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Synthesis of 2-aryl-6-methyl-5-nitroquinoline derivatives as potential prodrug systems for reductive activation

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Abstract

A range of novel 2-aryl-5-nitroquinolines have been synthesised as potential prodrug systems for bioreductive activation. Thus 5-nitroquinoline underwent vicarious nucleophilic substitution at C-6 with bromoform anion to give, after hydrolysis and reduction, the quinoline-6-methanol. Introduction of chlorine at C-2 was followed by palladium-catalysed Suzuki coupling to install the 2-aryl substituent. A fluorescent model 'drug', 7-hydroxy-4-methylcoumarin was coupled to the 6-hydroxymethyl group, and its fragmentation upon reduction of the nitro group was investigated.

1. Introduction

The development of prodrug systems for use in cancer therapy is of considerable interest to the medicinal chemistry community since such agents have the potential to improve tumour selectivity of chemotherapeutic agents thereby reducing unwanted side effects, and hence prodrugs have been developed that are converted by enzymes into active cytotoxic agents.[1] However, in order for the treatment to be selective, the enzyme needs to be present in cancer cells at significantly higher levels than normal cells. Conventional prodrug therapy relies upon the upregulation of the relevant enzymes in tumours, i.e., the enzyme is naturally overexpressed in tumour cells, but not in normal cells. More recent strategies have focused on targeted drug delivery mechanisms, whereby the activating enzyme is specifically delivered into the tumour cells by means of a tumour specific antibody or gene delivery system—antibody directed enzyme prodrug therapy (ADEPT) or gene directed enzyme prodrug therapy (GDEPT), respectively.

In many systems, the activating reaction is hydrolysis of the prodrug into its active form by enzymes such as carboxypeptidases, aminopeptidases, phosphatases, glucuronidases, etc.[1] However, a different but complementary strategy uses bioreduction of aromatic nitro compounds to trigger the formation of, or release of, a reactive species.[2–6] The bioreduction of the strongly electron-withdrawing nitro group into a hydroxylamino or amino group induces a dramatic change in reactivity of the aromatic ring that can be used to deliver cytotoxic species to tumours. Interest in this area stems from early work on tretazicar [5-(aziridin-1-yl)-2,4-dinitrobenzamide], formerly designated as CB1954, **1**, a compound that shows true antitumour selectivity. This compound undergoes reductive activation to the hydroxylamine **2**, subsequent acetylation of which generates a powerful electrophile **3** capable of cross-linking DNA (Scheme 1).[7] However, a more common tactic is to exploit the 'electronic switch' engendered by nitro reduction to trigger the fragmentation of the prodrug molecule into the biologically active drug, as illustrated by nitrobenzyl phosphoramide mustard **4**.[8] In this case the hydroxylamine **5** formed upon bioreduction initiates cleavage of the benzylic C–O bond to eliminate the free phosphoramide mustard **7** together with a highly electrophilic quinonemethide derivative

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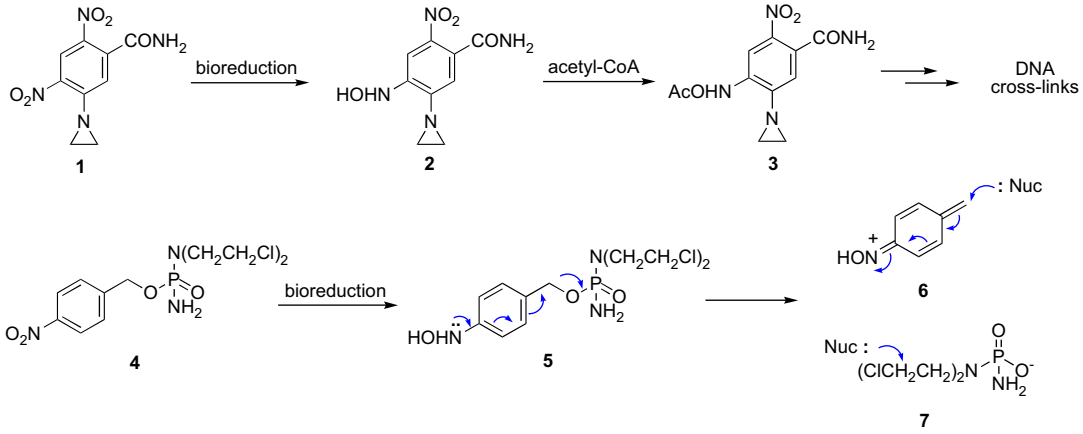


Scheme 1. Bioreductive activation of nitroarenes triggers formation of electrophilic species capable of alkylating DNA. Only bioreduction to the hydroxylamine is shown—reduction to the aniline would result in a similar fragmentation.

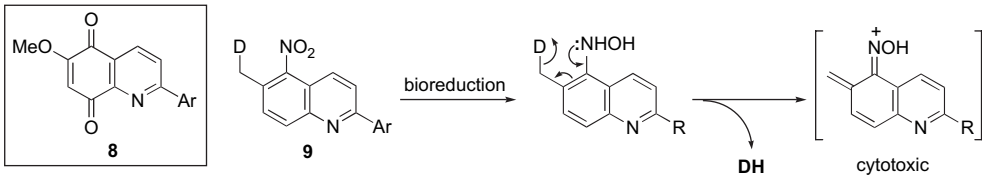
6; both **6** and **7** can act as electrophiles towards DNA (Scheme 1).

In conventional prodrug strategies, the aerobic bioreduction of nitroarenes can only be carried out by two endogenous enzymes (although other enzymes can reduce them under hypoxic conditions). These are the related flavoenzymes NAD(P)H quinone oxidoreductase 1 (NQO1), also known as DT-diaphorase or QR1 (EC 1.6.99.2), and NAD(P)H quinone oxidoreductase 2 (NQO2), now known as NRH quinone oxidoreductase 2 or QR2. However, an alternative bioreductive prodrug approach utilises an exogenous nitroreductase enzyme (NTR), isolated from *Escherichia coli*, that appears to be a much better nitroreductase than NQO1—tretazicar is reduced about 90-fold more rapidly by NTR than by NQO1—and a targeted drug delivery mechanism based on ADEPT or GDEPT.[6] As a result of these efforts, there are now a number of strategies based on the bioreduction of nitroarenes, including prodrugs based on 4-nitrobenzyl derivatives,[8,9] 4-nitrobenzyl carbamates,[10–13] 2-nitrophenyl acetates[14] and heteroaromatic nitro compounds (imidazoles, furans and thiophenes).[15–21] In view of this interest, we now report a new series of heteroaromatic nitro compounds, based on 5-nitroquinoline, as potential prodrug systems for bioreductive activation.

