Synthesis of Ascididemine and an Isomer

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Ascididemine (9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one) (**1**) and an isomer (9*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one) (**4**) have been synthesized starting from 1,4-dimethoxyacridone (**7**). The acridone was converted into 1,4-dimethoxy-9-ethynylacridine (**11**) by a triflate coupling. The ethynylacridine was converted in one-pot into 3*H*-6-methoxypyrido[2,3,4-*kl*]acridine (**15**) by reaction with sodium diformylamide; the mechanism of this key transformation is discussed. Conversion into 6*H*-4-bromopyrido[2,3,4-*kl*]acridin-6-one (**19**) and 6*H*-pyrido[2,3,4-*kl*]acridin-6-one (**17**), followed by reaction of each of these under high pressure conditions with acrolein *N,N*-dimethylhydrazone, gave ascididemine and its isomer, respectively.

Introduction

Many heterocyclic natural products derived from marine organisms[1] have striking biological activities. Their role as pharmaceutical lead compounds, along with their limited availability from natural sources, makes them prime candidates for the development of total synthetic routes for the production of alkaloids and their analogues. More than 35 such substances are known which have as a common structural feature a tetracyclic pyrido[2,3,4-*kl*]acridine system.[2] Ascididemine **1**,[3] kuanoniamine A **2**,[4] and shermilamine A **3**[5] are typical (Figure 1). In each type, the core tetracycle is condensed with another heterocyclic ring: pyridine, thiazole, or 1,4-thiazine in these three examples, respectively. From the biological point of view, members of this group have, amongst others, important antitumor activities.[6]

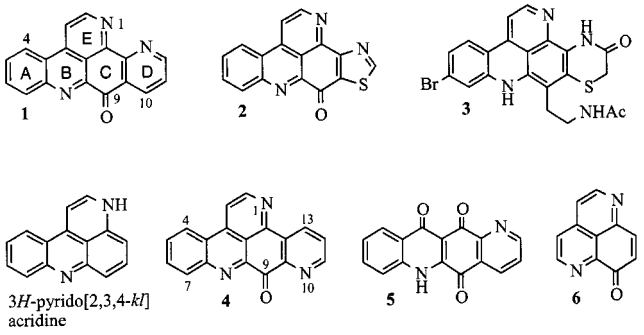

Figure 1. Structures of some naturally occurring pyrido[2,3,4-*kl*]acridines (**1**–**3**), synthetic analogues (**4**, **5**), and a synthetic model compound (**6**).

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Synthesis

We present here a full description of our total synthesis of ascididemine (9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (**1**) and of an isomer, 9*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one **(4)** in which the D ring nitrogen is at position 10 not position 13. The name "isoascididemine" has already been given to a synthetic, structural isomer (8*H*-benzo[*b*]pyrido[4,3,2-*de*]phenanthrolin-8-one) of ascididemine.[7] There have been three previous syntheses[8–10] of ascididemine, each of which adopted quite different strategies from that described here.

In our earliest work[11] in this area we prepared the tetracyclic pyridoacridinetrione **5**, which contains the A–D ring system of ascididemine, starting from 4-quinolone and methyl 3-formylpicolinate. This approach required a method for the addition of the "top" (E) ring so we conducted experiments which delineated an unambiguous method for adding this ring to such an intermediate, using a synthesis of 7-oxo-1,6-diazaphenalene **(6)**.[12] With this background, we began our synthesis of ascididemine from the known acridone **7**, readily available in two steps from 2-chlorobenzoic acid and 2,5-dimethoxyaniline.[13] Experiments aimed at producing the pyridine ring D first, by the introduction of a nitrogen into the electron-rich ring of **7**, were unsuccessful and will be described fully elsewhere. We therefore changed our synthetic route and the construction of the E ring was addressed first. Conversion of **7** into triflate **8** followed by palladium(0)-catalysed coupling with trimethylsilylacetylene proceeded in high yield giving **9**. Three quinones **10**, **12**, and **14** were prepared from **9** by CAN oxidation before and after desilylation (→ **11**) and after addition of methanol (→ **13**) to the alkyne (Scheme 1). Characteristic spectroscopic features for the quinones are: (1) the presence of two strong carbonyl stretching frequencies in the IR spectra, typical of the unsymmetrical quinones, and (2) the presence of pairs of doublets in the ^{1}H-NMR spectrum, with coupling constants of 10.2, 10.6 and 10.5 Hz,

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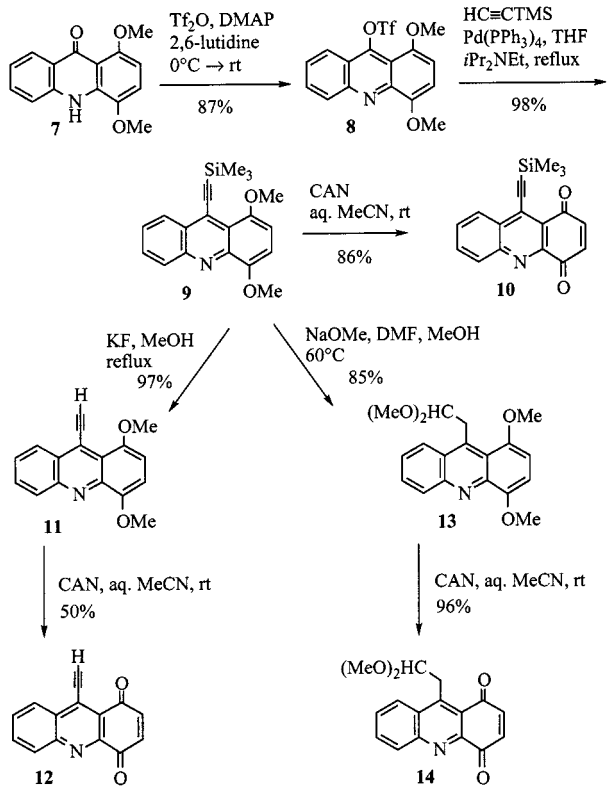
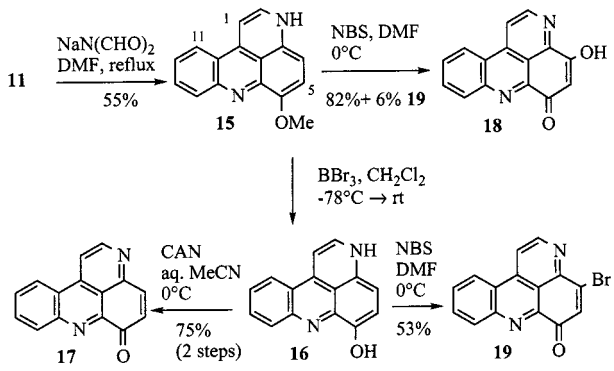
for **10**, **12** and **14**, respectively, corresponding to protons 2-H and 3-H. All attempts to introduce a nitrogen into any of these three quinones, and thus complete the E ring, were unsuccessful.[14]



