access acridones include (i) acid-induced cyclization of *N*-aryl anthranilic acids (or amides),[16a,17] (ii) hydrolysis of 9-chloroacridines[18] and oxidation of acridines[18-19] or acridinium salts,[20] (iii) copper-catalyzed (first reported by Deng,[21] Cheng,[22] Xu,[23] Zhu[23] and co-workers) or potassium *tert*-butoxide-mediated (reported by Zou and co-workers)[24] intramolecular *N*-arylation of *N*-substituted 2-aminobenzophenones,[25] (iv) copper-catalyzed oxidative cyclization of 2-(phenylamino)acetophenones studied in parallel by Zhou,[26] Fu,[19] Zhang[27] and co-workers, as well as Yang's scandium triflate-catalyzed[28] and Du/Zhao's (diacetoxyiodo)benzene-mediated[29] dehydrogenative cyclization of 2-(phenylamino)benzaldehydes, (v) Chen's tandem copper-catalyzed *N*-arylation/Friedel-Crafts reaction of methyl 2-aminobenzoates with diaryliodonium salts,[10] (vi) reactions involving *in situ* generated arynes (from 2-(trimethylsilyl)aryl triflates) such as Jiang's palladium-catalyzed multicomponent with 2-iodoanilines and carbon monoxide,[30] and Larock's cesium fluoride-mediated coupling with methyl 2-aminobenzoates,[31] (vii) Lei's palladium-copper co-catalyzed oxidative double C-H carbonylation of diphenylamines,[16d] (viii) palladium-catalyzed carbonylation/C-H activation sequence developed by Song, Liu and co-workers

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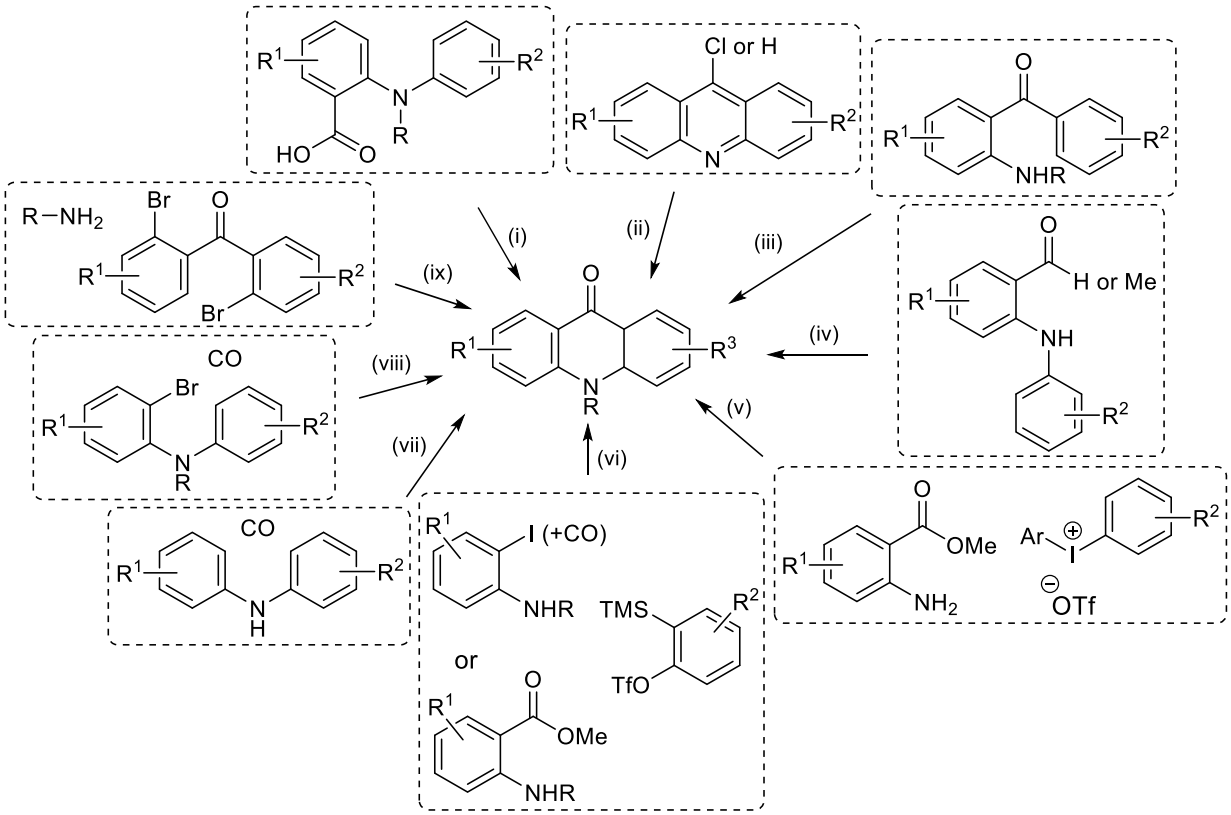
from 2-bromodiarylamines,[32] and (ix) Langer's palladium-catalyzed double amination of bis(2-bromophenyl) ketones.[33] As far as *N*-arylated acridones are concerned, they can be obtained either by a suitable choice of the precursors,[16a,21-22,25,32-33] or by post-functionalization of acridones[34] (Scheme 2).



Scheme 2. General ways reported in the literature to access acridones.

In 2018, we reported an easy synthesis of *N*-aryl isatins or acridines, both involving a copper-catalyzed C-N bond formation from 2-aminophenones.[35] As part of our studies dedicated to the development of short syntheses to access aromatic heterocycles of biological interest,[36] we here report our efforts to access both acridines and *N*-arylated acridones from a common precursor, 2-aminobenzaldehyde. We also document the photophysical properties of some of the prepared compounds, as well as their ability to inhibit the growth of melanoma cells.

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2. Results and Discussion

2.1. Syntheses of acridines

The secured synthesis of 2-aminobenzaldehyde reported in 2012[37] allowed organic chemists to involve it in copper-catalyzed *N*-arylation reactions, either with iodobenzenes as demonstrated for example by Li and co-workers by using potassium carbonate together with catalytic copper(I) iodide and glycine in dimethylformamide at 130 °C,[38] or with pinacol boronic esters as reported by Liu and Xu.[39] Inspired by previously reported *N*-arylation of 2-aminophenones,[40] and in line with our previous study,[35] 2-aminobenzaldehyde (**1**) was reacted with iodoarenes (iodobenzene, the three different iodoanisoles, and 3-iodopyridine) in the presence of potassium carbonate (2 equiv) and catalytic activated copper[41] at the reflux temperature of dibutyl ether to afford the expected products **2a-e** in moderate to good yields (Table 1, left). The diarylamines were next cyclized by using sulfuric acid in boiling acetic acid,[42] providing the acridines **3a-e** in high yields (Table 1, right). Our approach to access substituted acridines is complementary to those already reported in the literature. For example, Wu and Mu synthesized **3b** and **3d** them from 2-fluorobenzaldehyde by $ZnCl_2$-promoted intramolecular cyclization of 2-arylaminophenyl Schiff bases,[43] and Xu from 2-bromobenzaldehyde by palladium-catalyzed tandem coupling/cyclization.[9] In the case of 3-iodoanisole, two products **3c1** and **3c2** can be formed upon acid-mediated cyclization; they were respectively isolated in a 74:26 ratio in favor of the less hindered (entry 3). This result is rather consistent with previously reported trifluoroacetic acid-mediated cyclizations of 2-(3-methoxyphenylamino)benzaldehyde giving **3c1** and **3c2** in a 60:40 ratio.[44] In contrast, in the case of 3-iodopyridine for which two possible products can in theory be obtained, the one resulting from a cyclization at the 2 position of the pyridine ring (**3e**) was the only product isolated (entry 5). This result is particularly interesting since at present there is no efficient access to benzo[*b*][1,5]naphthyridine (**3e**) in the literature.[15]

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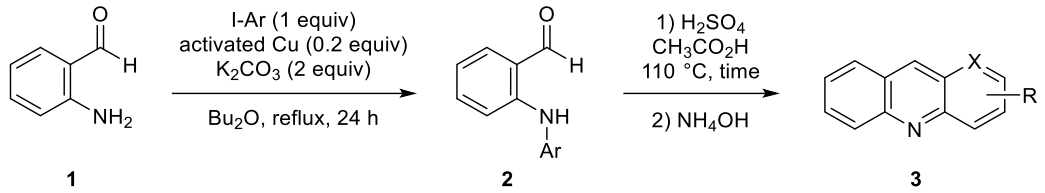
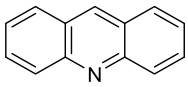
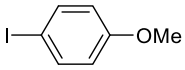
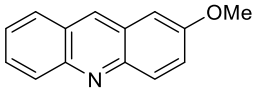
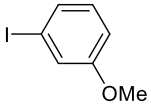
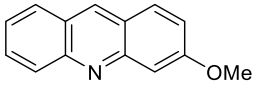
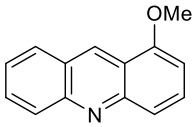
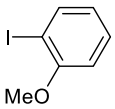
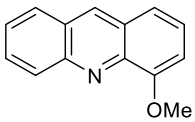
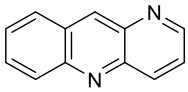
Table 1. *N*-arylation of 2-aminobenzaldehyde (**1**) to afford the *N*-arylamines **2**, and subsequent conversion to the acridines **3**.



Entry	I-Ar	**2**, Yield (%)[a]	Product **3** (time), Yield (%)[a]
1	I-Ph	**2a**, 71[35]	 **3a** (0.5 h), 94
2		**2b**, 78	 **3b** (1.5 h), 80
3		**2c**, 83	 **3c1** (3 h), 72  **3c2** (3 h), 25
4		**2d**, 76	 **3d** (3 h), 98
5		**2e**, 62	 **3e** (2 h), 83

[a] After purification (see experimental part).

The efficiency of the reaction led us to consider double *N*-arylation-cyclization sequences using diiodides. Kuninobu, Takai and co-workers showed that the pentacycle **3f2** could be synthesized from **2f2** in 76% yield by using catalytic indium(III) triflate in 1,2-dichloroethane at 150 °C for 24 h.[45] Wu, Mu and co-workers prepared both **3f1** and **3f2** from the corresponding 2-arylaminophenyl Schiff bases in 98 and 50% yield, respectively, by using zinc chloride in excess in tetrahydrofuran at 80 °C for 24 h.[43] By using conditions close to those of Table 1 for the *N*-arylation (0.4 equiv of activated copper, 3 equiv of potassium carbonate, reflux of dibutyl ether), but with an extended reaction time in order to allow the reaction to go to completion, 1,3-diiodobenzene reacted with an excess of 2-

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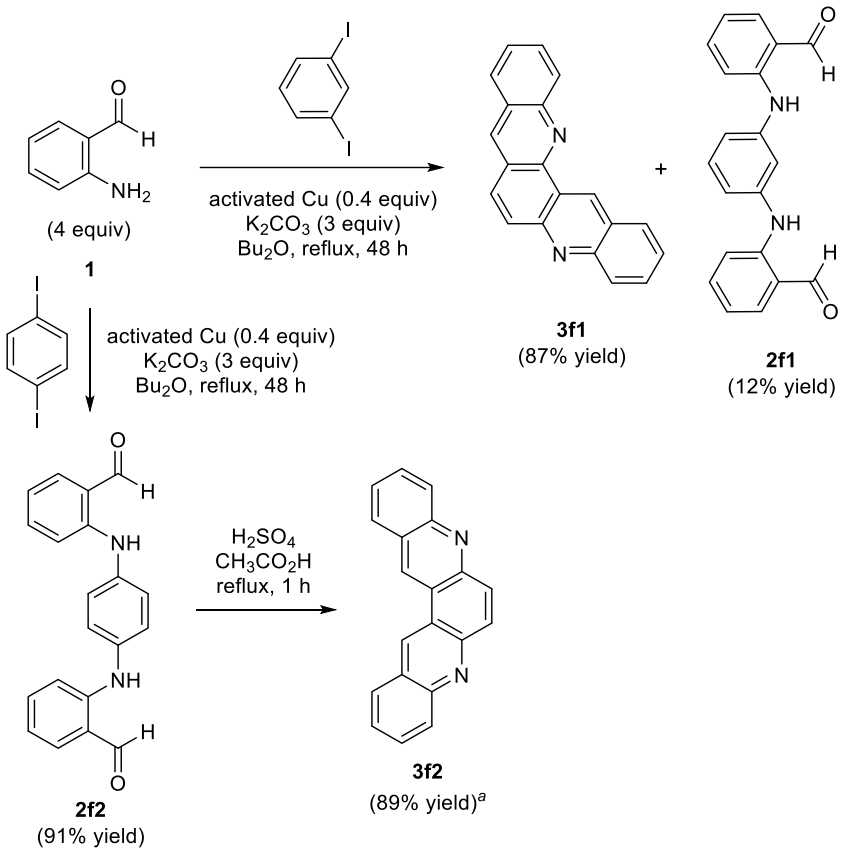
aminobenzaldehyde to directly lead to dibenzo[*b*,*j*][1,7]phenanthroline (**3f1**), isolated in 87% yield (Scheme 3, top). In contrast, using 1,4-diiodobenzene instead furnished the non-cyclized product **2f2** in 91% yield; the latter was converted to dibenzo[*b*,*j*][4,7]phenanthroline (**3f2**) in 89% yield by subsequent acid-mediated aromatic electrophilic substitution (sulfuric acid in boiling acetic acid) (Scheme 3, bottom). All these results are consistent with an easier cyclization from **2f1** which benefits from an additional well-located mesomeric electron-donating group.



Scheme 3. *N*-arylation of 2-aminobenzaldehyde (**1**) to afford, after cyclization, the pentacycles **3f1** and **3f2**. [a] No other isomer detected.

