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Novel quinolinequinone antitumor agents: structure-metabolism studies with NAD(P)H:quinone oxidoreductase (NQO1)

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Abstract—A series of quinolinequinones bearing various substituents has been synthesized, and the effects of substituents on the metabolism of the quinones by recombinant human NAD(P)H:quinone oxidoreductase (hNQO1) was studied. A range of quinolinequinones were selected for study, and were specifically designed to probe the effects of aryl substituents at C-2. A range of 28 quinolinequinones **2**–**29** was prepared using three general strategies: the palladium(0) catalyzed coupling of 2-chloroquinolines, the classical Friedländer synthesis and the double-Vilsmeier reaction of acetanilides. One example of an isoquinolinequinone **30** was also prepared, and the reduction potentials of the quinones were measured by cyclic voltammetry. For simple substituents R^2 at the quinoline 2-position, the rates of quinone metabolism by hNQO1 decrease for $R^2 = Cl > H \sim Me > Ph$. For aromatic substituents, the rate of reduction decreases dramatically for $R^2 = Ph > 1$-naphthyl > 2-naphthyl > 4-biphenyl. Compounds containing a pyridine substituent are the best substrates, and the rates decrease as $R^2 = 4$-pyridyl > 3-pyridyl > 2-pyridyl > 4-methyl-2-pyridyl > 5-methyl-2-pyridyl. The toxicity toward human colon carcinoma cells with either no detectable activity (H596 or BE-WT) or high NQO1 activity (H460 or BE-NQ) was also studied in representative quinones. Quinones that are good substrates for hNQO1 are more toxic to the NQO1 containing or expressing cell lines (H460 and BE-NQ) than the NQO1 deficient cell lines (H596 and BE-WT).

1. Introduction

NAD(P)H:quinone oxidoreductase (NQO1, EC 1.6.99.2), also known as DT-diaphorase, is an obligate 2-electron reductase that is characterized by its ability to use either NADH or NADPH as cofactor.[1,2] NQO1 catalyses the 2-electron reduction of quinones thereby bypassing the potentially toxic semiquinone and hence can protect cells against the toxic effects of quinones.[3] However NQO1 is also involved in the reductive activation of anticancer agents such as mitomycin C (MMC) which operate by the so-called bioreductive mechanism,[4–6] and a clear correlation between NQO1 activity and MMC sensitivity in human lung and breast cancer cell lines has been demonstrated.[7] The importance of NQO1 in the bioactivation of other cytotoxic quinones such as EO9,[8–10] azidiridinylbenzoquinones such as MeDZQ,[7,11] and the novel cyclopropamitosenes[12] is now well established, and the subject has been reviewed recently.[13,14]

We recently reported the results of two studies designed to correlate the rate of metabolism by NQO1 and toxicity towards human tumor cell lines with a series of indolequinones,[15,16] and NQO1 continues to generate interest because of its elevated levels in many tumors and tumor cell lines,[5,17] and its possible role in the stabilization of the tumor suppressor gene wild-type p53.[18–20] Thus other researchers have also studied the metabolism of quinones by NQO1,[21–27] and the induction and inhibition of the enzyme.[28–30] Advances have also been made in the immunohistochemical detection of NQO1 in normal and tumor tissue,[31–33] in understanding NQO1 gene expression,[34–36] and the polymorphism, resulting from a C to T base change at position 609, that occurs.[37,38]

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Recently the 3-dimensional structure of human NQO1 has been solved by two research groups, and resolved to 2.3 Å[39] and 1.7 Å[40] respectively. The structure of the complex of enzyme with duroquinone has also been solved,[40] and the studies highlight the structural changes that are necessary for control of access to the catalytic site that is required by the ping-pong mechanism in which NAD(P)H enters the catalytic site and reduces the flavin, $NAD(P)^+$ leaves thereby allowing the substrate to enter and be subsequently reduced by $FADH_2$. Although molecular modeling studies using a model of the human enzyme based on its homology to the previously determined structure of the rat enzyme have been useful in the design of new quinone substrates,[21,41,42] co-crystallization of an indolequinone substrate with the human protein has provided detailed structural information.[43] Likewise, structural studies on a related indolequinone have helped characterize a mechanism of NQO1 inhibition.[44]

One of the best substrates for NQO1 remains the naturally occurring antitumor antibiotic streptonigrin (SN) **1**. Streptonigrin, isolated from *Streptomyces flocculus* over 40 years ago, has activity against a broad range of tumors. It was studied clinically in the 1960s and 1970s as an antitumor agent, but its use was limited by reports of delayed myelotoxicity. Nevertheless, positive results were reported for SN both as a single agent and in combination chemotherapy. The biological properties of SN have been reviewed recently.[45] Hydroxyl radical ($HO^{\bullet}$) production following reduction of the quinolinequinone moiety of SN leads to DNA degradation and cytotoxicity, and an SN–metal–DNA complex is thought to be involved.[46,47] SN is an excellent substrate for NQO1,[48] and we have previously shown that it is selectively toxic to colon[49] and lung[50] cell lines with elevated NQO1, although its facile 2e-reduction by NQO1 may be independent from the hydroxyl radical production referred to above.

We now report the details of a study designed to examine the effects of functional group substitutions on the metabolism of a range of novel quinolinequinones **2–29** and one isoquinoline derivative **30** (Fig. 1) by recombinant hNQO1.[51] Although others have investigated the biological properties of quinolinequinones,[52,53] including analogues of SN,[47,54,55] the current work represents the first detailed study of the metabolism of such quinones by NQO1.

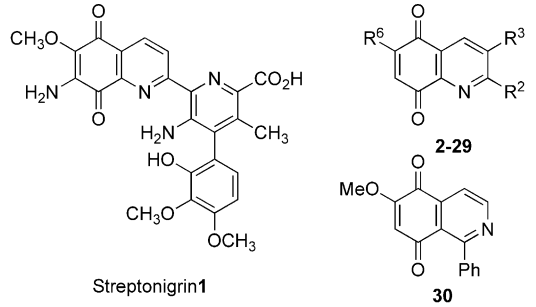


Figure 1.

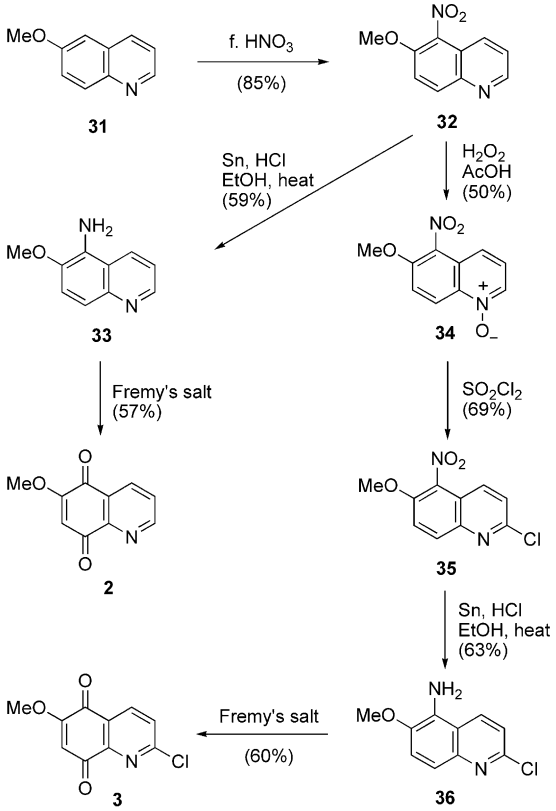
2. Results and discussion

2.1. Chemistry

A range of quinolinequinones was designed to explore the effect of substituents at C-2, and in particular variations in the aromatic ring at this position bearing in mind the presence of a substituted 2-pyridyl group at C-2 in SN **1**. We also looked at a smaller number of variations at C-6, and at the effect of introducing a substituent at C-3, a position that is unsubstituted in SN.

In order to prepare such a range of quinolinequinones, three strategies were adopted: the palladium(0) catalyzed coupling of 2-chloroquinoline derivatives, the classical Friedländer quinoline synthesis, and the 'double-Vilsmeier' reaction of acetanilides. The starting material for the first strategy was the commercially available 6-methoxyquinoline **31**. Thus nitration at C-5, followed by reduction of the nitro compound **32** and oxidation of the resulting 5-aminoquinoline **33** with Fremy's salt [potassium nitrosodisulfonate-$(KO_3S)_2NO$] gave the 6-methoxyquinoline-5,8-dione **2** (Scheme 1). The chlorine substituent at C-2 was introduced by oxidation of 6-methoxy-5-nitroquinoline **32** and treatment of the resulting *N*-oxide **34** with sulfuryl chloride to give the 2-chloroquinoline **35**. Subsequent reduction of the nitro group gave the 5-aminoquinoline **36**, oxidation of which gave the key 2-chloroquinolinequinone **3** (Scheme 1), a compound previously prepared by Kametani et al.[56]

The 2-methylquinolinequinone **4** was prepared slightly differently using the known reaction of 4-methoxy-2-



Scheme 1.

nitroaniline **37** with paraldehyde to give the 2-methylquinoline **38** albeit in poor yield.[57] Subsequent reduction of the nitro group, and treatment of the resulting 8-aminoquinoline **39** with Fremy's salt gave the desired quinone **4** (Scheme 2).

The 2-aryl-and-hetaryl-quinolinequinones **5**–**11**, **13**, **16** and **17** were prepared by palladium(0) catalyzed coupling reactions of the 2-chloroquinolinequinone **3** with areneboronic acids or arylstannanes under typical Suzuki or Stille reaction conditions (Scheme 3), although the yield in many of these reactions was poor to modest (Table 1).