Scheme 1. Synthesis of acridine quinones **10, 12,** and **14**

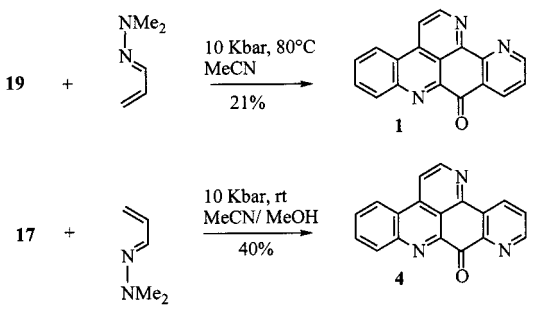
The route for construction of the "top" ring which had been successful in the model series involved reaction of an alkyne with sodium diformylamide giving an intermediate enamide which was subsequently oxidised to quinone and cyclised.[12] To our surprise and delight, reaction of alkyne **11** with $NaN(CHO)_2$[15] led directly to the desired tetracyclic system **15** without having to isolate an intermediate. The quinone-imine oxidation level was then readily achieved simply by *O*-demethylation (→ **16**) and subsequent CAN oxidation giving **17** (Scheme 2). The conversion of **11** into **15** is considered mechanistically later.



Scheme 2. Synthesis of 6*H*-4-hydroxy-, 6*H*-4-bromo- and 6*H*-pyrido[2,3,4-*kl*]acridin-6-ones **18**, **19** and **17**

Treatment of **15** with NBS gave hydroxypyridoacridinone **18** and only a trace of the anticipated and desired bromoquinone **19**. Demethylation of **15** gave phenol **16**, and now reaction with NBS produced the desired compound **19** in moderate yield, and without formation of the hydroxy compound. These results were reproducible, but are difficult to interpret. Clearly, in both brominations an oxidation has also occurred: possible explanations for this include *C*-bromination at the C-4 activated for both nitrogens, then hydrolysis,[16] or autoxidation of the substituted products during work up. It is not clear at what stage the hydroxyl group in **18** is introduced, however we could show that the bromoquinone imine is very easily transformed into the hydroxyquinone imine by treatment with aqueous base, monitored in a UV cell. Incidentally, this is strong evidence for the location of the bromine at C-4, where an addition/elimination mechanism is favoured. This conclusion was fully supported by extensive NOE, COSY and HMBC measurements which allowed a complete assignment of all ^{1}H- and ^{13}C-NMR signals in each of the tetracyclic compounds **15**–**19**. Compound **15** showed a positive NOE between 1-H and 11-H; H–H double resonance experiments permitted the assignments of signals for the protons of rings A and D, and finally, HMBC experiments were used for the assignment of the quaternary carbon signals and the hydrogen signals of the C ring. The position of the hydroxyl and bromine substituents at C-4 of **18** and **19** was unambiguously confirmed by the observation in both compounds of a correlation between the 5-H and both C-3a and C-6a.

The polarisation induced by a bromine atom has been utilised in other cases to control the orientation of cycloaddition of propenal *N,N*-dimethylhydrazone to a bromoquinone.[17,18] Accordingly, when **19** was reacted with the propenal derivative at 10 kbar and at 80°C, ascididemine (**1**) was obtained in 21% yield with spectroscopic properties identical to those of the natural product.[3] When we examined the quinone imine **17**, in which the polarising influence of the carbonyl group was expected to outweigh that of the imine, cycloaddition did indeed produce an isomer of ascididemine in 40% yield, assigned as structure **4**, and formed by reaction in the opposite regio sense. Interestingly, addition in the same regio sense was found by Kubo et al.[19] when 4-methoxyquinoline-5,8-dione and *ortho*-nitrocinnamaldehyde *N,N*-dimethylhydrazone were reacted. The conversions of **19** into **1** and of **17** into **4** appear to be the first examples of the fusion of a pyridine ring onto a qui-



Scheme 3. Aza-Diels–Alder cycloadditions

none imine (as opposed to a quinone or bromoquinone) using this aza-Diels–Alder chemistry.

A comprehensive assignment of the signals in the ^{1}H- and ^{13}C-NMR spectra of **4** utilised hetero correlation experiments, COSY, and long distance hetero correlation HMBC (Figure 2). The most important difference between the ^{1}H-NMR spectra of isomeric quinophenanthrolinones **1** and **4** is in the pattern of signals from the D ring protons: for **4**, the most deshielded doublet (J = 8.0 and 1.5 Hz) was at 9.08 ppm for 13-H whilst for **1** the most deshielded doublet (J = 4.8 and 1.8 Hz), at 9.20 ppm, corresponds to 12-H. The chemical shift of 13-H in **4** can be rationalised by invoking the anisotropic effect of the N-1 lone pair. More evidence for the structure of **4** came from HMBC experiments which revealed a correlation between 12-H (7.66 ppm) and C-13a (134.3 ppm), and a correlation between 13-H (9.08 ppm) and 11-H (8.79 ppm) with C-9a (147.5 ppm); finally in the same experiment the correlation between 13-H (9.08 ppm) and 2-H (8.93 ppm) with C-13b (148.0 ppm) confirms the orientation of the D ring.

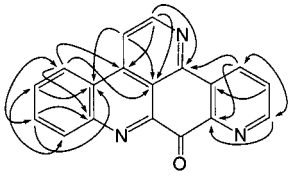


Figure 2. HMBC correlations for compound **4**

Mechanism of Formation of 15

We assume that the sequence of events in the conversion of **11** into **15** involves first, formation of an enamide **20** such as was actually isolated in the simpler series.[12] Base-catalysed deformylation (perhaps initiated by dimethylamine from the DMF) would lead to an anion **21** and an electrocyclic ring closure, seen best from the arrows on resonance contributor **22**, would provide **23** now requiring simple loss of methoxide (→ **24**) and finally deformylation, with formation of methyl formate (Scheme 4).