Our expertise in the field of deprotometalation-electrophilic trapping sequences from sensitive aromatic heterocycles,[46] and in copper-catalyzed *N*-arylation reactions of amides[47] and azoles[48] by aryl iodides, led us to study these reactions from acridine (**3a**). Indeed, acridine being so sensitive to nucleophilic attacks at its 9 position[49] that its deprotometalation followed by electrophilic trapping has, to our knowledge, never been reported. As a consequence, multistep approaches need to be followed

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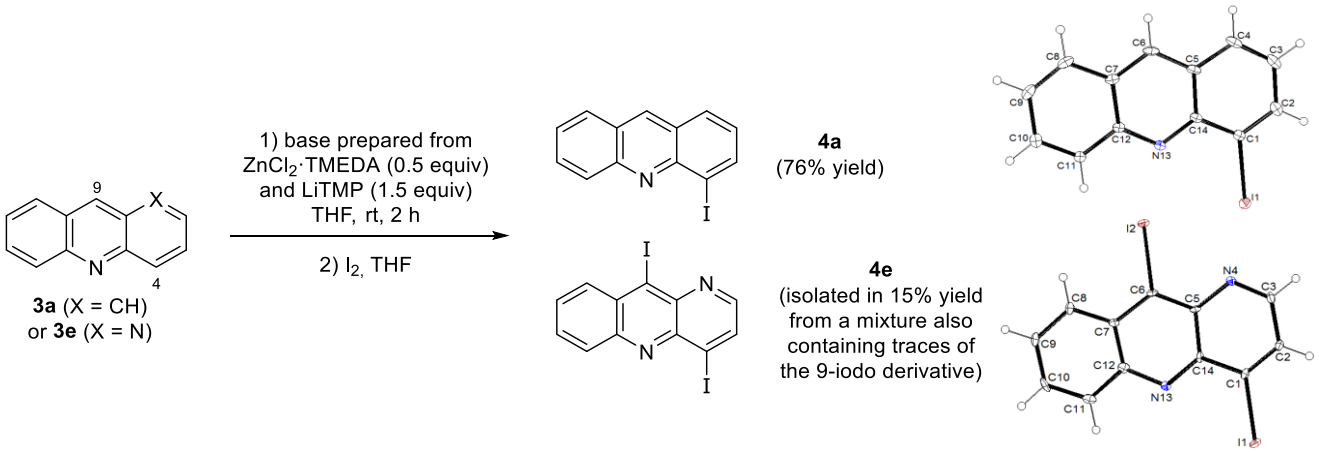
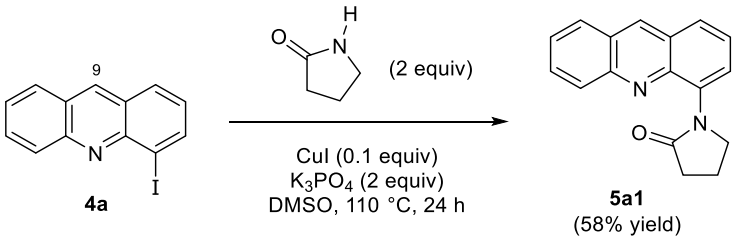
when halogenated acridones are required, as exemplified with the synthesis of 4-iodoacridine (**4a**) prepared from 4-bromoacridine (coming from the corresponding bromoaniline) by halogen/metal exchange followed by quenching with chlorotributylstannane and subsequent reaction with iodine.[50] By simply starting from acridine (**3a**), using our lithium-zinc base prepared *in situ* from $ZnCl_2 \cdot TMEDA$[51] (0.5 equiv) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP; 1.5 equiv)[46] chemoselectively led to the 9-arylmetal derivative which, upon iodolysis, furnished the 4-iodo derivative **4a** in 76% yield (Scheme 4, top). However, probably due to several possible deprotonation sites, a mixture was obtained by applying the same conditions to benzo[*b*][1,5]naphthyridine (**3e**); the 4,9-diiodo derivative **4e** was the only product isolated from a mixture also containing traces of the 9-iodo (Scheme 4, bottom).



Scheme 4. Functionalization of the tricycles **3a** and **3e** by a deprotometalation-iodolysis sequence and ORTEP diagrams (30% probability) of **4a** and **4e**.



Scheme 5. *N*-arylation of pyrrolidinone using 4-iodoacridine (**4a**).

Because of the paucity of *N*-(4-acridyl)amides and *N*-(4-acridyl)azoles in the literature, we were eager to develop an approach toward them. Therefore, we first attempted the reaction of pyrrolidinone with **4a** in the presence of potassium phosphate and catalytic copper(I) iodide in dimethyl sulfoxide (DMSO) at 110 °C. Under these conditions,[47] the expected coupled product was isolated in 58% yield

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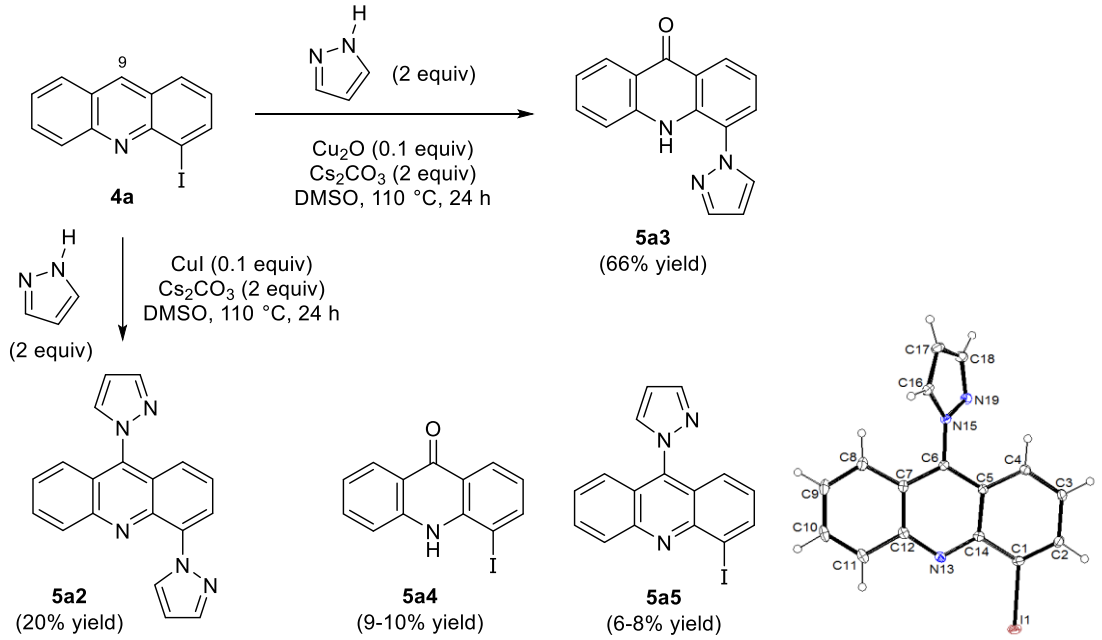
(Scheme 5). Next, we tried to *N*-arylate **4a** with pyrazole under conditions previously used for similar reactions (0.1 equiv of copper(I) source, 2 equiv of cesium carbonate, DMSO at 110 °C for 24 h).[48b] While copper(I) oxide proved better than copper(I) iodide, side reactions were observed. Indeed, the main product isolated (20% yield) was 4,9-di(*N*-pyrazolyl)acridine (**5a2**) by using the latter while 4-(*N*-pyrazolyl)-9-acridone (**5a3**) was formed as main compound (66% yield) with the former. Even if scarce, examples of acridine conversion into acridone have already been reported, for example by employing sodium hydride in DMSO.[52] In both cases, 4-iodo-9-acridone (**5a4**) and 4-iodo-9-(*N*-pyrazolyl)acridine (**5a5**) were also isolated in yields below 10% (Scheme 6).



Scheme 6. Attempts to *N*-arylate pyrazole using 4-iodoacridine (**4a**) in the presence of copper(I) salts and ORTEP diagram (30% probability) of **5a5**.

In order to determine if copper plays a role in the conversion of acridine to acridone, we performed the reaction from acridine (**3a**) and pyrazole without copper(I) source; under the same conditions, acridone (**5a6**) was also the main product (66% yield) while 9-(*N*-pyrazolyl)acridine (**5a7**) was isolated in 29% yield (Scheme 7, top). Formation of acridones could be explained by the sensitivity of acridines towards nucleophiles, and the presence of either residual water in DMSO[53] or carbonate.[54] As regards the addition of pyrazole onto the acridine ring, we replaced cesium carbonate by potassium phosphate

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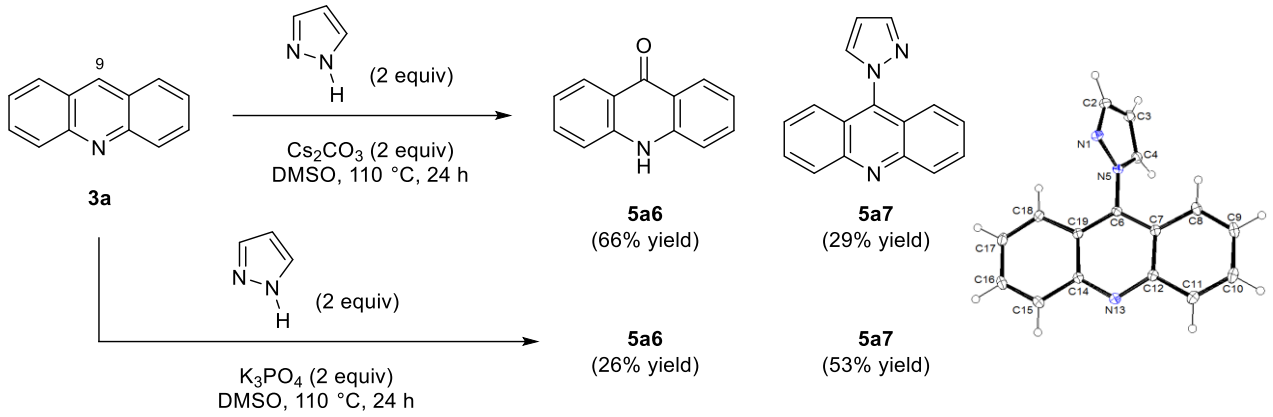
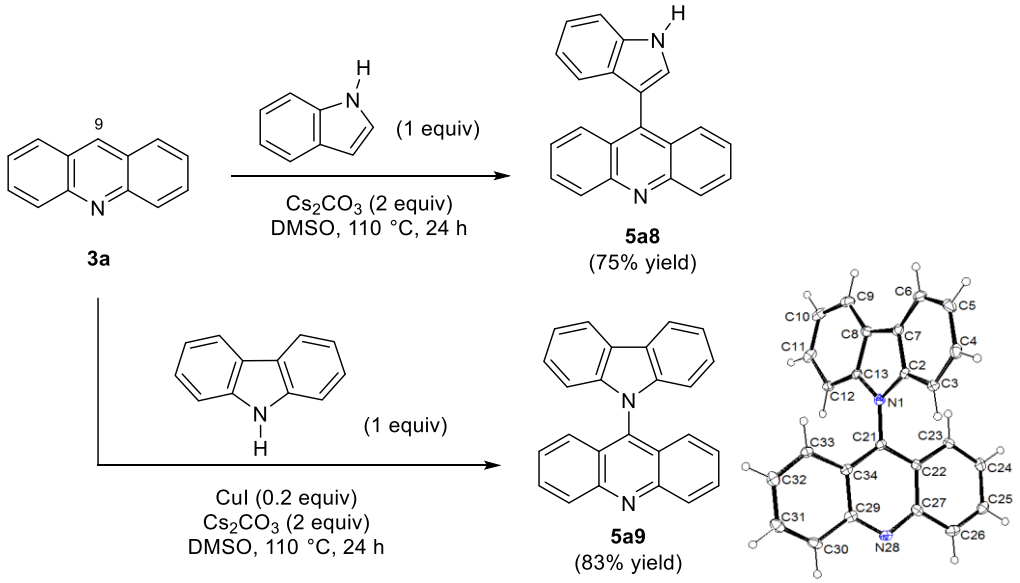
to see the impact of the base on the reaction. Under these conditions, the pyrazoloacridine **5a7** turned out to be the major product (isolated in 53% yield), and its structure was unambiguously established by X-ray diffraction (Scheme 7, bottom).



Scheme 7. Attempts to *N*-arylate pyrazole using acridine (**3a**) without copper(I) salts and ORTEP diagram (30% probability) of **5a7**.



Scheme 8. Attempts to arylate indole and carbazole using acridine (**3a**) and ORTEP diagram (30% probability) of **5a9**.

Although 9-(*N*-pyrazolyl)acridine (**5a7**) is new, the addition of other aromatic compounds onto acridine has already been documented.[55] As early as 1984, Takano and co-workers documented the reaction of 2,5-dimethylpyrrole, indole, imidazole and 2-methylimidazole with acridine upon heating at 160 °C (yields between 27 and 47%).[56] In contrast with the result observed here with pyrazole, there is

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no C-N bond formed in the reported examples since pyrrole and indole attack by their C3 carbon, and imidazoles by their C4. Thus, we tried a reaction from acridine and indole in the presence of cesium carbonate in DMSO at 110 °C. While it similarly led to 9-(3-indolyl)acridine (**5a8**) after 24 h, it was isolated in a higher 75% yield (Scheme 8, top).

A careful analysis of the literature data revealed 9-(*N*-carbazolyl)acridine (**5a9**) as the only *N*-(9-acridyl)azole reported. It was synthesized by photolysis of a 1:1 mixture of acridine and carbazole in acetonitrile, and isolated in 19% yield.[57] By repeating the protocol giving **5a8** but using carbazole instead of indole, no reaction was observed (starting materials recovered). However, in the presence of copper(I) iodide (0.2 equiv), the product was obtained in 83% yield after 24 h in DMSO at 110 °C (Scheme 8, bottom). However, replacing carbazole by 1,2,4-triazole, benzotriazole or azaindole did not allow the corresponding *N*-(9-acridyl)azoles to be formed under similar conditions (starting materials mainly recovered).

2.2. Syntheses of acridones

In the course of a study published recently, we observed that copper-catalyzed *N*,*N*-diarylation of thienylamines is possible by using an excess of aryl iodide in the presence of 1 equivalent of activated copper and 3 equivalents of base.[58] Hence, 2-aminobenzaldehyde (**1**) was similarly treated by the different iodoanisoles (2 equiv) at the reflux temperature of dibutyl ether until disappearance of the starting materials. The expected 2-(diarylamino)benzaldehydes **6b-d** were isolated in 14 to 63% yield, as a result of side reactions/degradation taking place in the course of the second, more difficult *N*-arylation step (Table 2, entries 1-3, left). To cyclize 2-(arylamino)benzaldehydes into acridones, reported methods are based on the use of scandium(III) triflate[28] and $PhI(OAc)_2$.[29] In our case, we simply treated **6b-d** with sulfuric acid in boiling acetic acid as before, and obtained the expected acridones **6b-d** in 40 to 71% yields (Table 2, entries 1-3, right). By using iodobenzene as aryl halide, we directly involved the *N*,*N*-diarylation crude product in the cyclization step to obtain *N*-phenyl-9-acridone (**7a**) in an overall 89% yield (Table 2, entry 4).

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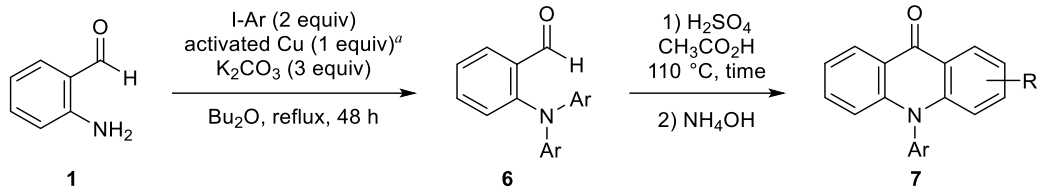
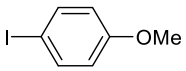
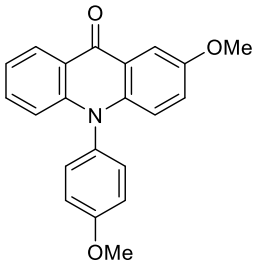
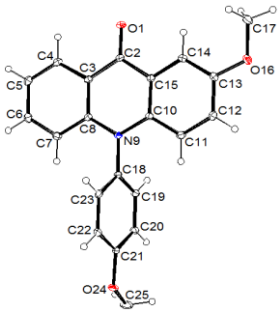
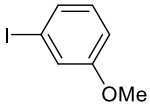
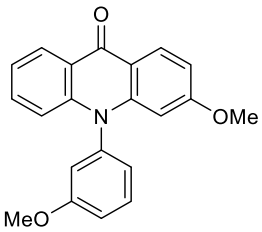
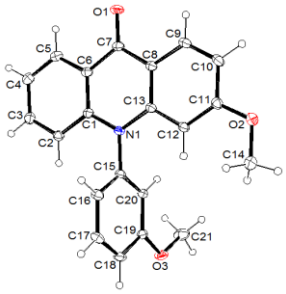
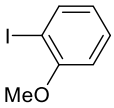
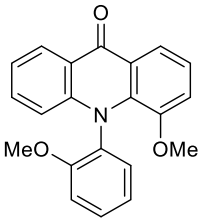
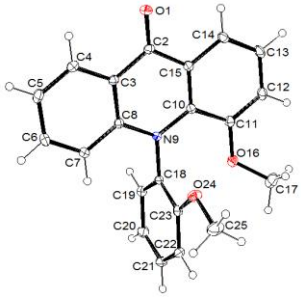
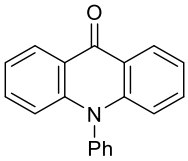
Table 2. Double *N*-arylation of 2-aminobenzaldehyde (**1**) to afford the diarylamines **6**, and subsequent conversion to the acridones **7**. ORTEP diagrams (30% probability) of **7b-d**.