The 2-(2-pyridyl)quinolinequinone **11** was also prepared using the Friedländer reaction. Thus catalytic hydrogenation of 2-benzenesulfonyloxy-3-methoxy-6-nitrobenzaldehyde **40** gave the corresponding *ortho*-aminobenzaldehyde which was immediately condensed with 2-acetylpyridine under Friedländer conditions.[58] This gave the 2-substituted quinolin-5-ol **41** in poor yield, the benzensulfonate ester being hydrolysed by treatment with aqueous ethanolic sodium hydroxide, readily oxidised to the quinone **11** (Scheme 4). Similarly, reaction of the *ortho*-aminobenzaldehyde with 2-acetyl-4-methylpyridine, 3-acetylpyridine and 4-acetylpyridine gave the 2-pyridylquinolin-5-ols **42**–**44** respectively in poor yield, oxidation of which gave the quinolinequinones **12**, **14** and **15** (Scheme 4).

The 4-indolyl substituted quinolinequinone **18** was also prepared by a palladium catalyzed coupling reaction, although it was carried out on the 2-chloro-6-methoxy-5-nitroquinoline **35** rather than the quinone **3**. Thus the indole-4-boronate **48**, prepared from 2-bromobenzaldehyde in four steps as shown in Scheme 5, was coupled to the 2-chloroquinoline **35** to give the indolylquinoline **49**. Reduction of the nitro and ester groups was then followed by the oxidation of the 5-aminoquinoline **51** to give the desired quinone **18** (Scheme 5).

The synthesis of a series of compounds possessing substituents other than a methoxy group at C-6 began with the displacement of the methoxy group in quinones **2** and **5** with secondary amines to give the quinones **19**–**21** as shown in Scheme 6.

The simple 2-phenyl-6-unsubstituted quinolinequinone **22** was prepared from 8-benzyloxy-2-quinolone **52** as shown in Scheme 7, by chlorination, Suzuki coupling of the resulting 2-chloroquinoline **53**, deprotection and oxidation of the quinolin-8-ol **55** with Fremy's salt.

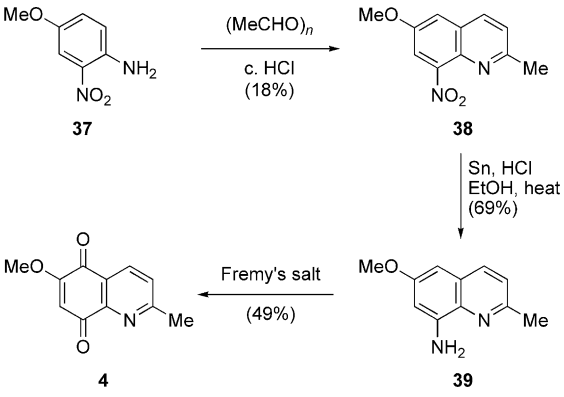
The synthesis of quinones bearing a substituent at C-3 started with 2,5-dimethoxyacetanilide **56** which underwent the 'double Vilsmeier' reaction upon treatment with phosphorus oxychloride in DMF to give the 2-chloroquinoline-3-carbaldehyde **57**.[59] Reduction of the aldehyde, reductive removal of the chlorine, and oxidative demethylation with cerium(IV) ammonium nitrate then gave the quinone **23** (Scheme 8).

The above sequence was readily modified to incorporate aryl or hetaryl groups at C-2. Thus Suzuki coupling of the 2-chloroquinoline-3-carbaldehyde **57** with benzeneboronic acid gave the 2-phenyl derivative **60**. Reduction

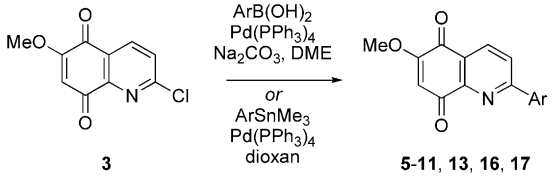
Table 1. Palladium(0) catalyzed coupling reactions of 2-chloro-6-methoxyquinoline-5,8-dione **3**

Ar	Method[a]	Product	Yield/%
Ph	A	5	24
2-Tolyl	A	6	44
4-Tolyl	A	7	42
4-Biphenyl	A	8	39
1-Naphthyl	A	9	18
2-Naphthyl	A	10	16
2-Pyridyl	B	11	88
5-Me-2-pyridyl	B	13	28
2-Thienyl	A	16	25
2-Benzofuranyl	A	17	20

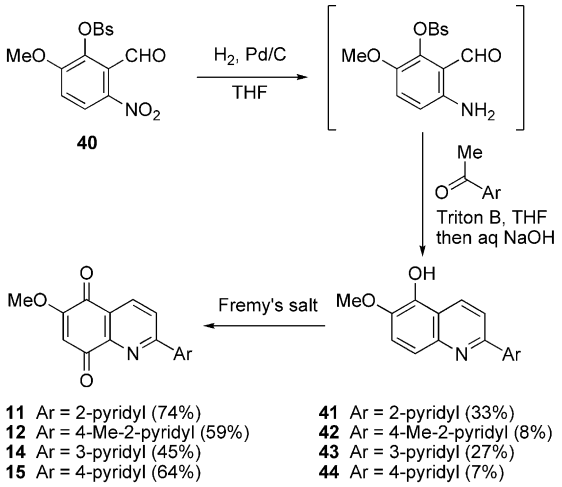
[a] Method: A, Suzuki coupling with $ArB(OH)_2$; B, Stille coupling with $ArSnMe_3$.



Scheme 2.



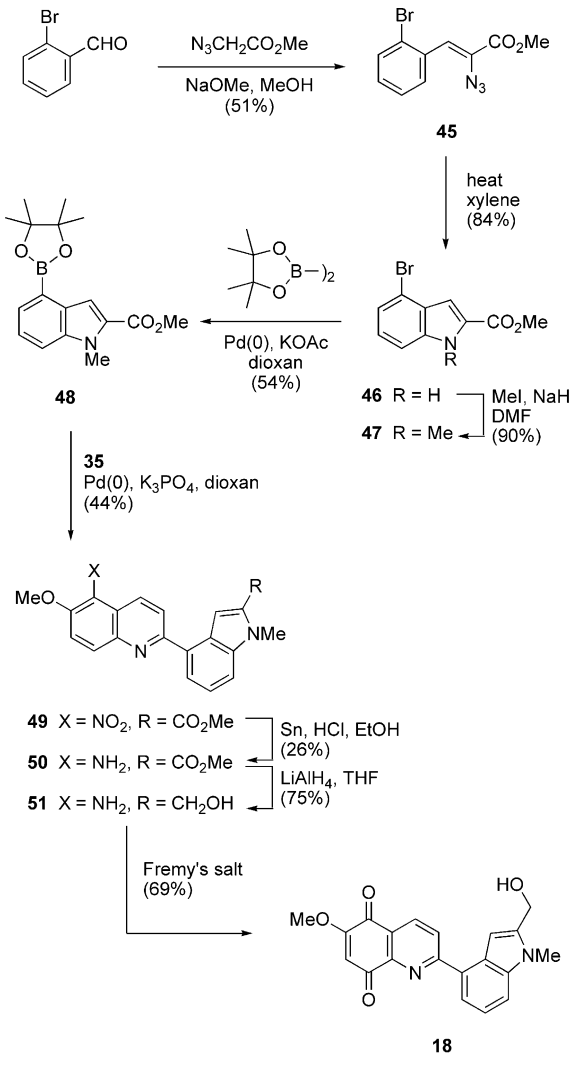
Scheme 3.



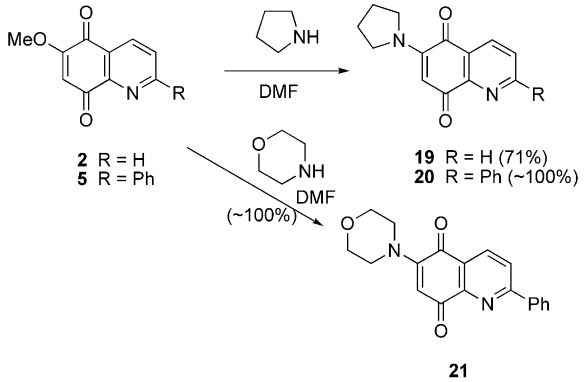
Scheme 4.

of the ester and oxidative demethylation of the 5,8-dimethoxyquinoline **61** gave the corresponding quinone **24** (Scheme 9). A similar sequence of reactions using 2-thienyl- and 2-benzofuranyl- boronic acids gave the corresponding quinones **25** and **26** (Scheme 9).