2. Results and discussion

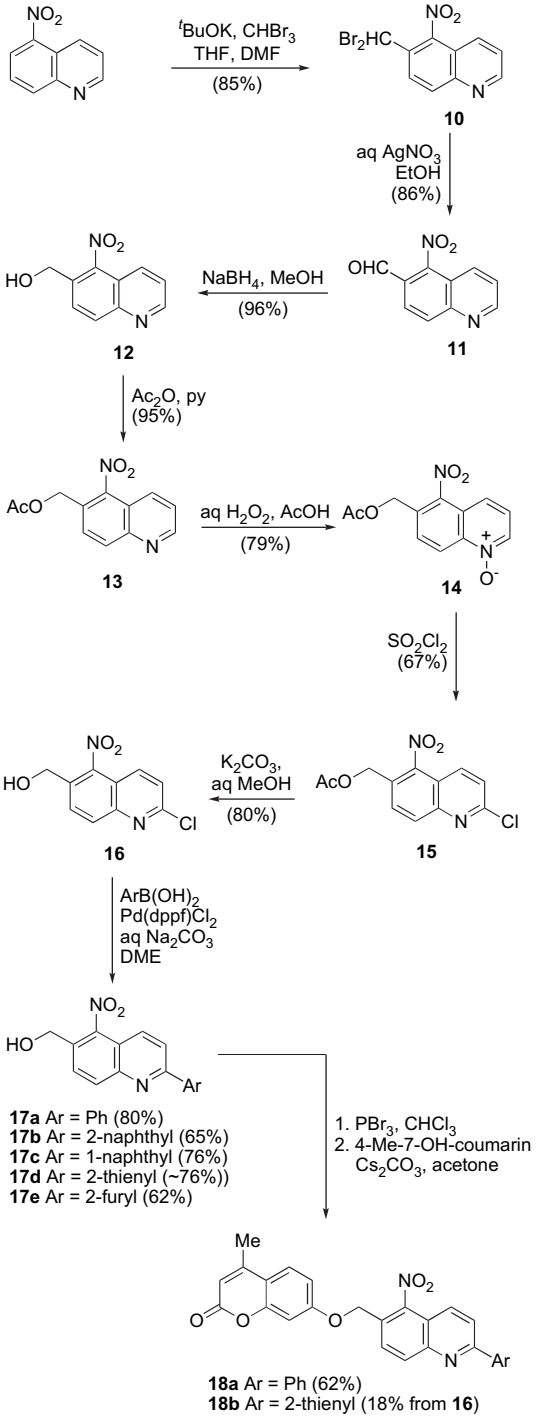
Our choice of nitroquinolines was influenced by our earlier work on quinolinequinones **8** (Scheme 2).[22,23] These simple quinones are excellent substrates for recombinant human NQO1 (hNQO1), and hence we speculated that other 2-arylquinoline derivatives such as 2-aryl-5-nitroquinolines **9** might also be the substrates for NQO1, and therefore represent a new family of potential bioreductively activated prodrug systems. The proposed fragmentation of such nitroquinolines **9** upon reductive activation is also shown in Scheme 2.

The starting point was the high yielding vicarious nucleophilic substitution reaction of commercially available 5-nitroquinoline with the anion derived from bromoform.[24,25] The resulting 6-dibromomethylquinoline **10** was readily converted into the quinoline-6-aldehyde **11** by treatment with aqueous ethanolic silver nitrate.[24] Reduction (96%) and acetylation (93%) then gave quinoline **13** ready for introduction of the 2-substituent. This was achieved by treatment of the corresponding *N*-oxide **14** with sulfuryl chloride (67%); final hydrolysis gave 2-chloro-5-nitroquinoline-6-methanol **16** (Scheme 3). A range of aryl substituents were introduced into the 2-position of the 2-chloroquinoline **16** in good yield by Suzuki coupling with commercially available boronic acids in the presence of $Pd(dppf)Cl_2$ catalyst to give the corresponding 2-aryl derivatives **17** (Scheme 3). In order to monitor the proposed bioreductive activation and subsequent fragmentation of nitroquinoline-based prodrug systems, we elected to incorporate a fluorescent model 'drug' moiety, namely 7-hydroxy-4-methylcoumarin. A similar approach has been used with 7-aminocoumarin derivatives using 4-nitrobenzyl carbamates.[26] Although the Mitsunobu coupling between the 7-hydroxycoumarin and the quinoline-6-methanol **17a** was unsuccessful, after some experimentation, it was found that conversion of **17a** into the corresponding bromide by treatment with phosphorus tribromide followed by reaction with 7-hydroxy-4-methylcoumarin in the presence of caesium carbonate as base gave the desired quinoline **18a** (Scheme 3).



Scheme 2. Structure of quinolinequinone substrates **8** for hNQO1, and proposed reductive fragmentation of 5-nitroquinolines **9** showing release of the drug D and formation of a cytotoxic species.

The thiophene derivative **18b** was similarly prepared, although in poor yield.



Scheme 3.

With the novel nitroquinolines available and a model drug molecule incorporated, it only remained to establish whether the desired fragmentation (Scheme 2) did indeed occur upon reduction of the nitro group. Thus, the nitroquinoline-coumarin conjugate **18a** was reduced chemically using zinc in acetic acid; following the reaction, which likely results in complete reduction of the nitro group to the aniline, the products were separated by chromatography to give the fluorescent 7-hydroxy-4-methylcoumarin (95%) and 5-amino-6-methyl-2-phenylquinoline **20** (95%) (Scheme 4) and identified by comparison with authentic sample obtained by independent synthesis as described in Section 3.4. It therefore appears that 5-nitroquinoline derivatives do undergo fragmentation upon reduction resulting in release of a phenolic leaving group from the 6-methyl position. Detailed biological evaluation of such systems is awaited.