Entry	I-Ar	**6**, Yield (%)[b]	Product **7** (time), Yield (%)[b]	
1		**6b**, 26[c]	 	**7b** (1 h), 71
2		**6c**, 14[d]	 	**7c** (2 h), 48
3		**6d**, 63	 	**7d** (1 h), 40
4	I-Ph	-[e]		**7a** (2 h), 89[f]

[a] Added by portions of 0.2 equivalent every 2 h. [b] After purification (see experimental part).
[c] Remaining **2b** was only isolated in 1% yield while starting 4-iodoanisole was detected.
[d] Remaining **2c** was only isolated in 9% yield. [e] Not isolated. [f] Yield for 2 steps.

Finally, we decided to check if this approach could be suitable to cyclize differently *N*,*N*-disubstituted 2-aminobenzaldehydes. For this purpose, we selected 2-(phenylamino)benzaldehyde (**2a**)

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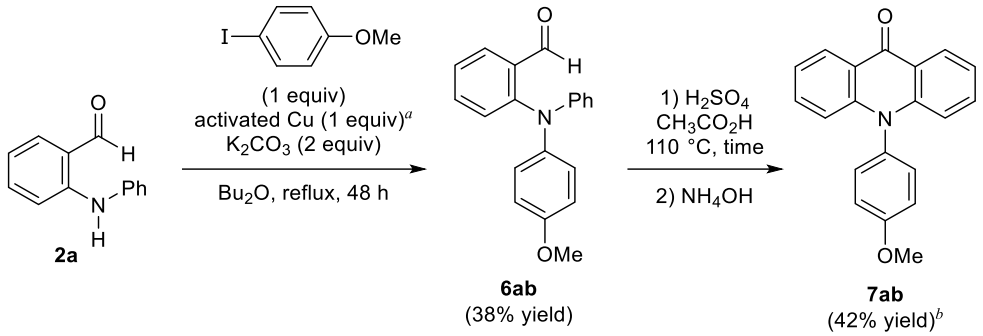
and carried out the second *N*-arylation with 4-iodoanisole. The cyclization of **6ab**, isolated in 38% yield, was performed as before to logically furnish as major compound the symmetrical *N*-(4-methoxyphenyl) derivative in 42% yield. The minor isomer, resulting from a less favored cyclization through electrophilic aromatic substitution at the 3-position of anisole, was only isolated in 3% yield (Scheme 9).



Scheme 9. Second *N*-arylation of 2-aminobenzaldehyde (**1**) to afford the diarylamine **6ab**, and subsequent conversion to the acridone **7ab**. [a] Added by portions of 0.2 equivalent every 2 h. [b] 2-Methoxy-*N*-phenyl-9-acridone was also isolated in 3% yield.

2.3. Photophysical properties

Acridine and acridone derivatives, especially when substituted with electron-donating groups, can display interesting fluorescence properties.[59] Thus, in view of potential applications as fluorescent probes in biological media, we performed a preliminary study of the photophysical properties of selected compounds. Their UV-visible absorption and emission properties were investigated in toluene, and the results are gathered in Table 3.

The three isomeric methoxyacridines **3c1**, **3c2** and **3d** exhibit a broad and structured lowest energy transition absorption band in the 300-450 nm range and emit in the violet-blue part of the visible (Figure 2). The maximum wavelengths of 1- (**3c2**) and 4-methoxy (**3d**) isomers are red-shifted by 8 and 9 nm compared with 3-methoxyacridine (**3c1**) respectively, whereas their emission band is red-shifted by 27 and 16 nm, respectively. Their fluorescence quantum yields are rather high (15-44%), and **3c2**, which is the most red-shifted is also the most emissive of the series.

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Table 3. Absorption and emission properties of selected acridines and acridones in toluene at 25 °C.

Compound	λ_{abs} [a] (nm)	ε_{max} [b] (M^{-1} cm^{-1})	λ_{em} [c] (nm)	Φ_F [d]	Stokes shift (cm^{-1}) [e]
3c1	348	-	429	0.15	5430
3c2	356	-	456	0.44	6160
3d	357	5100	445	0.20	5540
3f1	313, 328	50900	411, 421, 436, 464	0.04	6160
5a2	366, 398	6000	480	0.56	6490
5a7	362	11300	456	< 0.01	5700
5a3	399	8700	418, 440	0.31	1140
5a8	361, 384	8200	450	0.08	5480
5a9	362	10100	474	0.12	6530
7a	391	9000	398, 419	0.03	450
7c	377	9600	390, 409	0.01	880

[a] Absorption maximum. [b] Molar extinction coefficients at λ_{abs}. [c] Emission maximum. [d] Fluorescence quantum yield using as a standard quinine bisulfate in 0.5 M H_2SO_4 (Φ_F = 0.546). [e] Stokes shift = ($1/\lambda_{abs} - 1/\lambda_{em}$).

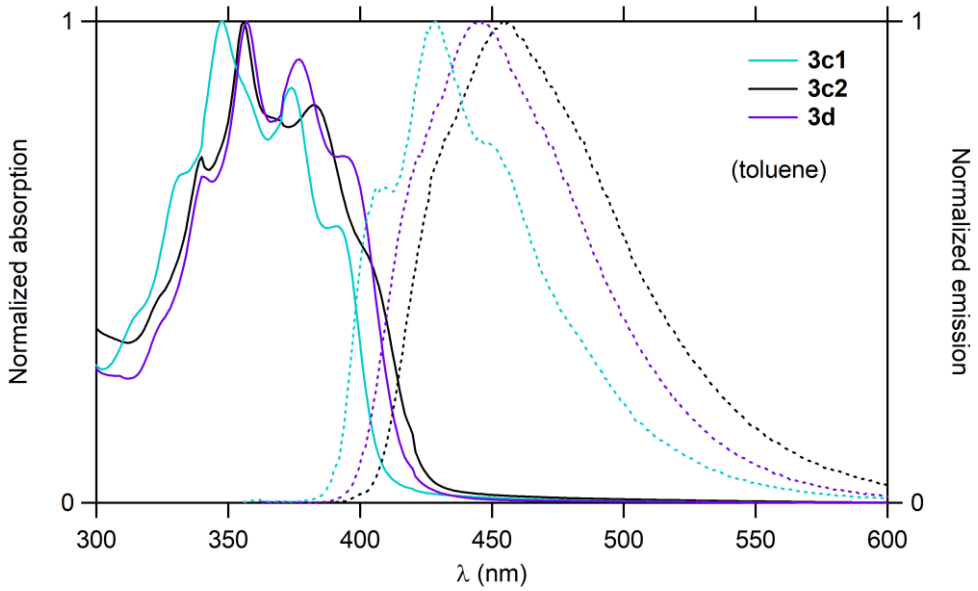

Figure 2. Absorption (solid line) and emission (dotted line) of methoxyacridines **3c1**, **3c2** and **3d** in toluene.

Dibenzophenanthroline **3f1** exhibits a structured absorption band with a maximum at 328 nm and also a structured emission band at 411 nm (Figure 3). However, it is pretty clear that the emission band

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is not the mirror image of the intense absorption band (ε ~ 50000 M^{-1} cm^{-1}) at 328 nm, but of a much less intense band (ε ~ 750 M^{-1} cm^{-1}) of lower energy with a maximum at 386 nm (see inset of Figure 3). The 0-0 transition is at 410 nm. The fluorescence quantum yield of **3f1** is low (4%), in agreement with a weakly allowed lowest-lying transition. As previously observed with other unsubstituted azarenes,[60] this weakly allowed absorption band can be assigned to a n-π* transition and the strongly allowed one to a π-π* transition.

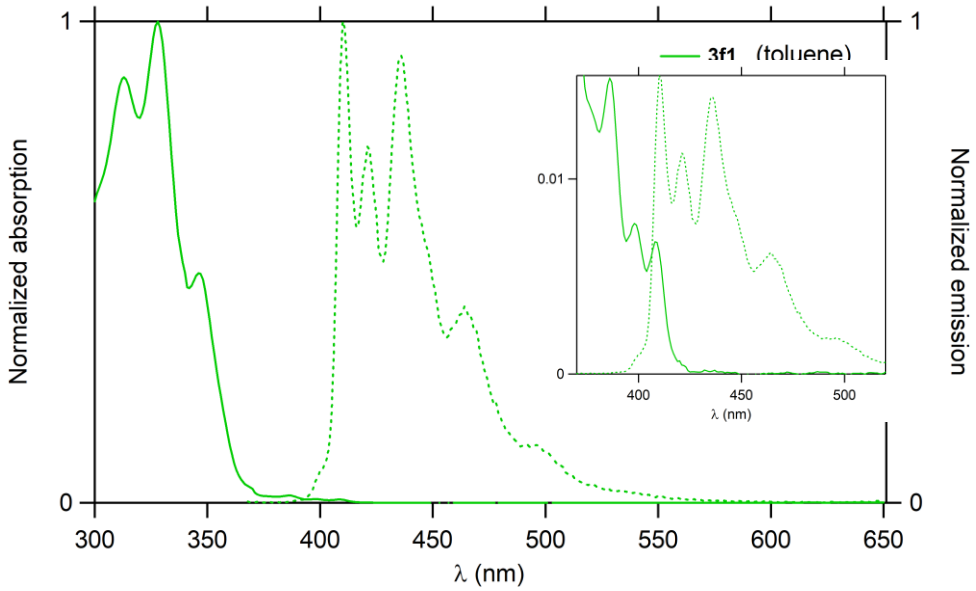

Figure 3. Absorption (solid line) and emission (dotted line) of dibenzophenanthroline **3f1** in toluene.

Four structurally-related acridines and an acridone with pyrazolyl, indolyl or carbazolyl substituents (**5a2**, **5a3**, **5a7**, **5a8** and **5a9**) have then been studied. These five compounds absorb in the near-UV and emit in the 400-600 nm range of the visible. The two compounds substituted with pyrazolyl groups at C4 position are better emitters (56% and 31% for **5a2** and **5a3**, respectively) than those bearing pyrazolyl (< 1% for **5a7**), indolyl (8% for **5a8**) or carbazolyl (12% for **5a9**) substituents at C9.

The four acridines (**5a2**, **5a7**, **5a8** and **5a9**) exhibit a broad emission band and a large Stokes shift (5500-6500 cm^{-1}), whereas acridone **5a3** has a structured emission band and a much smaller Stokes shift (1140 cm^{-1}) (Figure 4). This is indicative that the intramolecular charge transfer (ICT) process is more efficient with the former than with the latter. In the case of 4,9-dipyrazolylacridine **5a2**, this ICT

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process occurs from the two pyrazolyl groups to the nitrogen atom of the acridine. 9-Pyrazolyl-, 9-indolyl- and 9-carbazolylacridines have a similar behavior, but substitution at C9 is clearly less efficient than substitution at C4 to favor fluorescence, especially in the case of 9-pyrazolylacridine (**5a7**). 4,9-Dipyrazolylacridine (**5a2**) exhibits a broad absorption band of lowest energy at 398 nm that can be attributed to a charge transfer transition, and which is not present with **5a7**, explaining the very different quantum yields of these two compounds (Figure S1, Supporting Info). With acridone **5a3**, the electron-withdrawing group is obviously the carbonyl, and it seems that the nitrogens of the acridine and the pyrazolyl at C-4 are not donor enough to allow an efficient ICT.

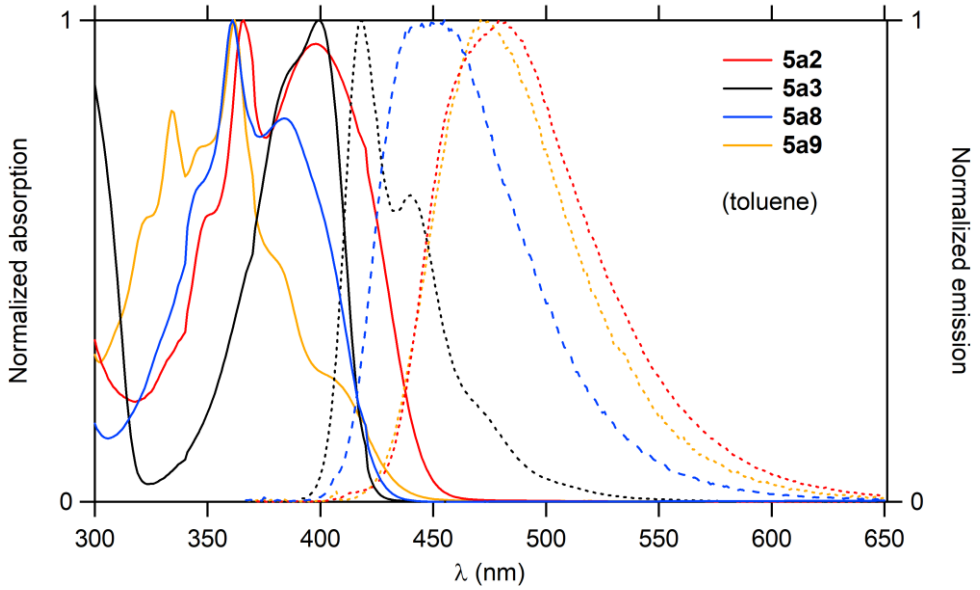

Figure 4. Absorption (solid line) and emission (dotted line) of acridines **5a2**, **5a8**, **5a9** and acridone **5a3** in toluene.

Compared to the two *N*-arylacridones **7a** and **7c**, 4-pyrazolylacridone **5a3** is red-shifted both in absorption and emission (Figure 5). It also exhibits a larger Stokes shift and a much higher fluorescence quantum yield (31%, instead of 3% and 1% for **7a** and **7c**, respectively). Substitution at the C-4 position of the acridone seems thus more efficient than *N*-substitution to favor ICT and fluorescence.