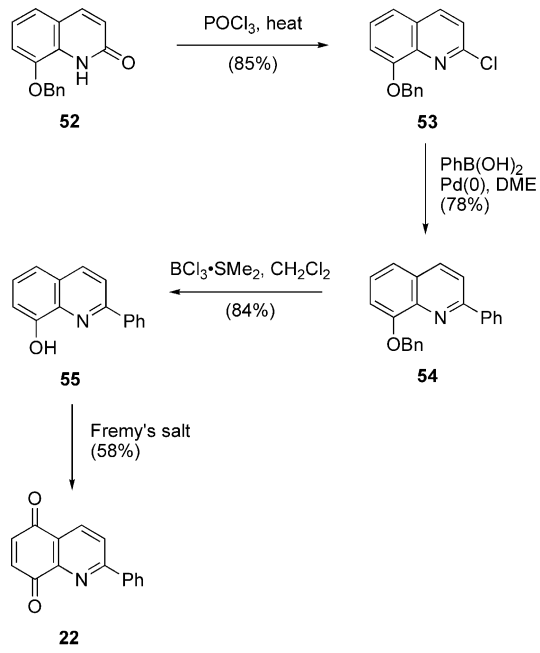
The acetate esters of quinones **24**–**26** were also prepared by acetylation of the alcohols **61**, **63** and **65** followed by



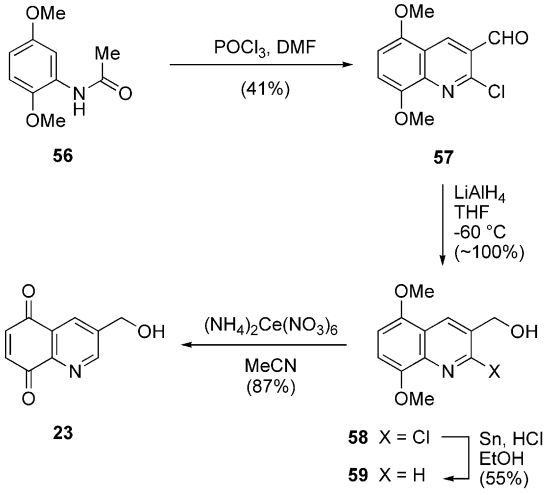
Scheme 5.



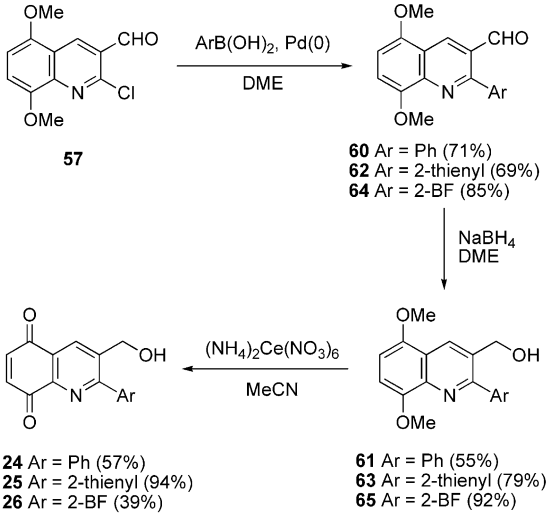
Scheme 6.



Scheme 7.



Scheme 8.



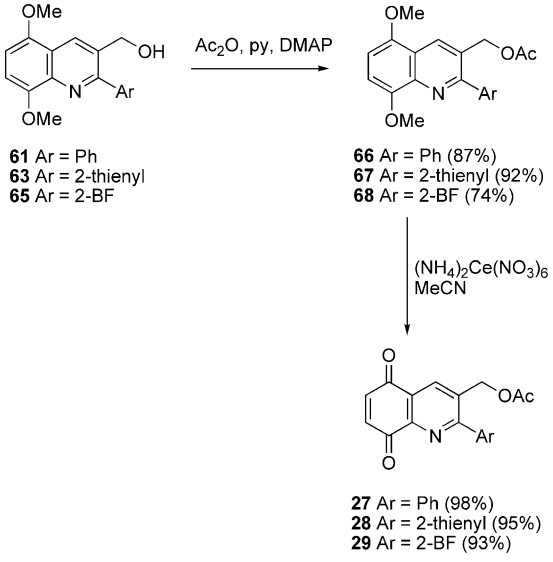
Scheme 9.

oxidation of the 5,8-dimethoxy compounds **66–68** to give the quinones **27–29** (Scheme 10). The structure of quinolinequinone **29** was confirmed by X-ray crystallography (Fig. 2).

Finally, a single example of an isoquinolinequinone was prepared following a literature procedure for related compounds.[60] The known phenethylamine derivative **69**[61] was benzoylated to give amide **70** which underwent Bischler–Napieralski cyclisation and debenzylation under the acidic conditions to give the isoquinolin-5-ol **71** in poor yield, oxidation of which gave the desired isoquinoline **30** (Scheme 11).

2.2. Electrochemistry

The main aim of this work was to study the enzymic 2e-reduction of quinolinequinones by NQO1. However, the reduction of quinones can also be readily studied in the laboratory using electrochemical techniques, and although this gives data related to the 1e-reduction, it does provide data on the relative ease of reduction of a series of quinones. Therefore electrochemical studies were performed on a number of the quinolinequinones using DMF as solvent and tetra-*n*-butyl ammonium tetrafluoroborate as the supporting electrolyte. $E_{1/2}$ values, determined from the (at least) quasi-reversible voltammograms recorded for the one-electron reduction of the quinolinequinones, show little variation over the range of potential sweep rates used. Thus, the $E_{1/2}$ values given in Table 2 are averages of the values determined from voltammograms recorded at potential sweep rates of 50, 100, 200, 300, 400 and 500 mV s^{-1}. The $E_{1/2}$ values, tabulated with reference to $E_{1/2}$ for ferrocene ($Fc^{+/0}$) to avoid liquid junction potential, are shown in Table 2.



Scheme 10.

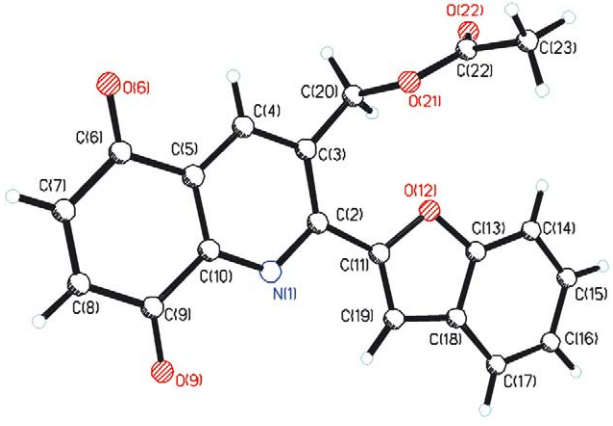
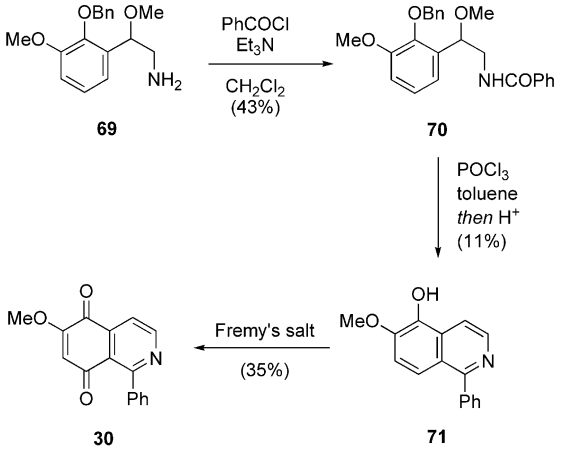


Figure 2. X-Ray crystal structure of 3-acetoxymethyl-2-(benzofuran-2-yl)quinoline-5,8-dione **29**.

With the exception of the three compounds indicated, all the quinolinequinones and the one isoquinolinequinone exhibited chemically reversible electrochemistry. All the 6-methoxyquinolinequinones have similar $E_{1/2}$ values, between −1.06 and −1.15 V, with those possessing the more electron-deficient rings at C-2, for example the various pyridyl derivatives, having the most positive $E_{1/2}$, that is, easiest to reduce. Not surprisingly, compounds **22–25** lacking the electron-releasing methoxy group at C-6 are somewhat easier to reduce than their 6-methoxy counterparts. Although electrochemical studies quickly identify compounds which are difficult to reduce, unfortunately, as discussed previously for indolequinones,[15,16,62] there is often little correlation between reduction potential and rate of reduction by NQO1. Nevertheless all the quinolinequinones investigated are easier to reduce than the previously studied indolequinones which have $E_{1/2}$ relative to $Fc^{+/0}$ in the range −1.20 to −1.50 V.[15,16]

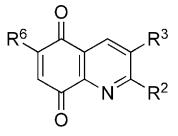
2.3. Biology

The metabolism of the quinones **1–30** by purified recombinant hNQO1 was studied using a spectrophotometic assay that employs cytochrome *c* as the terminal electron acceptor.[21] In our preliminary studies we used an alternative HPLC based assay,[51] but we now use the spectrophotometric assay because it gives initial rates of quinone metabolism. The assay uses cytochrome *c* as the terminal electron acceptor, and the initial reduction rates (μmol cytochrome *c* reduced/min/

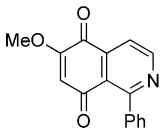


Scheme 11.