Biological Results

The cytotoxic activity of compounds **1**, **4** and **15–19** was tested in murine limphoma (P388D), human cell lung carcinoma (A549), human colon carcinoma (HT-29), and human melanoma (SK-MEL-28) cell lines and the results are detailed in Table 1. All those compounds present cytotoxic activity. A comparison of the activity of our tetracyclic compounds **15–19** with ascididemine **1** shows a minor activity for **16–19**, although **15** has a similar potency. Finally, the pentacyclic compound **4** presented an excellent cytotoxic activity, especially against human cell lung carcinoma (A-549) and human melanoma (MEL-28).

Table 1. Cytotoxic activity IC_{50} (μM) of compounds 1, 4, 15–19

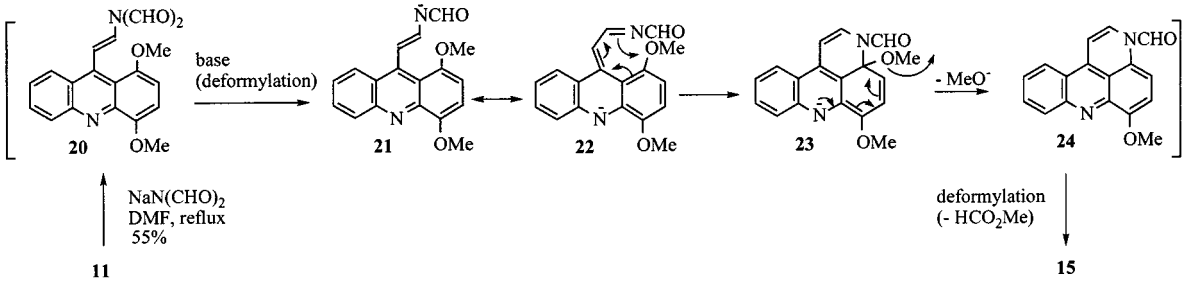
Compound	P-388D	A549	HT-29	SK-MEL-28
1[a] (ascididemine)	0.35	0.02	0.35	0.004
4	0.03	0.004	0.17	0.009
15	0.50	0.05	0.50	0.05
16	4.25	4.25	21.37	4.25
17	1.08	4.31	4.31	4.31
18	4.03	1.01	4.03	1.01
19	3.21	1.61	1.61	1.61

[a] Tested on related HCT-116 line cells.[3]

Experimental Section

General: Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica Gel 60 F_{254}, Merck 0.063–0.200 mm) and spots were located with UV light. Column chromatography was carried out on SiO_2 (silica Gel 60 SDS 0.060–0.2 mm). Flash chromatography was carried out on SiO_2 (silica Gel 60 A CC, Merck). Organic extracts were dried with anhydrous Na_2SO_4, and solutions were evaporated under reduced pressure in a rotatory evaporator. IR spectra were performed with a Nicolet 205 FT-IR. NMR spectra were measured with Varian Gemini 200 (200 MHz), Varian Gemini 300 (300 MHz) and Varian VXR-500 (500 MHz) spectrometers; data are given in δ referenced to TMS. Mass spectra were measured in the electron impact (EI) or chemical ionization (QI) mode with a Hewlett-Packard model 5989A. High resolution mass spectra were performed with an Autospec/VG by the Departament de Química Orgànica Biològica (C.S.I.C.) Barcelona. Elemental analyses were performed with a C. E. Instruments EA-1108 in the Serveis Científico-Tècnics de la Universitat de Barcelona.

2-[(2,5-Dimethoxyphenyl)amino]benzoic Acid:[13] A solution of 2,5-dimethoxyaniline (2.0 g, 13 mmol), 2-chlorobenzoic acid (1.0 g, 6.5 mmol), Cu powder (0.05 g, 0.8 mmol), and K_2CO_3 (1.8 g,



Scheme 4. Mechanism of formation of **15**

13 mmol) in amyl alcohol (10 mL) was stirred and refluxed for 1 h. The reaction mixture was allowed to cool to room temperature, H_2O (60 mL) was added and the organic solvent evaporated. H_2O (60 mL) was added and the aqueous solution was stirred for 15 min with charcoal, filtered through celite, and acidified with conc. HCl. The resulting precipitate was collected and dried to give 2-[(2,5-dimethoxyphenyl)amino]benzoic acid (1.5 g, 84%). m.p. 160–162 °C (CCl_4) (ref.[13] 162–163 °C). – IR (KBr): $\tilde{\nu}$ = 3451 cm^{-1} (s, OH), 3320 (s, NH), 1673 (s, CO), 1245 (s, C-Ar). – ^1H NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.58 (dd, *J* = 8.8 and 3.0 Hz, 1 H, H-4'), 6.78 (dd, *J* = 7.5 and 6.8 Hz, 1 H, H-5), 6.88 (d, *J* = 8.8 Hz, 1 H, H-3'), 7.04 (d, *J* = 3.0 Hz, 1 H, H-6'), 7.36 (m, 2 H, H-3 and H-4), 8.06 (d, *J* = 7.5 Hz, 1 H, H-6), 9.25 (br, 1 H, NH). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 55.6 (q, OCH_3), 56.3 (q, OCH_3), 107.1 (d, C-4'), 107.5 (d, C-6'), 112.1 (d, C-3'), 114.5 (d, C-3), 117.4 (d, C-5), 128.4 (s, C-1), 130.6 (s, C-1'), 132.6 (s, C-6), 134.8 (d, C-4), 145.8 (s, C-2'), 147.6 (s, C-2), 153.6 (s, C-5'), 166.0 (s, C=O). – MS (EI); *m/z* (%) = 274 [M + 1] (18), 273 [M^+] (100), 258 (38), 212 (41).

