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A Convenient New Route to 4-Substituted Benzo[de][3,6]Phenanthrolin-6(6H)-Ones: Important Intermediates in the Synthesis of Ring-A Analogues of the Cytotoxic Marine Alkaloid Ascididemin

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A CONVENIENT NEW ROUTE TO 4-SUBSTITUTED BENZO[*de*][3,6]PHENANTHROLIN-6(6*H*)-ONES: IMPORTANT INTERMEDIATES IN THE SYNTHESIS OF RING-A ANALOGUES OF THE CYTOTOXIC MARINE ALKALOID ASCIDIDEMIN.

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Abstract 4-ethylthio- and 4-(4"-methylphenylthio)benzo[*de*][3,6]phenanthrolin-6(6*H*)-one have been synthesised in 4 steps from benzoquinone and then readily converted to the 4-amino (**6d**) and 4-methoxy (**6c**) analogues by nucleophilic substitution. Further elaboration of **6d** leads to the synthesis of 11-hydroxyascididemin, which we have found to exhibit antiviral activity *in vitro*.

As part of an ongoing structure-activity relationship study of the cytotoxic marine alkaloid ascididemin[1] (**1**) we required an efficient synthesis of 4-substituted benzo[*de*][3,6]phenanthrolin-6(6*H*)-ones. One report of the synthesis of the parent alkaloid has been made by Kashman *et al.* using a low yielding biomimetic route,[2] while syntheses of the 4-amino and 4-methoxy analogues have recently been

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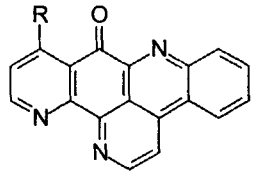
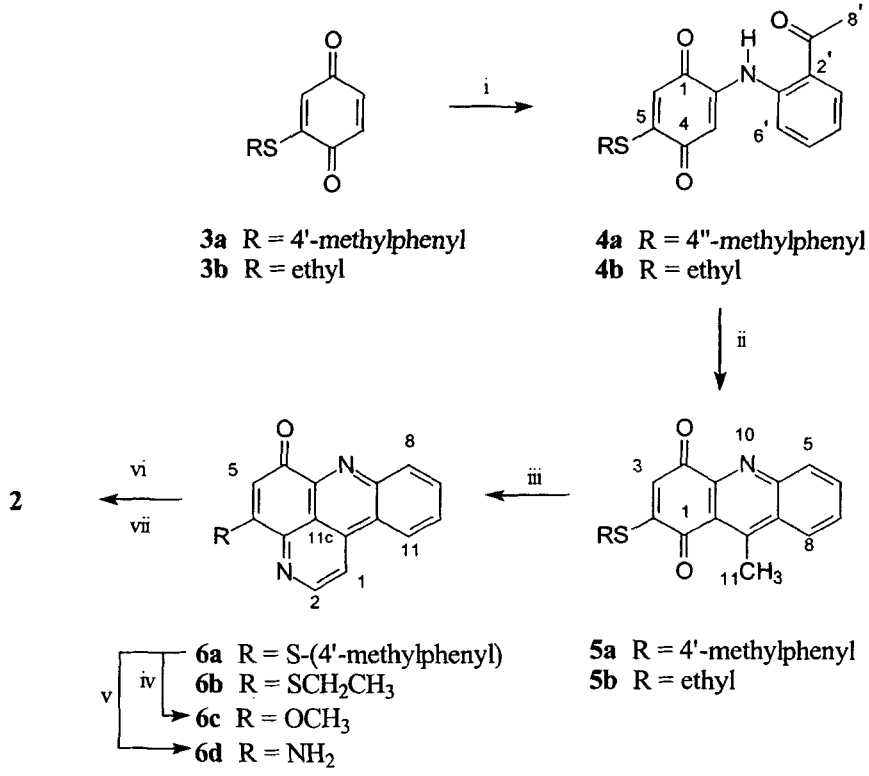
reported by Kubo *et al.*[3] Our project required the synthesis of a range of thio-, aza- and oxo-substituted analogues, but the route utilised by Kubo was not amenable to the synthesis of the thio-substituted analogues (see below). We now report a novel convenient synthetic route to the target alkaloids, further elaboration to the marine alkaloid 11-hydroxyascididemin (**2**) and comparative biological evaluation of ascididemin and 11-hydroxyascididemin.



