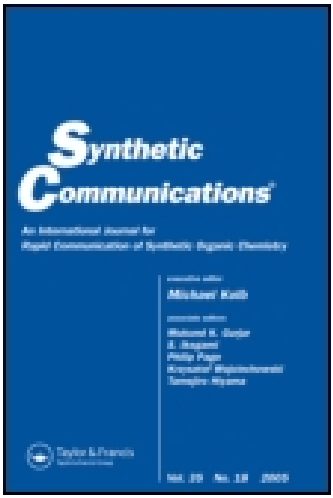

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Acridine-Quinone Systems—A Potential Electrochemical Fluorescent Switch

Verity J. Litchfield [a], Robert B. Smith [b], Anthony M. Franklin [a] & James Davis [a]

[a] Chemistry, School of Science and Technology, Clifton Campus, Nottingham Trent University, Nottingham, UK

[b] Centre for Materials Science, University of Central Lancashire, Preston, UK

Published online: 29 Sep 2008.

To cite this article: Verity J. Litchfield, Robert B. Smith, Anthony M. Franklin & James Davis (2008) Synthesis of Acridine-Quinone Systems—A Potential Electrochemical Fluorescent Switch, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:20, 3447-3455, DOI: 10.1080/00397910802154261

To link to this article: http://dx.doi.org/10.1080/00397910802154261

Synthetic Communications®, 38: 3447–3455, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802154261

Taylor & Francis
Taylor & Francis Group

Synthesis of Acridine–Quinone Systems—A Potential Electrochemical Fluorescent Switch

Verity J. Litchfield,[1] Robert B. Smith,[2] Anthony M. Franklin,[1] and James Davis[1]

[1]Chemistry, School of Science and Technology, Clifton Campus, Nottingham Trent University, Nottingham, UK
[2]Centre for Materials Science, University of Central Lancashire, Preston, UK

Abstract: The synthesis of various acridine-quinones is reported. The fluorescence-quenching quinone moiety has been incorporated into various acridine molecules, each having a different functionality at the ninth position of the acridine ring. It is envisaged that the quenching nature of the quinone will lead to the fluorescent properties of the acridine being controlled in a way similar to turning on a light switch.

Keywords: Acridine, fluorescence, oxidation, quinone, reduction

In our investigation into fluorescent electrochemical sensors, we have synthesized several 1,4-acridinequinones. Our study has been focused on a replacement for 1,4-napthoquinone **(1)**, which is a well-known electrochemical redox sensor,[1–3] in favor of a 1,4-acridinequinone **(2)** system. The conjugated quinone moiety itself is a well-established fluorescent quencher.[4,5] It is envisaged that upon Michael addition at the second or third position of the acridine ring system, with a human health biomarker such as glutathione, the conjugated system will undergo a reduction to a 1,4-diol **(3)** species. Once in this state, fluorescence will

Received April 15, 2008.
Address correspondence to Robert B. Smith, Centre for Materials Science, University of Central Lancashire, Preston, PR1 2HE, UK. E-mail: RBSmith@UCLan.ac.uk

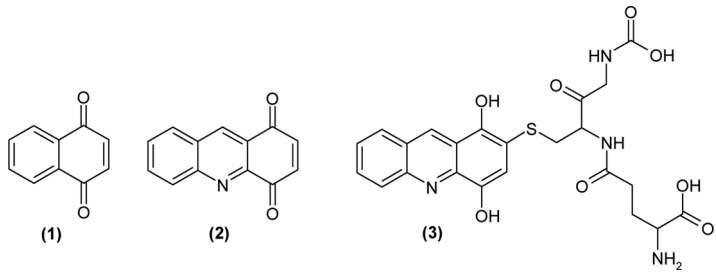

Figure 1. 1,4-Naphthoquinone **(1)**, 1,4-acridinequinone **(2)** and the formation of a 1,4-diol system upon attachment of glutathione to 1,4-acridinequinone **(3)**.

occur for a short period until air oxidation forces the 1,4-diol back to the quinone. The aforementioned compounds are shown in Fig. 1.