Table 2. Electrochemical reduction potentials[a] (DMF) (versus ferrocene) of quinolinequinones and their metabolism by recombinant human NQO1



2-29



30

	R^2	R^3	R^6	$E_{1/2}$ (V) *v* Fc	Reduction rate by hNQO1 (μmol/min/mg)
1	—	—	—	—	411±36
2	H	H	OMe	−1.11	337.3±42.2
3	Cl	H	OMe	−1.01	420.3±40.1
4	Me	H	OMe	−1.15	342.3±22.9
5	Ph	H	OMe	−1.11	313.7±58.8
6	2-Tolyl	H	OMe	−1.11	383.3±61.9
7	4-Tolyl	H	OMe	−1.10	236.7±33.5
8	4-Biphenyl	H	OMe	−1.09	0.4±0.1
9	1-Naphthyl	H	OMe	−1.10	87.4±8.0
10	2-Naphthyl	H	OMe	−1.09	16.8±15.5
11	2-Pyridyl	H	OMe	−1.09	446±39
12	4-Me-2-Pyridyl	H	OMe	−1.08	354.0±16.4
13	5-Me-2-Pyridyl	H	OMe	−1.09	279.5±13.5
14	3-Pyridyl	H	OMe	−1.08	568.7±59.7
15	4-Pyridyl	H	OMe	−1.05	653.0±51.2
16	2-Thienyl	H	OMe	−1.10	307.7±57.1
17	2-Benzofuranyl	H	OMe	−1.06	191.2±62.9
18	1-Me-2-CH_2OH-4-indolyl	H	OMe	−1.13	31.1±1.3
19	H	H	Pyrrolidinyl	−1.29	46.3±2.5
20	Ph	H	Pyrrolidinyl	*nr*	5.8±0.6
21	Ph	H	Morpholinyl	*nr*	6.6±0.5
22	Ph	H	H	−0.98	13.4±7.7
23	H	CH_2OH	H	−0.98	56.5±9.7
24	Ph	CH_2OH	H	−0.97	34.8±3.1
25	2-Thienyl	CH_2OH	H	−0.95	17.2±1.5
26	2-Benzofuranyl	CH_2OH	H	*nr*	16.1±4.6
27	Ph	CH_2OAc	H	—	61.9±10.8[b]
28	2-thienyl	CH_2OAc	H	—	4.2±2.2[b]
29	2-Benzofuranyl	CH_2OAc	H	—	2.9±0.9[b]
30	Ph	H	OMe	−1.04	446.3±35.9

[a] $E_{1/2}$ (±0.005V) values calculated as $(E_{pc}+E_{pa})/2$ are averages of the values determined from voltammograms recorded at potential sweep rates of 50, 100, 200, 300, 400 and 500 mVs^{-1}; E_{pc}, cathodic peak potential; E_{pa} anodic peak potential; *nr* = electrochemical reduction not reversible.
[b] The quinones inactivate the enzyme- see text.

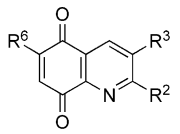
mg NQO1) (Table 2) were calculated from the linear portion (0–30 s) of the reaction graphs.

Three of the compounds evaluated caused inactivation of the enzyme: thus the 3-acetoxymethyl quinolinequinones **27–29** inactivated the enzyme to the extent of 78, 63 and 68%, respectively (data not shown). Since these compounds all contain a potential leaving group (acetate) that could be eliminated upon reduction of the quinone, it is likely that the inactivation is due to mechanism based inhibition of NQO1, a feature of previously studied indolequinones bearing potential leaving groups.[15,21,44]

Cytotoxicity studies were also performed on representative quinones with cell survival being measured using the MTT colorimeteric assay. In our previous work, we have used the non-small cell lung cancer (NSCLC) cell lines H460 (with high NQO1 activity) and H596 (with no measurable NQO1 activity). However, a better model has been developed by Winski et al. that utilizes the BE human colon carcinoma cell line stably transfected with human NQO1 cDNA.[34] Like the H596 cell line, the BE cells (BE-WT) have no measurable NQO1 activity whereas activity in the transfected cells (BE-NQ) was greater than 500 nmol min^{-1} mg^{-1} total cell protein using dichlorophenolindophenol as the standard electron acceptor. For this report we have compared the toxicity of representative quinones (Table 3) using both sets of cells.

Although the metabolism of streptonigrin itself by hNQO1 has been investigated,[48–50] there has been no similar study of quinolinequinones in general. Therefore the current work represents the first detailed study of the metabolism of such quinones by hNQO1. In general, the quinolinequinones studied were much better substrates for recombinant hNQO1 than related indolequinones,[15,16] this greater ease of reduction being borne out by the electrochemical data (see above). Within the series of 6-methoxy substituted quinones several trends are apparent from the metabolism data (Table 2). For simple substituents at the 2-position as in quinones **2–5**, the rates of metabolism by hNQO1 are $R^2 = Cl > H \sim Me > Ph$. For aromatic substituents at C-2, as in quinones **5–10**, the compounds possessing the smaller substituents are metabolized faster. Thus the rate of reduction decreases dramatically for $R^2 = Ph > 1$-naphthyl > 2-naphthyl > 4-biphenyl, with the last compound **8** with the large 4-biphenyl substituent being a

Table 3. Cytotoxicity of representative quinolinequinones towards NSCLC cell lines H596 (nomeasurable NQO1 activity) and H460 (high NQO1 activity), and BE human colon carcinoma cell lines BE-WT (no NQO1 activity) and BE-NQ (high NQO1 activity)



	R^2	R^3	R^6	H596 IC_{50} (μM)	H460 IC_{50} (μM)	BE-WT IC_{50} (μM)	BE-NQ IC_{50} (μM)
1	—	—	—	1.36±0.10	0.0143±0.001	2.12±0.20	0.11±0.02
2	H	H	OMe	>50	14.7±0.3	>50	32.8±6.1
3	Cl	H	OMe	30.1±2.0	16.8±0.4	41.0±4.0	12.5±1.3
5	Ph	H	OMe	49.0±1.7	15.3±0.4		
7	4-Tolyl	H	OMe	>50	14.7±0.3		
8	4-Biphenyl	H	OMe	>50	>50		
9	1-Naphthyl	H	OMe	28.0±0.7	31.3±0.8		
10	2-Naphthyl	H	OMe	>50	>50		
11	2-Pyridyl	H	OMe	25.9±1.3	7.2±0.6	25.2±0.8	8.2±0.6
13	5-Me-2-pyridyl	H	OMe	11.5±0.4	11.0±0.3		
16	2-Thienyl	H	OMe	36.5±1.2	14.3±0.3		
17	2-Benzofuranyl	H	OMe	>50	>50		
18	1-Me-2-CH_2OH-4-indolyl	H	OMe	13.0±0.8	15.9±1.5		
19	H	H	Pyrrolidinyl	>50	3.72	>50	>50
22	Ph	H	H	14.5±0.1	12.4±0.5		
27	Ph	CH_2OAc	H			15.1±0.5	16.2±0.8
28	2-Thienyl	CH_2OAc	H			15.1±0.7	15.3
29	2-Benzofuranyl	CH_2OAc	H			34.6±1.3	37.0±0.2

very poor substrate. The two tolyl substituted derivatives **6** and **7** exhibit rates of reduction by hNQO1 that are much closer to that of the phenyl derivative **5**. In the 6-methoxyquinolinequinones **11**–**18** containing heteroaromatic groups, the 2-thienyl derivative **16** is close to the 2-phenyl compound **5** both in terms of electrochemistry and rate of metabolism, a result that is perhaps not surprising given the similarity in electronic properties of benzene and thiophene rings. However it is the pyridine derivatives **11**–**15** that are the best substrates, with the 2-, 3- and 4-pyridyl compounds **11**, **14**, **15** being better substrates than SN itself. The reason for investigating such compounds was, of course, the presence of a 2-pyridyl group in SN, but it is clear that the 3- and 4-pyridyl substituents lead to faster metabolism. Within the series of five pyridyl quinolinequinones, the rates of metabolism are R^2 = 4-pyridyl > 3-pyridyl > 2-pyridyl > 4-methyl-2-pyridyl > 5-methyl-2-pyridyl.

A small number of variations at C-6 were investigated. For compounds which share a phenyl group at the 2-position (quinones **5**, **20**–**22**), the 6-methoxy compound **5** is by far the best substrate; the 6-unsubstituted compound **22** and the compounds possessing a secondary amine are all reduced less efficiently. The fact that replacement of a methoxy group by a more electron-releasing secondary amine deactivates the quinone towards reduction is hardly surprising, and was also observed throughout our studies on indolequinones.[15,16,62]

The quinones **23**–**29** bearing a substituent at the 3-position are all poor substrates by comparison with similarly 2-substituted derivatives. However, whether this is due to the presence of the 3-substituent or the absence of the 6-methoxy substituent is not clear, although the fact that **24** is a better substrate than **22** suggests the latter explanation. As discussed above, the quinones **27**–**29** bearing acetate leaving groups inactivate the enzyme (data not shown).

Finally the single example of an isoquinolinequinone **30** was investigated and found to be an excellent substrate.

Cytotoxicity data were obtained for selected quinolinequinones (Table 3). In comparison to SN, all the synthetic analogues are much less cytotoxic, since presumably they do not possess the metal-binding features that lead, after reduction, to hydroxyl radical production, and toxicity. As expected, quinones such as **2**, **5**, **11**, and **16** that are good substrates for hNQO1 are more toxic to the NQO1 containing or expressing cell lines (H460 and BE-NQ) than the NQO1 deficient cell lines (H596 and BE-WT). Quinones such as the biphenyl and naphthyl derivatives **8**–**10** which are poor substrates show no selectivity or have no measurable cytotoxicity (IC_{50} > 50 μM).

In conclusion, these findings further advance our understanding of the relationship between quinone structure and metabolism by NQO1. Based on the structure of streptonigrin, a naturally occurring cytotoxin known to be an excellent substrate for the enzyme, we have started to probe for the first time, the structure-metabolism relationships in simple quinolinequinones, thereby complementing the data on the better studied indolequinones.

3. Experimental

3.1. Chemistry

3.1.1. General information. Commercially available solvents and reagents were used throughout without

further purification unless otherwise mentioned. Light petroleum refers to the fraction that boils between 40 °C and 60 °C and was distilled over calcium chloride (anhydrous). Acetonitrile was distilled from CaH_2 under N_2.