1,4-Dimethoxyacridone[13] **(7):** PPA (15 g) was added to 2-[(2,5-dimethoxy-phenyl)amino]benzoic acid (1.5 g, 5.5 mmol) and the mixture was stirred at 100 °C for 3 h. The cooled mixture was poured into H_2O (150 mL) and made basic with conc. NH_3. The resulting precipitate was collected by filtration, dried and purified by column chromatography. Elution with CH_2Cl_2 afforded **7** (1.2 g, 85%) as a yellow solid; m.p. 222–223 °C (CH_2Cl_2) (ref.[13] 220–221 °C). – IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (s, NH), 1626 (s, CO), 1248 (s, C-Ar). – ^1H NMR (200 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 6.53 (d, *J* = 8.8 Hz, 1 H, H-2), 7.02 (d, *J* = 8.8 Hz, 1 H, H-3), 7.24 (dd, *J* = 8.0 and 7.9 Hz, 1 H, H-7), 7.29 (d, *J* = 8.4 Hz, 1 H, H-5), 7.61 (dd, *J* = 8.4 and 7.9 Hz, 1 H, H-6), 8.46 (d, *J* = 8.0 Hz, 1 H, H-8), 8.54 (br, 1 H, NH). – ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 56.0 (q, OCH_3), 56.1 (q, OCH_3), 100.3 (d, C-2), 111.8 (d, C-3), 112.2 (s, C-9a), 116.2 (d, C-5), 121.5 (d, C-8), 123.0 (s, C-8a), 127.2 (d, C-7), 132.8 (d, C-6), 133.4 (s, C-4a), 138.8 (s, C-10a), 140.3 (s, C-4), 154.3 (s, C-1), 177.7 (s, C=O). – MS (CI); *m/z* (%) = 296 [M + 41] (1), 284 [M + 29] (12), 256 [M + 1] (100), 255 [M^+] (25).

1,4-Dimethoxy-9-(trifluoromethylsulfonyloxy)acridine (8): To a solution of **7** (1.0 g, 3.9 mmol) in dry CH_2Cl_2 (18 mL) under N_2 were successively added DMAP (95 mg, 0.8 mmol), 2,6-lutidine (0.6 mL, 5.5 mmol) and Tf_2O (0.8 mL, 4.7 mmol); the reaction mixture was stirred at 0 °C for 2 h and then for 1 h at room temp. The solution was washed with H_2O, dried and evaporated to dryness. The residue was purified by column chromatography (hexane/CH_2Cl_2 1:1) to give **8** (1.3 g, 87%), as a yellow solid. – IR (KBr): $\tilde{\nu}$ = 1253 cm^{-1} (s, SO), 1030 (s, SO). – ^1H NMR (200 MHz, $CDCl_3$): δ = 4.04 (s, 3 H, OCH_3), 4.14 (s, 3 H, OCH_3), 6.83 (d, *J* = 8.4 Hz, 1 H, H-2), 7.01 (d, *J* = 8.4 Hz, 1 H, H-3), 7.68 (dd, *J* = 8.5 and 7.8 Hz, 1 H, H-7), 7.86 (dd, *J* = 8.5 and 7.8 Hz, 1 H, H-6), 8.22 (d, *J* = 8.5 Hz, 1 H, H-5), 8.43 (d, *J* = 8.5 Hz, 1 H, H-8). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 55.2 (q, OCH_3), 56.3 (q, OCH_3), 104.2 (d, C-2), 106.6 (d, C-3), 113.3 (s, C-9a), 118.5 (q, CF_3), 119.1 (s, C-8a), 120.7 (d, C-7), 122.5 (s, C-4a), 127.6 (d, C-6), 129.8 (d, C-8), 130.9 (d, C-5), 144.2 (s, C-10a), 147.2 (s, C-1), 148.7 (s, C-4), 148.8 (s, C-9). – MS (EI); *m/z* (%) = 388 [M + 1] (9), 387 [M^+] (42), 254 (100), 226 (69). – HRMS ($C_{16}H_{12}F_3NO_5S$): calcd. 387.0388; found 387.0394.

1,4-Dimethoxy-9-(trimethylsilylethynyl)acridine (9): To a solution of **8** (1.2 g, 3.1 mmol) in dry THF (10 mL) under N_2 were successively added $Pd(PPh_3)_4$ (0.3 g, 0.3 mmol), *i*Pr_2NEt (1.6 mL, 9.3 mmol) and trimethylsilylacetylene (1.3 mL, 9.3 mmol). The mixture was stirred at reflux for 5 h. After this time the solvent was evaporated and the residue was dissolved in CH_2Cl_2 and washed with water. The organic solution was dried and evaporated affording a residue which was purified by column chromatography. Elution with hexane/CH_2Cl_2 (1:1) gave **9** (1.0 g, 98%) as a red solid; m.p. 110–111 °C (CH_2Cl_2). – IR (film): $\tilde{\nu}$ = 2810 cm^{-1} (w, CC), 1608 (s, Ar), 1527 (m, Ar), 1468 (s, Ar). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.41 (s, 9 H, 3 CH_3), 3.99 (s, 3 H, OCH_3), 4.11 (s, 3 H, OCH_3), 6.75 (d, *J* = 8.4 Hz, 1 H, H-2), 6.93 (d, *J* = 8.4 Hz, 1 H, H-3), 7.63 (dd, *J* = 8.0 and 7.2 Hz, 1 H, H-7), 7.78 (dd, *J* = 8.4 and 7.2 Hz, 1 H, H-6), 8.35 (d, *J* = 8.4 Hz, 1 H, H-5), 8.64 (d, *J* = 8.0 Hz, 1 H, H-8). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 0.0 (q, CH_3), 55.8 (q, OCH_3), 56.1 (q, OCH_3), 101.5 (s, C–Si), 103.9 (d, C-2), 105.7 (d, C-3), 111.8 (s, C), 120.5 (s, C-9a), 126.4 (d, C-7), 126.9 (d, C-6), 127.5 (s, C-9), 129.9 (d, C-5), 130.0 (s, C-8a), 130.3 (d, C-8), 142.1 (s, C-4a), 147.0 (s, C-1), 149.4 (s, C-4 and C-10a). – MS (EI); *m/z* (%) = 336 [M + 1] (10), 335 [M^+] (36), 320 (100), 306 (13), 290 (10), 262 (14). – HRMS ($C_{20}H_{21}NO_2Si$): calcd. 335.1341; found 335.1336. – $C_{20}H_{21}NO_2Si·1/8CH_2Cl_2$ (346.10): calcd. C 69.84, H 6.19, N 4.05; found C 69.70, H 6.42, N 4.09.