The Ullmann–Goldberg condensation in DMF was employed using 1 equivalent of 2,5-dimethoxyaniline **(4)** to 1.5 equivalents of bromobenzoic acid **(5)** in the presence of potassium carbonate as base and a catalytic amount of copper bronze. This yielded 70% of 2-(2,5-dimethoxyphenyl)aminobenzoic acid **(6)**, which was purified by an acid/base wash. 1,4-Dimethylacrid-9-one **(7)** was formed in 59% yield upon the reaction of **6** with polyphosphoric acid (PPA), followed by a careful workup with ammonium hydroxide as in shown in Fig. 2. The reductive aromatization of **7** yielded 1,4-dimethoxyacridine **(8)** at 27% using conditions similar to those recorded by Lu et al.[6] and is shown in Fig. 3. Chlorination of **7** using oxalyl chloride in the presence of a catalytic amount of DMF yielded 64% of 1,4-dimethoxy-9-chloroacridine **(9)**. Heating **9** at 100 °C in DMF in the presence of potassium carbonate and phenol gave 1,4-dimethoxy-9-phenoxyacridine **(10)** as an orange solid in 48% yield.[7] The formation of 1,4-dimethoxy-9-aminoacridine **(11)** was recorded upon heating **9** in the presence of phenol and ammonium carbonate at 80 °C.[8] Oxidation of the 2,5-dimethoxy moieties with cerium ammonium nitrate (CAN) gave the acridine-1,4-quinones **(12a–e)**.[9] The aforementioned synthetic route can be seen in

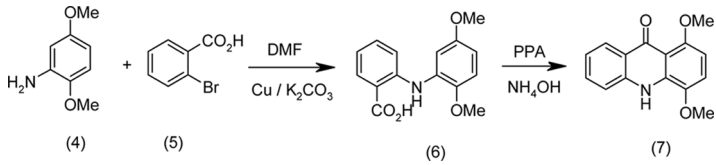

Figure 2. The Ullmann–Goldberg condensation to yield 2-(2,5-dimethoxyphenyl)-aminobenzoic acid **(6)** followed by ring closure to yield the 1,4-methoxyacrid-9-one **(7)**.

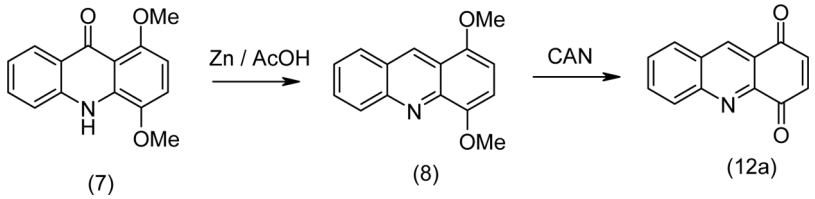

Figure 3. Reductive aromatization yields the 1,4-methoxyacridinine **(8)** and oxidation with CAN yields 1,4-acridininequinone **(12a)**.

Fig. 4. The structures of compounds **6–12** were determined using NMR spectroscopy and MS spectrometry data. The ^{13}C spectroscopy data for the 1,4-acridinequinones were not recorded because the samples were