Analytical thin layer chromatography (TLC) was carried out using Merck silica gel 60A plates. The plates were visualized under ultra-violet light and/or alkaline potassium permanganate or ninhydrin. Column chromatography was carried out using Merck Kieselgel 60, 230–400 mesh, with the specified eluent. Pressure was applied at the column head with hand bellows. Samples were applied as a saturated solution in an appropriate solvent or were pre-adsorbed onto a small quantity of silica.

Infra red spectra were recorded as KBr discs or using NaCl plates as stated, using a Nicolet Magna infra-red spectrometer 550. Ultra-violet spectra were recorded as solutions in spectroscopic grade methanol or acetonitrile as stated, on an ATI Unicam UV/Visible spectrometer (UV4). Proton magnetic resonance (^{1}H NMR) were recorded using Bruker AC300 (300 MHz), Bruker AV300 (300 MHz) and Bruker DRX400 (400 MHz) spectrometers. Carbon magnetic resonance (^{13}C NMR) were recorded on Bruker AC300 (75 MHz) and Bruker DRX400 (100 MHz) instruments. NMR spectra are referenced against residual undeuterated solvent. In the case of deuterated chloroform, this is 7.260 ppm. Signals are described as singlets (s), broad (br), doublets (d), triplets (t), quartets (q), multiplets (m), double doublets (dd) and double double doublets (ddd).

Mass spectra [electron impact (EI), chemical ionisation (CI), and field ionisation (FI)] were recorded on a Micromass GCT spectrometer, [electrospray (ES)] on a Micromass Platform LC Electrospray Mass Spectrometer or on a VAG Analytical ZAB-E instrument (EPSRC Mass Spectrometry Service at Swansea).

3.1.2. 6-Methoxyquinoline-5,8-dione (2). (a) 6-Methoxyquinoline 31 (10.0 g, 62.8 mmol) was added dropwise to fuming HNO_3 (126 mL) keeping the temperature between 0 and 10 °C. The mixture was stirred for 30 min before being poured onto ice. The precipitate was collected by filtration, washed with water and dried under vacuum. The crude product was recrystallized from methanol to give 6-methoxy-5-nitroquinoline **32** as pale yellow crystals (10.9 g, 85%), mp 198–199 °C (lit.,[63] mp 104–105 °C); δ_H (400 MHz; DMSO) 4.08 (3H, s), 7.80 (1H, dd, $J=8.8$, 4.4 Hz), 8.01 (1H, d, $J=9.5$ Hz), 8.28 (1H, d, $J=8.8$ Hz), 8.32 (1H, d, $J=9.5$ Hz), 9.01 (1H, dd, $J=4.4$, 1.3 Hz); δ_C (100 MHz; DMSO) 58.0 (Me), 119.3 (CH), 121.0 (C), 124.8 (CH), 131.6 (CH), 132.3 (CH), 134.3 (C), 139.4 (C), 148.9 (CH), 149.9 (C).

(b) Tin powder (2.5 g) and 3M HCl were added to a solution of 6-methoxy-5-nitroquinoline 32 (1.00 g, 4.9 mmol) in ethanol (150 mL). The mixture was heated under reflux for 1 h. After cooling the solution was decanted from the excess tin, neutralized with saturated $NaHCO_3$ solution and an equal volume of water was added. The mixture was stirred overnight in dichloromethane. The mixture was filtered through Celite and the layers were separated. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give 5-amino-6-methoxyquinoline **33** as a brown solid (0.50 g, 59%) (lit.,[64] mp 154–156 °C) which was used without purification, δ_H (300 MHz; $CDCl_3$) 3.98 (3H, s), 4.25 (2H, br), 7.29 (1H, dd, $J=8.4$, 3.9 Hz), 7.43 (1H, d, $J=9.0$ Hz), 7.59 (1H, d, $J=9.0$ Hz), 8.12 (1H, d, $J=8.4$ Hz), 8.76 (1H, m); δ_C (100 MHz; $CDCl_3$) 56.5 (Me), 116.4 (CH), 118.7 (C), 119.5 (CH), 129.0 (CH), 129.3 (C), 142.5 (C), 144.0 (C), 148.1 (CH); one CH not observed.

(c) To a solution of 5-amino-6-methoxyquinoline **33** (0.45 g, 2.6 mmol) in acetone (85 mL) was added a solution of Fremy's salt (1.14 g, 4.3 mmol) in dihydrogen phosphate buffer (0.3M; 100 mL). The mixture was stirred at room temperature for 1 h. A further solution of Fremy's salt (1.14 g, 4.3 mmol) in sodium dihydrogen phosphate buffer (0.3M; 100 mL) was added and the mixture was stirred for 1 h. The acetone was removed in vacuo, the resulting mixture was extracted with dichloromethane, the organic phase was dried (Na_2SO_4) and concentrated. The crude mixture was recystallized from ethyl acetate/light petroleum to give the *title compound* **2** as a light brown solid (0.27 g, 57%), mp 251–252 °C (from methanol) (lit.,[65] mp 250–251 °C), δ_H (300 MHz; $CDCl_3$) 3.95 (3H, s), 6.37 (1H, s), 7.67 (1H, dd, $J=7.8$, 4.8 Hz), 8.47 (1H, dd, $J=7.8$, 1.8 Hz), 9.05 (1H, dd, $J=4.8$, 1.8 Hz); δ_C (100 MHz; $CDCl_3$) 56.5 (Me), 110.6 (CH), 127.2 (CH), 127.9 (C), 134.6 (CH), 147.6 (C), 154.9 (CH), 160.1 (C), 179.5 (C), 182.9 (C).

3.1.3. 2-Chloro-6-methoxyquinoline-5,8-dione (3). (a) To a suspension of 6-methoxy-5-nitroquinoline 32 (5 g, 24 mmol) in acetic acid (25 mL) was added hydrogen peroxide (35%; 4 mL). The mixture was heated to 80 °C for 4 h. Further hydrogen peroxide (35%; 2 mL) was added and heating was continued for 3 h. After cooling the mixture was basified with NaOH (1 M) and extracted with dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate/2-propanol elution) to give 6-methoxy-5-nitroquinoline-*N*-oxide **34** as a yellow solid (2.65 g, 50%), mp 174–175 °C (from toluene/light petroleum)(lit.,[66] mp 182–184 °C), δ_H (300 MHz; $CDCl_3$) 4.10 (3H, s), 7.38 (1H, dd, $J=9.0$, 6.0 Hz), 7.56 (2H, m), 8.44 (1H, d, $J=6.0$ Hz), 8.91 (1H, d, $J=9.6$ Hz); δ_C (100 MHz; $CDCl_3$) 57.2 (Me), 116.4 (CH), 118.2 (CH), 123.9 (CH), 124.2 (C), 124.3 (CH), 134.4 (C), 135.9 (C), 150.8 (C); one CH unobserved.

(b) Sulfuryl chloride (37 mL) was added to 6-methoxy-5-nitroquinoline-*N*-oxide 34 (5.3 g, 24 mmol) and the mixture was heated to 60 °C for 3 h. After cooling the mixture was dissolved in dichloromethane and stirred in water for 1 h to dissolve any insoluble material. The layers were separated and the organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane elution) to give 2-chloro-6-methoxy-5-nitroquinoline **35** as a yellow solid (3.99 g, 69%), mp 152–

153 °C (from methanol) (lit.,[56] mp 151–153 °C), δ_H (300 MHz; $CDCl_3$) 4.07 (3H, s), 7.50 (1H, d, $J = 8.7$ Hz), 7.59 (1H, d, $J = 9.3$ Hz), 8.03 (1H, dd, $J = 8.7$, 0.9 Hz), 8.17 (1H, dd, $J = 9.3$, 0.9 Hz); δ_C (100 MHz; $CDCl_3$) 57.2 (Me), 117.3 (CH), 120.1 (C), 125.0 (CH), 132.2 (CH), 133.0 (CH), 134.7 (C), 141.7 (C), 149.5 (C), 150.0 (C).

(c) Tin powder (2.4 g) and HCl (3 M; 58 mL) were added to a suspension of 2-chloro-6-methoxy-5-nitroquinoline **35** (2 g, 8.4 mmol) in ethanol (200 mL) and the mixture was heated under reflux for 10 min. After cooling the mixture was neutralized with saturated $NaHCO_3$ solution and an equal volume of water was added. The mixture was stirred in dichloromethane for 3 h. The layers were separated and the organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane elution) to give 5-amino-2-chloro-6-methoxyquinoline **36** as a dark yellow solid (1.1 g, 63%), mp 93–95 °C (from ethyl acetate/light petroleum) (lit.,[56] mp 98–101 °C), δ_H (300 MHz; $CDCl_3$) 3.97 (3H, s), 4.27 (2H, br), 7.25 (1H, d, $J = 9.0$ Hz), 7.40 (1H, d, $J = 9.0$ Hz), 7.48 (1H, d, $J = 9.0$ Hz), 8.06 (1H, d, $J = 9.0$ Hz); δ_C (100 MHz; $CDCl_3$) 56.5 (Me), 116.9 (CH), 117.0 (C), 118.5 (CH), 120.4 (CH), 129.8 (C), 132.1 (CH), 143.0 (C), 143.4 (C), 148.3 (C).