1 R = H
2 R = OH

Reaction of 2-(4'-methylphenylthio)benzo[1,4]quinone (**3a**)[4] with *o*-amino acetophenone in the presence of cerium chloride[8] yielded adduct **4a** in 74% yield (Scheme I). Regiochemistry of amine addition was confirmed by ^{1}H-NMR spectroscopy, where the quinone protons were observed as singlets. Acid cyclisation of **4a** afforded 2-(4'-methylphenylthio)-9-methyl-acridine[1,4]dione (**5a**) in 97%. Attempted installation of the final pyridine ring using dimethylformamide diethylacetal (DMFDEA) methodology developed by Bracher for the synthesis of ascididemin[9] only afforded intractable mixtures which contained none of the desired product. However, using a one pot method recently reported by us,[10] final ring installation proceeded smoothly by reaction with paraformaldehyde and ammonium chloride in refluxing acetic acid to afford 4-(4'-



Scheme I.

i. *o*-aminoacetophenone, air, EtOH, $CeCl_3.7H_2O$. ii. H_2SO_4:HOAc (1:10), 100°C, 5 min. iii. $(CH_2O)_n$, NH_4Cl, HOAc, 100°C, 10 min. iv. NaOMe, MeOH, 65°C, 3 hr. v. NaN_3, aq. DMF, 100°C, 4 hr. vi. Meldrum's acid, $HC(OCH_3)_3$ vii. $(C_6H_5)O$, reflux, 30 min.

methylphenylthio)benzo[*de*][3,6]phenanthrolin-6(6*H*)-one (**6a**) in 87% yield. Complete structural assignment of **6a** was obtained by 2-D NMR spectroscopy and by a single crystal X-ray diffraction study.

To demonstrate the generality of this scheme we have also synthesised the 4-ethylthio analogue **6b** using similar methodology.[11] Functional group

interconversions to the known methylether (**6c**) and amino (**6d**) analogues[3] were readily achieved by reaction of **6a** with either sodium methoxide in methanol (98% yield) or with sodium azide in aqueous DMF (64% yield) respectively. Further elaboration of the 4-amino analogue **6d** to the cytotoxic marine alkaloid 11-hydroxyascidiidemin (**2**)[12] proceeded smoothly using methodology reported by Kubo.[3]

Both ascidiidemin and 11-hydroxyascidiidemin exhibited comparable levels of *in vitro* cytotoxicity towards the murine leukaemia cell line P388 (IC_{50} values of 0.4 and 2.3 μM respectively) and antibacterial activity towards *Bacillus subtilis* and *Escherichia coli* at doses of 20 μg per disc. In an *in vitro* antiviral assay which utilises the non-malignant African Green Monkey kidney cell line (BSC-1) as the viral host, ascidiidemin exhibited marked toxicity to the host cells with no detectable efficacy for antiviral activity. In direct contrast to this however, was the observation of negligible toxicity by 11-hydroxyascidiidemin towards the viral host cell line and moderate levels of antiviral activity towards both DNA (Herpes simplex type 1 (ATCC VR 733) (no detectable toxicity to viral host cells, complete viral inhibition at 10 μg/well)) and RNA (Polio virus type 1 (Pfizer vaccine strain) (no detectable toxicity, moderate viral inhibition at 10 μg/well)) viruses. 11-Hydroxyascidiidemin however failed to exhibit any protection against HIV-1 in testing at the NCI.

Experimental

NMR spectra were recorded on either a Bruker Avance DRX-400 spectrometer at

400 MHz for ^{1}H and 100 MHz for ^{13}C, or a Bruker AC200 spectrometer (200 MHz ^{1}H, 50 MHz ^{13}C) in $CDCl_3$ (unless otherwise specified) and the solvent signal was used as reference. Carbon resonance multiplicity was determined by using the DEPT pulse sequence. Coupling constants are quoted in hertz (Hz). ^{1}H and ^{13}C assignments for compounds **5a, b** and **6a-d** were made with the assistance of standard 2-D NMR experiments including gCOSY, gHSQC and gHMBC. Mass spectra were recorded on a VG-7070 mass spectrometer and infrared spectra were collected on a Perkin-Elmer 1600 FTIR spectrometer. Melting points were determined on a Reichert-Hofler block and are uncorrected. Elemental analyses were performed at the University of Otago.