1,4-Dihydro-1,4-dioxo-9-(trimethylsilylethynyl)acridine (10): A solution of CAN (438 mg, 0.8 mmol) in H_2O (1 mL) was added to a solution of **9** (124 mg, 0.4 mmol) in MeCN (3 mL) and the mixture was stirred for 10 min at room temp. After this time H_2O (5 mL) was added and the solution was extracted with CH_2Cl_2. The organic layer was dried and evaporated giving **10** (105 mg, 86%) as a black solid; m.p. 115–116 °C (CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 2810 cm^{-1} (w, CC), 1720 (s, CO), 1667 (s, CO), 1612 (m, Ar), 1249 (m, Ar). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.44 (s, 9 H, 3 CH_3), 7.13 (d, *J* = 10.2 Hz, 1 H, H-2), 7.22 (d, *J* = 10.2 Hz, 1 H, H-3), 7.83 (dd, *J* = 8.4 and 7.6 Hz, 1 H, H-7), 7.95 (dd, *J* = 8.6 and 7.6 Hz, 1 H, H-6), 8.44 (d, *J* = 8.6 Hz, 1 H, H-5), 8.60 (d, *J* = 8.4 Hz, 1 H, H-8). – ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = –0.2 (q, CH_3), 99.0 (s, C–Si), 116.9 (s, C), 127.8 (d, C-6), 129.8 (s, C-9a), 130.7 (d, C-7), 131.2 (s, C-9), 132.0 (d, C-5), 132.3 (s, C-8a), 133.2 (d, C-8), 138.6 (d, C-2), 140.6 (d, C-3), 146.6 (s, C-4a), 148.7 (s, C-10a), 183.0 (s, C=O), 183.1 (s, C=O). – MS (EI); *m/z* (%) = 306 [M + 1] (15), 305 [M^+] (48), 304 (54), 262 (100), 232 (34). – HRMS ($C_{18}H_{15}NO_2Si$): calcd. 305.0872; found 305.0877.

1,4-Dimethoxy-9-ethynylacridine (11): KF (0.5 g, 9.0 mmol) was added to a solution of **9** (1 g, 3.0 mmol) in MeOH (30 mL) and the mixture was stirred at reflux for 30 min. The solvent was evaporated and the residue was dissolved in CH_2Cl_2. The organic solution was washed with H_2O, dried and evaporated to give **11** (764 mg, 97%) as a brown solid; m.p. 155–157 °C (Et_2O). – IR (KBr): $\tilde{\nu}$ = 2100 cm^{-1} (w, CC), 1625 (m, Ar), 1460 (m, Ar). – ^1H NMR (200 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, OCH_3), 4.10 (s, 3 H, OCH_3), 4.20 (s, 1 H, CH), 6.75 (d, *J* = 8.4 Hz, 1 H, H-2), 6.92 (d, *J* = 8.4 Hz, 1 H, H-3), 7.62 (dd, *J* = 8.4 and 7.4 Hz, 1 H, H-7), 7.78 (dd, *J* = 8.6 and 7.4 Hz, 1 H, H-6), 8.36 (d, *J* = 8.6 Hz, 1 H, H-5), 8.66 (d, *J* = 8.4 Hz, 1 H, H-8). – ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 56.0 (q, OCH_3), 56.1 (q, OCH_3), 85.6 (s, C), 92.7 (d, CH), 104.1 (d, C-2), 105.8 (d, C-3), 121.0 (s, C-9a), 124.2 (s, C-9), 126.2 (d, C-6), 127.1 (d, C-7), 127.8 (s, C-8a), 130.0 (d, C-8), 130.4 (d, C-5), 141.3 (s, C-4a), 147.5 (s, C-1), 149.3 (s, C-10a), 149.5 (s, C-4). – MS (EI); *m/z* (%) = 264 [M + 1] (7), 263 [M^+] (35), 248 (100). – HRMS ($C_{17}H_{13}NO_2$): calcd. 263.0946; found 263.0940.

9-Ethynyl-1,4-dihydro-1,4-dioxoacridine (12): A solution of CAN (438 mg, 0.8 mmol) in H_2O (1 mL) was added to a solution of **11** (100 mg, 0.4 mmol) in MeCN (3 mL) and the mixture stirred for 10 min at room temp. H_2O (5 mL) was then added and the solution extracted with CH_2Cl_2. The organic layer was dried and evaporated affording a residue which was purified by column chromatography.

Elution with CH_2Cl_2 gave the quinone **12** (47 mg, 50%). IR (film): $\tilde{\nu}$ = 2160 cm^{-1} (w, CC), 1683 (s, CO), 1658 (s, CO), 1610 (m, Ar), 1342 (m, Ar). – ^1H NMR (200 MHz, $CDCl_3$): δ = 4.33 (s, 1 H, CCH), 7.16 (d, *J* = 10.6 Hz, 1 H, H-2), 7.25 (d, *J* = 10.6 Hz, 1 H, H-3), 7.85 (dd, *J* = 8.4 and 7.4 Hz, 1 H, H-7), 7.98 (dd, *J* = 8.4 and 7.4 Hz, 1 H, H-6), 8.47 (d, *J* = 8.4 Hz, 1 H, H-5), 8.65 (d, *J* = 8.4 Hz, 1 H, H-8). – ^{13}C NMR (75.4 MHz, $CDCl_3$): δ =129.4 (d, C-6), 132.1 (d, C-7), 132.3 (d, C-5), 133.0 (d, C-8), 138.6 (d, C-2), 141.1 (d, C-3). – MS (EI); *m*/*z* (%) = 235 [M + 2] (100), 234 [M + 1] (41), 233 [M^+] (25), 206 (18). – HRMS ($C_{15}H_7NO_2$): calcd. 233.0477; found 233.0471.

1,4-Dimethoxy-9-(2,2-dimethoxyethyl)acridine (13): A solution of **9** (300 mg, 0.9 mmol) in dry DMF (1.5 mL) was added to a solution of NaOMe (200 mg, 3.7 mmol) in dry MeOH (1.3 mL). The black mixture was stirred at 60 °C for 2 h, H_2O (4 mL) was added and the solution extracted with ether. The organic layer was washed with H_2O, dried and evaporated to give **13** (250 mg, 85%) as an orange oil. – IR (film): $\tilde{\nu}$ = 1625 cm^{-1} (s, Ar), 1463 (s, Ar), 1245 (s, Ar). – ^1H NMR (200 MHz, $CDCl_3$): δ = 3.27 (s, 6 H, 2 OCH_3), 3.92 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 4.20 (d, *J* = 5.0 Hz, 2 H, CH_2), 4.80 (t, *J* = 5.0 Hz, 1 H, $CH(OMe)_2$), 6.63 (d, *J* = 8.2 Hz, 1 H, H-2), 6.83 (d, *J* = 8.2 Hz, 1 H, H-3), 7.52 (dd, *J* = 8.8 and 7.4 Hz, 1 H, H-7), 7.73 (dd, *J* = 8.9 and 7.4 Hz, 1 H, H-6), 8.33 (d, *J* = 8.9 Hz, 1 H, H-5), 8.51 (d, *J* = 8.8 Hz, 1 H, H-8). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 33.9 (t, CH_2), 53.4 (q, 2 OCH_3), 54.3 (q, OCH_3), 55.1 (q, OCH_3), 101.5 (d, $CH(OMe)_2$), 104.0 (d, C-2), 106.0 (d, C-3), 118.8 (s, C-9a), 124.6 (d, C-6), 124.8 (d, C-7), 126.1 (s, C-8a), 128.5 (d, C-8), 129.4 (d, C-5), 141.2 (s, C-9), 141.4 (s, C-4a), 146.4 (s, C-10a), 148.5 (s, C-1), 149.4 (s, C-4). – MS (EI); *m*/*z* (%) = 328 [M + 1] (1), 327 [M^+] (5), 253 (16), 238 (19), 75 (100). – HRMS ($C_{19}H_{21}NO_4$): calcd. 327.1470; found 327.1457.

