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Synthesis of ABC Analogues of the Antitumour Antibiotic Streptonigrin

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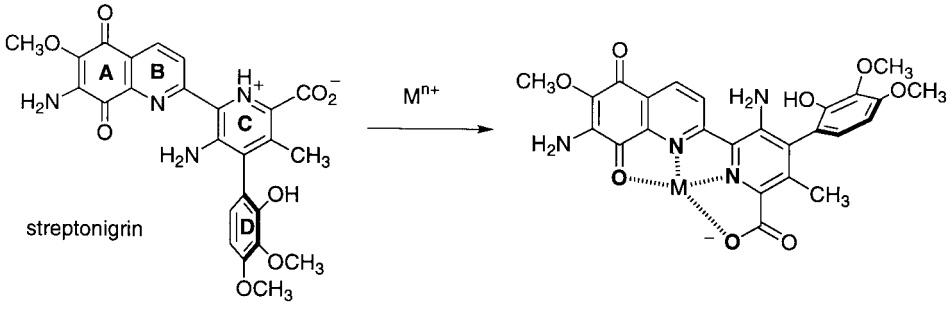
Abstract—ABC analogues of the antitumour antibiotic streptonigrin, that contain the key metal chelation site and redox-active quinone unit that are essential for biological activity, were prepared via palladium catalysed cross-coupling of 2-iodo-8-nitroquinoline or 2-iodo-6-methoxy-5-nitroquinoline with 2-trimethylstannio-6-methylpyridine. Mild oxidation of the pyridyl methyl group introduced the acid functional group on ring C and Fremy's salt oxidation afforded the quinone unit which was elaborated to give the 5-amino-6-methoxy substitution pattern present in streptonigrin.

Introduction

Streptonigrin (Scheme 1) is a highly functionalised aminoquinone antitumour antibiotic that has broad spectrum anticancer activity against a range of tumour lines.[1–4] The mechanism of antitumour action is believed to result from free radical-mediated DNA strand cleavage due to reductive activation of streptonigrin, in a process that involves metal ions and oxygen.[5–8] A large number of structure activity studies[4,9,10] have established the crucial role of the quinoline-5,8-dione AB ring system, the carboxylic acid on ring C as well as the pyridyl nitrogens in rings B and C, i.e., the redox active quinone ring and the key metal binding site (Scheme 1). The role of ring D is not fully understood but is not believed to be essential as derivatives lacking this ring maintain activity, although activity is modified with respect to the parent drug.[11,12] The combination of peripheral functional groups are also important and alterations to ring A substituents has a marked influence on activity,[12] presumably as these groups affect the redox chemistry of this ring.[13]

We have synthesised a number of model ligands based on the streptonigrin skeleton and carried out detailed spectroscopic studies to establish unequivocally the site of metal binding.[14–17] For all metals studied, 1:1 bipyridyl complexes are formed (Scheme 1).[10,16] The stabilities of these complexes are highly influenced by the flanking carbonyl groups of the quinone and carboxylic acid. In addition, the zwitterionic nature of streptonigrin[18] is important for solubility and provision of a substituent at the 6-position of ring C which effectively provides a 6,6′-disubstituted-2,2′-bipyridyl chelation site. Based on these studies, we have proposed that the preparation of stable metal chelates of streptonigrin, or ABC analogues of streptonigrin, may provide potentially useful new generation anticancer drugs.[10]



Scheme 1.

Keywords: quinolinones; antitumour compounds; bicyclic heterocyclic compounds; coupling reactions.
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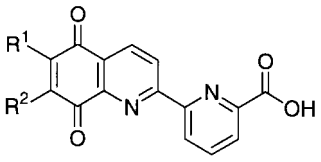
This paper describes the synthesis of analogues of the general structure **1**, which contain the redox active quinone group, the 6,6′-disubstituted bipyridyl chelation site and a range of substituents on ring A, including the 5-amino-6-methoxy substitution pattern present in streptonigrin. The key chemistry centres on biaryl couplings of 2-iodoquinolines and provides access to a range of ABC analogues of streptonigrin.