(d) To a solution of 5-amino-2-chloro-6-methoxyquinoline **36** (1.4 g, 6.7 mmol) in acetone (250 mL) was added a solution of Fremy's salt (3.1 g, 11 mmol) in sodium dihydrogen phosphate buffer (0.3M; 250 mL). The mixture was stirred at room temperature for 1.5 h. The acetone was removed in vacuo, the residue extracted with dichloromethane, the organic phase dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (dichloromethane elution) to give the title compound **3** as a yellow solid (1.0 g, 60%), mp 227–229 °C (from ethyl acetate/light petroleum) (lit.,[56] mp 226–227 °C), δ_H (300 MHz; $CDCl_3$) 3.95 (3H, s), 6.36 (1H, s), 7.68 (1H, d, $J = 8.4$ Hz), 8.39 (1H, d, $J = 8.4$ Hz); δ_C (100 MHz; $CDCl_3$) 56.7 (Me), 110.4 (CH), 126.6 (C), 128.5 (CH), 137.2 (CH), 147.7 (C), 157.6 (C), 160.0 (C), 178.6 (C), 181.4 (C).

3.1.4. 6-Methoxy-2-methylquinoline-5,8-dione (4). (a) Concentrated HCl (2 mL) was added to a mixture of paraldehyde (0.80 mL, 6.0 mmol) and 4-methoxy-2-nitroaniline **37** (0.5 g, 3.0 mmol). The reaction mixture was heated until an exothermic reaction occurred and the heating was stopped. The reaction mixture was stirred at room temperature for 0.5 h followed by heating under reflux for 4 h. The reaction mixture was cooled to room temperature and neutralized with NaOH solution (1 M). The precipitate formed was collected by filtration and purified by column chromatography (dichloromethane elution) to yield 6-methoxy-2-methyl-8-nitroquinoline **38** as a pale yellow solid (0.1 g, 18%), mp 184–185 °C (lit.,[57] mp 186–187 °C), δ_H (300 MHz; $CDCl_3$) 2.74 (3H, s), 3.97 (3H, s), 7.25 (1H, d, $J = 2.8$ Hz), 7.37 (1H, d, $J = 8.5$ Hz), 7.63 (1H, d, $J = 2.8$ Hz), 8.01 (1H, d, J 8.5 Hz); δ_C (100 MHz; $CDCl_3$) 25.5 (Me), 56.1 (Me), 109.4 (CH), 115.7 (CH), 124.0 (CH), 128.2 (C), 134.7 (CH), 135.0 (C), 155.5 (C), 159.3 (C), one C unobserved.

(b) Tin powder (0.1 g) and HCl (3 M; 3 mL) were added to a solution of 6-methoxy-2-methyl-8-nitroquinoline **38** (0.09 g, 0.40 mmol) in ethanol (10 mL). The reaction mixture was heated under reflux for 20 min. After cooling, the reaction mixture was neutralized with saturated $NaHCO_3$ solution and an equal volume of water was added. The mixture was stirred in dichloromethane for 2 h. The separated organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane elution) to give 8-amino-6-methoxy-2-methylquinoline **39** as a yellow solid (0.05 g, 69%) (lit.,[57] mp 102 °C), used without further purification, δ_H (300 MHz; $CDCl_3$) 2.69 (3H, s), 3.88 (3H, s), 5.00 (2H, br), 6.47 (1H, d, $J = 2.5$ Hz), 6.58 (1H, d, $J = 2.5$ Hz), 7.22 (1H, d, $J = 8.5$ Hz), 7.86 (1H, d, $J = 8.5$ Hz).

(c) To a solution of 8-amino-2-methyl-6-methoxyquinoline (0.05 g, 0.30 mmol) in acetone (11 mL) was added a solution of Fremy's salt (0.1 g, 0.49 mmol) in dihydrogen phosphate buffer (pH 6, 0.3 M; 11 mL). The reaction mixture was stirred at room temperature for 2 h. The acetone was removed in vacuo, the resulting mixture was extracted with dichloromethane (3×10 mL), the organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (9:1) elution] to give the *title compound* **4** as a dark yellow solid (0.03 g, 49%), mp 211–212 °C (lit.,[67] mp 204–206 °C), δ_H (300 MHz; $CDCl_3$) 2.79 (3H, s), 3.94 (3H, s), 6.34 (1H, s), 7.53 (1H, d, $J = 8.0$ Hz), 8.35 (1H, d, $J = 8.0$ Hz); δ_C (100 MHz; $CDCl_3$) 25.4 (Me), 56.6 (Me), 110.3 (CH), 125.8 (C), 127.3 (CH), 134.9 (CH), 147.2 (C), 160.0 (C), 165.5 (C), 179.6 (C), 183.5 (C).

3.2. Palladium(0) catalyzed coupling reactions of 2-chloro-6-methoxyquinoline-5,8-dione 3; preparation of quinones 5–11, 13, 16, 17

3.2.1. General procedure for Suzuki coupling. A solution of 2-chloro-6-methoxyquinoline-5,8-dione 3 (0.3 g, 1.3 mmol) in 1,2-dimethoxyethane (32 mL) was degassed under reduced pressure. $Pd(PPh_3)_4$ (0.08 g) was added and the solution was degassed further. The mixture was stirred under a nitrogen atmosphere for 10 min. Na_2CO_3 solution (2 M; 3 mL) was added followed by the boronic acid (2.0 mmol). The mixture was heated under reflux for 24 h. After cooling the mixture was poured into dichloromethane and washed with water (×3). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography.

3.2.2. 6-Methoxy-2-phenylquinoline-5,8-dione (5). 24% yield, mp 225–227 °C, (Found: C, 70.5; H, 4.0; N, 5.0. $C_{16}H_{11}NO_3.0.4H_2O$ requires C, 70.5; H, 4.4; N, 5.1%); (Found: M^+, 265.0734. $C_{16}H_{11}NO_3$ requires 265.0739); λ_{max}(MeOH)/nm 228 (log ε 4.47), 262 (4.66), 304 (4.72); ν_{max} (Nujol)/cm^{-1} 1683, 1657, 1611, 1591; δ_H (300 MHz; $CDCl_3$) 3.95 (3H, s), 6.37 (1H, s), 7.50–7.53

(3H, m), 8.07 (1H, d, $J=8.4$ Hz), 8.17–8.20 (2H, m), 8.49 (1H, d, $J=8.4$ Hz); δ_C (100.6 MHz; $CDCl_3$) 56.6 (Me), 110.6 (CH), 123.5 (CH), 126.3 (C), 127.8 (CH), 129.0 (CH), 130.8 (CH), 135.5 (CH), 137.3 (C), 147.7 (C), 160.1 (C), 162.3 (C), 179.5 (C), 183.1 (C); *m*/*z* (EI) 265 (M^+, 9%), 252 (3), 236 (2), 224 (3), 207 (3), 179 (3), 83 (100).

3.2.3. 6-Methoxy-2-(2-tolyl)quinoline-5,8-dione (6). 44% yield, mp 206–207 °C, (Found: M^+, 279.0892. $C_{17}H_{13}NO_3$ requires 279.0895); λ_{max} (MeCN)/nm 310 (log ε 4.01), 357 (3.23); ν_{max} (KBr)/cm^{-1} 1672, 1607, 1585; δ_H (300 MHz; $CDCl_3$) 2.43 (3H, s), 3.97 (3H, s), 6.39 (1H, s), 7.30–7.39 (3H, m), 7.47–7.50 (1H, m), 7.78 (1H, d, $J=8.2$ Hz), 8.52 (1H, d, $J=8.2$ Hz); δ_C (100 MHz; $CDCl_3$) 20.5 (Me), 56.7 (Me), 110.7 (CH), 126.0 (C), 126.1 (CH), 127.6 (CH), 129.5 (CH), 129.9 (CH), 131.1 (CH), 134.9 (CH), 136.3 (C), 138.7 (C), 147.2 (C), 160.1 (C), 165.6 (C), 179.6 (C), 183.1 (C); *m*/*z* (EI) 279 (M^+, 76%), 278 (72), 264 (28), 250 (34), 236 (100) 167 (28), 166 (59), 139 (34).

3.2.4. 6-Methoxy-2-(4-tolyl)quinoline-5,8-dione (7). 42% yield, mp 205–207 °C, (Found: C, 72.8; H, 4.8; N, 5.0. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.7; N, 5.0%); (Found: M^+, 279.0896. $C_{17}H_{13}NO_3$ requires 279.0895); λ_{max} (MeOH)/nm 230 (log ε 4.27), 264 (4.34), 310 (4.45); $\nu_{max}(CHCl_3)$/cm^{-1} 1680, 1669, 1608, 1577; δ_H (400 MHz; $CDCl_3$) 2.42 (3H, s), 3.94 (3H, s), 6.35 (1H, s), 7.31 (2H, d, $J=8.4$ Hz), 8.03 (1H, d, $J=8.4$ Hz), 8.09 (2H, d, $J=8.4$ Hz), 8.45 (1H, d, $J=8.4$ Hz); δ_C (100 MHz; $CDCl_3$) 21.4 (Me), 56.2 (Me), 110.6 (CH), 123.0 (CH), 126.1 (C), 127.7 (CH), 129.7 (CH), 134.5 (C), 135.4 (CH), 141.3 (C), 147.6 (C), 160.1 (C), 162.2 (C), 179.5 (C), 183.2 (C); *m*/*z* (EI) 279 (M^+, 100%), 250 (21), 221 (31), 180 (27).