3. Experimental section

3.1. General procedures

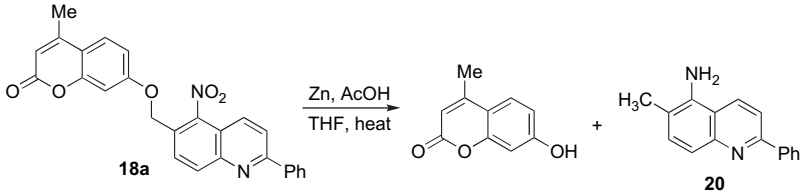
Commercially available reagents and solvents were used throughout without further purification, except tetrahydrofuran, dichloromethane and diethyl ether, which were freshly distilled. Light petroleum refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. All reactions were carried out under a nitrogen atmosphere. Thin layer chromatography was carried out on Merck Kieselgel 60GF_{254} aluminium foil backed plates. The plates were visualised under UV light or by potassium permanganate stain. Flash chromatography was carried out using Merck Kieselgel 60H silica or Matrix silica 60, with the eluent specified. IR spectra were recorded using a Nicolet Magna FT-550 spectrometer. Spectra were recorded as films between NaCl plates or as KBr disks. ^{1}H and ^{13}C NMR spectra were recorded using Bruker AC300, AC400, AV400 and DRX500 machines (^{1}H frequencies 300, 400 and 500 MHz, ^{13}C frequencies 75, 100 and 125 MHz, respectively); chemical shifts are quoted in parts per million and coupling constants, *J*, are quoted in hertz. In the ^{13}C spectra, signals corresponding to CH, CH_2 or Me groups, as assigned from DEPT, are noted; all others are C. High and low resolution mass spectra were carried out on a Micromass GCT TOF high resolution mass spectrometer.

3.1.1. General procedure A: Suzuki biaryl cross-coupling reactions

A solution of 2-chloro-5-nitroquinoline-6-methanol **16** (0.500 g, 2.1 mmol) and arylboronic acid (2.5 mmol) in 1,2-dimethoxyethane (45 mL) was degassed under reduced pressure and flushed with nitrogen. Pd(dppf)Cl_2 (0.077 g, 0.1 mmol) was added and the system was degassed again. Finally sodium carbonate (0.890 g, 8.4 mmol) dissolved in water (5 mL) was added and the mixture was heated under reflux for 1–3 h. After cooling, 1,2-dimethoxyethane was removed in vacuo, dichloromethane (50 mL) was added and the organic layer washed with water (3×30 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo, and the crude product purified by column chromatography.

3.1.2. General procedure B: bromination reactions

To a solution of 2-aryl-5-nitroquinoline-6-methanol **17** (1.2 mmol) in tetrahydrofuran (7 mL) and chloroform (2 mL) was added phosphorus tribromide (0.12 mL, 1.2 mmol) at 0 °C. The reaction mixture was then heated to 50 °C and left



Scheme 4.

to stir overnight. After cooling, the solvents were removed in vacuo and the residue was partitioned between saturated sodium hydrogen carbonate solution (10 mL) and ethyl acetate (10 mL). The aqueous phase was further extracted with ethyl acetate (2×10 mL). The organic phases were combined, dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The crude product was then purified by column chromatography.

3.1.3. General procedure C: alkylation reactions

A solution of 7-hydroxy-4-methylcoumarin (0.070 g, 0.4 mmol) in acetone (4 mL) was treated with caesium carbonate (0.240 g, 0.7 mmol) and stirred at room temperature for 15 min. The solution was then cooled to 0 °C and the 6-bromomethylquinoline (0.4 mmol) dissolved in acetone (4 mL) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 1 h. The acetone was then removed in vacuo, the residue partitioned between water (25 mL) and dichloromethane (10 mL) and the layers were separated. The organic phase was dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo to give the crude product. Purification was specific to each compound.

3.2. Nitroquinolines

3.2.1. 6-(Dibromomethyl)-5-nitroquinoline **10**

To a well-stirred solution of potassium *tert*-butoxide (13.2 g, 117 mmol), in a mixture of dry THF (12 mL) and dry DMF (9 mL) cooled to around −73 °C, a solution of 5-nitroquinoline (4.8 g, 27 mmol) and bromoform (7.6 g, 30 mmol) in dry DMF (14 mL) was added dropwise, being careful that the temperature did not exceed −68 °C. The mixture was allowed to stir for 1 min and then acidified with acetic acid (15 mL). After allowing the mixture to return to room temperature it was poured into water (900 mL) and the aqueous solution was extracted with dichloromethane (3×250 mL). The combined organic extracts were washed with water (3×350 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (1:1) to give the *title compound* as a yellow solid (7.9 g, 85%), mp 106–108 °C (from ethanol) (lit.[24] mp 108–109 °C). ν_{max} (KBr)/cm^{-1} 1593, 1524 (NO_2), 1346 (NO_2); δ_H (300 MHz; DMSO-d_6) 7.52 (1H, s, $CHBr_2$), 7.80 (1H, dd, *J* 8.7, 4.2, H-3), 8.23 (1H, d, *J* 8.7, H-4), 8.34 (1H, d, *J* 9.1, ArH), 8.42 (1H, d, *J* 9.1, ArH), 9.11 (1H, d, *J* 4.2, H-2).

3.2.2. 5-Nitroquinoline-6-carbaldehyde **11**

To a solution of 6-(dibromomethyl)-5-nitroquinoline **10** (4.0 g, 11.6 mmol) in ethanol (200 mL) was added a solution of silver nitrate (4.1 g, 24.1 mmol) in hot (60 °C) distilled water (25 mL), and the reaction mixture was heated under reflux for 2 h. After cooling, concentrated hydrochloric acid was added (25 mL) and solvent was removed in vacuo. The residue was treated with saturated sodium hydrogen carbonate solution, extracted with dichloromethane (3×250 mL) and the organic phases were washed with water (150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the *title compound* as a brown solid (2.0 g, 86%), mp 159–160 °C (from light petroleum/ethyl acetate) (lit.[24] mp 156–158 °C). ν_{max} (KBr)/cm^{-1} 1699 (C=O), 1612, 1529 (NO_2), 1344 (NO_2); δ_H (300 MHz; $CDCl_3$) 7.62 (1H, dd, *J* 8.7, 4.1, H-3), 8.17 (1H, d, *J* 8.9, ArH), 8.26 (1H, d, *J* 8.9, ArH), 8.35 (1H, d, *J* 8.7, H-4), 9.08 (1H, d, *J* 4.1, H-2), 10.15 (1H, s, CHO); *m/z* (EI) 202 (M^+, 10%), 155 (60), 144 (96), 115 (57), 102 (78), 101 (94), 99 (49), 90 (42), 89 (97), 52 (40), 51 (81).