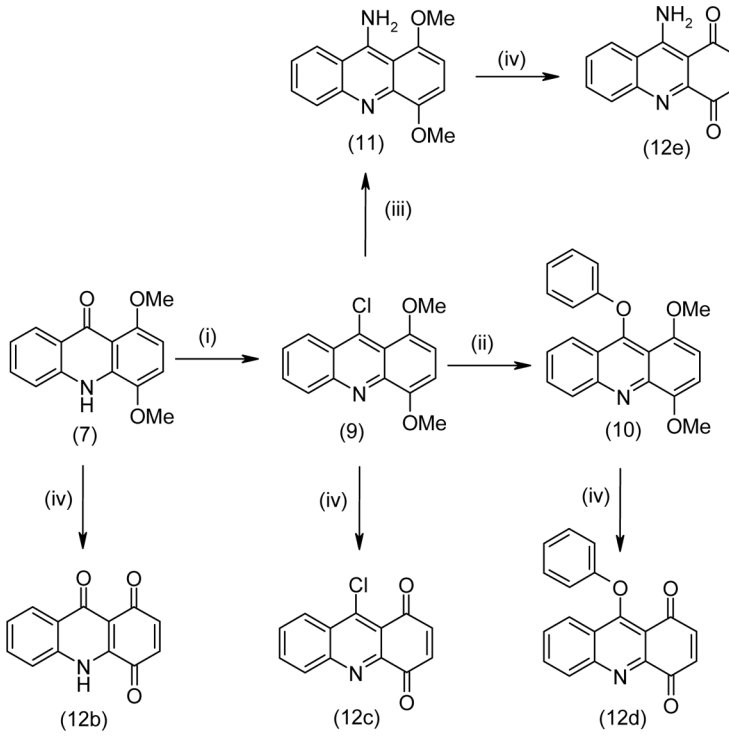

Figure 4. The stepwise synthetic route to yield the acridinequinones **(12b–12e)**: (i) Oxalyl chloride/DMF, (ii) phenol/K_2CO_3, (iii) $NH_2(CO)_3$/phenol, (iv) CAN/MeCN.

very dilute. As further evidence for the presence of the 1,4-acridinequinones, no peaks were observed around 3–4 ppm in the ^{1}H NMR spectrum. Also, there was no evidence of the methoxy moieties being present when these compounds were studied using infrared spectroscopy. An expected lack of fluorescence was also noted.

In summary, we have designed a convenient and efficient route for the synthesis of a series of 1,4-acridine-quinones. This method can be used if other substrates are required to be attached to the ninth position of the acridine ring such as amino acids.

EXPERIMENTAL

NMR spectra were measured on a Jeol ECX 400-MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Mass spectra were recorded on a Micromass Platform liquid chromatography mass spectrometry-electrospray ionization (LCMS-ESI) and an Agilent gas chromatography-mass spectrometry (GC-MS) (6850NGC and 5975XL-MSD). All chemicals and solvents were bought from either Sigma Aldrich or Apollo Synthesis and used without further purification.

2-(2,5-Dimethoxyphenyl)aminobenzoic Acid (6)

A mixture of 2,5-dimethoxyaniline (1.53 g, 10 mmol), 2-bromobenzoic acid (3.01 g, 15 mmol), copper bronze (0.13 g, 2 mmol), and potassium carbonate (2.76 g, 20 mmol) were refluxed in DMF (40 ml) for 6 h. The brown solution was poured over ice and treated with sodium hydroxide solution until the pH was 10. The brown solution was heated to 80 °C, activated charcoal was added, and after 5 min of stirring the solution was filtered and treated with hydrochloric acid untill the pH was 5. The green precipitate produced was filtered and dried to yield 2-(2,5-dimethoxyphenyl)aminobenzoic acid **6** (1.90 g, 70%) as a green solid.

^{1}H NMR (d_6-DMSO): 3.68 (s, 3H, O-C$\underline{H}_3$), 3.75 (s, 3H, O-C$\underline{H}_3$), 6.55 (d, 1H, $J = 8.8$ Hz, Ar-$\underline{H}$), 6.77 (t, 1H, $J = 7.6$ Hz, Ar-H), 6.96–6.94 (m, 2H, Ar-H), 7.28 (d, 1H, $J = 8.5$ Hz, Ar-$\underline{H}$), 7.39 (t, 1H, $J = 7.8$ Hz, Ar-H), 7.90 (d, 1H, $J = 8.0$ Hz, Ar-H), 9.64 (brs, 1H, COO$\underline{H}$). ^{13}C NMR (d_6-DMSO): 55.32, 56.16, 106.17, 106.72, 112.51, 113.25, 114.09, 117.58, 130.34, 131.92, 134.15, 144.89, 146.19, 153.33, 169.76. IR (ATR): 3319, 2885, 2824, 2640, 1576, 1026, 738. LCMS-ESI (m/z) 274 [M–H].