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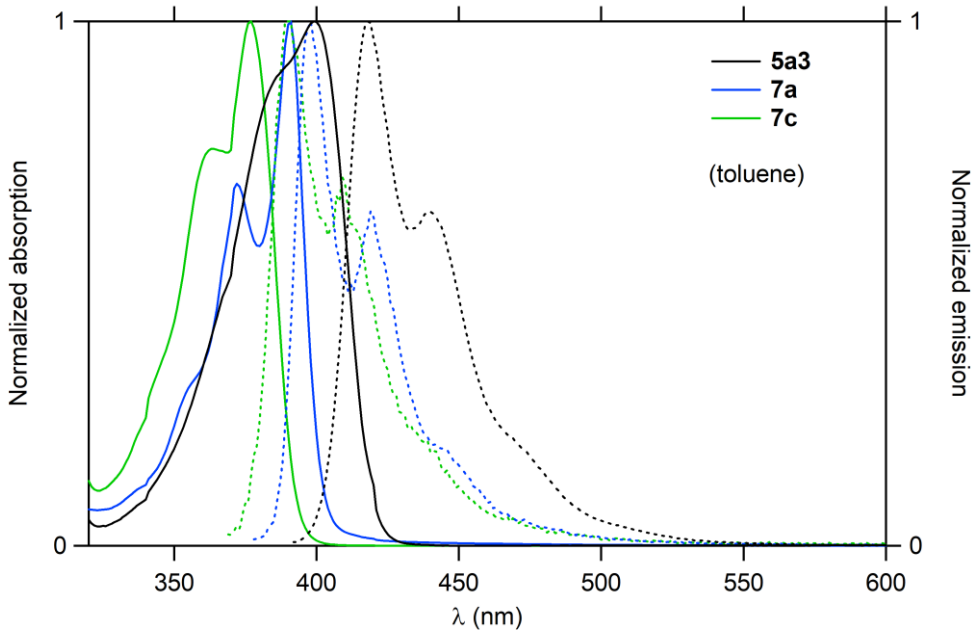

Figure 5. Absorption (solid line) and emission (dotted line) of acridones **5a3**, **7a** and **7c** in toluene.

Although this is only a preliminary study, the results obtained allowed us to derive some interesting structure-property relationships, which will help us design new acridines and acridones with optimized fluorescence properties.

2.4. Biological evaluation on melanoma cell lines

Fifteen compounds among those synthesized (**2a**, **3e**, **2f2**, **3f1**, **3f2**, **5a1**, **5a2**, **5a3**, **5a7**, **5a8**, **5a9**, **6d**, **6ab**, **7b**, **7d**) were evaluated for their antiproliferative activity against A2058 melanoma cells that are highly invasive human epithelial adherent melanoma cells considered as very resistant to anticancer drugs. With a mortality rate very high,[61] there is an important need to identify other pharmacological targets and to develop new drugs. The selected cell lines possess natural and acquired resistance to chemotherapy and radiotherapy; hence, they are suitable to evaluate the antiproliferative activity of our molecules.

Most of the tested compounds exerted an antiproliferative activity in A2058 melanoma cells (Figure 6), the best results being obtained for 9-(3-indolyl)acridine (**5a8**) and the dibenzophenanthroline **3f1**. When compared with pentacycles already evaluated on the same target,[35] the bare analog **3f1** exhibits a

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similar behavior. As regards the 9-substituted acridines, the 3-indolyl group is responsible for the highest antiproliferative activity when compared with *N*-carbazolyl and *N*-pyrazolyl. These two compounds can therefore be considered as a promising starting point for further functionalization toward more active molecules.

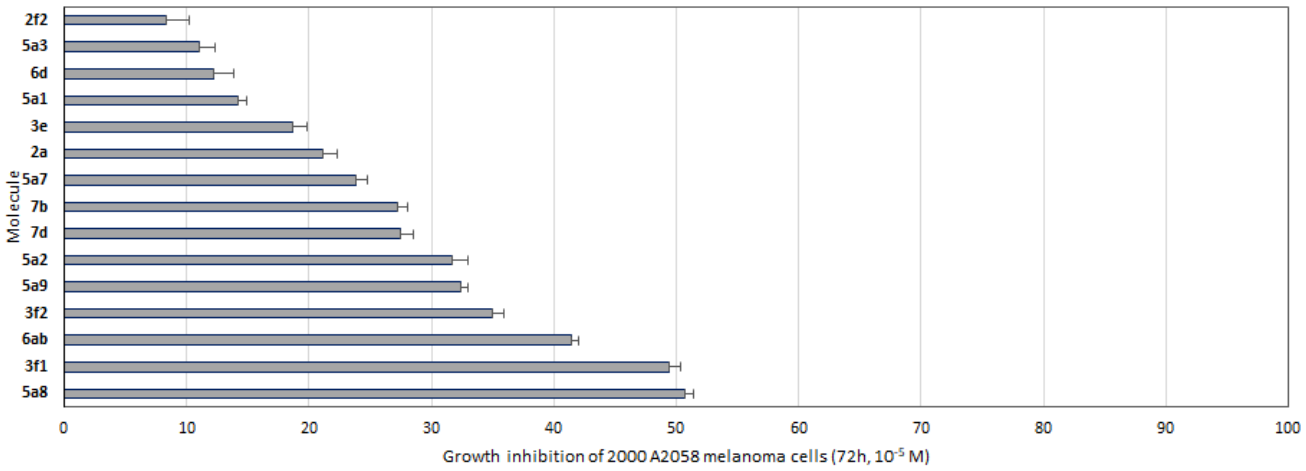

Figure 6: Antiproliferative activity of some of the synthesized compounds at 10^{-5} M after 72 h in A2058 human melanoma cells.

3. Conclusion

Thus, by starting from a common substrate, 2-aminobenzaldehyde, we developed a general entry to both acridines and acridones. Besides, while methods to introduce specific substituents at the 4 position of acridine exist, for example by Friedel & Crafts alkylation,[62] or with recourse to rhodium,[63] nickel,[64] cobalt[65] or iridium[66] catalysis, we here reported a short access to the iodo derivative which can be used for different post-functionalizations, as demonstrated in the present study. In addition, direct introduction of an aromatic heterocycle at the 9 position of acridine was improved, notably through copper catalysis.

Finally, the compounds identified as promising for their antiproliferative activity showed significant fluorescence properties.

4. Experimental

4.1. General

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Column chromatography separations were achieved on silica gel (40-63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded either on a Bruker Avance III spectrometer at 300 MHz and 75 MHz respectively, or on a Bruker Avance III HD spectrometer at 500 MHz and 126 MHz respectively. ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak and ^{13}C chemical shifts are relative to the central peak of the solvent signal.[67] Microanalyses were performed on a Thermo Fisher Flash EA 1112 elemental analyzer. 2-Aminobenzaldehyde,[37] activated Cu[41] and $ZnCl_2 \cdot TMEDA$[51] were prepared as described previously.

Crystallography. The samples were studied with monochromatized Mo-Kα radiation (λ = 0.71073 Å, multilayered monochromator). The X-ray diffraction data of the compounds **4a**, **4e**, **5a5**, **5a7**, **5a9**, **7b**, **7c** and **7d** were collected at T = 150(2) K by using a D8 VENTURE Bruker AXS diffractometer equipped with a (CMOS) PHOTON 100 detector. The structures were solved by dual-space algorithm using the *SHELXT* program,[68] and then refined with full-matrix least-square methods based on F^2 (*SHELXL*).[69] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions and treated as riding on their parent atom with constrained thermal parameters. The molecular diagrams were generated by ORTEP-3 (version 2.02).[70]

4.2. *N*-arylation of 2-aminobenzaldehyde (1)

4.2.1. General procedure 1 for the *N*-arylation reactions. This reaction was performed under an argon atmosphere. The *N*-arylated substrates were prepared by slightly modifying a literature procedure.[40] To 2-aminobenzaldehyde (**1**; 0.12 g, 1.0 mmol) and the required iodide (1 equiv, 1.0 mmol) in Bu_2O (1 mL) were successively added activated Cu (0.20 equiv, 13 mg, 0.20 mmol) and K_2CO_3 (2 equiv, 0.29 g, 2.0 mmol). The reaction mixture was degassed and refluxed under argon for 24 h. After cooling to room temperature, it was concentrated. Purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

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4.2.2. 2-(Phenylamino)benzaldehyde (2a) was obtained according to the general procedure 1 by using iodobenzene (0.11 mL) as reported previously.[35] Purification by column chromatography over silica gel (heptane-CH_2Cl_2 85:15; R_f (petroleum ether-ethyl acetate 90:10) = 0.76) gave **2a** in 71% yield (0.20 g) as a yellow solid: mp 78 °C (lit.[71] 74-76 °C, after similar purification by column chromatography); IR (ATR): 698, 748, 822, 899, 1118, 1155, 1185, 1314, 1185, 1314, 1398, 1422, 1450, 1491, 1519, 1571, 1591, 1649, 2757, 2837, 2925, 3038, 3279 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.84 (t, 1H, *J* = 7.3 Hz), 7.16 (t, 1H, *J* = 7.1 Hz), 7.23-7.42 (m, 6H), 7.58 (d, 1H, *J* = 7.6 Hz), 9.92 (s, 1H, CHO), 10.04 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 113.0 (CH), 117.2 (CH), 119.5 (C), 123.2 (2CH), 124.5 (CH), 129.5 (2CH), 135.6 (CH), 136.7 (CH), 139.7 (C), 147.8 (C), 194.3 (CH, CHO). The NMR data are close to those reported previously.[72]

4.2.3. 2-(4-Methoxyphenylamino)benzaldehyde (2b) was obtained according to the general procedure 1 by using 4-iodoanisole (0.23 g). Purification by column chromatography over silica gel (petroleum ether-AcOEt 70:30) gave **2b** in 78% yield (0.19 g) as a yellow solid: mp 61-62 °C (lit.[44] 62-63 °C, after similar purification by column chromatography); IR (ATR): 659, 748, 795, 839, 899, 1032, 1117, 1155, 1180, 1239, 1295, 1323, 1398, 1438, 1457, 1509, 1574, 1605, 1652, 2746, 2834, 2933, 3001, 3290 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3H, OMe), 6.77 (ddd, 1H, *J* = 7.9, 7.1 and 1.0 Hz, H5), 6.90-6.95 (m, 2H), 6.97 (d, 1H, *J* = 8.6 Hz, H3), 7.17-7.22 (m, 2H), 7.31 (dddd, 1H, *J* = 8.7, 7.1, 1.7 and 0.4 Hz, H4), 7.54 (dd, 1H, *J* = 7.8 and 1.6 Hz, H6), 9.83 (br s, 1H, NH), 9.90 (d, 1H, *J* = 0.5 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 112.7 (CH), 114.9 (2CH), 116.5 (CH), 119.0 (C), 126.2 (2CH), 132.4 (C), 135.7 (CH), 136.6 (CH), 149.4 (C), 157.3 (C), 194.2 (CH, CHO). The ^1H NMR data are close to those reported previously.[44]

4.2.4. 2-(3-Methoxyphenylamino)benzaldehyde (2c) was obtained according to the general procedure 1 by using 3-iodoanisole (0.23 g). Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 85:15) = 0.63) gave **2c** in 83% yield (0.20 g) as a yellow solid: mp 72-74 °C (lit.[44] 68-69 °C, after recrystallization from MeOH-H_2O); IR (ATR): 660, 693, 747, 763, 789, 846, 870,

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958, 1039, 1080, 1116, 1153, 1166, 1184, 1196, 1261, 1306, 1327, 1397, 1405, 1435, 1454, 1470, 1489, 1521, 1574, 1592, 1652, 2757, 2834, 2933, 2957, 2996, 3272 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H, OMe), 6.70 (dd, 1H, *J* = 8.2 and 2.3 Hz), 6.81-6.89 (m, 3H), 7.24-7.30 (m, 2H), 7.37 (ddd, 1H, *J* = 8.4, 7.0 and 1.4 Hz, H4), 7.57 (dd, 1H, *J* = 7.7 and 1.5 Hz, H6), 9.90 (s, 1H, CHO), 10.00 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.5 (CH_3), 108.8 (CH), 110.1 (CH), 113.4 (CH), 115.4 (CH), 117.4 (CH), 119.6 (C), 130.2 (CH), 135.7 (CH), 136.7 (CH), 141.1 (C), 147.7 (C), 160.8 (C), 194.4 (CH, CHO). The ^{1}H NMR data are close to those reported previously.[44]

4.2.5. 2-(2-Methoxyphenylamino)benzaldehyde (2d) was obtained according to the general procedure 1 by using 2-iodoanisole (0.23 g). Purification by column chromatography over silica gel (petroleum ether-AcOEt 90:10) gave **2d** in 76% yield (0.19 g) as a yellow solid: mp 68-70 °C (lit.[44] 67-69 °C); IR (ATR): 669, 749, 782, 835, 905, 1021, 1040, 1115, 1163, 1186, 1250, 1294, 1328, 1407, 1452, 1492, 1515, 1573, 1590, 1652, 2770, 2837, 2937, 3010, 3062, 3269 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H, OMe), 6.83 (ddd, 1H, *J* = 7.9, 7.0 and 1.1 Hz), 6.94-6.99 (m, 2H), 7.08-7.13 (m, 1H), 7.28 (d, 1H, *J* = 8.6 Hz), 7.37 (ddd, 1H, *J* = 8.3, 7.0 and 1.3 Hz), 7.46-7.49 (m, 1H), 7.56 (dd, 1H, *J* = 7.7 and 1.5 Hz), 9.93 (d, 1H, *J* = 0.4 Hz, CHO), 10.03 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 111.4 (CH), 113.1 (CH), 117.1 (CH), 120.0 (C), 120.5 (CH), 121.8 (CH), 124.4 (CH), 129.0 (C), 135.3 (CH), 136.6 (CH), 147.2 (C), 151.8 (C), 194.0 (CH, CHO). The ^{1}H NMR data are close to those reported previously.[44]

4.2.6. 2-(3-Pyridylamino)benzaldehyde (2e) was obtained according to the general procedure 1 by using 3-iodopyridine (0.205 g). Purification by column chromatography over silica gel (R_f (AcOEt-petroleum ether 50:50) = 0.41) gave **2e** in 62% yield (0.13 g) as a yellow oil: IR (ATR): 666, 707, 750, 784, 833, 899, 1021, 1042, 1117, 1158, 1187, 1224, 1315, 1398, 1456, 1481, 1512, 1570, 1582, 1659, 2748, 2830, 3035, 3276 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.90 (ddd, 1H, *J* = 7.8, 7.3 and 0.93 Hz, H4 or H5), 7.17 (d, 1H, *J* = 8.5 Hz, H3), 7.30 (dd, 1H, *J* = 8.1 and 4.7 Hz, H5'), 7.39 (ddd, 1H, *J* = 8.5, 7.2 and 1.4 Hz, H4 or H5), 7.59-7.62 (m, 2H, H6 and H4'), 8.39 (d, 1H, *J* = 3.6 Hz, H6'), 8.60 (br s, 1H, H2'), 9.92

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(d, 1H, J = 0.5 Hz, CHO), 10.00 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 112.7 (CH), 118.3 (CH), 120.0 (C), 123.9 (C), 129.8 (CH), 135.7 (CH), 136.6 (CH), 136.7 (CH), 144.8 (CH), 145.2 (CH), 146.9 (C), 194.5 (CH, CHO). The NMR data are close to those reported previously.[73]