3.2.3. 5-Nitroquinoline-6-methanol **12**

To a solution of 5-nitroquinoline-6-carbaldehyde **11** (1.7 g, 8.2 mmol) in wet methanol (200 mL) was added sodium borohydride (0.5 g, 13 mmol) portionwise. The reaction was stirred at room temperature for 1 h. The reaction mixture was quenched with hydrochloric acid (2 M) until pH 7 was achieved and the solvent removed in vacuo. The residue was partitioned between ethyl acetate (100 mL) and water (50 mL), the layers were separated, the organic layer was dried ($MgSO_4$) and concentrated in vacuo to give the *title compound* as a yellow solid (1.6 g, 96%), R_f 0.13 (light petroleum/ethyl acetate 1:1); mp 105–107 °C (from ethanol). (Found: C, 58.53; H, 3.70; N, 13.72. $C_{10}H_8N_2O_3$ requires C, 58.82; H, 3.95; N, 13.72%.) (Found: MH^+, 205.0621. $C_{10}H_8N_2O_3$+H requires 205.0613.) ν_{max} (KBr)/cm^{-1} 3176 (OH), 1594, 1516 (NO_2), 1354 (NO_2); δ_H (300 MHz; $CDCl_3$) 2.97 (1H, br s, OH), 4.86 (2H, s, CH_2), 7.50 (1H, dd, *J* 8.6, 4.1, H-3), 7.89 (1H, d, *J* 8.8, ArH), 8.15 (1H, d, *J* 8.6, H-4), 8.21 (1H, d, *J* 8.8, ArH), 8.91 (1H, d, *J* 4.1, H-2); δ_C (75 MHz; $CDCl_3$) 61.5 (CH_2), 120.6 (C), 123.9 (CH), 129.4 (CH), 131.3 (CH), 133.2 (C), 133.6 (CH), 145.6 (C), 147.4 (C), 151.9 (CH); *m/z* (CI) 205 (MH^+, 49%), 203 (21), 201 (32), 188 (60), 173 (32), 158 (15), 157 (10), 130 (12), 129 (10).

3.2.4. 6-Acetoxymethyl-5-nitroquinoline **13**

Acetic anhydride (12 mL) and pyridine (24 mL) were added to 5-nitroquinoline-6-methanol **12** (1.6 g, 7.8 mmol) in acetonitrile (40 mL). The reaction mixture was stirred at room temperature for 1 h and quenched with saturated sodium hydrogen carbonate solution (150 mL). The aqueous layer was

extracted with dichloromethane (3×50 mL). The combined organic phases were washed with copper sulfate solution (10%; 3×60 mL) and saturated aqueous brine solution (20 mL), dried ($MgSO_4$) and concentrated in vacuo to give the *title compound* as an orange solid (1.8 g, 95%), R_f 0.24 (light petroleum/ethyl acetate 1:1); mp 64–65 °C (from light petroleum/ethyl acetate). (Found: C, 58.45; H, 4.06; N, 11.36. $C_{12}H_{10}N_2O_4$ requires C, 58.54; H, 4.09; N, 11.38%.) (Found: MH^+, 247.0721. $C_{12}H_{10}N_2O_4$+H requires 247.0719.) ν_{max} (KBr)/cm^{-1} 2956, 1737 (C=O), 1625, 1595, 1523 (NO_2), 1349 (NO_2); δ_H (300 MHz; DMSO-d_6) 2.08 (3H, s, Me), 5.35 (2H, s, CH_2), 7.77 (1H, dd, *J* 8.7, 4.1, H-3), 7.98 (1H, d, *J* 8.9, ArH), 8.28 (1H, d, *J* 8.7, H-4), 8.34 (1H, d, *J* 8.9, ArH), 9.09 (1H, d, *J* 4.1, H-2); δ_C (75 MHz; DMSO-d_6) 20.7 (Me), 61.7 (CH_2), 119.9 (C), 124.8 (CH), 128.8 (C), 130.7 (CH), 131.7 (CH), 132.6 (CH), 145.1 (C), 145.5 (C), 151.8 (CH), 170.3 (C); *m/z* (CI) 247 (MH^+, 19%), 189 (24), 188 (28), 187 (100), 173 (16), 171 (17), 61 (40).

3.2.5. 6-Acetoxymethyl-5-nitroquinoline-N-oxide **14**

To a solution of 6-acetoxymethyl-5-nitroquinoline **13** (0.43 g, 1.8 mmol) in acetic acid (2 mL) was added hydrogen peroxide (35%; 0.8 mL). The mixture was heated to 80 °C for 4 h. After cooling, the mixture was poured into water (10 mL) and neutralised with saturated sodium hydrogen carbonate solution (35 mL). The aqueous mixture was extracted with dichloromethane (3×60 mL), the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography eluting with ethyl acetate/methanol (19:1) to give the *title compound* as a yellow solid (0.37 g, 79%), R_f 0.11 (ethyl acetate); mp 101–102 °C (from ethyl acetate/light petroleum). (Found: M^+, 262.0590. $C_{12}H_{10}N_2O_5$ requires 262.0592.) ν_{max} (KBr)/cm^{-1} 3080, 1739 (C=O), 1569, 1527 (NO_2), 1352 (NO_2), 1262, 1191, 1055; δ_H (300 MHz; $CDCl_3$) 2.14 (3H, s, Me), 5.33 (2H, s, CH_2), 7.47 (1H, dd, *J* 8.9, 6.0, H-3), 7.69 (1H, d, *J* 8.9, H-4), 7.85 (1H, d, *J* 9.0, ArH), 7.98 (1H, d, *J* 6.0, H-2), 8.92 (1H, d, *J* 9.0, ArH); δ_C (75 MHz; $CDCl_3$) 21.0 (Me), 61.8 (CH_2), 119.9 (CH), 123.6 (C), 123.7 (CH), 124.1 (CH), 130.0 (CH), 130.6 (C), 136.8 (CH), 141.7 (C), 146.6 (C), 170.6 (C); *m/z* (EI) 262 (M^+, 58%), 216 (53), 200 (27), 186 (18), 175 (44), 173 (24), 157 (20), 145 (20), 130 (29), 129 (40), 128 (34), 127 (16), 115 (25), 103 (27), 102 (24), 90 (19).