1,4-Dimethoxyacridin-9-one (7)

A mixture of **6** (20 g, 73 mmol) and polyphosphoric acid (60 ml) was stirred at 120 °C for 3 h. Upon cooling to 60 °C, distilled water (100 ml) was added slowly to yield a brown solution, which upon careful addition of aqueous ammonium hydroxide produced a yellow precipitate. When the solution achieved a pH of 8, the yellow solid was filtered to yield 1,4-dimethoxyacridin-9-one **7** (11.05 g, 59%) as a yellow solid, which was dried under vacuum in a desiccator.

^{1}H NMR (d_6-DMSO): 3.77 (s, 3H, O-C$\underline{H}_3$), 3.94 (s, 3H, O-C$\underline{H}_3$), 6.55 (d, 1H, $J = 8.8$ Hz, Ar-$\underline{H}$), 7.16–7.20 (m, 2H, Ar-H), 7.61 (t, 1H, $J = 7.7$ Hz, Ar-$\underline{H}$), 7.77 (d, 1H, $J = 8.4$ Hz, Ar-$\underline{H}$), 8.12 (d, 1H, $J = 8.2$ Hz, Ar-H), 10.83 (brs, 1H, N$\underline{H}$). ^{13}C NMR (d_6-DMSO): 55.88, 56.34, 101.06, 111.72, 112.95, 117.72, 121.11, 122.34, 125.79, 132.57, 133.66, 139.73, 141.04, 153.70, 157.98. IR (ATR): 3319, 2885, 2824, 2640, 1576, 1026, 738. LCMS-ESI (m/z) 273 [M–H].

1,4-Dimethoxyacridine (8)

Zinc dust (13.33 g, 0.2 mol) in was added to a suspension of **7** (2 g, 7.8 mmol) in glacial acetic acid (235 ml) one portion. The reaction mixture was refluxed for 6 h and a color change was observed (yellow to red). The reaction mixture was cooled to room temperature and extracted with ethyl acetate, and the organic phase was washed with a mixture of saturated solution of $NaHCO_3$ and distilled water. The organic layer was removed, dried over sodium sulphate, and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel with diethyl ether as eluent to yield 1,4-dimethoxyacridine **8** (0.31 g, 27%) as a yellow solid.

^{1}H NMR ($CDCl_3$): 4.04 (s, 3H, O-C$\underline{H}_3$), 4.12 (s, 3H, O-C$\underline{H}_3$), 6.66 (d, 1H, $J = 8.2$ Hz, Ar-$\underline{H}$), 6.92 (d, 1H, $J = 8.3$ Hz, Ar-$\underline{H}$), 7.55 (t, 1H, $J = 7.0$ Hz, Ar-$\underline{H}$), 7.78 (t, 1H, $J = 7.0$ Hz, Ar-$\underline{H}$), 8.03 (d, 1H, $J = 8.4$ Hz, Ar-$\underline{H}$), 8.39 (d, 1H, $J = 8.8$ Hz, Ar-$\underline{H}$), 9.17 (s, 1H, Ar-$\underline{H}$). ^{13}C NMR ($CDCl_3$): 55.17, 56.09, 100.82, 105.79, 120.98, 125.09, 126.13, 128.38, 120.02, 130.18, 131.44, 142.06, 148.12, 148.80, 149.21. IR (ATR): 2831, 1733, 1628, 1579, 1531, 797. GCMS-EI (m/z) 239 [M–H].

1,4-Dimethoxy-9-chloroacridine (9)

Into a round-bottomed flask charged with **7** (5.10 g, 20 mmol) in toluene (200 ml), DMF (20 drops) and oxalyl chloride (5.14 ml, 60 mmol) were

added. The reaction was heated at 60 °C for 3 h, allowed to cool, and filtered. Ammonium hydroxide (35%) was added to the cooled reaction mixture with slight stirring until the solution went from purple to yellow. The yellow solution was transferred into a separating funnel and washed with a minimum amount of water until the organic layer was pH 7. The organic layer was removed, dried with sodium sulphate, and evaporated to dryness to yield 1,4-dimethoxy-9-chloroacridine **9** (3.5 g, 64%) as a yellow solid.