2-(2'-acetylphenylamino)-5-(4"-methylphenylthio)benzo[1,4]quinone (4a). A mixture of *o*-aminoacetophenone (0.44 g, 3.3 mmol), quinone **3a** (0.9 g, 3.9 mmol), $CeCl_3.7H_2O$ (0.56 g, 1.5 mmol) and EtOH (60 mL) was stirred at room temperature for 8 days. Dark red crystalline product (**4a**), which precipitated out of solution, was removed by filtration every 2 days, washed and recrystallised to afford **4a** (1.1 g, 74%). mp 165-167°C (dark red needles from ethanol). EIMS m/z (%) 363 (M^+, 100), 345 (35), 321 (65), 320 (65). HREIMS *m/z* 363.0934 (calcd for $C_{21}H_{17}NO_3S$, 363.0929). Anal. calcd for $C_{21}H_{17}NO_3S$: C, 69.40; H, 4.71; N, 3.85; found C, 69.62; H, 5.03; N, 3.85 %. IR (KBr) 1659, 1650, 1614, 1557, 1520, 1453 cm^{-1}. ^{1}H-NMR δ 11.04 (1H, s), 7.93 (1H, d, *J*=7.9), 7.56 (2H, m), 7.39 (2H, d, *J*=8.1), 7.29 (2H, d, *J*=8.1), 7.17 (1H, m), 6.48 (1H, s), 5.85 (1H, s), 2.65 (3H,

s), 2.42 (3H, s). ^{13}C-NMR δ 201.2 (0), 183.4 (0), 179.8 (0), 159.3 (0), 142.9 (0), 140.9 (0), 139.9 (0), 135.3 (1), 134.1 (1), 132.3 (1), 131.1 (1), 125.7 (0), 123.9 (0), 123.7 (1), 122.0 (1), 120.6 (1), 102.5 (1), 28.4 (3), 21.3 (3).

2-(4'-methylphenylthio)-9-methyl-acridine[1,4]dione (5a). A solution of **4a** (204 mg, 0.56 mmol) in CH_3CO_2H-H_2SO_4 (10:1, 5 mL) was heated at 100 °C for 5 min. The reaction mixture was cooled, diluted with water, neutralised with aq. NH_3 solution, extracted with CH_2Cl_2 (3 x 100 mL). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with $CHCl_3$) to afford **5a** (188 mg, 97%). mp >300°C (decomp.) (yellow needles from $CHCl_3$). EIMS m/z (%) 345 (M^+, 100), 289 (35), 288 (40), 274 (20), 254 (25). HREIMS *m/z* 345.0824 (calcd for $C_{21}H_{15}NO_2S$, 345.0824). Anal. calcd for $C_{21}H_{15}NO_2S$: C, 73.02; H, 4.38; N, 4.06; found C, 72.83; H, 4.72; N, 4.10%. IR (KBr) 1660, 1576, 1560, 1492 cm^{-1}. ^{1}H-NMR δ 8.38 (1H, dm, *J*=8.5, H-5), 8.32 (1H, dm, *J*=8.6, H-8), 7.74 (1H, br dd, *J*=8.4, 8.4, H-7), 7.58 (1H, br dd, *J*=8.2, 8.2, H-6), 7.42 (2H, d, *J*=8.1, H-13/17), 7.30 (2H, d, *J*=7.9, H-14/16), 6.35 (1H, s, H-3), 3.21 (3H, s, H-11), 2.42 (3H, s, H-18). ^{13}C-NMR δ 183.7 (d, *J*=9, C-1), 180.1 (s, C-4), 160.6 (d, *J*=3, C-2), 151.7 (m, C-9), 148.3 (dd, *J*=8, 2, C-10a), 147.2 (d, *J*=6, C-4a), 141.2 (dd, *J*=13, 6, C-15), 135.5 (dd, *J*=164, 6, C-13/17), 132.6 (dd, *J*=163, 8, C-7), 129.1 (s, C-8a), 128.3 (d, *J*=169, C-3), 125.4 (dd, *J*=164, 7, C-8), 123.5 (d, *J*=8, C-12), 123.2 (m, C-9a), 21.3 (qm, *J*=127, C-18), 16.1 (q, *J*=130, C-11). A crystal structure of **5a** has also been secured, details of which will be presented elsewhere.[13]

4-(4'-methylphenylthio)benzo[*de*][3,6]phenanthrolin-6(6*H*)-one (6a).