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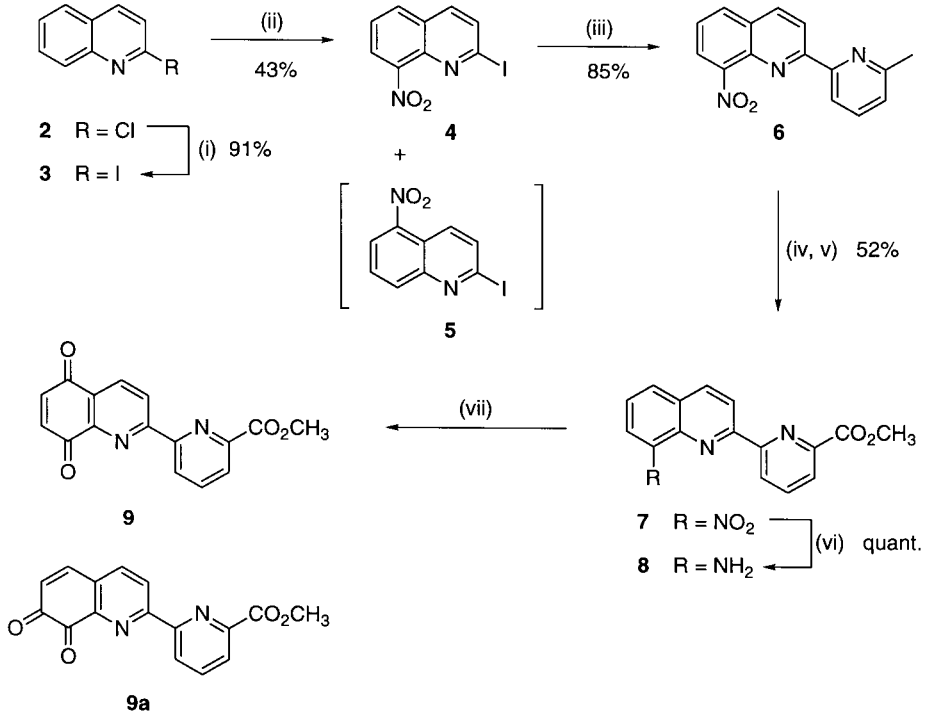
Results and Discussion

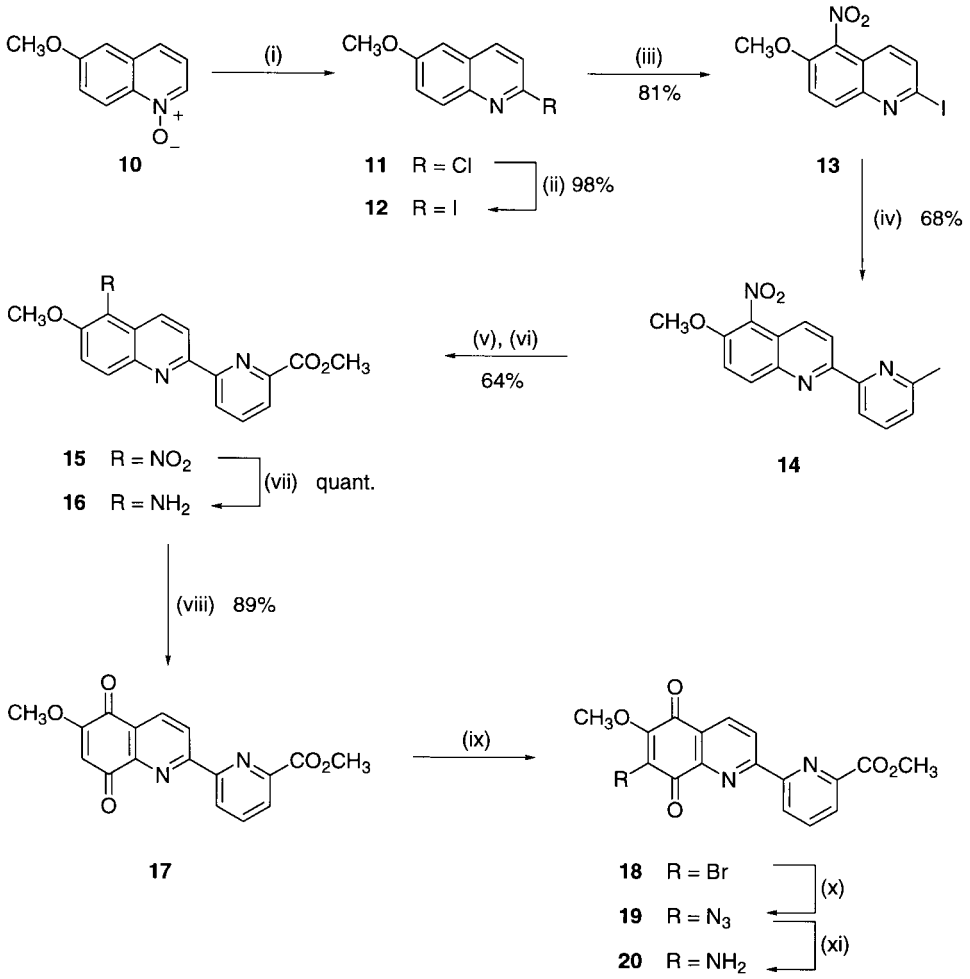
The strategy for the synthesis of the ABC analogues of streptonigrin **1** centred on metal catalysed cross couplings of suitably substituted quinolyl and pyridyl precursors. A number of ABC analogues of streptonigrin have been prepared,[12,19–22] with an intramolecular condensation reaction (Friedlander quinoline synthesis) used to construct the quinoline ring B, functionalised with ring C. More recently, metal catalysed coupling reactions to form the B–C biaryl bond have been investigated,[21–24] but these methods have been used to prepare analogues that either lack the key carboxylic acid in the 6-position of ring C or do not allow ready functionalisation of ring A. A range of new functionalised pyridine intermediates suitable for metal catalysed cross-coupling reactions under either Stille or Suzuki conditions, and elaboration into streptonigrin analogues, have been reported,[25–29] but no analogues incorporating both the carboxylic acid and ring A substitution pattern of streptonigrin have been synthesised from these intermediates.