3.2.6. 6-Acetoxymethyl-2-chloro-5-nitroquinoline **15**

Sulfuryl chloride (3 mL) was added to 6-acetoxymethyl-5-nitroquinoline-*N*-oxide **14** (0.17 g, 0.7 mmol) and the mixture was heated to 60 °C for 3.5 h. After cooling, dichloromethane (15 mL) and water (15 mL) were added to the mixture and the mixture was stirred for 1 h to dissolve any insoluble material. The layers were separated and the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give the crude product as a brown oil (0.12 g, 67%). δ_H (300 MHz; $CDCl_3$) 2.07 (3H, s, Me), 5.29 (2H, s, CH_2), 7.50 (1H, d, *J* 8.9, ArH), 7.78 (1H, d, *J* 8.9, ArH), 8.11 (1H, d, *J* 8.6, ArH), 8.14 (1H, d, *J* 8.6, ArH). No further characterisation was carried out and the compound was used directly in the next step.

3.2.7. 2-Chloro-5-nitroquinoline-6-methanol **16**

To a solution of 6-acetoxymethyl-2-chloro-5-nitroquinoline **15** (4.0 g, 14.3 mmol) in 70% aqueous methanol (300 mL) was added potassium carbonate (7.9 g, 57.0 mmol). The reaction mixture was stirred at room temperature for 1 h. The methanol was then removed in vacuo, dichloromethane (100 mL) and water (50 mL) were added, and the layers were separated. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (4:1) to give the *title compound* as an off-white solid (2.72 g, 80%), R_f 0.38 (light petroleum/ethyl acetate 1:1); mp 116–118 °C (from dichloromethane/hexane). (Found: C, 50.67; H, 2.98; N, 11.80. $C_{10}H_7ClN_2O_3$ requires C, 50.42; H, 2.96; N, 11.74%.) (Found: M^+, 238.0138. $C_{10}H_7^{35}ClN_2O_3$ requires 238.0145.) ν_{max} (KBr)/cm^{-1} 3430 (OH), 1628, 1588, 1525 (NO_2), 1364 (NO_2), 821; δ_H (300 MHz; DMSO-d_6) 4.76 (2H, s, CH_2), 5.81 (1H, s, OH), 7.79 (1H, d, *J* 9.0, ArH), 8.07 (1H, d, *J* 8.9, ArH), 8.25 (1H, d, *J* 8.9, ArH), 8.30 (1H, d, *J* 9.0, ArH); δ_C (75 MHz; DMSO-d_6) 59.6 (CH_2), 118.8 (C), 125.4 (CH), 130.7 (CH), 131.8 (CH), 134.5 (CH), 134.8 (C), 144.5 (C), 146.3 (C), 151.6 (C); *m/z* (EI) 240/238 (M^+, 6/16%), 220 (30), 193 (15), 178/176 (39/87), 166 (44), 163 (53), 162 (80), 161 (17), 151 (23), 150 (27), 149 (54), 141 (65), 129 (75), 128 (96), 127 (95), 102 (50).

3.2.8. 5-Nitro-2-phenylquinoline-6-methanol **17a**

2-Chloro-5-nitroquinoline-6-methanol **16** (0.500 g, 2.0 mmol) was reacted with benzeneboronic acid (0.270 g, 2.2 mmol) following the general procedure A. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (1:1) to give the *title compound* as a colourless solid (0.470 g, 80%), R_f 0.46 (light petroleum/ethyl acetate 4:1); mp 154–156 °C (from ethyl acetate/ethanol). (Found: C, 68.14; H, 4.31; N, 9.95. $C_{16}H_{12}N_2O_3$ requires C, 68.56; H, 4.32; N, 9.99%.) (Found: MH^+, 281.0918. $C_{16}H_{12}N_2O_3$+H requires 281.0926.) ν_{max} (KBr)/cm^{-1} 3206 (OH), 2923, 2849, 1597, 1582, 1520 (NO_2), 1468, 1354 (NO_2), 1071; δ_H (300 MHz; DMSO-d_6) 4.77 (2H, d, *J* 5.7, CH_2), 5.80 (1H, t, *J* 5.7, OH), 7.56–7.63 (3H, m, ArH), 8.03 (1H, d, *J* 8.9, ArH), 8.33 (1H, d, *J* 8.9, ArH), 8.30–8.34 (4H, m, ArH); δ_C (75 MHz; DMSO-d_6) 59.7 (CH_2), 118.7 (C), 121.6 (CH), 127.8 (CH), 129.4 (CH), 129.6 (CH), 130.7 (CH), 131.6 (CH), 132.9 (CH), 133.7 (C), 137.9 (C), 144.7 (C), 146.7 (C), 157.5 (C); *m/z* (CI) 281 (MH^+, 59%), 263 (100), 268 (39), 250 (19), 249 (62).

3.2.9. 2-(Naphth-2-yl)-5-nitroquinoline-6-methanol **17b**

2-Chloro-5-nitroquinoline-6-methanol **16** (0.500 g, 2.0 mmol) was reacted with 2-naphthaleneboronic acid (0.400 g, 2.2 mmol) following the general procedure A. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (1:1) to give the *title compound* as a colourless solid (0.450 g, 65%), R_f 0.36 (light petroleum/ethyl acetate 4:1); mp 205–207 °C (from ethyl acetate/ethanol). (Found: MH^+, 331.1082. $C_{20}H_{14}N_2O_3$+H requires 331.1078.) ν_{max} (KBr)/cm^{-1} 3418 (OH), 2958, 1622, 1592, 1537 (NO_2), 1365 (NO_2); δ_H (400 MHz; DMSO-d_6)

4.78 (2H, d, *J* 5.6, CH_2), 5.78 (1H, t, *J* 5.6, OH), 7.60–7.62 (2H, m, ArH), 7.99–8.05 (2H, m, ArH), 8.10–8.13 (2H, m, ArH), 8.33–8.40 (2H, m, ArH), 8.47–8.53 (2H, m, ArH), 8.80 (1H, s, ArH); δ_C (100 MHz; DMSO-d_6) 59.3 (CH_2), 118.4 (C), 121.5 (CH), 124.4 (CH), 126.7 (CH), 127.4 (CH), 127.4 (CH), 127.6 (CH), 128.6 (CH), 128.9 (CH), 129.3 (CH), 131.2 (CH), 132.5 (CH), 133.0 (C), 133.4 (C), 133.8 (C), 134.9 (C), 144.3 (C), 146.4 (C), 157.4 (C); *m/z* (CI) 331 (MH^+, 83%), 330 (26), 314 (37), 313 (100), 298 (14), 297 (24), 270 (13).