A mixture of **5a** (50 mg, 0.145 mmol), NH_4Cl (233 mg, 4.35 mmol) and paraformaldehyde (22 mg, 0.725 mmol) were heated in acetic acid (25 mL) at 100°C for 10 mins. The purple solution was then made alkaline with 1N NaOH and extracted with CH_2Cl_2 (3 x 100 mL). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2) to afford **6a** (45 mg, 87%). mp 291–292°C (decomp.) (yellow plates from aq. MeOH). EIMS m/z (%) 354 (M^+, 100), 339 (20), 325 (50), 311 (20). HREIMS *m/z* 354.0819 (calcd for $C_{22}H_{14}N_2OS$, 354.0827). Anal. calcd for $C_{22}H_{14}N_2OS{\bullet}H_2O$: C, 70.95; H, 4.33; N, 7.53; found C, 70.90; H, 4.43; N, 7.50%. IR (KBr) 1644, 1596, 1550 cm^{-1}. ^{1}H-NMR δ 8.99 (1H, d, *J*=5.8, H-2), 8.53 (1H, dd, *J*=8.0, 1.0, H-11), 8.48 (1H, dd, *J*=8.0, 1.0, H-8), 8.41 (1H, d, *J*=5.8, H-1), 7.91 (1H, ddd, *J*=8.3, 8.3, 1.2), 7.84 (1H, ddd, *J*=8.3, 8.3, 1.2), 7.51 (2H, d, *J*=8.0, 2H-13), 7.31 (2H, d, *J*=8.0, 2H-14), 6.23 (1H, s, H-5), 2.43 (3H, s, 3H-16). ^{13}C-NMR δ 180.1 (s, C-6), 160.9 (d, *J*=7, C-4), 149.4 (dd, *J*=10, 10, C-3a), 148.2 (dd, *J*=183, 2, C-2), 146.5 (d, *J*=5, C-6a), 145.8 (dd, *J*=10, 7, C-7a), 141.1 (m, C-15), 136.8 (m, C-11b), 135.9 (m, 2C-13), 132.9 (dd, *J*=165, 7, C-8), 131.7 (dd, *J*=163, 9, C-9), 131.1 (m, 2C-14), 130.5 (dd, *J*=163, 9, C-10), 124.8 (d, *J*=168, C-5), 122.8 (dd, *J*=160, 7, C-11), 122.7 (m, C-11a), 117.3 (dd, *J*=165, 8, C-1), 116.1 (d, *J*=6, C-11c), 21.4 (qdd, *J*=126, 4, 4, C-16). The single crystal x-ray data were collected at 203(2) K on a Siemens-SMART-CCD system using Mo Kα (λ 0.71073 Å) monochromated radiation. Crystal data: yellow prizms from $CHCl_3$, $C_{22}H_{14}N_2OS$, crystal

dimensions 0.25x0.22x0.12 mm, a = 9.0848(2), b = 8.9141(3), c = 20.7939(5) Å, β = 101.535(1)°, V = 1649.9 Å^3, D_{cal} = 1.427 g.cm^{-3}, space group monoclinic, $P2_1/c$, (Z=4), $F(000)$ = 736, μ = 0.21 mm^{-1}. Frame data were collected in the range of 2.0–28.2° ($-11 \leq h \leq 11$; $0 \leq k \leq 11$; $0 \leq l \leq 27$) and processed. The processed hkl data were absorption corrected using the program SADABS. Hydrogen atoms were inserted at calculated positions using a riding model with thermal parameters equal to 1.2U of their carrier atoms. Anisotropic thermal parameters were assigned to non-hydrogen atoms and the refinement on 235 least-squares parameters converged with R_1=0.0421, wR^2 = 0.0953, and GOF = 1.055 for 3054 reflections with $I>2\sigma(I)$. In the final difference map, the electron density fluctuated in the range 0.288 to –0.347 e.Å^{-3}. Copies of the crystallographic data (excluding structure factors) are available, free of charge, on application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 33603: email: deposit@ccdc.cam.ac. uk).

4-methoxybenzo[*de*][3,6]phenanthrolin-6(6*H*)-one (6c).