^{1}H NMR ($CDCl_3$): 3.98 (s, 3H, O-C$\underline{H}_3$), 4.10 (s, 3H, O-C$\underline{H}_3$), 6.80 (d, 1H, $J = 8.5$ Hz, Ar-$\underline{H}$), 6.91 (d, 1H, $J = 8.5$ Hz, Ar-$\underline{H}$), 7.63 (t, 1H, $J = 7.7$ Hz, Ar-$\underline{H}$), 7.63 (t, 1H, $J = 7.7$ Hz, Ar-$\underline{H}$), 8.34 (d, 1H, $J = 8.7$ Hz, Ar-$\underline{H}$), 8.58 (d, 1H, $J = 8.8$ Hz, Ar-$\underline{H}$). ^{13}C NMR ($CDCl_3$): 56.25, 56.51, 105.11, 106.03, 118.54, 124.82, 127.17, 128.17, 128.98, 130.24, 130.37, 140.10, 142.92, 147.48, 149.55. IR (ATR): 2960, 2935, 2837, 1623, 1456, 1076, 812, 757 GCMS-EI (m/z) 273 [M–H].

1,4-Dimethoxy-9-phenoxyacridine (10)

Into a round-bottomed flask charged with phenol (1.14 g, 15 mmol) and potassium carbonate (2.07 g, 15 mmol), dry DMF (25 ml) was added, and the mixture was stirred for 30 min under nitrogen. Upon the addition of **9** (1.36 g, 5 mmol), the reaction mixture was heated to 100 °C for 6 h. The reaction mixture was transferred to a separating funnel; dichloromethane (DCM) (100 ml) was added. The mixture was washed with 1 M NaOH (aq) (5 × 100 ml). The organic layer was removed, dried with sodium sulphate, and evaporated to dryness, leaving a brown solid. The addition of ethyl acetate (50 ml) left an orange solid, which was filtered and air dried to yield 1,4-dimethoxy-9-phenoxyacridine **10** (0.81 g, 48%).

^{1}H NMR ($CDCl_3$): 3.63 (s, 3H, O-C$\underline{H}_3$), 4.13 (s, 3H, O-C$\underline{H}_3$), 6.62 (d, 1H, $J = 8.4$ Hz, Ar-$\underline{H}$), 6.74 (d, 2H, $J = 8.6$ Hz, Ar-$\underline{H}$), 6.94 (d, 1H, $J = 8.4$ Hz, Ar-$\underline{H}$), 6.99 (t, 1H, $J = 7.4$ Hz, Ar-$\underline{H}$), 7.24 (t, 2H, $J = 8.1$ Hz, Ar-$\underline{H}$), 7.48 (t, 1H, $J = 7.6$ Hz, Ar-$\underline{H}$), 7.74 (t, 1H, $J = 7.7$ Hz, Ar-$\underline{H}$), 8.19 (d, 1H, $J = 8.7$ Hz, Ar-$\underline{H}$), 8.39 (d, 1H, $J = 8.8$ Hz, Ar-$\underline{H}$). NMR ($CDCl_3$): 55.99, 56.19, 103.05, 106.30, 114.82, 121.55, 121.81, 122.73, 126.20, 129.43, 129.90, 130.65, 144.15, 148.87, 149.21, 149.39, 155.29, 159.94. IR (ATR): 3045, 2832, 1626, 1488, 754. LCMS-ESI (m/z) 332 [M–H].

1,4-Dimethoxy-9-aminoacridine (11)

Into a round-bottomed flask charged with phenol (34.8 g, 0.37 mol) and ammonium carbonate (0.8 g, 8.5 mmol), **9** (2 g, 7.5 mmol) was added. The reaction mixture was heated at 80 °C for 2 h. The reaction mixture was

transferred to a separating funnel; DCM (100 ml) was added. The mixture was washed with 2 M NaOH (aq) (10 × 100 ml). The organic layer was removed, dried with sodium sulphate, and evaporated to dryness to yield 1,4-dimethoxy-9-aminoacridine **11** (1.46 g, 79%) as a feathery yellow solid.