A Stille coupling using the stannane derived from commercially available 2-chloroquinoline **2** was initially trialed on the unsubstituted ABC system **1** (R^1=R^2=H). However, generation of the stannane using standard lithium halogen exchange[30] followed by treatment with trimethyltin chloride was unsuccessful, which was attributed to the low reactivity of the chloride and the inability to generate the lithium salt in good yield. Reaction of the sodium salt of trimethyltin chloride with 2-chloroquinoline has been reported to give the corresponding stannane in 75% yield.[25] However, in our hands, poor and irreproducible yields of the same stannane were obtained. While changing the solvent from THF, used in the literature method,[25] to DME improved the reaction, the yield was still poor and separation of unreacted starting material from the product was difficult. Hence the reverse Stille coupling partners were used to construct the quinoline pyridine biaryl bond.

While the low reactivity of aryl chlorides such as 2-chloroquinoline **2** in Stille couplings is well established, higher yields may be obtained under Negishi conditions. However, coupling of 2-trimethylstannio-6-methylpyridine and 2-chloroquinoline under either standard Pd^0 or Ni^0 catalysis,[31,32] gave poor overall yields of the coupled product **6**. Hence 2-chloroquinoline was converted to the more reactive iodo derivative **3** in excellent yield (91%), by treatment with sodium iodide in the presence of acetyl chloride[33] (Scheme 2); this derivative coupled smoothly with a range of stannanes to give the biaryl products in good yields.



Scheme 2. (i) NaI, AcCl, CH_3CN; (ii) H_2SO_4, KNO_3; (iii) $PdCl_2(PPh_3)_2$, 2-trimethylstannio-6-methylpyridine, THF; (iv) CrO_3, H_2SO_4; (v) MeOH, cat. H_2SO_4; (vi) H_2, Pd/C, MeOH; (vii) Fremy's salt, MeOH, phosphate buffer (pH 7.1, 0.05 M).



Scheme 3. (i) $POCl_3$; (ii) NaI, AcCl, CH_3CN; (iii) H_2SO_4, HNO_3, 0°C; (iv) $PdCl_2(PPh_3)_2$, 2-trimethylstannio-6-methylpyridine, THF; (v) SeO_2, pyridine; (vi) MeOH, cat. H_2SO_4; (vii) H_2, Pd-C, EtOH, EtOAc; (viii) Fremy's salt, MeOH, phosphate buffer (pH 7.2, 0.05 M); (ix) Br_2, $CHCl_3$; (x) NaN_3, DMF, MeOH; (xi) H_2, Pd/C, EtOH, EtOAc.

Functionalisation or activation of quinolines at the 2-position has typically been via the pyridone or *N*-oxide. The iodo group does not appear to have been widely used to activate the 2-position to facilitate biaryl couplings, but they have been recently used to form activated zinc reagents that are readily coupled with a range of organic electrophiles.[34]

Nitration of 2-iodoquinoline **3** under mild conditions yielded a mixture of the 8-nitro and 5-nitro isomers, **4** and **5** respectively, which were assigned from NOESY experiments. In the case of the 8-nitro isomer **4**, NOEs were detected from H4 to both H3 and H5, while for the 5-nitro isomer **5**, H4 gave an NOE only to H3. The 8-isomer **4** (formed in 43% yield) was coupled to 2-trimethylstannio-6-methylpyridine under Stille conditions to afford the required ABC skeleton **6**. Oxidation of the ring C methyl group in **6** with CrO_3 afforded the carboxylic acid which was isolated as the methyl ester **7** for purification purposes. Nitroquinoline **7** was converted into the corresponding amine **8** which was oxidised with potassium nitrosodisulfonate (Fremy's salt)[35] to give a number of products. Analysis of the ^1H NMR and mass spectrum of the crude product was consistent with formation of both the desired *para*-quinone **9** as well as some *ortho*-quinone **9a** and other unidentified products. However, quinones **9** and **9a** could not be separated by crystallisation and were unstable to chromatography on silica.