3.2.10. 2-(Naphth-1-yl)-5-nitroquinoline-6-methanol *17c*

2-Chloro-5-nitroquinoline-6-methanol **16** (0.500 g, 2.0 mmol) was reacted with 1-naphthaleneboronic acid (0.400 g, 2.2 mmol) following the general procedure A. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (1:1) to give the *title compound* as a colourless solid (0.525 g, 76%), R_f 0.38 (light petroleum/ethyl acetate 4:1); mp 202–204 °C (from ethyl acetate/ethanol). (Found: MH^+, 331.1096. $C_{20}H_{14}N_2O_3$+H requires 331.1082.) ν_{max} (KBr)/cm^{-1} 3306 (OH), 3063, 2922, 2863, 1591, 1555, 1524 (NO_2), 1356 (NO_2), 1080; δ_H (300 MHz; DMSO-d_6) 4.81 (2H, d, *J* 5.7, CH_2), 5.84 (1H, t, *J* 5.7, OH), 7.53–7.81 (4H, m, ArH), 8.02–8.17 (5H, m, ArH), 8.37 (1H, d, *J* 2.3, ArH), 8.39 (1H, d, *J* 2.3, ArH); δ_C (75 MHz; DMSO-d_6) 59.7 (CH_2), 118.5 (C), 125.6 (CH), 125.8 (CH), 126.0 (CH), 126.6 (CH), 127.3 (CH), 128.6 (CH), 128.9 (CH), 129.6 (CH), 130.0 (CH), 130.7 (C), 131.2 (CH), 132.9 (CH), 133.8 (C), 134.0 (C), 137.4 (C), 144.7 (C), 146.6 (C), 160.2 (C); *m/z* (CI) 331 (MH^+, 64%), 330 (18), 314 (36), 313 (100), 300 (33), 298 (26), 285 (16), 271 (13).

3.2.11. 5-Nitro-2-(2-thienyl)quinoline-6-methanol *17d*

2-Chloro-5-nitroquinoline-6-methanol **16** (0.500 g, 2.0 mmol) was reacted with 2-thiophene boronic acid (0.320 g, 2.1 mmol) following the general procedure A. Complete purification of this compound proved to be difficult, and therefore the crude product (0.447 g, 76%) was used in the next step without further purification or characterisation.

3.2.12. 2-(Fur-2-yl)-5-nitroquinoline-6-methanol *17e*

2-Chloro-5-nitroquinoline-6-methanol **16** (0.500 g, 2.0 mmol) was reacted with 2-furan boronic acid (0.280 g, 2.4 mmol) following the general procedure A. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (7:3) to give the *title compound* as a pale yellow solid (0.350 g, 62%), R_f 0.36 (light petroleum/ethyl acetate 1:1); mp 179–181 °C (from methanol/hexane). (Found: M^+, 270.0643. $C_{14}H_{10}N_2O_4$ requires 270.0641.) ν_{max} ($CHCl_3$)/cm^{-1} 3606 (OH), 1602, 1496 (NO_2), 1354 (NO_2), 1072, 1010; δ_H (300 MHz; $CDCl_3$) 2.57 (1H, br s, OH), 4.87 (2H, s, CH_2), 6.62 (1H, dd, *J* 3.5, 1.7, ArH), 7.30 (1H, d, *J* 3.5, ArH), 7.66 (1H, dd, *J* 1.4, 0.8, ArH), 7.89 (1H, d, *J* 8.9, ArH), 7.94 (1H, d, *J* 9.1, ArH), 8.21 (1H, dd, *J* 9.1, 0.8, ArH), 8.27 (1H, d, *J* 8.9, ArH); δ_C (75 MHz; $CDCl_3$) 61.5 (CH_2), 112.0 (CH), 112.8 (CH), 119.0 (C), 120.0 (CH), 129.6 (CH), 131.5 (CH), 131.9 (C), 133.2 (CH), 145.2 (CH), 147.3 (C), 150.2 (C), 152.6 (C), one C unobserved; *m/z* (EI) 270 (M^+, 79%), 238 (20), 222 (25), 208 (34), 196 (87), 195 (41), 194 (50), 179 (51), 176 (29), 167 (100), 140 (64), 139 (49).

3.2.13. 6-Bromomethyl-5-nitro-2-phenylquinoline

5-Nitro-2-phenylquinoline-6-methanol **17a** (0.560 g, 2.0 mmol) was treated with phosphorus tribromide (0.2 mL, 2.2 mmol) following the general procedure B. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (4:1) to give the *title compound* as a colourless solid (0.651 g, 95%), R_f 0.68 (light petroleum/ethyl acetate 4:1); mp 156–158 °C (from ethyl acetate/light petroleum). (Found: C, 56.00; H, 3.25; N, 8.07. $C_{16}H_{11}BrN_2O_2$ requires C, 56.00; H, 3.23; N, 8.16%.) (Found: M^+, 341.9988. $C_{16}H_{11}^{79}BrN_2O_2$ requires 342.0004.) ν_{max} (KBr)/cm^{-1} 1597, 1539, 1520 (NO_2), 1446, 1359 (NO_2), 799; δ_H (300 MHz; $CDCl_3$) 4.58 (2H, s, CH_2), 7.43–7.51 (3H, m, ArH), 7.72 (1H, d, *J* 8.9, ArH), 7.96 (1H, d, *J* 8.9, ArH), 8.09–8.15 (3H, m, ArH), 8.23 (1H, d, *J* 8.9, ArH); δ_C (75 MHz; $CDCl_3$) 27.0 (CH_2), 119.6 (C), 121.9 (CH), 128.1 (CH), 128.4 (C), 129.5 (CH), 130.8 (CH), 131.2 (CH), 131.9 (CH), 134.1 (C), 138.5 (CH), 146.6 (C), 148.1 (C), 159.5 (C); *m/z* (FI) 344/342 (M^+, 94/100%).