^{1}H NMR ($CDCl_3$): 3.99 (s, 3H, O-C$\underline{H}_3$), 4.04 (s, 3H, O-C$\underline{H}_3$), 6.49 (d, 1H, $J = 8.4$ Hz, Ar-$\underline{H}$), 6.81 (d, 1H, $J = 8.4$ Hz, Ar-$\underline{H}$), 6.96 (br s, 2H, N$\underline{H}_2$), 7.35 (t, 1H, $J = 7.6$ Hz, Ar-$\underline{H}$), 7.65 (t, 1H, $J = 7.7$ Hz, Ar-$\underline{H}$), 7.84 (d, 1H, $J = 8.5$ Hz, Ar-$\underline{H}$), 8.16 (d, 1H, $J = 8.5$ Hz, Ar-$\underline{H}$). NMR ($CDCl_3$): 55.46, 55.82, 98.82, 105.48, 106.90, 113.89, 122.00, 122.74, 128.76, 129.93, 142.70, 147.41, 148.86, 151.09, 151.47. IR (ATR): 3446, 2831, 1636, 1534, 1374, 786. LCMS-ESI (m/z) 255 [M–H].

Preparation of 1,4-Acridinequinones (12a) (General Procedure)

Into a round-bottom flask charged with 1,4-dimethoxyacridine (**8**) (4 mmol) and cerium ammonium nitrate (CAN) (15 mmol), acetonitrile (40 ml) and water (20 ml) were added. The solution was stirred for 20 min at 0 °C and then poured into brine and extracted with chloroform. The organic layer was removed, concentrated under reduced pressure, and purified on silica gel using chloroform as eluent. The first fraction was collected and evaporated to dryness to yield a bright red solid, which was the 1,4-acridinequinone.

Data

1,4-Acridinequinone (12a)

Yielded 83% as a red solid. ^{1}H NMR ($CDCl_3$): 7.19 (AB-quart, 1H, $J = 10.5$ Hz, Ar-$\underline{H}$), 7.30 (AB-quart, 1H, $J = 11.0$ Hz, Ar-$\underline{H}$), 7.78 (t, 1H, $J = 7.6$ Hz, Ar-$\underline{H}$), 7.97 (t, 1H, $J = 7.5$ Hz, Ar-$\underline{H}$), 8.10 (d, 1H, $J = 8.1$ Hz, Ar-$\underline{H}$), 8.47 (d, 1H, $J = 8.6$ Hz), 9.00 (s, 1H Ar-$\underline{H}$). LCMS-ESI (m/z) 210 [M–H].

Acridine-1,4,9-trione (12b)

Yielded 45% as a red solid. ^{1}H NMR (d_6-DMSO): 6.80 (AB-quart, 1H, $J = 9.8$ Hz, Ar-$\underline{H}$), 7.03 (AB-quart, 1H, $J = 9.3$ Hz, Ar-$\underline{H}$), 7.46 (t, 2H, $J = 7.2$ Hz, Ar-$\underline{H}$), 7.75 (t, 1H, $J = 7.0$ Hz, Ar-$\underline{H}$), 8.06 (d, 1H, $J = 6.7$ Hz, Ar-$\underline{H}$), 8.15 (d, 1H, $J = 6.4$ Hz), 12.36 (brs, 1H, N$\underline{H}$). LCMS-ESI (m/z) 226 [M–H].

9-Chloro-1,4-acridinequinone (12c)

Yielded 88% as a red solid. ^{1}H NMR ($CDCl_3$): 7.15 (AB-quart, 1H, $J = 10.6$ Hz, Ar-H), 7.23 (AB-quart, 1H, $J = 10.4$ Hz, Ar-H), 7.88 (t, 2H, $J = 7.2$ Hz, Ar-H), 8.00 (t, 1H, $J = 7.0$ Hz, Ar-H), 8.47 (d, 1H, $J = 8.5$ Hz, Ar-H), 8.62 (d, 1H, $J = 8.6$ Hz). LCMS-ESI (m/z) 244 [M–H].