3.2.5. 2-(4-Biphenyl)-6-methoxyquinoline-5.8-dione (8). 39% yield, mp 313–314 °C (from methanol), (Found: M^+, 341.1049. $C_{22}H_{15}NO_3$ requires 341.1052); λ_{max} (MeOH)/nm 228 (log ε 3.57), 272 (3.47), 320 (3.60); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1680, 1659, 1608, 1577; δ_H (400 MHz; CD_2Cl_2) 3.95 (3H, s), 6.36 (1H, s), 7.43 (1H, m), 7.50 (2H, m), 7.72 (2H, m), 7.81 (2H, m), 8.16 (1H, d, $J=8.2$ Hz), 8.30 (2H, m), 8.49 (1H, d, $J=8.2$ Hz); δ_C (100 MHz; $CDCl_3$) 56.1 (Me), 110.1 (CH), 122.9 (CH), 125.8 (C), 126.4 (CH), 126.9 (CH), 127.4 (CH), 127.7 (CH), 128.3 (CH), 135.0 (CH), 135.6 (C), 139.3 (C), 142.8 (C), 147.1 (C), 159.6 (C), 161.0 (C), 178.3 (C), 182.6 (C); *m*/*z* (EI) 341 (M^+, 29%), 127 (24), 85 (72), 84 (88), 83 (100), 69 (35).

3.2.6. 6-Methoxy-2-(1-naphthyl)quinoline-5.8-dione (9). 18% yield, mp 224–225 °C (from methanol/chloroform), (Found: C, 75.1; H, 3.9; N, 4.3. $C_{20}H_{13}NO_3.0.2H_2O$ requires C, 75.3; H, 4.2; N, 4.4%); (Found: M^+, 315.0900. $C_{20}H_{13}NO_3$ requires 315.0895); λ_{max} (MeOH)/nm 242 (log ε 4.29), 270 (4.19), 316 (3.92); ν_{max} (Nujol)/cm^{-1} 1675, 1669, 1618, 1577; δ_H (300 MHz; MeOH-d_4) 3.99 (3H, s), 6.49 (1H, s), 7.51–7.53 (2H, m), 7.62–7.64 (1H, m), 7.72 (1H, d, $J=9.0$ Hz), 7.95–8.06 (4H, m), 8.61 (1H, d, $J=9.0$ Hz); δ_C (100 MHz; MeOH-d_4) 55.9 (Me), 109.9 (CH), 124.7 (CH), 124.9 (CH), 125.9 (CH), 126.6 (CH), 126.7 (C), 127.8 (CH), 128.2 (CH), 128.8 (CH), 129.9 (CH), 130.7 (C), 133.9 (C), 134.9 (CH), 136.7 (C), 160.9 (C), 164.0 (C), 183.4 (C); two ArC unobserved; *m*/*z* (EI) 315 (M^+, 100%), 302 (29), 272 (20), 228 (6), 204 (5), 152 (8), 83 (20), 69 (18).

3.2.7. 6-Methoxy-2-(2-naphthyl)quinoline-5,8-dione (10). 16% yield, mp 279–280 °C, (Found: C, 72.6; H, 4.1; N, 4.2. $C_{20}H_{13}NO_3.0.8H_2O$ requires C, 72.8; H, 4.5; N, 4.3%); (Found: M^+, 315.0893. $C_{20}H_{13}NO_3$ requires 315.0895); λ_{max} (MeOH)/nm 236 (log ε 4.29), 260 (4.38), 316 (4.26); $\nu_{max}(CHCl_3)$/cm^{-1} 1675, 1659, 1608, 1582; δ_H (400 MHz; $CDCl_3$) 3.95 (3H, s), 6.38 (1H, s), 7.54–7.56 (2H, m), 7.81–7.91 (1H, m), 7.96–8.04 (2H, m), 8.22 (1H, d, $J=8.0$ Hz), 8.29 (1H, dd, $J=8.0$, 2.0 Hz), 8.52 (1H, d, $J=8.8$ Hz), 8.70 (1H, s); δ_C (100 MHz; $CDCl_3$) 56.5 (Me), 110.6 (CH), 123.7 (CH), 124.5(CH), 126.3 (C), 126.6 (CH), 127.5 (CH), 127.7 (CH), 128.1 (CH), 128.8 (CH), 129.1 (CH), 133.2 (C), 134.5 (C), 134.6 (C), 135.5 (CH), 147.7 (C), 160.2 (C), 162.1 (C), 179.4 (C), 183.1 (C); *m*/*z* (EI) 315 (M^+, 100%), 257 (44), 216 (25), 153 (37).

3.2.8. 6-Methoxy-2-(2-pyridyl)quinoline-5,8-dione (11) (Method 1). A solution of 2-chloro-6-methoxyquinoline-5,8-dione **3** (0.25 g, 1.1 mmol) and 2-trimethylstannylpyridine (0.32 g, 1.3 mmol) in 1,4-dioxane (30 mL) was degassed under reduced pressure. $Pd(PPh_3)_4$ (0.1 g) was added and the solution was degassed further. The solution was heated under reflux for 17 h. After cooling the mixture was poured into dichloromethane and was washed with water (×3). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane elution) to give the title compound 11 as a yellow solid (0.26 g, 88%), mp 274–275 °C (from methanol/dichloromethane) (lit.,[58] mp 260 °C; lit.,[68] mp 262–264 °C), δ_H (300 MHz; $CDCl_3$) 3.96 (3H, s), 6.38 (1H, s), 7.38–7.42 (1H, m), 7.88 (1H, m), 8.56 (1H, d, $J=8.4$ Hz), 8.69–8.72 (2H, m), 8.80 (1H, d, $J=8.4$ Hz); δ_C (100 MHz; $CDCl_3$) 56.6 (Me), 110.7 (CH), 122.9 (CH), 124.3 (CH), 125.1 (CH), 127.6 (C), 135.6 (CH), 137.1 (CH), 147.3 (C), 149.4 (CH), 154.1 (C), 160.2 (C), 160.8 (C), 179.5 (C), 183.0 (C).

3.2.9. 6-Methoxy-2-(5-methyl-2-pyridyl)quinoline-5,8-dione (13). A solution of 2-chloro-6-methoxyquinoline-5,8-dione 3 (0.25 g, 1.1 mmol) and 5-methyl-2-trimethylstannylpyridine (0.36 g, 1.3 mmol) in 1,4-dioxane (35 mL) was degassed under reduced pressure. $Pd(PPh_3)_4$ (0.1 g) was added and the solution was degassed further. The solution was heated under reflux for 20 h. After cooling, the mixture was poured into dichloromethane and was washed with water (×3). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane elution) to give the *title compound* **13** as a yellow solid (86 mg, 28%), mp 277–278 °C (from methanol/dichloromethane), (Found: M^+, 280.0856. $C_{16}H_{12}N_2O_3$ requires 280.0848); λ_{max} (MeOH)/nm 260 (log ε 3.56), 304 (3.79); $\nu_{max}(CHCl_3)$/cm^{-1} 1680, 1659, 1608, 1582; δ_H (300 MHz; $CDCl_3$) 2.41 (3H, s), 3.94 (3H, s), 6.36 (1H, s), 7.65–7.69 (1H, m), 8.51–8.53 (2H,

m), 8.59 (1H, d, $J=8.1$ Hz), 8.75 (1H, d, $J=8.1$ Hz); δ_C (100 MHz; $CDCl_3$) 20.9 (Me), 56.6 (Me), 110.6 (CH), 122.5 (CH), 124.0 (CH), 127.4 (C), 135.3 (C), 135.6 (CH), 137.6 (CH), 149.9 (CH), 151.6 (C), 160.2 (C), 161.0 (C), 171.0 (C), 183.0 (C); *m*/*z* (EI) 280 (M^+, 100%), 267 (25), 251 (20), 222 (39), 194(22), 181 (35).

3.2.10. 6-Methoxy-2-(2-thienyl)quinoline-5,8-dione (16). 25% yield, mp 208–209 °C, (Found: C, 61.7; H, 3.2; N, 5.0. $C_{14}H_9NO_3S$ requires C, 62.0; H, 3.3; N, 5.2%); (Found: M^+, 271.0301. $C_{14}H_9NO_3S$ requires 271.0303; λ_{max} (MeOH)/nm 258 (log ε 4.18), 324 (4.38), 400 (3.43); ν_{max} ($CHCl_3$)/cm^{-1} 1675, 1659, 1613, 1577; δ_H (400 MHz; $CDCl_3$) 3.94 (3H, s), 6.33 (1H, s), 7.18 (1H, dd, $J=5.2$, 3.6 Hz) 7.57 (1H, dd, $J=5.2$, 1.2 Hz), 7.84 (1H, dd, $J=3.6$, 1.2 Hz), 7.91 (1H, d, $J=8.4$ Hz), 8.41 (1H, d, $J=8.4$ Hz); δ_C (100 MHz; $CDCl_3$) 56.5 (Me), 110.4 (CH), 121.8 (CH), 125.9 (C), 128.0 (CH), 128.6 (CH), 131.0 (CH), 135.4 (CH), 143.0 (C), 147.8 (C), 157.3 (C), 160.1 (C), 179.1 (C), 182.7 (C); *m*/*z* (EI) 271 (M^+, 100%), 258 (54), 213 (32), 172 (50), 83 (58), 69 (55).