4.2.7. Dibenzo[*b,j*][1,7]phenanthroline (3f1). To 2-aminobenzaldehyde (**1**; 0.48 g, 4.0 mmol) and 1,3-diiodobenzene (1 equiv, 1.0 mmol) in Bu_2O (1 mL) were successively added, under an argon atmosphere, activated Cu (0.40 equiv, 26 mg, 0.40 mmol) and K_2CO_3 (3 equiv, 0.43 g, 3.0 mmol). The reaction mixture was degassed and refluxed under argon for 48 h. After cooling to room temperature, it was concentrated. Purification by column chromatography over silica gel (R_f (CH_2Cl_2-AcOEt 95:5) = 0.30) gave **3f1** in 87% yield (0.24 g) as a yellow solid: mp 208-210 °C (lit.[74] 219 °C, after recrystallization from ligroin); IR (ATR): 737, 748, 810, 820, 856, 921, 950, 1014, 1077, 1117, 1230, 1315, 1424, 1453, 1493, 1558, 1608, 1679, 2925, 3044 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (dtd, 2H, J = 8.1, 7.0 and 1.1 Hz), 7.87 (dddd, 2H, J = 8.5, 6.8, 3.1 and 1.5 Hz), 7.93 (s, 2H), 8.03 (dd, 1H, J = 8.2 and 0.6 Hz), 8.22 (d, 1H, J = 8.2 Hz), 8.31 (dd, 1H, J = 8.6 and 0.7 Hz), 8.39 (d, 1H, J = 8.6 Hz), 8.59 (s, 1H), 10.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 124.6 (C), 125.8 (C), 126.5 (CH), 126.7 (CH), 127.1 (C), 127.5 (C), 128.1 (CH), 129.2 (CH), 129.3 (CH), 129.4 (CH), 129.7 (CH), 130.3 (CH), 130.9 (CH), 131.3 (CH), 133.9 (CH), 135.3 (CH), 147.8 (C), 147.9 (C), 149.1 (C), 151.2 (C). The NMR data are close to those reported previously.[43] ***N,N'*-(1,3-phenylene)bis(2-aminobenzaldehyde) (2f1)**[75] was similarly isolated (R_f (petroleum ether-AcOEt 85:15) = 0.63) in 12% yield (40 mg) as a yellow oil: IR (ATR): 662, 691, 748, 812, 841, 871, 910, 990, 1041, 1062, 1080, 1117, 1156, 1194, 1261, 1314, 1397, 1456, 1473, 1514, 1576, 1653, 2745, 2833, 3059, 3273 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.86 (ddd, 2H, J = 7.9, 7.1 and 1.1 Hz, H5 and H5'), 7.05 (dd, 2H, J = 8.0 and 2.1 Hz, H3 and H3'), 7.21 (t, 1H, J = 2.0 Hz, H1"), 7.29 (d, 2H, J = 8.5 Hz, H3"), 7.35 (t, 1H, J = 7.9 Hz, H4"), 7.39 (ddd, 2H, J = 8.6, 7.1 and 1.3 Hz, H4 and H4'), 7.58 (dd, 2H, J = 7.7 and 1.6 Hz, H6 and H6'), 9.90 (d, 2H, J = 0.5 Hz, CHO), 10.03 (br s, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 113.3 (2CH), 117.0, 117.6 (2CH), 118.8 (2CH), 119.7, 130.4, 135.7 (2CH), 136.8 (2CH), 141.1, 147.5, 194.5 (2CH, CHO). In addition, *N*-(3-iodophenyl)-2-

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aminobenzaldehyde was detected by NMR: ^{1}H NMR ($CDCl_3$) δ 6.89 (td, 1H, *J* = 7.4 and 0.9 Hz), 7.08 (t, 1H, *J* = 7.9 Hz), 7.22-7.25 (m, 2H), 7.40 (ddd, 1H, *J* = 8.6, 7.2 and 1.4 Hz), 7.46 (d, 1H, *J* = 7.8 Hz), 7.59 (dd, 1H, *J* = 7.7 and 1.6 Hz), 7.65 (t, 1H, *J* = 1.7 Hz), 9.90 (s, 1H, CHO), 9.99 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 94.7 (C, C3'), 113.2 (CH), 118.1 (CH), 119.9 (C), 122.1 (CH), 131.0 (CH), 131.5 (CH), 133.2 (CH), 135.8 (CH), 136.8 (CH), 141.3 (C), 147.0 (C), 194.5 (CH, CHO).

4.2.8. *N,N'*-(1,4-phenylene)-2,2'-bis(2-aminobenzaldehyde) (2f2).[45] To 2-aminobenzaldehyde (0.48 g, 4.0 mmol) and 1,4-diiodobenzene (1 equiv, 1.0 mmol) in Bu_2O (1 mL) were successively added, under an argon atmosphere, activated Cu (0.40 equiv, 26 mg, 0.40 mmol) and K_2CO_3 (3 equiv, 0.43 g, 3.0 mmol). The reaction mixture was degassed and refluxed under argon for 48 h. After cooling to room temperature, it was concentrated. Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 85:15) = 0.68) gave **2f2** in 91% yield (0.30 g) as a yellow solid: mp 214 °C; IR (ATR): 666, 707, 729, 784, 833, 899, 1021, 1042, 1117, 1158, 1187, 1224, 1315, 1398, 1456, 1481, 1512, 1570, 1582, 1659, 2748, 2830, 3035, 3276 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.84 (ddd, 2H, *J* = 7.9, 7.4 and 1.0 Hz, H5 and H5'), 7.20 (d, 2H, *J* = 8.5 Hz, H3 and H3'), 7.29 (s, 4H, H2"), 7.38 (ddd, 2H, *J* = 8.6, 7.2 and 1.6 Hz, H4 and H4'), 7.58 (dd, 2H, *J* = 7.8, 1.6 Hz, H6 and H6'), 9.91 (s, 2H, CHO), 10.00 (br s, 2H, NH); ^{13}C NMR ($CDCl_3$) δ 113.0 (2CH), 117.2 (2CH), 119.5 (2C), 124.6 (4CH, C2"), 135.7 (2CH), 136.3 (2C), 136.8 (2CH), 148.1 (2C), 194.4 (2CH, CHO).

4.3. Conversion of the *N*-arylated 2-aminobenzaldehydes (2) into acridines

4.3.1. General procedure 2 for the cyclization reactions giving acridines. The cyclized products were prepared by adapting a literature procedure.[42] To the required *N*-arylated 2-aminobenzaldehyde (**2**; 1.0 mmol) in CH_3CO_2H (3 mL) was added 96% H_2SO_4 (2.8 mmol, 0.15 mL). The reaction mixture was stirred at 110 °C. The reaction time is given in the product description. After cooling to room temperature, water (5 mL) was added and the reaction mixture was basified using 25% NH_4OH. Extraction using AcOEt (3x20 mL), drying over $MgSO_4$, removal of the solvent and purification by

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chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

4.3.2. Acridine (3a) was obtained according to the general procedure 2 (reaction time: 30 min) from **2a** (0.20 g). Purification by column chromatography over silica gel (heptane-AcOEt 70:30) gave **3a** in 94% yield (0.17 g) as a yellow solid: mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (ddd, 2H, *J* = 8.2, 6.6 and 1.1 Hz, H2 and H7), 7.79 (ddd, 2H, *J* = 8.8, 6.6 and 1.4 Hz, H3 and H6), 8.02 (d, 2H, *J* = 8.5 Hz, H1 and H8), 8.25 (dd, 2H, *J* = 8.8 and 0.8 Hz, H4 and H5), 8.79 (s, 1H, H9). These data are similar to those obtained for a commercial sample.

4.3.3. 2-Methoxyacridine (3b) was obtained according to the general procedure 2 (reaction time: 1.5 h) from **2b** (0.23 g). Purification by column chromatography over silica gel (heptane-AcOEt 70:30) gave **3b** in 80% yield (0.17 g) as a beige solid: mp 92-94 °C (lit.[76] 89-91 °C, after recrystallization from Et_2O-hexane); IR (ATR): 749, 782, 826, 845, 907, 959, 1026, 1114, 1136, 1169, 1217, 1275, 1313, 1408, 1431, 1470, 1481, 1520, 1564, 1582, 1633, 2925, 3371 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H, OMe), 7.17 (d, 1H, *J* = 2.7 Hz, H1), 7.48 (dd, 1H, *J* = 9.5 and 2.8 Hz, H3), 7.50-7.55 (m, 1H, H7), 7.69-7.75 (m, 1H, H6), 7.96 (dt, 1H, *J* = 8.4 and 0.6 Hz, H8), 8.14 (d, 1H, *J* = 9.5 Hz, H4), 8.21 (d, 1H, *J* = 8.6 Hz, H5), 8.63 (s, 1H, H9); ^{13}C NMR ($CDCl_3$) δ 55.6 (CH_3), 103.2 (CH), 125.7 (CH), 125.9 (CH), 127.0 (C), 127.6 (C), 127.7 (CH), 129.2 (CH), 129.5 (CH), 131.1 (CH), 133.8 (CH), 146.4 (C), 147.6 (C), 157.2 (C). The ^{1}H NMR data are close to those reported previously.[76]

4.3.4. 3-Methoxyacridine (3c1) was obtained according to the general procedure 2 (reaction time: 3 h) from **2c** (0.23 g). Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 80:20) = 0.25) gave **3c1** in 72% yield (0.15 g) as an orange solid: mp 87-88 °C (lit.[44] 88-89 °C); IR (ATR): 745, 777, 805, 844, 855, 914, 958, 968, 1015, 1131, 1144, 1173, 1208, 1278, 1294, 1309, 1409, 1433, 1449, 1481, 1519, 1563, 1615, 1633, 1724, 2925, 3052 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H, OMe), 7.21 (dd, 1H, *J* = 9.2 and 2.4 Hz), 7.46-7.51 (m, 2H), 7.76 (ddd, 1H, *J* = 8.7, 6.7 and 1.4 Hz), 7.86 (d, 1H, *J* = 9.2 Hz), 7.96 (dd, 1H, *J* = 8.4 and 1.2 Hz), 8.18 (d, 1H, J = 8.8 Hz), 8.67 (s, 1H, H9);

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^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3), 105.1 (CH), 121.4 (CH), 124.9 (CH), 125.6 (C), 128.4 (CH), 128.6 (CH), 128.9 (C), 129.5 (CH), 130.6 (CH), 131.0 (C), 136.1 (CH), 150.8 (C), 161.7 (C). The ^{1}H NMR data are close to those reported previously.[44] **1-Methoxyacridine (3c2)** was similarly obtained (R_f (petroleum ether-AcOEt 80:20) = 0.40) in 25% yield (52 mg) as a yellow solid: mp 114-115 °C (lit.[44] 121-122 °C, after similar purification by column chromatography); IR (ATR): 736, 751, 809, 862, 914, 923, 963, 972, 1059, 1085, 1135, 1180, 1233, 1251, 1264, 1315, 1385, 1402, 1438, 1453, 1469, 1524, 1560, 1619, 1628, 1722, 1823, 1941, 2851, 2923, 2963, 3015, 3048 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.09 (s, 3H, OMe), 6.78 (d, 1H, *J* = 7.4 Hz), 7.53 (ddd, 1H, *J* = 8.1, 6.6, 1.0 Hz), 7.68 (dd, 1H, *J* = 8.9 and 7.5 Hz), 7.79 (ddd, 1H, *J* = 8.7, 6.6 and 1.4 Hz), 7.82 (dt, 1H, *J* = 8.9 and 0.7 Hz), 8.03 (dt, 1H, *J* = 8.4 and 0.6 Hz), 8.22 (dd, 1H, *J* = 8.8 and 0.8 Hz), 9.21 (s, 1H, H9); ^{13}C NMR ($CDCl_3$) δ 56.0 (CH_3), 101.8 (CH), 120.5 (C), 121.7 (CH), 125.6 (CH), 126.1 (C), 128.9 (CH), 129.3 (CH), 130.5 (CH), 130.7 (CH), 131.7 (CH), 149.2 (C), 149.8 (C), 155.5 (C). The ^{1}H NMR data are close to those reported previously.[44]

4.3.5. 4-Methoxyacridine (3d) was obtained according to the general procedure 2 (reaction time: 3 h) from **2d** (0.23 g). Purification by column chromatography over silica gel (R_f (heptane-AcOEt 60:40) = 0.34) gave **3d** in 98% yield (0.21 g) as a yellow solid: mp 134-136 °C (lit.[77] 131-135 °C); IR (ATR): 719, 735, 757, 768, 854, 937, 965, 978, 1011, 1068, 1094, 1126, 1144, 1179, 1225, 1245, 1267, 1320, 1367, 1403, 1464, 1491, 1523, 1560, 1626, 1719, 1919, 2925, 3005, 3058 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.16 (s, 3H, OMe), 7.04 (d, 1H, *J* = 7.5 Hz), 7.44 (t, 1H, *J* = 8.0 Hz), 7.54 (ddd, 1H, *J* = 8.1, 6.6 and 0.9 Hz), 7.57 (dd, 1H, *J* = 7.6 and 0.8 Hz), 7.76 (ddd, 1H, *J* = 8.8, 6.6 and 1.4 Hz), 7.98 (d, 1H, *J* = 8.4 Hz), 8.40 (d, 1H, *J* = 8.8 Hz), 8.73 (s, 1H, H9); ^{13}C NMR ($CDCl_3$) δ 56.3 (CH_3), 106.7 (CH), 120.2 (CH), 125.8 (CH), 126.2 (CH), 127.0 (C), 127.7 (C), 128.0 (CH), 130.0 (CH), 130.4 (CH), 135.9 (CH), 142.3 (C), 148.3 (C), 155.3 (C).

4.3.6. Benzo[*b*][1,5]naphthyridine (3e) was obtained according to the general procedure 2 (reaction time: 2 h) from **2e** (0.20 g). Purification by column chromatography over silica gel (AcOEt-heptane 50:50) gave **3e** in 83% yield (0.15 g) as a white solid: mp 106 °C (lit.[78] 106-107 °C); IR (ATR): 666,

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707, 751, 784, 833, 899, 1021, 1042, 1117, 1158, 1187, 1224, 1315, 1398, 1456, 1481, 1512, 1570, 1582, 1659, 2748, 2830, 3035, 3276 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (ddd, 1H, *J* = 8.0, 7.5 and 0.78 Hz, H7), 7.68 (dd, 1H, *J* = 8.8 and 3.9 Hz, H3), 7.84 (ddd, 1H, *J* = 8.1, 6.6 and 1.3 Hz, H6), 8.09 (d, 1H, *J* = 8.5 Hz, H8), 8.26 (d, 1H, *J* = 8.8 Hz, H5), 8.53 (d, 1H, *J* = 8.8 Hz, H4), 9.01 (s, 1H, H9), 9.06 (dd, 1H, *J* = 3.8 and 1.5 Hz, H2); ^{13}C NMR ($CDCl_3$) δ 124.9 (CH), 126.8 (CH), 128.8 (CH), 128.8 (C), 129.6 (CH), 131.2 (CH), 136.8 (CH), 137.5 (CH), 140.6 (C), 145.0 (C), 149.5 (C), 152.1 (CH). The ^1H NMR data are close to those reported previously.[78]

4.3.7. Dibenzo[*b,j*][4,7]phenanthroline (3f2). To *N,N'*-(1,4-phenylene)-2,2'-bis(2-aminobenzaldehyde) (**2f2**; 0.33 g, 1.0 mmol) in CH_3CO_2H (3 mL) was added 96% H_2SO_4 (5.6 mmol, 0.30 mL). The reaction mixture was stirred at 110 °C for 1 h. After cooling to room temperature, water (5 mL) was added and the reaction mixture was basified using 25% NH_4OH. Extraction using AcOEt (3x20 mL), drying over $MgSO_4$, removal of the solvent and purification by column chromatography over silica gel (heptane-AcOEt 80:20) gave **3f2** in 89% yield (0.25 g) as a yellow solid: mp 240 °C (lit.[45] 244-245 °C); IR (ATR): 666, 752, 782, 804, 834, 859, 903, 957, 1013, 1095, 1131, 1190, 1259, 1322, 1378, 1455, 1480, 1504, 1556, 1620, 1663, 1734, 2853, 2920, 3053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (t, 2H, *J* = 7.4 Hz, H2 and H11), 7.87 (ddd, 2H, *J* = 8.2, 7.7 and 1.2 Hz, H3 and H10), 8.14 (d, 2H, *J* = 8.2 Hz, H1 and H12), 8.22 (s, 2H, H6 and H7), 8.31 (d, 2H, *J* = 8.7 Hz, H4 and H9), 9.46 (s, 2H, H13 and H14); ^{13}C NMR ($CDCl_3$) δ 123.8 (2C), 126.8 (2C), 127.0 (2CH), 128.3 (2CH), 129.5 (2CH), 130.6 (2CH), 130.6 (2CH), 134.4 (2CH), 148.5 (2C), 149.2 (2C). The NMR data are close to those reported previously.[45]