9-Phenoxy-1,4-acridinequinone (12d)

Yielded 50% as a red solid. ^{1}H NMR ($CDCl_3$): 6.87 (d, 2H, $J =$ 7.8 Hz, Ar-H), 6.94 (AB-quart, 1H, $J = 10.4$ Hz, Ar-H), 7.09 (t, 1H, $J = 7.4$ Hz, Ar-H), 7.18 (AB-quart, 1H, $J = 10.4$ Hz, Ar-H), 7.31 (t, 2H, $J = 8.1$ Hz, Ar-H), 7.72 (t, 1H, $J = 7.1$ Hz, Ar-H), 7.98 (t, 1H, $J =$ 7.0 Hz, Ar-H), 8.27 (d, 1H, $J = 8.5$ Hz, Ar-H), 8.50 (d, 1H, $J = 8.6$ Hz). LCMS-ESI (m/z) 302 [M–H].

9-Amino-1,4-acridinequinone (12e)

Yielded 11% as a brown solid. ^{1}H NMR ($CDCl_3$): 7.01 (AB-quart, 1H, $J = 10.6$ Hz, Ar-H), 7.05 (AB-quart, 1H, $J = 10.5$ Hz, Ar-H), 7.65 (t, 1H, $J = 7.8$ Hz, Ar-H), 7.85 (t, 1H, $J = 7.5$ Hz, Ar-H), 7.94 (d, 1H, $J = 8.2$ Hz, Ar-H), 8.30 (d, 1H, $J = 8.3$ Hz). LCMS-ESI (m/z) 244 [M–H].

REFERENCES

1. Sjoelin, A. M.; Livingstone, D. R. Redox cycling of aromatic hydrocarbon quinones catalyzed by digestive gland microsomes of the common mussel (*Mytilus edulis* L.). *Aquatic Toxicol.* **1997**, *38*, 83–99.
2. Smith, R. B.; Canton, C.; Lawrence, N. S.; Livingstone, C.; Davis, J. Molecular anchors–mimicking metabolic processes in thiol analysis. *New J. Chem.* **2006**, *30*, 1718–1724.
3. Villalba, M. M.; Litchfield, V. J.; Smith, R. B.; Franklin, A. M.; Livingstone, C.; Davis, J. A chromatographic tool for preparing combinatorial quinone-thiol conjugate libraries. *J. Biochem. Bioph. Methods* **2007**, *70*, 797–802.
4. Ilos, R. A.; Harlev, E.; Bittner, S. A novel all-organic chemical and electrochemical fluorescent switch. *Tetrahedron Lett.* **2005**, *46*, 8427–8430.
5. Sutovsky, Y.; Likhtenshtein, G. I.; Bittner, S. Synthesis and photochemical behavior of donor–acceptor systems obtained from chloro-1,4-naphthoquinone attached to trans-aminostilbenes. *Tetrahedron* **2003**, *59*, 2939–2945.

6. Lu, L.; Chen, Q.; Zhu, X.; Chen, C. A convenient synthesis of alkoxyanthracenes from alkoxy-9,10-anthraquinones. *Synthesis* **2003**, *16*, 2464–2466.
7. Sanchez, I.; Reches, R.; Caignard, D. H.; Renard, P.; Pujol, M. D. Synthesis and biological evaluation of modified acridines: The effect of N- and O-substituent in the nitrogenated ring on antitumor activity. *Eur. J. Med. Chem.* **2006**, *41*, 340–352.
8. Lin, G.; Midha, K. K.; Hawes, E. M. Synthesis of the piperidinone metabolites of piperidine type phenothiazine antipsychotic drugs via ruthenium tetroxide oxidation. *J. Heterocycl. Chem.* **1991**, *28*, 215–219.
9. Horiguchi, Y.; Sakuma, S.; Suzuki, H.; Sano, T. Synthesis of benzacridine and pyridoacridine via Diels–Alder reaction of acridonequinone. *Heterocycles* **2000**, *153*, 1305–1316.