The strategy to assemble the ABC ring system outlined in Scheme 2 was applied to the synthesis of analogue **20** but incorporated the 6-methoxy group in the starting quinoline. In addition to providing the functional group present in streptonigrin it was anticipated that the methoxy group would direct both the nitration and Fremy's salt oxidation to give exclusively the required *para*-quinone. Thus, 6-methoxyquinoline was converted into 2-chloro-6-methoxyquinoline **11** via the *N*-oxide **10** under standard conditions. The corresponding iodoquinoline **12** was nitrated regioselectively to give exclusively the 5-nitro isomer **13** which underwent a Stille coupling to give the pyridylquinoline **14** (Scheme 3).

Oxidation of **14** using CrO_3 (i.e., identical conditions to those used to convert the unsubstituted analogue **6** into the ester **7**; Scheme 2) resulted in concomitant degradation of ring A under a variety of reaction conditions. While the susceptibility of the carbocyclic ring of quinolines to

oxidative degradation has been noted and is enhanced by the presence of electron withdrawing groups,[36] selective oxidation of alkyl substituents can be carried out with milder selenium reagents.[37] However, oxidation of **14** with selenium dioxide in dioxane afforded only minor amounts of the aldehyde and unreacted starting material. While I_2/*t*-BuI/DMSO reagents have been reported to be selective for oxidation of methyl to formyl groups in heteroaromatic derivatives,[38] this method also gave trace amounts of aldehyde and mainly unreacted starting material.

In the case of **14**, selective oxidation of the methyl group to the carboxylic acid was achieved using selenium dioxide in pyridine.[39] The success of the oxidation depended critically on the number of equivalents of selenium dioxide used (optimal 4 equiv.), reaction time (5 days) and removal of all selenium residues prior to esterification to the more soluble methyl ester **15**. Reduction to the amine **16** followed by immediate Fremy's salt oxidation in phosphate buffered solution (pH 7.2) afforded the dione **17** in 83% yield from **15**. Introduction of the amino group by initial bromination to give **18**, conversion to the azide **19** and reduction to the amine **20** followed the route of Liao et al.[40] using modified reaction conditions. Due to the instability of the quinones on silica, the intermediate bromide **18** and azide **19** were not isolated and characterised but were converted directly to the final 7-amino-6-methoxy-2-pyridylquinoline-5,8-dione **20**, which contains the same substitution pattern as the AB ring system of streptonigrin.

Experimental

General experimental procedures

Melting points were determined on a Reichert heating stage and are uncorrected. Microanalyses were performed by the Microanalytical unit at the University of Otago, New Zealand. Infra-red spectra (IR) were recorded on a Perkin–Elmer 1600 series Fourier transform spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC 200F spectrometer at 200 MHz, referenced to residual solvent protons unless otherwise stated. Low resolution EI mass spectra were recorded on a Kratos MS902 double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV. High resolution spectra were recorded at a nominal resolution of 5000 referenced to perfluorokerosene.

2-Iodo-8-nitroquinoline 4

To a solution of 2-iodoquinoline[33] **3** (2.1 g, 0.008 mol) in H_2SO_4 (4.4 mL, 18 M) was added KNO_3 (1.1 g, 0.010 mol) in portions at 0°C. The reaction was warmed to room temperature and stirred overnight. The mixture was poured onto ice and extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with $NaHCO_3$ (100 mL, saturated), dried over Na_2SO_4 and the solvent removed to give the crude product which was purified by chromatography (SiO_2, 1:1, ethyl acetate:hexanes). The first band was collected and the solvent removed under vacuum to give 2-iodo-5-nitroquinoline **5** as a yellow solid (1.08 g, 45%), mp 116.5–119.0°C. IR (KBr) ν_{max} 1324, 1514 (NO_2) cm^{-1}. HRMS: $C_9H_5N_2O_2I$ requires 299.9396; found, 299.9393. ^{1}H NMR (400 MHz, C_6D_6): δ 6.64 (1H, t, $J_{7,6}$= 8.1 Hz, $J_{7,8}$=8.1 Hz, H_7), 7.10 (1H, d, $J_{3,4}$=9.0 Hz, H_3), 7.52 (1H, d, $J_{8,7}$=8.1 Hz, H_8), 7.77 (1H, d, $J_{6,7}$=8.1 Hz, H_6), 7.86 (1H, d, $J_{4,3}$=9.0 Hz, H_4). Mass Spectrum: *m/z* 300 (M^+, 43%), 173 (M-I, 55), 127 (100). The second band was collected and the solvent removed under vacuum to give 2-iodo-8-nitroquinoline **4** as a pale yellow solid (1.03 g, 43%), mp 126.0–127.5°C. IR (KBr) ν_{max} 1351, 1520 (NO_2) cm^{-1}. HRMS: $C_9H_5N_2O_2I$ requires 299.9396; found, 299.9408. ^{1}H NMR (400 MHz, C_6D_6): δ 6.66 (1H, d, $J_{4,3}$=8.5 Hz, H_4), 6.70 (1H, t, $J_{6,5}$=7.8 Hz, $J_{6,7}$=7.8 Hz, H_6), 6.98 (1H, d, $J_{5,6}$=7.8 Hz, H_5), 7.19 (1H, d, $J_{3,4}$= 8.5 Hz, H_3), 7.27 (1H, d, $J_{7,6}$=7.8 Hz, H_7). Mass Spectrum: *m/z* 300 (M^+ 74%), 173 (M−I, 89), 127 (100).