4.4. Deprotometalation-iodolysis of acridine (3a) and benzo[*b*][1,5]naphthyridine (3e)

4.4.1. 4-Iodoacridine (4a)[50] was obtained by adapting a procedure reported previously.[48a] To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (2-3 mL) were successively added BuLi (about 1.6 M hexanes solution, 1.5 mmol) and, 5 min later, $ZnCl_2$·TMEDA (0.13 g, 0.50 mmol). The reaction mixture was stirred for 15 min at 0 °C before

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introduction of acridine (**3a**; 0.18 g, 1.0 mmol) at 0-10 °C. After 2 h at room temperature, a solution of I_2 (0.38 g, 1.5 mmol) in THF (4 mL) was added. The reaction mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (4 mL) and extraction with AcOEt (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography over silica gel (R_f (AcOEt-heptane 20:80) = 0.73) gave **4a** in 76% yield (0.23 g) as a yellow solid: mp 120-124 °C; IR (ATR): 660, 735, 756, 921, 1307, 1456, 1505, 1609 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21 (dd, 1H, *J* = 8.3 and 7.1 Hz, H2), 7.55 (ddd, 1H, *J* = 8.0, 6.7 and 1.0 Hz, H7), 7.80 (ddd, 1H, *J* = 8.8, 6.6 and 1.4 Hz, H6), 7.95 (dd, 1H, *J* = 8.5 and 1.2 Hz, H1), 7.99 (d, 1H, *J* = 8.5 Hz, H8), 8.36 (dd, 1H, *J* = 8.8 and 0.7 Hz, H5), 8.44 (dd, 1H, *J* = 7.1 and 1.2 Hz, H3), 8.66 (s, 1H, H9); ^{13}C NMR ($CDCl_3$) δ 104.2 (C, C4), 126.5 (C), 126.5 (CH), 126.6 (CH), 127.1 (C), 127.9 (CH), 129.3 (CH), 130.1 (CH), 130.7 (CH), 137.0 (CH), 140.8 (CH), 147.1 (C), 149.8 (C). **Crystal data for 4a.** $C_{13}H_8IN$, M = 305.10, monoclinic, $P\ 2_1/c$, a = 4.6787(7), b = 12.4539(17), c = 18.228(3) Å, β = 94.359(5) °, V = 1059.0(3) $Å^3$, Z = 4, d = 1.914 g cm^{-3}, μ = 2.985 mm^{-1}. A final refinement on F^2 with 2426 unique intensities and 136 parameters converged at $\omega R(F^2)$ = 0.0543 ($R(F)$ = 0.0240) for 2177 observed reflections with $I > 2\sigma(I)$. CCDC 2011443.

4.4.2. 4,9-Diiodobenzo[*b*][1,5]naphthyridine (4e) was obtained by adapting a procedure reported previously.[48a] To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (2-3 mL) were successively added BuLi (about 1.6 M hexanes solution, 1.5 mmol) and, 5 min later, $ZnCl_2$·TMEDA (0.13 g, 0.50 mmol). The reaction mixture was stirred for 15 min at 0 °C before introduction of benzo[*b*][1,5]naphthyridine (**3e**; 0.18 g, 1.0 mmol) at 0-10 °C. After 2 h at room temperature, a solution of I_2 (0.38 g, 1.5 mmol) in THF (4 mL) was added. The reaction mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (4 mL) and extraction with AcOEt (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 85:15) = 0.60) gave **4e** in 15% yield (65 mg) as an orange solid: mp 232 °C;

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IR (ATR): 679, 751, 793, 847, 857, 927, 1046, 1120, 1147, 1173, 1239, 1260, 1311, 1373, 1393, 1456, 1492, 1532, 1579, 1619, 1695, 1948, 2851, 2919, 3061 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (ddd, 1H, *J* = 8.4, 6.7 and 1.0 Hz, H6 or H7), 7.88 (ddd, 1H, *J* = 8.3, 6.7 and 1.2 Hz, H6 or H7), 8.34 (d, 1H, *J* = 8.7 Hz, H5 or H8), 8.39 (d, 1H, *J* = 4.2 Hz, H3), 8.45 (d, 1H, *J* = 8.8 Hz, H5 or H8), 8.65 (d, 1H, *J* = 4.2 Hz, H2); ^{13}C NMR ($CDCl_3$) δ 117.2 (C), 124.0 (C), 129.3 (CH), 130.5 (CH), 131.7 (CH), 133.0 (C), 133.2 (CH), 136.2 (CH), 140.6 (C), 143.1 (C), 149.4 (C), 152.0 (CH). **Crystal data for 4e.** $C_{12}H_6I_2N_2$, *M* = 431.99, monoclinic, *P* $2_1/n$, *a* = 14.3375(16), *b* = 4.2116(5), *c* = 20.411(2) Å, *β* = 109.389(4) °, *V* = 1162.6(2) $Å^3$, *Z* = 4, *d* = 2.468 g cm^{-3}, *μ* = 5.381 mm^{-1}. A final refinement on F^2 with 2661 unique intensities and 128 parameters converged at $\omega R(F^2)$ = 0.1050 ($R(F)$ = 0.0571) for 2029 observed reflections with $I > 2\sigma(I)$. CCDC 2011444. **9-Iodobenzo[*b*][1,5]naphthyridine** was identified by NMR (<10% estimated yield) from a mixture similarly obtained: ^1H NMR ($CDCl_3$) δ 7.66-7.74 (m, 2H, H3 and H7), 7.82-7.88 (m, 1H, H6), 8.22 (d, 1H, *J* = 8.7 Hz, H5 or H8), 8.45 (d, 1H, *J* = 8.8 Hz, H5 or H8), 8.50 (dd, 1H, *J* = 8.7 and 1.4 Hz, H4), 9.14 (d, 1H, *J* = 2.7 Hz, H2).

4.5. *N*-Arylation of pyrrolidinone using 4-iodoacridine (4a)

***N*-(4-acridyl)-2-pyrrolidinone (5a1)** was obtained by adapting a procedure reported previously.[47] A mixture of CuI (19 mg, 0.10 mmol), K_3PO_4 (0.42 g, 2.0 mmol), 2-pyrrolidinone (0.17 g, 2.0 mmol) and 4-iodoacridine (**4a**; 0.31 g, 1.0 mmol) in DMSO (2 mL) was degassed and stirred under argon at 110 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered over celite®. After addition of H_2O (25 mL) to the filtrate and extraction with Et_2O (3x10 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography over silica gel (R_f (AcOEt) = 0.44) gave **5a1** in 58% yield (0.15 g) as a yellow solid: mp 182-184 °C; IR (ATR): 666, 733, 766, 808, 858, 916, 1042, 1074, 1129, 1149, 1223, 1260, 1287, 1323, 1415, 1467, 1523, 1579, 1617, 1681, 2878 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (quint, 2H, *J* = 7.5 Hz, H4'), 2.76 (t, 2H, *J* = 8.0 Hz, H3'), 4.30 (t, 2H, *J* = 7.0 Hz, H5'), 7.51-7.57 (m, 2H, H2 and H7), 7.76 (ddd, 1H, *J* = 8.1, 6.7 and 1.1 Hz, H6), 7.82 (dd, 1H, *J* = 7.1 and 1.0 Hz, H3), 7.95 (d, 1H, *J*

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= 8.9 Hz, H1 or H8), 7.98 (d, 1H, J = 9.0 Hz, H1 or H8), 8.20 (d, 1H, J = 8.8 Hz, H5), 8.77 (s, 1H, H9); ^{13}C NMR ($CDCl_3$) δ 19.5 (CH_2), 32.0 (CH_2), 51.8 (CH_2), 125.4 (CH), 126.1 (CH), 126.7 (C), 127.7 (C), 127.9 (CH), 128.1 (CH), 129.0 (CH), 130.2 (CH), 130.4 (CH), 136.2 (C), 136.3 (CH), 144.9 (C), 148.6 (C), 176.3 (C). Anal. Calcd for $C_{17}H_{14}N_2O$ (262.31): C, 77.84; H, 5.38; N, 10.68. Found: C, 78.01; H, 5.71; N, 10.32%.

4.6. *N*-Arylation of pyrazole using 4-iodoacridine (4a)

4.6.1. 4,9-Di(*N*-pyrazolyl)acridine (5a2). A mixture of 4-iodoacridine (**4a**; 0.31 g, 1.0 mmol), CuI (19 mg, 0.10 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), pyrazole (0.14 g, 2.0 mmol) and DMSO (0.5 mL) was stirred for 24 h at 110 °C. After cooling to room temperature, the reaction mixture was diluted with AcOEt (10 mL) and filtered over celite®. After washing with AcOEt and removal of the solvent, purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 80:20) = 0.44) gave **5a2** in 20% yield (62 mg) as a yellowish solid: mp 140-142 °C; IR (ATR): 665, 725, 736, 748, 758, 806, 817, 863, 889, 928, 952, 1014, 1039, 1078, 1194, 1260, 1329, 1359, 1390, 1401, 1435, 1445, 1467, 1517, 1565, 1626, 1718, 1948, 2850, 2919, 2961, 3103, 3162 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.54 (dd, 1H, J = 2.3 and 1.9 Hz, H4'), 6.67 (t, 1H, J = 2.1 Hz, H4"), 7.46-7.58 (m, 4H, H1, H2, H7, H8), 7.72-7.78 (m, 1H, H6), 7.77 (d, 1H, J = 1.4 Hz, H5'), 7.86 (d, 1H, J = 2.4 Hz, H3"), 7.95 (d, 1H, J = 1.7 Hz, H5"), 8.24 (d, 1H, J = 8.8 Hz, H5), 8.28 (dd, 1H, J = 7.2 and 1.4 Hz, H3), 9.11 (d, 1H, J = 2.5 Hz, H3'); ^{13}C NMR ($CDCl_3$) δ 106.9 (CH), 107.4 (CH), 121.9 (CH), 123.1 (C), 123.4 (CH), 123.9 (CH), 124.1 (C), 127.2 (CH), 128.2 (CH), 130.3 (CH), 130.9 (CH), 133.7 (CH), 134.3 (CH), 137.0 (C), 141.0 (CH), 142.0 (CH), 142.0 (C), 142.3 (C), 149.1 (C). **4-Iodo-9-(*N*-pyrazolyl)acridine (5a5)** was similarly isolated (R_f (petroleum ether-AcOEt 80:20) = 0.66) in 8% yield (30 mg) as a yellow solid: mp 150-152 °C; IR (ATR): 760, 804, 880, 1045, 1087, 1381, 1654, 2893, 2974, 3340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.72 (t, 1H, J = 2.1 Hz, H4'), 7.22 (dd, 1H, J = 8.7 and 7.2 Hz, H2), 7.55-7.63 (m, 3H, H1, H7 and H8), 7.82-7.88 (m, 2H, H6 and H3'), 8.01 (d, 1H, J = 1.7 Hz, H5'), 8.44 (d, 1H, J = 8.8 Hz, H5), 8.49 (dd, 1H, J = 7.1 and 0.9 Hz, H3). **Crystal data for 5a5.** $C_{16}H_{10}IN_3$, M = 371.17,

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orthorhombic, *P b c a*, a = 13.207(2), b = 11.6806(16), c = 17.774(3) Å, V = 2742.0(7) Å^3, Z = 8, d = 1.798 g cm^{-3}, μ = 2.328 mm^{-1}. A final refinement on F^2 with 3143 unique intensities and 182 parameters converged at $\omega R(F^2)$ = 0.0656 ($R(F)$ = 0.0270) for 2781 observed reflections with $I > 2\sigma(I)$. CCDC 2011445.

4.6.2. 4-(*N*-pyrazolyl)-9-acridone (5a3) was obtained by adapting a procedure reported previously.[48b] A mixture of 4-iodoacridine (**4a**; 0.31 g, 1.0 mmol), Cu_2O (0.10 g, 0.10 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), pyrazole (0.14 g, 2.0 mmol) and DMSO (0.5 mL) was stirred for 24 h at 110 °C. After cooling to room temperature, the reaction mixture was diluted with AcOEt (10 mL) and filtered over celite®. After washing with AcOEt and removal of the solvent, purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 80:20) = 0.17) gave **5a3** in 66% yield (0.17 g) as a yellow solid: mp 190-192 °C; IR (ATR): 690, 746, 824, 871, 884, 916, 933, 968, 1053, 1065, 1076, 1107, 1128, 1173, 1246, 1260, 1322, 1336, 1392, 1414, 1434, 1457, 1475, 1486, 1529, 1589, 1602, 1619, 1637, 1730, 2854, 2924, 3114 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.62 (t, 1H, J = 2.2 Hz, H4'), 7.27-7.32 (m, 2H, H2 and H7), 7.38 (d, 1H, J = 8.3 Hz, H5), 7.67 (ddd, 1H, J = 8.4, 7.0 and 1.5 Hz, H6), 7.72 (dd, 1H, J = 7.7 and 1.3 Hz, H3), 7.94 (d, 1H, J = 1.7 Hz, H5'), 8.04 (d, 1H, J = 2.5 Hz, H3'), 8.49 (m, 2H, H1 and H8), 11.65 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 107.7 (CH), 117.8 (CH), 120.4 (CH), 121.4 (C), 122.1 (CH), 123.6 (C), 124.1 (CH), 126.5 (CH), 126.8 (C), 127.2 (CH), 129.9 (CH), 133.8 (CH), 134.0 (C), 140.4 (C), 141.5 (CH), 178.0 (C). Anal. Calcd for $C_{16}H_{11}N_3O$ (261.28): C, 73.55; H, 4.24; N, 16.08. Found: C, 73.40; H, 4.47; N, 15.96%. **4-Iodo-9-acridone (5a4)** was similarly isolated (R_f (petroleum ether-AcOEt 80:20) = 0.37) in 10% yield (32 mg) as a beige solid: mp 260-262 °C; IR (ATR): 659, 724, 750, 778, 814, 842, 863, 898, 1041, 1109, 1119, 1158, 1190, 1237, 1315, 1396, 1443, 1458, 1482, 1517, 1579, 1607, 1651, 1690, 2750, 2830, 2922, 3288 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.04 (t, 1H, J = 7.8 Hz, H2 or H7), 7.32 (t, 1H, J = 7.6 Hz, H2 or H7), 7.41 (d, 1H, J = 8.2 Hz, H5), 7.71 (ddd, 1H, J = 8.4, 7.1 and 1.5 Hz, H6), 8.13 (dd, 1H, J = 7.6 and 1.4 Hz, H3), 8.35 (br s, 1H, NH), 8.44-8.50 (m, 2H, H1 and H8); ^{13}C NMR ($CDCl_3$) δ 85.7 (C, C4), 117.0 (CH), 121.1 (C),

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122.5 (C), 122.6 (CH), 123.1 (CH), 127.5 (CH), 128.3 (CH), 134.1 (CH), 139.8 (C), 140.2 (C), 143.4 (CH), 178.1 (C, C=O).