3.2.14. 6-Bromomethyl-5-nitro-2-(thien-2-yl)quinoline

The impure 5-nitro-2-(2-thienyl)quinoline-6-methanol **17d** (0.20 g, 0.7 mmol) was treated with phosphorus tribromide (0.07 mL, 0.7 mmol) following the general procedure B. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (4:1) to give the *title compound* as a bright yellow solid (0.195 g, 61% over 2 steps), R_f 0.67 (light petroleum/ethyl acetate 4:1); mp 179–181 °C (from chloroform). (Found: MH^+, 348.9631. $C_{14}H_9^{79}BrN_2O_2$ +H requires 348.9646.) ν_{max} (KBr)/cm^{-1} 1596, 1580, 1523 (NO_2), 1456, 1445, 1364 (NO_2), 1099, 752; δ_H (300 MHz; DMSO-d_6) 4.95 (2H, s, CH_2), 7.35 (1H, dd, *J* 5.1, 3.8, ArH), 7.93 (1H, d, *J* 5.1, ArH), 8.07 (1H, d, *J* 8.9, ArH), 8.20 (1H, d, *J* 3.8, ArH), 8.31 (1H, d, *J* 8.9, ArH), 8.33 (1H, d, *J* 9.1, ArH), 8.41 (1H, d, *J* 9.1, ArH); δ_C (75 MHz; DMSO-d_6) 28.0 (CH_2), 118.8 (C), 121.0 (CH), 128.3 (C), 129.3 (CH), 129.3 (CH), 131.7 (CH), 131.8 (CH), 132.2 (CH), 132.8 (CH), 143.6 (C), 146.2 (C), 147.1 (C), 154.1 (C); *m/z* (CI) 351/349 (MH^+, 14/13%), 271 (25), 270 (16), 269 (100), 253 (7).

3.2.15. 6-(4-Methylcoumarin-7-yloxyl)methyl-5-nitro-2-phenylquinoline *18a*

7-Hydroxy-4-methylcoumarin (0.093 g, 0.5 mmol) was reacted with 6-bromomethyl-5-nitro-2-phenylquinoline (0.200 g, 0.6 mmol) following the general procedure C. The crude product was stirred in water (50 mL) for 30 min and then filtered. The solid was then stirred in ethyl acetate for 30 min and then filtered to give the *title compound* as a colourless solid (0.200 g, 65%), R_f 0.58 (light petroleum/ethyl acetate 4:1); mp 244–246 °C (from tetrahydrofuran/ethyl acetate). (Found: C, 70.99; H, 4.04; N, 6.18. $C_{26}H_{18}N_2O_5$ requires C, 71.23; H, 4.14; N, 6.39%.) (Found: M^+, 438.1211. $C_{26}H_{18}N_2O_5$ requires 438.1216.) ν_{max} (KBr)/cm^{-1} 2983,

2922, 2863, 1724 (C=O), 1617, 1598, 1582, 1470, 1454, 1073; δ_H (500 MHz; DMSO-d_6) 2.40 (3H, s, Me), 5.58 (2H, s, CH_2), 6.24 (1H, s, CH), 7.04 (1H, dd, *J* 8.8, 2.4, ArH), 7.13 (1H, d, *J* 2.4, ArH), 7.57–7.62 (3H, m, ArH), 7.73 (1H, d, *J* 8.8, ArH), 8.13 (1H, d, *J* 8.8, ArH), 8.31–8.33 (2H, m, ArH), 8.37 (1H, d, *J* 9.2, ArH), 8.40 (1H, d, *J* 9.2, ArH), 8.42 (1H, d, *J* 8.8, ArH); δ_C (125 MHz; DMSO-d_6) 18.4 (Me), 67.0 (CH_2), 102.6 (CH), 112.2 (CH), 113.0 (CH), 114.6 (C), 119.1 (C), 122.1 (CH), 127.1 (CH), 127.8 (C), 128.0 (CH), 129.5 (CH), 130.3 (CH), 130.9 (CH), 131.9 (CH), 133.5 (CH), 138.1 (C), 146.1 (C), 147.6 (C), 153.5 (C), 155.2 (C), 158.6 (C), 160.3 (C), 161.2 (C); *m/z* (EI) 438 (M^+, 7%), 264 (22), 263 (100), 246 (15), 219 (18), 205 (66), 204 (74), 176 (20), 148 (27), 147 (44).

3.2.16. 6-(4-Methylcoumarin-7-yloxyl)methyl-5-nitro-2-(thien-2-yl)quinoline ***18b***

7-Hydroxy-4-methylcoumarin (0.048 g, 0.3 mmol) was reacted with 6-bromomethyl-5-nitro-2-(2-thienyl)quinoline (0.100 g, 0.3 mmol) following the general procedure C. The crude product was purified by stirring in cold tetrahydrofuran and collecting the solid to give the *title compound* as a colourless solid (0.038 g, 30%), mp 240–242 °C (from chloroform/hexane). (Found: M^+, 444.0789. $C_{24}H_{16}N_2O_5S$ requires 444.0780.) ν_{max} (KBr)/cm^{-1} 2923, 2854, 1714 (C=O), 1609, 1529 (NO_2), 1472, 1392 (NO_2), 1282, 1268, 1074; δ_H (300 MHz; DMSO-d_6) 2.44 (3H, s, Me), 5.59 (2H, s, CH_2), 6.29 (1H, s, ArH), 7.05–7.09 (1H, m, ArH), 7.17–7.15 (1H, m, ArH), 7.30–7.33 (1H, m, ArH), 7.77 (1H, d, *J* 8.9, ArH), 7.89 (1H, d, *J* 4.5, ArH), 8.11–8.17 (2H, m, ArH), 8.30–8.40 (3H, m, ArH); *m/z* (EI) 444 (M^+, 11%), 270 (25), 269 (100), 252 (27), 211 (95), 210 (43), 176 (41), 148 (41), 147 (36), 140 (12), 128 (30), 91 (21).

3.3. Chemical reduction reactions

To a solution of 6-(4-methylcoumarin-7-yloxyl)methyl-5-nitro-2-phenylquinoline **18a** (0.004 g, 9.1 μmol) in THF (5 mL) and acetic acid (0.001 mL, 36.5 μmol) was added zinc dust (0.002 g, 63.9 μmol) and the reaction mixture heated under reflux for 16 h. After cooling, the mixture was diluted with water (10 mL) and neutralised with saturated sodium hydrogen carbonate solution (0.5 mL). The mixture was extracted with dichloromethane (3×10 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (9:1) to give 5-amino-6-methyl-2-phenylquinoline **20** as a bright yellow solid (0.0015 g, 95%) and 4-methyl-7-hydroxycoumarin as a colourless solid (0.002 g, 95%); both compounds were comparable to authentic samples.