2-(6′-Methyl-2′-pyridyl)-8-nitroquinoline 6

2-Iodo-8-nitroquinoline **4** (500 mg, 1.67 mmol), 2-trimethylstannio-6-methylpyridine[30] (640 mg, 2.5 mmol) and $PdCl_2(PPh_3)_2$ (120 mg, 0.17 mmol) in THF (10 mL) were refluxed for 16 h under a nitrogen atmosphere. The solvent was removed and the residue dissolved in DCM (50 mL). The mixture was washed with KF (50 mL, saturated), dried over Na_2SO_4 and the solvent removed under vacuum. The residue was purified by chromatography (SiO_2, 4:1, DCM:hexanes) yielding the title compound **6** as a white solid (390 mg, 85%), mp 125.5–127.0°C. $C_{15}H_{11}N_3O_2$ requires, C 67.9, H 4.2, N 15.8%; found, C 67.7, H 3.9, N 16.0%. IR (KBr) ν_{max} 1530, 1240 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.69 (3H, s, CH_3), 7.27 (1H, m, H_5), 7.64 – 7.56 (1H, dd, $J_{6,7}$ and $J_{6,5}$=7.52, 7.42 Hz, H_6), 7.79 (1H, t, $J_{4',3'}$ and $J_{4',5'}$=7.8 Hz, $H_{4'}$), 8.06 (2H, m, $H_{3',5'}$), 8.36 (1H, d, $J_{3,4}$=8.8 Hz, H_3), 8.52 (1H, m, H_7), 8.84 (1H, d, $J_{4,3}$=8.8 Hz, H_4). Mass Spectrum: *m/z* 265 (M^+, 72%), 219 (M-NO_2, 20), 83 (100).

2-(6′-Methoxycarbonyl-2′-pyridyl)-8-nitroquinoline 7

2-(6′-Methyl-2′-pyridyl)-8-nitroquinoline **6** (200 mg, 0.754 mmol) was dissolved in H_2SO_4 (1 mL, 18 M), cooled to 0°C and CrO_3 (300 mg, 3.02 mmol) was added in portions over a 1 h period. The mixture was allowed to warm to room temperature and heated to 75°C for 4 h. The reaction mixture was cooled, poured into methanol (100 mL) and refluxed overnight, under a nitrogen atmosphere. The mixture was cooled and the solvent removed under vacuum. The residue basified with NaOH (1 M) and extracted with DCM (2×50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under vacuum. The residue was purified by chromatography (SiO_2, 4:1, DCM:hexanes) yielding unreacted starting material, followed by the title compound **7** as a white solid (120 mg, 52%), mp 214.0–215.5°C. $C_{16}H_{11}N_3O_4$ requires C 62.1, H 3.6, N 13.6%; found, C 62.0, H 3.4, N 13.5%. IR (KBr) ν_{max} 1740 (CO_2CH_3), 1530, 1200 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.04 (3H, s, CO_2CH_3), 7.62 (1H, t, $J_{4',3'}$ and $J_{4',5'}$=7.9 Hz, $H_{4'}$), 7.97–8.09 (3H, m, $H_{5',5,6}$), 8.19 (1H, m, $H_{3'}$), 8.38 (1H, d, $J_{3,4}$=8.7 Hz, H_3), 8.88 (1H, m, H_7), 8.90 (1H, $J_{4,3}$=8.7 Hz, H_4). Mass Spectrum: *m/z* 310 ($M+1^+$, 7%), 251 (M−CO_2CH_3, 47), 149 (100%).