A freshly prepared solution of sodium methoxide in methanol (methanol (75 mL) and Na metal (29 mg, 1.2 mmol)) was used to dissolve **6a** (44 mg, 0.12 mmol). The solution was stirred under nitrogen at 65°C for 3 hrs, after which time water (500 mL) was added. The solution was made neutral with 1N H_2SO_4 and extracted with CH_2Cl_2 (3 x 100 mL). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2-MeOH, 10:1) to afford **6c** (32 mg, 98%). DEIMS m/z (%) 262 (M^+, 100), 233 (60), 205 (80),

204 (50). HRDEIMS *m/z* 262.0735 (calcd for $C_{16}H_{10}N_2O_2$, 262.0742). ^{1}H-NMR δ 9.08 (1H, d, *J*=5.6, H-2), 8.61 (1H, dd, *J*=8.0, 1.0, H-11), 8.58 (1H, dd, *J*=8.4, 1.0, H-8), 8.48 (1H, d, *J*=5.7, H-1), 7.97 (1H, ddd, *J*=7.5, 7.5, 1.2, H-9), 7.89 (1H, ddd, *J*=7.1, 7.1, 1.3, H-10), 4.13 (3H, s, OCH_3). ^{13}C-NMR δ 183.0 (d, *J*=2, C-6), 165.6 (m, C-4), 148.7 (d, *J*=183, C-2), 147.3 (dd, *J*=11, 7, C-3a), 146.2 (d, *J*=4, C-6a), 145.7 (dd, *J*=8, 8, C-7a), 137.1 (m, C-11b), 133.2 (dd, *J*=165, 7, C-8), 131.8 (dd, *J*=163, 9, C-9), 130.5 (dd, *J*=162, 8, C-10), 122.9 (dd, *J*=7, 7, C-11a), 122.8 (dd, *J*=160, 8, C-11), 117.5 (dd, *J*=165, 8, C-1), 116.7 (m, C-11c), 107.5 (d, *J*=164, C-5), 57.0 (q, *J*=147, OCH_3).

4-aminobenzo[*de*][3,6]phenanthrolin-6(6*H*)-one (6d).

Sodium azide (38.4 mg, 0.59 mmol) in H_2O (5 mL) was added to a solution of **6a** (42 mg, 0.12 mmol) in DMF (15 mL) and the whole was heated at 100°C for 4 hrs. Water (250 mL) was added and extracted with $CHCl_3$ (5 x 100 mL), the organic extracts were combined and washed with water (10 x 100 mL). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with $CHCl_3$-MeOH 10:1) to afford **6d** (18 mg, 64%). mp >300°C (decomp.) (orange-red needles from MeOH) (lit.,[3] mp 285°C (decomp.)). EIMS m/z (%) 247 (M^+, 80), 219 (80). HREIMS *m/z* 247.0743 (calcd for $C_{15}H_9N_3O$, 247.0746). ^{1}H-NMR (dmso-d_6) δ 8.98 (1H, d, *J*=5.6, H-2), 8.85 (1H, d, *J*=7.8, H-11), 8.82 (1H, d, *J*=5.8, H-1), 8.30 (1H, d, *J*=8.0, H-8), 7.98 (1H, ddd, *J*=8.3, 8.3, 1.1, H-9), 7.88 (1H, ddd, *J*=7.1, 7.1, 0.8, H-10), 7.67 (2H, br s, NH_2), 5.99 (1H, s, H-5). ^{13}C-NMR (dmso-d_6) δ 178.6 (s, C-6), 154.6 (s, C-4),

148.0 (d, *J*=6, C-6a), 147.6 (d, *J*=183, C-2), 146.2 (m, C-3a), 145.0 (dd, *J*=8, 6, C-7a), 136.2 (m, C-11b), 131.6 (dd, *J*=163, 9, C-9), 131.4 (dd, *J*=163, 7, C-8), 129.6 (dd, *J*=163, 8, C-10), 123.9 (dd, *J*=163, 8, C-11), 122.1 (m, C-11a), 118.4 (dd, *J*=168, 8, C-1), 116.6 (d, *J*=6, C-11c), 101.7 (dt, *J*=160, 2, C-5).