3.4. Independent synthesis of 5-amino-6-methyl-2-phenylquinoline ***20***

(a) To a solution of 6-methyl-5-nitroquinoline (6.7 g, 35.6 mmol) in acetic acid (37 mL) was added hydrogen peroxide (35%; 9 mL). The mixture was heated to 80 °C for 4 h. After cooling, the mixture was basified with sodium hydroxide solution (1 M) and extracted with dichloromethane (3×60 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give *6-methyl-5-nitroquinoline-N-oxide* as a yellow solid (5.91 g, 81%), R_f 0.10 (ethyl acetate); mp 196–198 °C. (Found: M^+, 204.0534. $C_{10}H_8N_2O_3$ requires 204.0535.) ν_{max} (KBr)/cm^{-1} 3050, 2987, 2922, 1622, 1574, 1528, 1355, 1267; δ_H (300 MHz; $CDCl_3$) 2.57 (3H, s, Me), 7.43 (1H, dd, *J* 8.8, 6.1, ArH), 7.60 (1H, d, *J* 8.8, ArH), 7.66 (1H, d, *J* 9.0, ArH), 8.54 (1H, d, *J* 6.1, ArH), 8.82 (1H, d, *J* 9.0, ArH); δ_C (75 MHz; $CDCl_3$) 18.5 (Me), 119.5 (CH), 122.8 (CH), 123.6 (C), 123.7 (CH), 132.0 (C), 133.0 (CH), 136.2 (CH), 140.7 (C), 147.4 (C); *m/z* (EI) 204 (M^+, 73%), 188 (81), 171 (71), 143 (91), 142 (100), 141 (71), 115 (68), 77 (49).

(b) Sulfuryl chloride (46 mL) was added to 6-methyl-5-nitroquinoline-*N*-oxide (6.5 g, 32.0 mmol) and the mixture was heated to 60 °C for 3.5 h. After cooling, dichloromethane (200 mL) and water (200 mL) were added to the reaction mixture and the mixture was stirred for 1 h to dissolve any insoluble material. The layers were separated and the organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was recrystallised from dichloromethane/light petroleum to give *2-chloro-6-methyl-5-nitroquinoline* as a colourless solid (4.0 g, 56%), R_f 0.60 (light petroleum/ethyl acetate 4:1); mp 171–173 °C (from dichloromethane/light petroleum). (Found: M^+, 222.0198. $C_{10}H_7^{35}ClN_2O_2$ requires 222.0196.) ν_{max} (KBr)/cm^{-1} 3079, 1583, 1515, 1453, 1365, 817; δ_H (300 MHz; $CDCl_3$) 2.49 (3H, s, Me), 7.45 (1H, d, *J* 8.9, ArH), 7.58 (1H, d, *J* 8.7, ArH), 8.00 (1H, d, *J* 8.9, ArH), 8.01 (1H, d, *J* 8.7, ArH); δ_C (75 MHz; $CDCl_3$) 18.6 (Me), 119.5 (C), 125.0 (CH), 130.1 (C), 131.8 (CH), 133.5 (CH), 133.5 (CH), 146.5 (C), 147.0 (C), 152.1 (C); *m/z* (EI) 224/222 (M^+, 25/55%), 205 (85), 192 (51), 191 (36), 178 (37), 177 (98), 142 (51), 141 (62), 140 (100), 128 (35), 113 (41), 63 (29).

(c) A solution of 2-chloro-6-methyl-5-nitroquinoline (0.350 g, 1.6 mmol) in 1,2-dimethoxyethane (33 mL) was degassed under reduced pressure and flushed with nitrogen. $Pd(dppf)Cl_2$ (0.192 g, 0.26 mmol) was added and the system was degassed again. The solution was stirred for 10 min. Potassium carbonate (0.906 g, 6.6 mmol) was added, which was followed by benzeneboronic acid (0.160 g, 1.3 mmol) and the mixture was heated under reflux for 24 h. After cooling, the mixture was diluted with ether (70 mL) and washed with water (3×20 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography eluting with light petroleum/ethyl acetate (4:1) to give *6-methyl-5-nitro-2-phenylquinoline* as a colourless solid (0.291 g, 84%), R_f 0.70 (light petroleum/ethyl acetate 4:1); mp 102–104 °C (from light petroleum/ethyl acetate). (Found: MH^+, 265.0977. $C_{16}H_{12}N_2O_2$+H requires 265.0977.) ν_{max} (KBr)/cm^{-1} 2924, 2848, 1599, 1517 (NO_2), 1490, 1471, 1369 (NO_2); δ_H (400 MHz; $CDCl_3$) 2.56 (3H, s, Me), 7.48–7.56 (3H, m, ArH), 7.60 (1H, d, *J* 8.7, ArH), 7.98–8.01 (1H, m, ArH), 8.16–8.18 (3H, m, ArH), 8.21 (1H, d, *J* 8.7, ArH); δ_C (100 MHz; $CDCl_3$) 18.2 (Me), 119.3 (C), 121.1 (CH), 127.6

(CH), 128.7 (C), 129.0 (CH), 130.0 (CH), 130.8 (CH), 131.9 (CH), 132.6 (CH), 138.5 (C), 146.6 (C), 146.7 (C), 157.9 (C); *m/z* (CI) 265 (MH^+, 100%), 235 (12).

(d) A stirred solution of 6-methyl-5-nitro-2-phenylquinoline (0.150 g, 0.57 mmol) and palladium on carbon (10%; 0.030 g, 0.03 mmol) in methanol (15 mL) was placed under a hydrogen atmosphere for 16 h at room temperature. The crude reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography eluting with dichloromethane/ethyl acetate (1:0 to 9:1 elution) to give the *title compound* as a bright yellow solid (0.122 g, 92%), R_f 0.46 (light petroleum/ethyl acetate 1:1); mp 154–156 °C (from dichloromethane/hexane). (Found: MH^+, 235.1228. $C_{16}H_{14}N_2$+H requires 235.1235.) ν_{max} ($CHCl_3$)/cm^{-1} 3487 (NH), 3410 (NH), 2970, 1623, 1592, 1564, 1406, 1368; δ_H (400 MHz; $CDCl_3$) 2.35 (3H, s, Me), 4.11 (2H, br s, NH_2), 7.43–7.47 (1H, m, ArH), 7.46 (1H, d, *J* 8.5, ArH), 7.50–7.54 (2H, m, ArH), 7.61 (1H, d, *J* 8.5, ArH), 7.77 (1H, d, *J* 8.8, ArH), 8.14–8.17 (2H, m, ArH), 8.20 (1H, d, *J* 8.8, ArH); δ_C (100 MHz; $CDCl_3$) 17.6 (Me), 116.7 (C), 117.0 (C), 117.3 (CH), 119.6 (CH), 127.5 (CH), 128.8 (CH), 129.2 (CH), 129.9 (CH), 133.2 (CH), 139.0 (C), 139.5 (C), 147.7 (C), 156.0 (C); *m/z* (ES) 235 (MH^+, 100%).

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