1,4-Dihydro-1,4-dioxo-9-(2,2-dimethoxyethyl)acridine (14): To a solution of acetal **13** (229 mg, 0.7 mmol) in MeCN (4.5 mL) was added a solution of CAN (767 mg, 1.4 mmol) in H_2O (1.5 mL). The mixture was stirred for 10 min at room temp., H_2O (5 mL) was added, and the solution was extracted with CH_2Cl_2. The organic solution was dried and evaporated to give **14** (200 mg, 96%) as a black oil. – IR (film): $\tilde{\nu}$ = 1682 cm^{-1} (s, CO), 1662 (s, CO), 1269 (m, Ar), 1115 (s, Ar). – ^1H NMR (200 MHz, $CDCl_3$): δ = 3.38 (s, 6 H, 2 OCH_3), 4.07 (d, *J* = 5.4 Hz, 2 H, CH_2), 4.69 (t, *J* = 5.4 Hz, 1 H, $CH(OMe)_2$), 7.09 (d, *J* = 10.5 Hz, 1 H, H-2), 7.20 (d, *J* = 10.5 Hz, 1 H, H-3), 7.76 (dd, *J* = 8.4 and 7.1 Hz, 1 H, H-7), 7.91 (dd, *J* = 8.0 and 7.1 Hz, 1 H, H-6), 8.41 (d, *J* = 8.0 Hz, 1 H, H-5), 8.51 (d, *J* = 8.4 Hz, 1 H, H-8). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 33.1 (t, CH_2), 54.9 (q, 2 OCH_3), 105.2 (d, $CH(OMe)_2$), 123.5 (s, C-8a), 127.3 (d, C-6), 129.4 (d, C-7), 130.0 (s, C-9a), 131.9 (d, C-8), 132.6 (d, C-5), 137.9 (d, C-2), 141.6 (d, C-3), 146.8 (s, C-9), 148.1 (s, C-4a), 149.7 (s, C-10a), 183.8 (s, C=O), 186.4 (s, C=O). – MS (EI); *m*/*z* (%) = 299 [M + 2] (1), 297 [M^+] (1), 267 (45), 235 (66), 222 (28), 83 (100).

6-Methoxy-3*H*-pyrido[2,3,4-*kl*]acridine (15): Sodium diformylamide[15] (190 mg, 2.0 mmol) was added to a solution of **11** (217 mg, 0.8 mmol) in dry DMF (2 mL) and the mixture was stirred at reflux for 30 min. The solvent was removed and the residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic solution was dried and evaporated affording a residue which was purified by column chromatography. Elution with CH_2Cl_2/MeOH (99:2) gave **15** (109.5 mg, 55%); m.p. 148–150 °C (EtOAc). – IR (KBr): $\tilde{\nu}$ = 1686 cm^{-1} (s, C=N), 1599 (s, Ar), 1573 (s, Ar), 1460 (s, Ar). – ^1H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 6.75 (d, *J* = 7.8 Hz, 1 H, H-8), 6.85 (dd, *J* = 8.0 and 7.5 Hz, 1 H, H-10), 6.99 (d, *J* = 5.0 Hz, 1 H, H-1), 7.18 (dd, *J* = 7.8 and 7.5 Hz, 1 H, H-9), 7.20 (d, *J* = 9.0 Hz, 1 H, H-4), 7.23 (d, *J* = 9.0 Hz, 1 H, H-5), 7.66 (d, *J* = 8.0 Hz, 1 H, H-11), 8.37 (d, *J* = 5.0 Hz, 1 H, H-2). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 56.3 (q, OCH_3), 106.1 (d, C-1), 115.1 (d, C-4), 115.3 (d, C-5), 115.6 (d, C-8), 117.4 (s, C-11a), 118.7 (s, C-11c), 121.0 (d, C-10), 123.9 (d, C-11), 125.2 (s, C-6), 131.5 (d, C-9), 137.2 (s, C-6a), 139.2 (2s, C-7a and C-11), 144.5 (s, C-3a), 150.3 (d, C-2). – MS (EI); *m*/*z* (%) = 249 [M + 1] (11), 248 [M^+] (45), 234 (21), 233 (100). – HRMS ($C_{16}H_{12}N_2O$): calcd. 248.0949; found 248.0938. – $C_{16}H_{12}N_2O{\cdot}0.5CH_3CO_2C_2H_5$ (292.35): calcd. C 73.95, H 5.52, N 9.58; found C 73.67, H 5.42, N, 9.64.