4.7. 9-(*N*-pyrazolyl)acridine (5a7). A mixture of acridine (**3a**; 0.18 g, 1.0 mmol), K_3PO_4 (0.42 g, 2.0 mmol), pyrazole (0.14 g, 2.0 mmol) and DMSO (0.5 mL) was stirred for 24 h at 110 °C. After cooling to room temperature, the reaction mixture was diluted with AcOEt (10 mL) and filtered over celite®. After washing with AcOEt and removal of the solvent, purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 50:50) = 0.63) gave **5a7** in 53% yield (0.13 g) as a yellow solid: mp 202-204 °C; IR (ATR): 659, 730, 813, 863, 898, 1040, 1087, 1110, 1120, 1158, 1193, 1237, 1314, 1395, 1443, 1458, 1484, 1511, 1576, 1607, 1651, 2750, 2830, 3090, 3292 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.72 (t, 1H, *J* = 2.1 Hz, H4'), 7.54 (ddd, 2H, *J* = 8.7, 6.5 and 0.9 Hz, H2 and H7), 7.63 (dd, 2H, *J* = 8.7 and 0.7 Hz, H1 and H8), 7.82 (ddd, 2H, *J* = 8.7, 6.5 and 1.4 Hz, H3 and H6), 7.88 (d, 1H, *J* = 2.3 Hz, H3'), 8.01 (d, 1H, *J* = 1.7 Hz, H5'), 8.31 (d, 2H, *J* = 8.8 Hz, H4 and H5); ^{13}C NMR ($CDCl_3$) δ 107.2 (CH, C4'), 123.2 (2C, Ca and Cd), 123.5 (2CH, C2 and C7), 127.5 (2CH, C1 and C8), 129.8 (2CH, C4 and C5), 130.7 (2CH, C3 and C6), 133.6 (CH, C3'), 141.6 (C, C9), 141.8 (CH, C5'), 149.7 (2C, Cb and Cc). **Crystal data for 5a7.** $C_{16}H_{11}N_3$, *M* = 245.28, triclinic, *P* -1, *a* = 7.2487(7), *b* = 8.6301(10), *c* = 11.1761(11) Å, *α* = 68.695(4), *β* = 86.059(4), *γ* = 66.381(4) °, *V* = 594.38(11) $Å^3$, *Z* = 2, *d* = 1.370 g cm^{-3}, *μ* = 0.084 mm^{-1}. A final refinement on F^2 with 2729 unique intensities and 173 parameters converged at $\omega R(F^2)$ = 0.1017 ($R(F)$ = 0.0383) for 2308 observed reflections with $I > 2\sigma(I)$. CCDC 2011446. **Acridone** (**5a6**) was similarly isolated (R_f (petroleum ether-AcOEt 50:50) = 0.47) in 26% yield (51 mg) as a yellow solid: mp > 300 °C; IR (ATR): 671, 706, 748, 814, 848, 936, 1022, 1103, 1157, 1262, 1342, 1470, 1529, 1552, 1595, 1634, 1728, 2946, 2990, 3030, 3097 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 7.25 (ddd, 2H, *J* = 8.0, 7.0 and 1.0 Hz, H2 and H7), 7.52 (d, 2H, *J* = 8.4 Hz, H4 and H5), 7.69 (ddd, 2H, *J* = 8.4, 7.0 and 1.5 Hz, H3 and H6), 8.34 (dd, 2H, *J* = 8.1 and 1.2 Hz, H1 and H8), 10.63 (br s, 1H, NH). These data are similar to those obtained for a commercial sample.

4.8. Respective *C*- and *N*-Arylation of indole and carbazole using acridine (3a)

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4.8.1. 9-(3-Indolyl)acridine (5a8). A mixture of acridine (**3a**; 0.18 g, 1.0 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), indole (0.12 g, 1.0 mmol) and DMSO (0.5 mL) was stirred for 24 h at 110 °C. After cooling to room temperature, the reaction mixture was diluted with AcOEt (10 mL) and filtered over celite®. After washing with AcOEt and removal of the solvent, purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 60:40) = 0.50) gave **5a8** in 75% yield (0.24 g) as an orange solid: mp 266 °C (lit.[79] 257-258 °C, after similar purification by column chromatography); IR (ATR): 657, 770, 778, 813, 842, 863, 898, 1015, 1041, 1109, 1120, 1157, 1190, 1236, 1314, 1395, 1442, 1457, 1483, 1516, 1576, 1607, 1650, 2750, 2831, 3289 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (t, 1H, *J* = 7.3 Hz, H5' or H6'), 7.17 (d, 1H, *J* = 7.7 Hz, H4' or H7'), 7.32 (ddd, 1H, *J* = 8.0, 7.5 and 1.0 Hz, H5' or H6'), 7.39 (ddd, 2H, *J* = 8.0, 6.5 and 0.7 Hz, H2 and H7), 7.49 (d, 1H, *J* = 2.5 Hz, H2'), 7.59 (d, 1H, *J* = 8.2 Hz, H4' or H7'), 7.76 (ddd, 2H, *J* = 8.2, 6.6 and 1.2 Hz, H3 and H6), 7.97 (d, 2H, *J* = 8.7 Hz, H1 and H8), 8.29 (d, 2H, *J* = 8.7 Hz, H4 and H5), 8.81 (br s, 1H, NH); ^1H NMR ($(CD_3)_2SO$) δ 6.96-7.00 (m, 2H), 7.22 (ddd, 1H, *J* = 8.1, 5.2 and 2.9 Hz, H5' or H6'), 7.47 (ddd, 2H, *J* = 8.5, 6.5 and 0.9 Hz, H2 and H7), 7.62 (d, 1H, *J* = 8.2 Hz, H4' or H7'), 7.79 (d, 1H, *J* = 2.4 Hz, H2'), 7.83 (ddd, 2H, *J* = 8.4, 6.5 and 1.2 Hz, H3 and H6), 7.92 (d, 2H, *J* = 8.7 Hz, H1 and H8), 8.21 (d, 2H, *J* = 8.7 Hz, H4 and H5), 11.84 (s, 1H, NH); ^{13}C NMR ($(CD_3)_2SO$) δ 108.4 (C), 112.1 (CH), 118.9 (CH), 119.8 (CH), 121.8 (CH), 125.4 (2CH, C2 and C7), 125.5 (2C, Ca and Cd), 127.1 (2CH, C1 and C8), 127.2 (CH, C2'), 127.8 (C), 129.4 (2CH), 130.0 (2CH), 136.2 (C), 141.2 (C), 148.4 (2C, Cb and Cc). The NMR data are similar to those reported previously.[79]

4.8.2. 9-(*N*-carbazolyl)acridine (5a9). A mixture of acridine (**3a**; 0.18 g, 1.0 mmol), Cs_2CO_3 (0.65 g, 2.0 mmol), CuI (36 mg, 0.2 mmol), carbazole (0.17 g, 1.0 mmol) and DMSO (0.5 mL) was stirred for 24 h at 110 °C. After cooling to room temperature, the reaction mixture was diluted with AcOEt (10 mL) and filtered over celite®. After washing with AcOEt and removal of the solvent, purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 85:15) = 0.41) gave **5a9** in 83% yield (0.29 g) as a greenish solid: mp 258-260 °C (lit.[57] 257-259 °C); IR (ATR): 722, 744, 857, 1012,

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1148, 1229, 1313, 1332, 1420, 1448, 1476, 1490, 1518, 1555, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.76 (dd, 2H, *J* = 7.1 and 1.2 Hz), 7.31 (td, 2H, *J* = 7.3 and 1.4 Hz), 7.35 (dd, 2H, *J* = 7.3 and 1.3 Hz), 7.37-7.39 (m, 4H), 7.83 (ddd, 2H, *J* = 8.7, 4.7 and 3.2 Hz), 8.29 (dd, 2H, *J* = 6.9 and 1.6 Hz), 8.42 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 110.4 (2CH), 120.6 (2CH), 120.7 (2CH), 123.6 (2C), 123.9 (2CH), 124.6 (2C), 126.5 (2CH), 127.2 (2CH), 130.3 (2CH), 130.8 (2CH), 139.6 (C, C9), 142.3 (2C), 150.2 (2C). **Crystal data for 5a9.** $C_{25}H_{16}N_2$, *M* = 344.40, monoclinic, *P* $2_1/c$, *a* = 11.3761(5), *b* = 11.8575(5), *c* = 12.5585(5) Å, *β* = 93.323(2) °, *V* = 1691.19(12) $Å^3$, *Z* = 4, *d* = 1.353 g cm^{-3}, *μ* = 0.080 mm^{-1}. A final refinement on F^2 with 3882 unique intensities and 244 parameters converged at $\omega R(F^2)$ = 0.1638 ($R(F)$ = 0.0693) for 3349 observed reflections with $I > 2\sigma(I)$. CCDC 2011447. These data are as reported previously.[57]

4.9. Double *N*-arylation of 2-aminobenzaldehyde (1)

4.9.1. General procedure 3 for the double *N*-arylation reactions. This reaction was performed under an argon atmosphere by adapting a procedure reported previously.[58] To 2-aminobenzaldehyde (**1**; 0.12 g, 1.0 mmol) and the required iodide (2.0 mmol) in Bu_2O (1 mL) were successively added activated Cu (13 mg, 0.20 mmol) and K_2CO_3 (0.43 g, 3.0 mmol). The reaction mixture was degassed and refluxed under argon for 48 h. During this time, activated Cu (4 x 13 mg, 4 x 0.20 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the reaction mixture was concentrated. Purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

4.9.2. 2-[*N*,*N*-di(4-methoxyphenyl)]aminobenzaldehyde (6b) was obtained according to the general procedure 3 by using 4-iodoanisole (0.47 g). Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 90:10) = 0.30) gave **6b** in 26% yield (87 mg) as a yellow solid: mp 103-104 °C; IR (ATR): 721, 761, 783, 811, 828, 1021, 1107, 1151, 1169, 1181, 1238, 1265, 1311, 1399, 1450, 1473, 1501, 1593, 1686, 2762, 2840, 2933, 2966, 3007 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 6H, OMe), 6.76-6.81 (m, 4H), 6.92-6.97 (m, 4H), 7.04 (d, 1H, *J* = 8.1 Hz, H3), 7.15 (t, 1H, *J* = 7.5 Hz,

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H4 or H5), 7.46 (ddd, 1H, J = 8.2, 7.4 and 1.7 Hz, H4 or H5), 7.82 (dd, 1H, J = 7.8 and 1.6 Hz, H6), 10.2 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 55.7 ($2CH_3$), 115.0 (4CH), 124.2 (CH), 124.7 (4CH), 127.4 (CH), 129.2 (CH), 130.7 (C), 135.1 (CH), 143.1 (2C, C1'), 151.4 (C), 155.6 (2C, C4'), 190.9 (CHO). Anal. Calcd for $C_{21}H_{19}NO_3$ (333.39): C, 75.66; H, 5.74; N, 4.20. Found: C, 75.72; H, 5.75; N, 4.18%.

4.9.3. 2-[*N*,*N*-di(3-methoxyphenyl)]aminobenzaldehyde (6c) was obtained according to the general procedure 3 by using 3-iodoanisole (0.47 g). Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 90:10) = 0.36) gave **6c** in 14% yield (0.13 g) as an orange oil: IR (ATR): 688, 721, 759, 823, 1027, 1038, 1107, 1152, 1163, 1207, 1238, 1266, 1311, 1397, 1450, 1474, 1488, 1592, 1687, 2762, 2837, 2965, 3006 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 6H, OMe), 6.54-6.63 (m, 6H), 7.11-7.18 (m, 3H), 7.27 (tt, 1H, J = 7.5 and 0.9 Hz), 7.54 (ddd, 1H, J = 8.1, 7.3 and 1.7 Hz), 7.89 (dd, 1H, J = 7.8 and 1.5 Hz), 10.21 (d, 1H, J = 0.8 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 55.3 ($2CH_3$), 108.2 (2CH), 109.3 (2CH), 115.6 (2CH), 125.7 (CH), 129.0 (CH), 129.2 (CH), 130.2 (2CH), 132.1 (C), 135.5 (CH), 149.9 (2C, C1'), 150.2 (C), 160.6 (2C, C3'), 190.8 (CH, CHO). Anal. Calcd for $C_{21}H_{19}NO_3$ (333.39): C, 75.66; H, 5.74; N, 4.20. Found: C, 75.61; H, 5.60; N, 4.13%.

4.9.4. 2-[*N*,*N*-di(2-methoxyphenyl)]aminobenzaldehyde (6d) was obtained according to the general procedure 3 by using 2-iodoanisole (0.47 g). Purification by column chromatography over silica gel (R_f (heptane-AcOEt 70:30) = 0.66) gave **6d** in 63% yield (0.21 g) as a yellow solid: mp 114 °C; IR (ATR): 703, 746, 795, 827, 1024, 1047, 1097, 1116, 1156, 1185, 1234, 1258, 1291, 1309, 1391, 1455, 1475, 1494, 1592, 1684, 2836, 2937, 3063 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 6H, OMe), 6.81-6.90 (m, 6H), 6.94 (dd, 1H, J = 8.2, 0.7 Hz), 7.05-7.12 (m, 3H), 7.38 (ddd, 1H, J = 8.2, 7.3 and 1.7 Hz), 7.78 (dd, 1H, J = 7.7 and 1.7 Hz, H6), 10.20 (d, 1H, J = 0.7 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 56.0 ($2CH_3$), 113.4 (2CH), 121.4 (2CH), 123.2 (CH), 124.8 (CH), 125.2 (2CH), 126.2 (2CH), 128.5 (CH), 129.4 (C), 134.2 (CH), 138.6 (2C, C1'), 152.5 (C), 153.5 (2C, C2'), 191.8 (CH, CHO). Anal. Calcd for $C_{21}H_{19}NO_3$ (333.39): C, 75.66; H, 5.74; N, 4.20. Found: C, 75.59; H, 5.65; N, 4.09%.

4.10. Conversion of the *N*,*N*-arylated 2-aminobenzaldehydes (6) into acridones

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4.10.1. General procedure 4 for the cyclization reactions giving acridones. To the required *N*,*N*-diarylated 2-aminobenzaldehyde (1.0 mmol) in CH_3CO_2H (3 mL) was added 96% H_2SO_4 (2.8 mmol, 0.15 mL). The reaction mixture was stirred at 110 °C. The reaction time is given in the product description. After cooling to room temperature, water (5 mL) was added and the reaction mixture was basified using 25% NH_4OH. Extraction using AcOEt (3x20 mL), drying over $MgSO_4$, removal of the solvent and purification by chromatography on silica gel (the eluent is given in the product description) led to the expected compound.