2-(6′-Methoxycarbonyl-2′-pyridyl)-5,8-quinolinedione 9 and 2-(6′-methoxycarbonyl-2′-pyridyl)-7,8-quinolinedione 9a

2-(6′-Methoxycarbonyl-2′-pyridyl)-8-nitroquinoline **7** (150 mg, 0.485 mmol) was dissolved in methanol (50 mL). Palladium-on-charcoal (15 mg) was added and the mixture was stirred, in the dark, under a hydrogen atmosphere for 20 h. The mixture was filtered through celite, eluting with ethyl acetate and the solvent removed to yield 8-amino-2-(6′-methoxycarbonyl-2′-pyridyl)quinoline **8** in quantitative yield as an orange oil which solidified on standing. The crude product **8** (135 mg, 0.483 mmol) was dissolved in methanol (9 mL) and added to a solution of Fremy's salt (519 mg, 1.93 mmol) in KH_2PO_4 (9 mL, 0.05 M, pH 7.1) under a nitrogen atmosphere. The mixture was stirred, in the dark, under a nitrogen atmosphere, for 19 h and poured onto water. The mixture was extracted with DCM (3×40 mL), dried over Na_2SO_4 and the solvent removed to yield the crude product as a purple solid (136 mg), which contained several products, including quinones **9** and **9a**, which were tentatively assigned by ^{1}H NMR and mass spectral data. Mass Spectrum: *m/z* 293 ($M-1^+$ 3%), 279 (M-CH_3,14), 247 ($M-CO_2CH_3$, 7), 43 (100).

2-Iodo-6-methoxyquinoline 12

To a solution of 2-chloro-6-methoxyquinoline[41] **11** (500 mg, 2.58 mmol), sodium iodide (600 mg, 4.00 mmol) and acetonitrile (2.9 mL) was added acetyl chloride (0.39 mL, 5.42 mmol). The solution refluxed overnight, under a nitrogen atmosphere and quenched with water. The mixture was extracted with DCM (100 mL) and washed with a solution of 10% K_2CO_3/10% $Na_2S_2O_3$ (100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under vacuum. The crude product was dissolved in DCM and filtered through SiO_2, eluting with DCM. Removal of the solvent under vacuum yielded 2-iodo-6-methoxyquinoline **12** as a yellow solid (720 mg, 98%), mp 146.0–147.0°C. HRMS: $C_{10}H_8ONI$ requires 284.9651; found, 284.9652. ^{1}H NMR ($CDCl_3$): δ 3.92 (3H, s, OCH_3), 7.04 (1H, d, $J_{5,7}$=2.6 Hz, H_5), 7.36 (1H, dd, $J_{7,5}$=2.8 Hz, $J_{7,8}$=9.1 Hz, H_7), 7.71 (2H, m, $H_{3,4}$), 8.05 (1H, d, $J_{8,7}$=9.1 Hz, H_8). Mass Spectrum: *m/z* 285 (M^+ 67%), 158 ($M-I$, 100).

2-Iodo-6-methoxy-5-nitroquinoline 13

2-Iodo-6-methoxyquinoline **12** (310 mg, 1.08 mmol) was dissolved in H_2SO_4 (1.2 mL, 18 M) and stirred at 0°C. Concentrated HNO_3 (0.21 mL, 1.63 mmol) was added dropwise over 10 min and the mixture was stirred for a further 10 min at 0°C. The reaction mixture was poured onto ice and basified with NaOH (2 M), with cooling. The aqueous mixture was extracted with DCM (2×50 mL), the combined organic layers were dried over Na_2SO_4 and the solvent removed under vacuum. The crude product was dissolved in DCM and filtered through SiO_2 eluting with DCM. Removal of the solvent under vacuum yielded the title compound **13** as a white solid (290 mg, 81%), mp 171.5–173.0°C. HRMS: $C_{10}H_7O_3N_2I$ requires 329.9501; found, 329.9462. ^{1}H NMR ($CDCl_3$): δ 4.08 (3H, s, OCH_3), 7.57 (1H, d, $J_{3,4}$=9.4 Hz, H_3), 7.68 (1H, d, $J_{7,8}$=9.0 Hz, H_7), 7.83 (1H, d, $J_{8,7}$=9.0 Hz, H_8), 8.2 (1H, d, $J_{4,3}$=9.4 Hz, H_4). Mass Spectrum: *m/z* 330 (M^+ 100%), 203 (M−I+H, 71), 127 (I, 51).