6-Hydroxy-3*H*-pyrido[2,3,4-*kl*]acridine (16) and 6*H*-Pyrido[2,3,4-*kl*]acridin-6-one (17) :[20] BBr_3 (8.3 mL, 8.3 mmol) was added to a solution of **15** (0.4 g, 1.6 mmol) in CH_2Cl_2 (20 mL) cooled at –78 °C and maintained under nitrogen. The reaction temperature was increased gradually to –30 °C during 90 min and then to room temperature during 30 min. The reaction mixture was neutralised with saturated aq. Na_2CO_3 and extracted with CH_2Cl_2. The organic solution was dried and evaporated to give **16** as a gum. – IR (KBr): $\tilde{\nu}$ = 3430 cm^{-1} (s, OH and NH), 1588 (s, Ar), 1318 (s, Ar), 1052 (s, Ar). – ^1H NMR (300 MHz, CD_3OD): δ = 6.92 (d, *J* = 8.7 Hz, 1 H, H-4), 7.04 (d, *J* = 6.5 Hz, 1 H, H-1), 7.09 (dd, *J* = 8.5 and 7.1 Hz, 1 H, H-10), 7.28 (d, *J* = 8.4 Hz, 1 H, H-8), 7.33 (d, *J* = 8.7 Hz, 1 H, H-5), 7.51 (dd, *J* = 8.4 and 7.1 Hz, 1 H, H-9), 7.79 (d, *J* = 8.5 Hz, 1 H, H-11), 7.93 (d, *J* = 6.5 Hz, 1 H, H-2). – ^{13}C NMR (75.4 MHz, CD_3OD): δ = 104.1 (d, C-1), 106.1 (d, C-4), 116.3 (s, C-11a), 118.6 (d, C-5), 121.1 (s, C-6b), 121.6 (d, C-8), 124.0 (d, C-10), 126.1 (d, C-11), 127.0 (s, C-11b), 132.9 (s, C-7a), 136.1 (d, C-9), 139.5 (s, C-6a), 141.8 (s, C-3a), 143.2 (d, C-2), 150.3 (s, C-6). – MS (EI); *m*/*z* (%) = 235 [M + 1] (26), 234 [M^+] (100), 205 (27), 117 (17). – HRMS ($C_{15}H_{10}N_2O$): calcd. 234.0793; found 234.0790. The hydroxyacridine was dissolved in MeCN (12 mL) and a solution of CAN (883 mg, 0.2 mmol) in H_2O (4 mL) was added. The reaction mixture was stirred for 15 min at 0 °C, diluted with H_2O (10 mL) and extracted with CH_2Cl_2. The organic solution was dried and evaporated to give **17** (281 mg, 75%) as a yellow solid; m.p. >300 °C (CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 1664 cm^{-1} (s, CO), 1610 (s, Ar), 1384 (s, Ar). – ^1H NMR (500 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 10.5 Hz, 1 H, H-5), 7.87 (d, *J* = 10.5 Hz, 1 H, H-4), 7.91 (t, *J* = 7.5 Hz, 1 H, H-10), 7.98 (t, *J* = 7.5 Hz, 1 H, H-9), 8.39 (d, *J* = 6.0 Hz, 1 H, H-1), 8.59 (d, *J* = 7.5 Hz, 1 H, H-8), 8.62 (d, *J* = 7.5 Hz, 1 H, H-11), 9.00 (d, *J* = 6.0 Hz, 1 H, H-2). – ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 116.3 (d, C-1), 118.2 (s, C-11c), 122.8 (d, C-11), 123.2 (s, C-11a), 130.6 (d, C-10), 131.6 (d, C-9), 133.1 (2d, C-5 and C-8), 136.8 (s, C-11b), 143.1 (d, C-4), 145.8 (s, C-6a), 146.1 (s, C-7a), 149.1 (d, C-2), 151.1 (s, C-3a), 183.6 (s, C=O). – MS (EI); *m*/*z* (%) = 234 [M + 2] (17), 233 [M + 1] (32), 232 [M^+] (65), 204 (100). – HRMS ($C_{15}H_8N_2O$): calcd. 232.0637; found 232.0631.

4-Hydroxy-6*H*-pyrido[2,3,4-*kl*]acridin-6-one (18) and 4-Bromo-6*H*-pyrido[2,3,4-*kl*]acridin-6-one (19): NBS (35 mg, 0.2 mmol) was added to a solution of **15** (50 mg, 0.2 mmol) in DMF (5 mL) cooled to 0 °C and the mixture was stirred for 30 min. The solvent was evaporated at reduced pressure and the residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic solution was dried and evaporated to give a crude product which was purified by column chromatography. Elution with hexane/CH_2Cl_2 (1:1) gave **19** (4 mg, 6%); m.p. 132–133 °C (CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 1697 cm^{-1} (s, CO), 1658 (s, Ar), 1180 (s, Ar). – ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55 (s, 1 H, H-5), 7.93 (ddd, *J* = 8.0, 7.5, and 1.0 Hz, 1 H, H-10), 7.99 (ddd, *J* = 8.0, 7.5, and 1.0 Hz, 1 H, H-9), 8.47 (d, *J* = 5.5 Hz, 1 H, H-1), 8.55 (dd, *J* = 8.0 and 1.0 Hz, 1 H, H-8), 8.62 (dd, *J* = 8.0 and 1.0 Hz, 1 H, H-11), 9.10 (d, *J* = 5.5 Hz, 1 H, H-2). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 116.6 (d, C-1), 121.8 (s, C-11a), 122.0 (d, C-11), 130.0 (d, C-10), 131.5 (d, C-9), 131.9 (d,

C-8), 134.9 (s, C-4), 135.1 (d, C-5), 136.1 (s, C-11b), 142.9 (s, C-6b), 144.3 (s, C-6a), 144.6 (s, C-7a), 147.8 (d, C-2), 148.1 (s, C-3a), 180.0 (s, C=O). – MS (EI); *m/z* (%) = 312 [M + 2] (57), 310 [M^+] (44), 284 (50), 282 (50), 232 (30), 231 (16), 83 (100). – HRMS ($C_{15}H_7BrN_2O$): calcd. 309.9742; found 309.9736.

Elution with CH_2Cl_2/MeOH (99:1) gave **18** (41 mg, 82%) as a solid; m.p. 137–138 °C (CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 3520 cm^{-1} (s, OH), 1708 (s, CO), 1665 (s, Ar), 1579 (s, Ar). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16 (s, 1 H, H-5), 7.94 (dd, *J* = 8.5 and 8.0 Hz, 1 H, H-10), 8.01 (dd, *J* = 8.5 and 8.0 Hz, 1 H, H-9), 8.39 (d, *J* = 5.5 Hz, 1 H, H-1), 8.64 (d, *J* = 8.5 Hz, 2 H, H-8 and H-11), 8.78 (d, *J* = 5.5 Hz, 1 H, H-2). – ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 116.6 (d, C-1), 118.9 (s, C-6b), 122.8 (d, C-11), 123.5 (s, C-11a), 130.9 (d, C-10), 131.8 (d, C-9), 132.1 (d, C-5), 133.4 (d, C-8), 137.2 (s, C-11b), 146.0 (s, C-7a), 146.4 (s, C-6a), 148.6 (d, C-2), 151.0 (s, C-3a), 177.0 (s, C-4), 183.2 (s, C=O). – MS (EI); *m/z* (%) = 249 [M + 1] (100), 248 [M^+] (5), 205 (35). – HRMS ($C_{15}H_8N_2O_2$): calcd. 248.0936; found 248.0940.