4.10.2. 2-Methoxy-*N*-(4-methoxyphenyl)-9-acridone (7b) was obtained according to the general procedure 4 (reaction time: 1 h) from **6b** (0.33 g). Purification by column chromatography over silica gel (R_f (heptane-AcOEt 70:30) = 0.41) gave **7b** in 71% yield (0.24 g) as a yellow solid: mp 198-200 °C; IR (ATR): 755, 837, 1034, 1111, 1157, 1249, 1275, 1293, 1340, 1465, 1482, 1495, 1510, 1599, 1632, 2931 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.78 (d, 1H, *J* = 9.3 Hz, H4), 6.82 (d, 1H, *J* = 8.7 Hz, H5), 7.15 (dd, 1H, *J* = 9.3 and 3.1 Hz, H3), 7.15-7.20 (m, 2H, 4-$MeOC_6H_4$), 7.23-7.29 (m, 3H, H7, 4-$MeOC_6H_4$), 7.49 (ddd, 1H, *J* = 8.7, 6.9 and 1.7 Hz, H6), 7.98 (d, 1H, *J* = 3.1 Hz, H1), 8.58 (dd, 1H, *J* = 8.1 and 1.4 Hz, H8); ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3), 56.0 (CH_3), 106.1 (CH), 116.2 (2CH), 116.9 (CH), 118.8 (CH), 121.2 (C), 121.3 (CH), 122.6 (C), 124.3 (CH), 127.3 (CH), 131.2 (2CH), 131.7 (C), 133.1 (CH), 138.6 (C), 143.2 (C), 154.8 (C), 160.3 (C), 177.8 (C). **Crystal data for 7b.** $C_{21}H_{17}NO_3$, *M* = 331.36, triclinic, *P* -1, *a* = 9.0841(8), *b* = 10.1698(10), *c* = 10.2554(9) Å, *α* = 67.744(3), *β* = 76.968(3), *γ* = 66.831(3) °, *V* = 802.86(13) $Å^3$, *Z* = 2, *d* = 1.371 g cm^{-3}, *μ* = 0.092 mm^{-1}. A final refinement on F^2 with 3659 unique intensities and 228 parameters converged at $\omega R(F^2) = 0.1105$ ($R(F) = 0.0402$) for 3201 observed reflections with $I > 2\sigma(I)$. CCDC 2011448.

4.10.3. 3-Methoxy-*N*-(3-methoxyphenyl)-9-acridone (7c) was obtained according to the general procedure 4 (reaction time: 2 h) from **6c** (0.33 g). Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 50:50) = 0.50) gave **7c** in 48% yield (0.16 g) as a beige solid: mp 186

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°C; IR (ATR): 670, 721, 755, 782, 803, 824, 885, 991, 1035, 1101, 1150, 1183, 1223, 1249, 1275, 1307, 1335, 1379, 1442, 1465, 1519, 1558, 1588, 1714, 1939, 2838, 2921, 3055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H, OMe), 3.89 (s, 3H, OMe), 6.21 (s, 1H), 6.81 (d, 1H, *J* = 8.5 Hz), 6.90 (d, 1H, *J* = 9.2 Hz, H2), 6.93 (s, 1H), 7.00 (d, 1H, *J* = 7.6 Hz), 7.21 (d, 1H, *J* = 8.3 Hz), 7.30 (d, 1H, *J* = 7.4 Hz), 7.51 (t, 1H, *J* = 7.6 Hz), 7.63 (t, 1H, *J* = 8.0 Hz), 8.54 (d, 1H, *J* = 9.0 Hz, H1), 8.59 (d, 1H, *J* = 8.2 Hz, H8); ^{13}C NMR ($CDCl_3$) δ 55.4 (CH_3), 55.7 (CH_3), 99.8 (CH), 110.2 (CH), 115.2 (CH), 115.7 (CH), 116.5 (C), 116.8 (CH), 121.6 (CH), 121.9 (CH), 122.0 (C), 127.2 (CH), 129.5 (CH), 131.8 (CH), 133.0 (CH), 140.1 (C), 143.2 (C), 145.0 (C), 161.9 (C), 163.8 (C), 177.3 (C, C=O). **Crystal data for 7c.** $C_{21}H_{17}NO_3$, *M* = 331.36, triclinic, *P* -1, *a* = 7.6096(8), *b* = 9.7782(9), *c* = 11.0303(11) Å, *α* = 84.157(3), *β* = 88.102(3), *γ* = 83.174(3) °, *V* = 810.51(14) $Å^3$, *Z* = 2, *d* = 1.358 g cm^{-3}, *μ* = 0.091 mm^{-1}. A final refinement on F^2 with 3671 unique intensities and 228 parameters converged at $\omega R(F^2)$ = 0.1046 ($R(F)$ = 0.0388) for 3258 observed reflections with $I > 2\sigma(I)$. CCDC 2011449.

4.10.4. 4-Methoxy-*N*-(2-methoxyphenyl)-9-acridone (7d) was obtained according to the general procedure 4 (reaction time: 1 h) from **6d** (0.33 g). Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 70:30) = 0.59) gave **7d** in 40% yield (0.13 g) as a yellow solid: mp 138-140 °C; IR (ATR): 732, 756, 1026, 1259, 1435, 1462, 1497, 1593, 1685, 2937 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.34 (s, 3H, OMe), 3.71 (s, 3H, OMe), 6.81 (d, 1H, *J* = 8.5 Hz), 7.03-7.10 (m, 3H), 7.17 (dd, 1H, *J* = 7.6 and 1.7 Hz), 7.22 (t, 1H, *J* = 7.9 Hz), 7.25 (td, 1H, *J* = 7.0 and 1.0 Hz), 7.43-7.49 (m, 2H), 8.26 (dd, 1H, *J* = 8.0 and 1.6 Hz), 8.54 (dd, 1H, *J* = 8.0 and 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 55.9 (CH_3), 57.2 (CH_3), 111.4 (CH), 117.3 (CH), 117.3 (CH), 120.0 (CH), 120.9 (CH), 121.7 (CH), 121.8 (CH), 124.5 (C), 127.1 (CH), 129.6 (CH), 129.7 (CH), 132.6 (C), 133.4 (CH), 134.6 (C), 144.1 (C), 149.6 (C), 156.5 (C), 178.4 (C, C=O), 1C not seen. **Crystal data for 7d.** $C_{21}H_{17}NO_3$, *M* = 331.36, monoclinic, $P\,2_1/n$, *a* = 10.1573(11), *b* = 11.0792(12), *c* = 15.0055(13) Å, *β* = 98.292(3) °, *V* = 1671.0(3) $Å^3$, *Z* = 4, *d* = 1.317 g cm^{-3}, *μ* = 0.088 mm^{-1}. A final refinement on F^2 with 3764 unique

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intensities and 228 parameters converged at $\omega R(F^2)$ = 0.1022 ($R(F)$ = 0.0424) for 2928 observed reflections with $I > 2\sigma(I)$. CCDC 2011450.

4.11. *N*-Phenyl-9-acridone (7a). It was obtained according to the general procedure 3 (not isolated) and 4 (reaction time: 2 h) by using iodobenzene (0.22 mL). Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 50:50) = 0.33) gave **7a** in 89% yield (0.24 g) as a yellow solid: mp 274-275 °C (lit.[80] 276-277 °C); IR (ATR): 671, 705, 746, 762, 775, 849, 934, 942, 1038, 1075, 1162, 1176, 1273, 1304, 1346, 1358, 1457, 1481, 1597, 1632, 1717, 2850, 2920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.76 (d, 2H, *J* = 8.6 Hz, H4 and H5), 7.28 (td, 2H, *J* = 7.1 and 0.8 Hz, H2 and H7), 7.36-7.39 (m, 2H, Ph), 7.50 (ddd, 2H, *J* = 8.6, 7.0 and 1.7 Hz, H3 and H6), 7.64-7.73 (m, 3H, Ph), 8.59 (dd, 2H, *J* = 8.0 and 1.5 Hz, H1 and H8); ^{13}C NMR ($CDCl_3$) δ 116.9 (2CH), 121.7 (2CH), 122.0 (2C), 127.4 (2CH), 129.7 (CH, C4'), 130.2 (2CH), 131.2 (2CH), 133.4 (2CH), 139.1 (C), 143.3 (2C), 178.3 (C, C=O). The NMR data are as reported previously.[81]

4.12. 2-[(*N*-4-methoxyphenyl-*N*-phenyl)amino]benzaldehyde (6ab) was prepared under an argon atmosphere by adapting a procedure reported previously.[58] To 2-(phenylamino)benzaldehyde (**2a**; 0.22 g, 1.0 mmol) and 4-iodoanisole (0.23 g, 1.0 mmol) in Bu_2O (1 mL) were successively added activated Cu (13 mg, 0.20 mmol) and K_2CO_3 (0.28 g, 2.0 mmol). The reaction mixture was degassed and refluxed under argon for 48 h. During this time, activated Cu (4 x 13 mg, 4 x 0.20 mmol) was added after 2, 4, 6 and 8 h of heating. After cooling to room temperature, the reaction mixture was concentrated. Purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 80:20) = 0.55) gave **6ab** in 38% yield (0.12 g) as a yellow solid: mp 94 °C; IR (ATR): 665, 697, 749, 779, 795, 872, 956, 967, 998, 1029, 1053, 1089, 1117, 1140, 1154, 1200, 1239, 1263, 1316, 1370, 1399, 1451, 1479, 1508, 1576, 1607, 1657, 2748, 2850, 2919, 3317 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H, OMe), 6.81-6.84 (m, 2H, 4-methoxyphenyl), 6.92-6.95 (m, 3H), 7.01-7.04 (m, 2H), 7.11 (d, 1H, *J* = 8.1 Hz, H3), 7.18-7.25 (m, 3H, H4 or H5 and Ph), 7.51 (t, 1H, *J* = 7.6 Hz, H4 or H5), 7.86 (d, 1H, *J* = 7.7 Hz, H6), 10.24 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 55.6 (CH_3), 115.1 (2CH), 121.6 (2CH), 122.1

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(CH), 125.0 (CH), 126.0 (2CH), 128.4 (CH), 129.3 (CH), 129.6 (2CH), 131.5 (C), 135.4 (CH), 142.0 (C), 149.8 (C), 150.8 (C), 156.2 (C), 191.0 (CH, CHO). Anal. Calcd for $C_{20}H_{17}NO_2$ (303.36): C, 79.19; H, 5.65; N, 4.62. Found: C, 79.25; H, 5.64; N, 4.67%.

4.13. *N*-(4-methoxyphenyl)-9-acridone (7ab). To 2-[(*N*-4-methoxyphenyl-*N*-phenyl)amino]benzaldehyde (**6ab**; 0.30 g, 1.0 mmol) in CH_3CO_2H (3 mL) was added 96% H_2SO_4 (2.8 mmol, 0.15 mL). The reaction mixture was stirred at 110 °C for 2 h. After cooling to room temperature, water (5 mL) was added and the reaction mixture was basified using 25% NH_4OH. Extraction using AcOEt (3x20 mL), drying over $MgSO_4$, removal of the solvent and purification by column chromatography over silica gel (R_f (petroleum ether-AcOEt 60:40) = 0.69) gave **7ab** in 42% yield (0.13 g) as a yellow solid: mp 230-232 °C; IR (ATR): 672, 708, 725, 747, 803, 833, 937, 1035, 1104, 1160, 1177, 1247, 1272, 1293, 1309, 1358, 1456, 1482, 1511, 1596, 1632, 1714, 1919, 2832, 2926, 2956, 2998, 3039 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (s, 3H, OMe), 6.82 (d, 2H, *J* = 8.6 Hz, H4 and H5), 7.17-7.20 (m, 2H, 4-$MeOC_6H_4$), 7.24-7.29 (m, 4H, H2, H7, 4-$MeOC_6H_4$), 7.50 (ddd, 2H, *J* = 8.6, 7.0 and 1.6 Hz, H3 and H6), 8.58 (dd, 2H, *J* = 8.0, 1.5 Hz, H1 and H8); ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3), 116.3 (2CH), 117.0 (2CH), 121.6 (2CH), 122.0 (2C), 127.4 (2CH), 131.1 (2CH), 131.5 (C), 133.4 (2CH), 143.7 (2C), 160.3 (C, C4'), 178.3 (C, C=O). The NMR data are as reported previously.[22] **2-Methoxy-*N*-phenyl-9-acridone** was similarly obtained (R_f (petroleum ether-AcOEt 60:40) = 0.55) in 3% yield (9 mg) and identified by NMR: ^1H NMR ($CDCl_3$) δ 3.95 (s, 3H, OMe), 6.73 (d, 1H, *J* = 9.3 Hz, H4), 6.77 (d, 1H, *J* = 8.8 Hz, H5), 7.12-7.29 (m, 2H, H3 and H7), 7.37 (d, 2H, *J* = 6.9 Hz), 7.46-7.53 (m, 1H, H6), 7.64-7.73 (m, 3H), 7.99 (d, 1H, *J* = 3.1 Hz, H1), 8.60 (dd, 1H, *J* = 7.8 and 1.4 Hz, H8). These data are similar to those recorded previously.[82]

4.14. Antiproliferative activity

The antiproliferative activity of compounds was evaluated on melanoma cell line A2058 (ATCC® CRL-11147) as previously described.[35] A2058 are highly invasive human epithelial adherent melanoma cells, derived from lymph nodes metastatic cells obtained from a 43 years male patient. They are

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tumorigenic at 100% frequency in nude mice. All cell culture experiments were performed at 37 °C. Cells were grown to confluence in 75 cm² flasks in DMEM supplemented with 10% fetal calf serum (FCS) and 1% penicillin-streptomycin (Dominique Dutscher, France) in a 5% CO_2 humidified atmosphere. Molecules are solubilized in DMSO at 10^{-3} M and diluted in the cell culture medium to obtain 2.10^{-5} M solutions. Confluent cells are trypsinized and centrifuged in FCS at 1500 g for 5 min. The supernatant containing trypsin is discarded and the cell pellet is suspended in cell culture medium to obtain a 4.104 cell.mL^{-1} suspension. At t0, 50 µL of the 2.10^{-5} M molecules solutions are deposited in a 96-wells flat bottom microplate, and 50 µL of the cell suspension were added. The 2000 cells are then grown for 72 h in the cell culture medium containing 10^{-5} M molecules. At t72, 20µL of a 5g.L^{-1} MTT solution are added in each well of the microplate, allowing living cells containing a functional mitochondrial succinate deshydrogenase to metabolize MTT to the corresponding blue formazan salt for 4 h. The cell culture medium is then removed using an Eppendorf epMotion 5070 pipeting robot (Eppendorf, France) and formazan crystals were dissolved in 200 µL DMSO. Microplates are placed at 37 °C for 5 min to solubilize formazan crystals. The absorbance is read at 550 nm using a VERSAmax microplate reader (Molecular devices, France). The percentage of growth inhibition is calculated as GI (%) = 100 - ((A550 nm sample – A550 nm BG) / (A550 nm control – A550 nm BG)) x 100 with:

- A550 nm sample: median absorbance of 8 wells containing cells treated with 10-5 M molecule
- A550 nm BG: median background absorbance of 8 wells containing control cell culture medium + 1% DMSO
- A550 nm control: median absorbance of 8 wells containing cells grown in control cell culture medium + 1% DMSO.

Data are expressed as GI (%) + sem (%) from 3 independent assays.

Acknowledgments. We thank the Algerian Direction Générale de la Recherche Scientifique et du Développement Technologique and Agence Thématique de Recherche en Sciences et Technologie (S.

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Z.), and the French Centre National de la Recherche Scientifique (F. M.). We acknowledge FEDER founds (D8 VENTURE Bruker AXS diffractometer) and Thermofisher (generous gift of 2,2,6,6-tetramethylpiperidine). L. P. and V. T. thank the French Cancer League (Comité 17 and Comité 86) for financial support and the Cancéropôle Grand Ouest (axis: Marine Molecules, Metabolism and Cancer 3MC) for scientific support. We also thank Frédéric Lassagne for his help all along the study. This research has been partly performed as part of the CNRS PICS project "Bimetallic synergy for the functionalization of heteroaromatics".

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

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