6-Methoxy-2-(6′-methyl-2′-pyridyl)-5-nitroquinoline 14

2-Iodo-6-methoxy-5-nitroquinoline **13** (250 mg, 0.76 mmol), 2-trimethylstannio-6-methylpyridine[30] (290 mg, 1.14 mmol) and $PdCl_2(PPh_3)_2$ (50 mg, 0.08 mmol) were refluxed in THF (10 mL), under a nitrogen atmosphere, for 16 h. The reaction was cooled and the solvent removed under vacuum. The residue was dissolved in DCM (20 mL), washed with KF (20 mL, saturated), dried over Na_2SO_4 and the solvent removed under vacuum. The residue was purified by chromatography (SiO_2, DCM) yielding the title compound **14** as a yellow solid (150 mg, 68%), mp 154.0–155.5°C. HRMS: $C_{16}H_{13}N_3O_3$ requires 295.0957; found, 295.0957. IR (KBr) ν_{max} 1530, 1269 (NO_2) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.66 (3H, s, CH_3), 4.07 (3H, s, OCH_3), 7.22 (1H, d, $J_{5',4'}$=7.7 Hz, $H_{5'}$), 7.55 (1H, d, $J_{3,4}$=9.4 Hz, H_3), 7.74 (1H, t, $J_{4',3'}$ and $J_{4',5'}$=7.7 Hz, $H_{4'}$), 8.14 (1H, d, $J_{7,8}$= 9.0 Hz, H_7), 8.28 (1H, d, $J_{4,3}$=9.4 Hz, H_4), 8.35 (1H, d, $J_{3',4'}$=7.7 Hz, $H_{3'}$), 8.7 (1H, d, $J_{8,7}$=9.0 Hz, H_8). Mass Spectrum: *m/z* 295 (M^+ 100%), 219 [($M-NO_2$ -CH_3O) +1, 37].

2-(6′-Methoxycarbonyl-2′-pyridyl)-6-methoxy-5-nitroquinoline 15

6-Methoxy-2-(6′-methyl-2′-pyridyl)-5-nitroquinoline **14** (300 mg, 1.0 mmol) and selenium dioxide (452 mg, 4.1 mmol) were dissolved in pyridine (10 mL). The mixture was refluxed, under a nitrogen atmosphere, for 5 days and the solvent was removed under vacuum. The residue was dissolved in methanol, filtered and the solvent removed under vacuum. Residual pyridine was azeotropically removed with methanol and the residue was dissolved in dry methanol (150 mL). The mixture was acidified with H_2SO_4 (18 M) and refluxed under a nitrogen atmosphere, for 20 h. The mixture was basified with $NaHCO_3$ (saturated) and the volume was reduced under vacuum. Water (150 mL) was added and the solution extracted with DCM (5×50 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed to yield the crude product as a brown solid (220 mg, 64%). The solid was recrystallised (DCM/hexanes) to yield the title compound **15** as a yellow solid (165 mg, 48%), mp 226.5–228°C. $C_{17}H_{13}N_3O_5$ requires C 60.2, H 3.9, N 12.4%; found, C 60.1, H 3.9, N 12.5%. IR (KBr) ν_{max} 1531, 1268 (NO_2), 1726 (CO_2CH_3) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.06 (3H, s, CO_2CH_3), 4.11 (3H, s, OCH_3), 7.60 (1H, d, $J_{3,4}$=9.6 Hz, H_3), 8.03 (1H, t, $J_{4',3'}$ and $J_{4',5'}$=8.0 Hz, $H_{4'}$), 8.20 (2H, d, $J_{7,8}$ and $J_{3',4'}$=8.0 Hz, H_7 and $H_{3'}$), 8.33 (1H, d, $J_{4,3}$=9.6 Hz, H_4), 8.81 (2H, d, $J_{8,7}$ and $J_{5',4'}$=8.0 Hz, H_8 and $H_{5'}$). Mass Spectrum: *m/z* 339 (M^+ 25%), 281 ($M-CO_2CH_3$, 60), 45 (100).

2-(6′-Methoxycarbonyl-2′-pyridyl)-6-methoxy-5,8-quinolinedione 17

2-(6′-Methoxycarbonyl-2′-pyridyl)-6-methoxy-5-nitroquinoline **15** (100 mg, 0.295 mmol) was suspended in ethanol (200 mL) and ethyl acetate (40 mL). Palladium-on-charcoal (50 mg) was added and the mixture was stirred, in the dark,