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11. 2-(2'-acetylphenylamino)-5-ethylthio)benzo[1,4]quinone **(4b)** was prepared using quinone **3b**[4] and the procedure for **4a** given above. Yield 48%. Mp 170–171°C (dark red needles from EtOH). EIMS m/z (%) 301 (M^+, 100), 283 (60), 259 (40), 186 (60). HREIMS *m/z* 301.0774 (calcd for $C_{16}H_{15}NO_3S$, 301.0774). Anal. calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65; found C, 63.57; H, 5.29; N, 4.84%. IR (KBr) 1656, 1614, 1582 cm^{-1}. ^{1}H-NMR δ 11.12 (1H, s), 7.92 (1H, br d, *J*=7.8), 7.54 (2H, m), 7.16 (1H, m), 6.45 (1H, s), 6.34 (1H, s), 2.80 (2H, q, *J*=7.5), 2.65 (3H, s), 1.40 (3H, t, *J*=7.4). ^{13}C-NMR δ 201.2 (0), 183.1 (0), 179.3 (0), 157.1 (0), 143.1 (0), 139.9 (0), 134.1 (1), 132.3 (1), 125.8 (0), 123.1 (1), 120.9 (1), 120.6 (1), 102.9 (1), 28.4 (3), 24.6 (3), 12.33 (2). 2-ethylthio-9-methyl-acridine[1,4]dione **(5b)** was synthesised using quinone **4b** and the procedure for **5a** given above. Yield 81%. Mp 211-212°C (yellow prizms from $CHCl_3$). EIMS m/z (%) 283 (M^+, 100), 268 (24), 256 (23), 254 (50). HREIMS *m/z* 283.0667 (calcd for $C_{16}H_{13}NO_2S$, 283.0666). Anal. calcd for $C_{21}H_{17}NO_3S$: C, 67.82; H, 4.62; N, 4.94; found C, 68.05; H, 4.64; N, 4.92%. IR (KBr) 1660, 1577, 1560 cm^{-1}. ^{1}H-NMR δ 8.36 (1H, d, *J*=8.4, H-5), 8.27 (1H, d, *J*=8.6, H-8), 7.85 (1H, ddd, *J*=8.3, 6.8, 1.3, H-6), 7.71 (1H, ddd, *J*=8.4, 6.8, 1.3, H-7), 6.82 (1H, s, H-3), 3.17 (3H, s, H-11), 2.88 (2H, q, *J*=7.4, H-12), 1.43 (3H, t, *J*=7.5, H-13). ^{13}C-NMR δ 183.6 (d, *J*=9, C-1), 179.9 (s, C-4), 158.5 (s, C-2), 151.6 (m, C-9), 148.4 (dd, *J*=6, C-10a), 147.2 (d, *J*=4, C-4a), 132.5 (dd, *J*=163, 9, C-6), 132.2 (dd, *J*=166, 8, C-5), 129.4 (dd, *J*=163, 9, C-7), 129.2 (m, C-8a), 127.2 (d, *J*=167, C-3), 125.4 (dd, *J*=161, 7, C-8), 123.43 (m, C-9a), 24.9 (tq, *J*=141, 4, C-12), 16.1 (q, *J*=130, C-11), 12.43 (qt, *J*=129, 4, C-13). A crystal structure of **5b** has also been secured, details of which will be presented elsewhere.[13] 4-ethylthiobenzo[*de*][3,6]phenanthrolin-6(6*H*)-one **(6b)** was synthesised using quinone **5b** and the procedure for **6a** given above. Yield 81%.

Mp 228–229°C (yellow/tan powder from MeOH). EIMS m/z (%) 292 (M^+, 50), 259 (100), 204 (43). HREIMS *m/z* 292.0665 (calcd for $C_{17}H_{12}N_2OS$, 292.0670). IR (KBr) 1644, 1595, 1542 cm^{-1}. ^{1}H-NMR δ 8.98 (1H, d, *J*=5.8, H-2), 8.60 (1H, dd, *J*=8.1, 1.4, H-8), 8.55 (1H, dd, *J*=8.2, 1.3, H-11), 8.44 (1H, d, *J*=5.8, H-1), 7.96 (1H, ddd, *J*=8.1, 7.1, 1.3, H-9), 7.88 (1H, ddd, *J*=8.2, 7.1, 1.4, H-10), 6.80 (1H, s, H-5), 3.04 (2H, q, *J*=7.5, H-12), 1.50 (3H, t, *J*=7.5, H-13). ^{13}C-NMR δ 179.8 (C-6), 158.9 (C-4), 149.6 (C-3a), 148.2 (C-2), 146.5 (C-6a), 145.9 (C-7a), 136.9 (C-11b), 133.1 (C-8), 131.8 (C-9), 130.5 (C-10), 123.6 (C-5), 122.8 (C-11), 122.8 (C-11a), 117.2 (C-1), 116.4 (C-11c), 25.2 (C-12), 12.6 (C-13).

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