4-Bromo-6*H*-pyrido[2,3,4-*kl*]acridin-6-one (19): NBS (17 mg, 0.1 mmol) was added to a solution of **16** (23 mg, 0.1 mmol) in DMF (3 mL) cooled at 0 °C and the mixture was stirred for 30 min. The solvent was evaporated at reduced pressure and the residue was dissolved in CH_2Cl_2 and washed with H_2O. The organic solution was dried and evaporated to give crude material which was purified by column chromatography. Elution with CH_2Cl_2/MeOH (99:1) gave the bromoacridinone **19** (15 mg, 53%).

Ascididemine (9*H*-Quino[4,3,2-*de*][1,10]phenanthrolin-9-one) (1): A solution of propenal dimethylhydrazone[7] (19 mg, 0.2 mmol) and bromopyridoacridinone **19** (15 mg, 0.05 mmol) in a dry MeCN (2 mL) was maintained at 10 Kbar and 80 °C for 18 h. The solvent was evaporated at reduced pressure and the residue dissolved in MeCN (3 mL) then a solution of CAN (53 mg, 0.1 mmol) in H_2O (1 mL) was added. The mixture was stirred at 0 °C for 15 min. After this time H_2O (5 mL) was added and the solution was extracted with CH_2Cl_2. The organic solution was dried and evaporated giving a residue which was purified by column chromatography. Elution with CH_2Cl_2/MeOH (97:3) afforded ascididemine (3 mg, 21%). – IR (film) $\tilde{\nu}$ = 1707 cm^{-1} (s, CO), 1683 (s, CN), 1578 (s, Ar), 1413 (s, Ar). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 8.0 and 4.8 Hz, 1 H, H-11), 7.98 (ddd, *J* = 8.2, 7.7 and 1.3 Hz, 1 H, H-5), 8.06 (ddd, *J* = 8.2, 7.7 and 1.3 Hz, 1 H, H-6), 8.59 (d, *J* = 5.6 Hz, 1 H, H-3), 8.67 (dd, *J* = 7.7 and 1.3 Hz, 1 H, H-7), 8.74 (dd, *J* = 7.7 and 1.3 Hz, 1 H, H-4), 8.83 (dd, *J* = 8.0 and 1.8 Hz, H-10), 9.20 (dd, *J* = 4.8 and 1.8 Hz, 1 H, H-12), 9.32 (d, *J* = 5.6 Hz, 1 H, H-2). – ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 117.0 (d, C-3), 118.1 (s, C-13c), 123.0 (d, C-4), 123.5 (s, C-3b), 125.7 (d, C-11), 129.7 (s, C-9a), 131.0 (d, C-5), 132.0 (d, C-6), 132.7 (d, C-7), 136.6 (d, C-10), 138.0 (s, C-3a), 145.5 (s, C-7a), 146.5 (s, C-8a), 149.6 (d, C-2), 152.1 (s, C-13b), 155.4 (d, C-12), 157.0 (s, C-13a). – MS (EI); *m/z* (%) = 284 [M + 1] (22), 283 [M^+] (83), 227 (14), 255 (100). – HRMS ($C_{18}H_9N_3O$): calcd. 283.0746; found 283.0743.

9*H*-Quino[4,3,2-*de*][1,7]phenanthrolin-9-one (4): A solution of propenal dimethylhydrazone[7] (95 mg, 1 mmol) and pyridoacridinone **17** (45 mg, 0.2 mmol) in a dry mixture of MeCN/MeOH (1:1, 3 mL) was maintained at 10 Kbar and room temperature for 24 h. The solvent was then evaporated at reduced pressure. The residue was dissolved in MeCN (3 mL) and a solution of CAN (213 mg, 0.4 mmol) in H_2O (1 mL) was added. The mixture was stirred at 0 °C for 15 min. After this time H_2O was added and the solution was extracted with CH_2Cl_2. The organic solution was dried and evaporated giving a residue which was purified by column chromatography. Elution with CH_2Cl_2/MeOH (99:1) afforded the pyridoacridone **17** (7 mg) and with CH_2Cl_2/MeOH (98:2) **4** (22 mg, 40%) as an orange foam. – IR (KBr): $\tilde{\nu}$ = 1691 cm^{-1} (s, CO), 1650 (s, Ar), 1600 (s, Ar), 1580 (s, Ar). – ^{1}H NMR [500 MHz, $CDCl_3$/CD_3OD (3.5:1.5)]: δ = 7.66 (dd, *J* = 8.0 and 4.5 Hz, 1 H, H-12), 7.80 (ddd, *J* = 8.0, 7.5 and 1.0 Hz, 1 H, H-5), 7.86 (ddd, *J* = 8.0, 7.5 and 1.0 Hz, 1 H, H-6), 8.39 (d, *J* = 5.5 Hz, 1 H, H-3), 8.40 (dd, *J* = 8.0 and 1.0 Hz, 1 H, H-7), 8.56 (dd, *J* = 8.0 and 1.0 Hz, 1 H, H-4), 8.79 (dd, *J* = 4.5 and 1.5 Hz, 1 H, H-11), 8.93 (d, *J* = 5.5 Hz, 1 H, H-2), 9.08 (dd, *J* = 8.0 and 1.5 Hz, 1 H, H-13). – ^{13}C NMR [75.4 MHz, $CDCl_3$/CD_3OD (3.5:1.5)]: δ = 117.1 (d, C-3), 117.5 (s, C-13c), 123.7 (d, C-4), 124.1 (s, C-3b), 129.3 (d, C-12), 131.6 (d, C-5), 132.7 (d, C-6), 132.9 (d, C-7), 134.3 (s, C-13a), 135.0 (d, C-13), 138.6 (s, C-3a), 146.0 (s, C-7a), 147.5 (s, C-9a), 148.0 (s, C-13b), 149.4 (s, C-8a), 149.7 (d, C-2), 152.8 (d, C-11), 181.3 (s, C-9). – MS (EI); *m/z* (%) = 285 [M + 2] (57), 284 [M + 1] (37), 283 [M^+] (72), 255 (100), 228 (40), 201 (34), 175 (13). – HRMS ($C_{18}H_9N_3O$): calcd. 283.0746; found 283.0747.

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