under a hydrogen atmosphere for 42 h. The mixture was filtered through Celite, eluting with ethyl acetate and the solvent removed to yield an orange residue. The residue was dissolved in methanol (15 mL) and added to a solution of potassium nitrosodisulfonate (Fremy's salt) (610 mg, 2.27 mmol) in KH_2PO_4 (15 mL, 0.05 M, pH 7.24) under a nitrogen atmosphere. The mixture was stirred, in the dark, under a nitrogen atmosphere for 72 h and poured onto water (300 mL). The mixture was extracted with DCM (3×40 mL), dried over Na_2SO_4 and the solvent removed to yield the title compound **17** as a brown solid (85 mg, 89%), mp 258.0–260.0°C. IR (KBr) ν_{max} 1643, 1685 (quinone), 1726 (CO_2CH_3) cm^{-1}. HRMS: $C_{17}H_{12}N_2O_5$ requires 324.0746; found, 324.0745. ^1H NMR ($CDCl_3$): δ 3.97 (3H, s, CO_2CH_3), 4.05 (3H, s, OCH_3), 6.40 (1H, s, H_7), 8.04 (1H, t, $J_{4',3'}$ and $J_{4',5'}$=8.0 Hz, $H_{4'}$), 8.22 (1H, dd, $J_{3',4'}$=8.0 Hz, $J_{3',5'}$=1.6 Hz, $H_{3'}$), 8.59 (1H, d, $J_{3,4}$=8.0 Hz, H_3), 8.90 (1H, dd, $J_{5',4'}$=8.0 Hz, $J_{5',3'}$=1.6 Hz, $H_{5'}$), 8.95 (1H, d, $J_{4,3}$=8.0 Hz, H_4). Mass Spectrum: *m/z* 324 (M^+ 12%), 266 ($M-CO_2CH_3$,100).

7-Amino-2-(6′-methoxycarbonyl-2′-pyridyl)-6-methoxy-5,8-quinolinedione 20

2-(6′-Methoxycarbonyl-2′-pyridyl)-6-methoxy-5,8-quinolinedione **17** (69 mg, 0.21 mmol) was dissolved in chloroform (7 mL) and bromine (22 mL, 0.42 mmol) was added. The mixture was stoppered and stirred in the dark for 21 h. Water (50 mL) was added and the product was extracted with DCM (2×25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed to yield the crude brominated product **18** as a yellow solid in quantitative yield which was carried through to the next step without purification. Crude 7-bromo-2-(6′-methoxycarbonyl-2′-pyridyl)-6-methoxy-5,8-quinolinedione **18** (85 mg, 0.21 mmol) was dissolved in methanol (7 mL) and DMF (7 mL). Sodium azide (21 mg, 0.32 mmol, 1.5 equiv.) was added and the mixture was stirred under an argon atmosphere, in the dark, for 20 h. Water (40 mL) was added and the mixture extracted with DCM (3×25 mL). The combined organic extracts were reduced in volume to 5 mL, washed with water (5×40 mL) and dried over Na_2SO_4. The solvent was removed to yield the crude azide **19** as a brown solid (75 mg, 96%) which was not purified but converted directly to the amine. 7-Azido-2-(6′-methoxycarbonyl-2′-pyridyl)-6-methoxy-5,8-quinolinedione **19** (75 mg, 0.21 mmol) was suspended in ethyl acetate (20 mL) and ethanol (60 mL). Palladium-on-charcoal (20 mg) was added and the mixture was stirred under an hydrogen atmosphere, in the dark, for 18 h. The mixture was filtered through Celite, eluting with ethyl acetate and the solvent removed to yield the crude product as a red–brown solid (50 mg, 69%). Purification by chromatography (basic alumina, DCM) afforded pure **20** as a red solid, mp 175.0–177.5°C. IR (KBr) ν_{max} 1643, 1684 (quinone), 1724 (CO_2CH_3), 3512, 3689 (NH_2) cm^{-1}. HRMS: $C_{17}H_{13}N_3O_5$ requires 339.0855; found, 339.0855. ^1H NMR ($CDCl_3$): δ 4.05 (3H, s, CO_2CH_3), 4.10 (3H, s, OCH_3), 5.22 (2H, s, NH_2), 8.03 (1H, t, $J_{4',3'}$ and $J_{4',5'}$=8.0 Hz, $H_{4'}$), 8.21 (1H, dd, $J_{3',4'}$=8.0 Hz, $J_{3',5'}$=1.6 Hz, $H_{3'}$), 8.50 (1H, d, $J_{3,4}$=8.0 Hz, H_3), 8.84 (1H, dd, $J_{5',4'}$=8.0 Hz, $J_{5',3'}$= 1.6 Hz, $H_{5'}$), 8.88 (1H, d, $J_{4,3}$=8.0 Hz, H_4). Mass Spectrum: *m/z* 339 (M^+ 100%), 280 (M-CO_2CH_3, 19), 266 (78).

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