3.2.11. 2-(2-Benzofuranyl)-6-methoxy-quinoline-5,8-dione (17). 20% yield, mp 299–301 °C, (Found: C, 67.3; H, 3.6; N, 4.2. $C_{18}H_{11}NO_4.0.8H_2O$ requires C, 67.6; H, 3.9; N, 4.4%); (Found: M^+, 305.0689. $C_{18}H_{11}NO_4$ requires 305.0688); λ_{max} (MeOH)/nm 246 (log ε 4.23), 336 (4.36); ν_{max} ($CHCl_3$)/cm^{-1} 1680, 1654, 1608, 1577; δ_H (300 MHz; $CDCl_3$) 3.95 (3H, s), 6.37 (1H, s), 7.29 (1H, m), 7.37–7.43 (1H, m), 7.57 (1H, dd, $J=8.4$, 0.9 Hz), 7.68–7.71 (1H, m), 7.87 (1H, d, $J=0.9$ Hz), 8.20 (1H, d, $J=8.4$ Hz), 8.52 (1H, d, $J=8.4$ Hz); δ_C (100 MHz; $CDCl_3$) 56.1 (Me), 108.7 (CH), 110.0 (CH), 111.1 (CH), 121.8 (CH), 121.9 (CH), 123.1 (CH), 125.9 (C), 126.0 (CH), 127.8 (C), 135.2 (CH), 147.4 (C), 152.9 (C), 155.2 (C), 159.7 (C), 182.1 (C); two C unobserved; *m*/*z* (EI) 305 (M^+, 100%), 247 (22), 206 (26), 84 (37).

3.3. Preparation of quinones 11, 12, 14, 15 by the Friedländer reaction

3.3.1. 6-Methoxy-2-(2-pyridyl)quinoline-5,8-dione (11) (Method 2). (a) A solution of 2-benzenesulfonyloxy-3-methoxy-6-nitrobenzaldehyde **40**[69] (1.0 g, 3.0 mmol) in THF (25 mL) was hydrogenated over 10% Pd/C (0.5 g). After 5 h the mixture was filtered and the filtrate was immediately used in the Friedländer condensation. To a stirred solution of 2-acetylpyridine (0.5 mL, 4.5 mmol) and Triton B (10 drops) was added a solution of the aminoaldehyde in THF under an atmosphere of nitrogen. The solution was stirred at room temperature for 20 h, during which additional Triton B (10 drops) was added. The reaction mixture was neutralized with HCl (1 M) and extracted with chloroform (3×10 mL). The chloroform extract was washed with brine (3×5 mL), dried (Na_2SO_4) and concentrated in vacuo. A stirred mixture of the residue and 15% NaOH solution (20 mL) in ethanol (20 mL) was heated under reflux overnight. The solution was cooled, diluted with water, and washed with chloroform (2×10 mL). The aqueous layer was separated, neutralized with dilute HCl, and extracted with chloroform (3×10 mL). The chloroform extract was washed with brine (3×5 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (8:2) elution) to give 6-methoxy-2,2-pyridylquinolin-5-ol **41** as a yellow solid (0.2 g, 33%) (lit.,[58] mp 184–185 °C) used directly in the next step.

(b) A solution of the above pyridylquinoline **41** (0.07 g, 0.3 mmol) in methanol (40 mL) was added to a stirred solution of Fremy's salt (1.0 g, 3.5 mmol) in dihydrogen phosphate buffer (pH 6, 0.3 M; 40 mL). The solution was stirred at room temperature overnight, diluted with water and the crystalline solid which precipitated was collected. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (8:2) elution) to give the title compound **11** as a yellow solid (0.08 g, 74%), data given above.

3.3.2. 6-Methoxy-2-(4-methyl-2-pyridyl)quinoline-5,8-dione (12). (a) A solution of 2-benzenesulfonyloxy-3-methoxy-6-nitrobenzaldehyde 40 (1.0 g, 3.0 mmol) in THF (40 mL) was hydrogenated over 10% Pd/C (0.5 g). After 2 h the mixture was filtered and the filtrate was used immediately in the Friedländer condensation. To a stirred solution of 2-acetyl-4-methylpyridine (0.6 g, 4.5 mmol) and Triton B (10 drops) was added a solution of the aminoaldehyde in THF under an atmosphere of nitrogen. The solution was stirred at room temperature for 19 h, during which additional Triton B (10 drops) was added. The reaction mixture was neutralized with HCl (1 M) and extracted with chloroform (3×20 mL). The chloroform extract was washed with brine (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. A stirred mixture of the residue and 15% NaOH solution (20 mL) in ethanol (20 mL) was heated under reflux overnight. The solution was cooled, diluted with water, and washed with chloroform (3×10 mL). The aqueous layer was separated, neutralized with dilute HCl, and extracted with chloroform (3×20 mL). The chloroform extract was washed with brine (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (8:2) elution) to give 6-methoxy-2-(4-methyl-2-pyridyl)quinolin-5-ol 42 as a yellow solid (61.8 mg, 8%), used directly in the next step.

(b) A solution of the pyridylquinoline 42 (0.06 g, 0.23 mmol) in methanol (32 mL) was added to a stirred solution of Fremy's salt (0.8 g, 2.9 mmol) in dihydrogen phosphate buffer (pH 6, 0.3 M; 32 mL). The solution was stirred at room temperature overnight and diluted with water, and the crystalline solid which precipitated was collected. The solid was recrystallized from dichloromethane to yield the *title compound* **12** as a yellow solid (0.04 g, 59%), mp 250 °C, (Found: M^+, 280.0850. $C_{16}H_{12}N_2O_3$ requires 280.0848); λ_{max} (MeCN)/nm 288 (log ε 4.04), 304 (4.01), 356 (3.15), 428 (2.14); ν_{max}(KBr)/cm^{-1} 3062, 2938, 2850, 1680, 1675, 1607, 1585; δ_H (400 MHz; $CDCl_3$) 2.47 (3H, s) 3.95 (3H, s), 6.38 (1H, s), 7.22 (1H, s), 8.53 (3H, m), 8.79 (1H, d, $J=8.0$ Hz); δ_C (100 MHz; $CDCl_3$) 21.2 (Me) 56.7 (Me), 110.7 (CH), 123.7 (CH), 124.6 (CH), 126.2 (CH), 127.6 (C), 135.7 (CH), 147.3 (C), 148.7 (C), 149.2 (CH), 153.7

(C), 160.3 (C), 161.0 (C), 179.5 (C), 183.2 (C); *m*/*z* (EI) 280 (M^+, 100%), 265 (13), 252 (17), 196 (11), 181 (28), 170 (11), 128 (14), 118 (13), 115 (23), 104 (63), 91 (54).

3.3.3. 6-Methoxy-2-(3-pyridyl)quinoline-5,8-dione (14). (a) A solution of 2-benzenesulfonyloxy-3-methoxy-6-nitrobenzaldehyde 40 (1.0 g, 3.0 mmol) in THF (35 mL) was hydrogenated over 10% Pd/C (0.5 g). After 5 h the mixture was filtered and the filtrate was used immediately in the Friedländer condensation. To a stirred solution of 3-acetylpyridine (0.5 g, 4.5 mmol) and Triton B (10 drops) was added a solution of the aminoaldehyde in THF under an atmosphere of nitrogen. The solution was stirred at room temperature for 20 h, during which additional Triton B (10 drops) was added. The reaction mixture was neutralized with HCl (1 M) and extracted with chloroform (3×15 mL). The chloroform extract was washed with brine (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. A stirred mixture of the residue and 15% NaOH solution (20 mL) in ethanol (20 mL) was heated under reflux overnight. The solution was cooled, diluted with water, and washed with chloroform (3×10 mL). The aqueous layer was separated, neutralized with dilute HCl, and extracted with chloroform (3×15 mL). The chloroform extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (8:2) elution) to give 6-methoxy-2-(3-pyridyl)quinolin-5-ol **43** as a yellow solid (0.2 g, 27%), (Found: M^+, 252.0901. $C_{15}H_{12}N_2O_2$ requires 252.0899); ν_{max}(KBr)/cm^{-1} 3287, 3069, 2996, 2938, 2836, 1621, 1578; δ_H (400 MHz; $CDCl_3$) 4.03 (3H, s), 6.46 (1H, br), 7.46 (1H, ddd, *J* = 0.7, 4.8, 7.9 Hz), 7.51 (1H, d, *J* 9.1 Hz), 7.76 (1H, d, *J* = 9.1 Hz), 7.83 (1H, d, *J* = 8.9 Hz), 8.50 (1H, ddd, *J* = 1.6, 2.2, 7.9 Hz), 8.61 (1H, d, *J* = 8.9 Hz), 8.69 (1H, dd, *J* = 1.6, 4.8 Hz), 9.35 (1H, dd, *J* = 0.7, 2.2 Hz); δ_C (100 MHz; $CDCl_3$) 57.0 (Me), 116.6 (CH), 117.6 (CH), 118.2 (C), 121.2 (CH), 123.7 (CH), 131.3 (CH), 135.0 (CH), 135.4 (C), 139.2 (C), 141.9 (C), 143.8 (C), 148.5 (CH), 149.7 (CH), 152.9 (C); *m*/*z* (EI) 252 (M^+, 97%), 237 (100), 149 (15), 97 (17), 85 (32), 71 (37), 57 (44), 55 (26).

(b) A solution of the pyridylquinoline **43** (0.1 g, 0.50 mmol) in methanol (70 mL) was added to a stirred solution of Fremy's salt (1.9 g, 6.7 mmol) in dihydrogen phosphate buffer (pH 6, 0.3 M; 70 mL). The solution was stirred at room temperature overnight, diluted with water and the crystalline solid which precipitated was collected. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (8:2) elution) to give the *title compound* **14** as a yellow solid (0.06 g, 45%), mp 182–184 °C, (Found: M^+, 266.0689. $C_{15}H_{10}N_2O_3$ requires 266.0691); λ_{max} (MeCN)/nm 288 (log ε 3.98), 304 (3.95), 356 (3.15), 428 (2.39); ν_{max}(KBr)/cm^{-1} 3040, 2938, 2836, 1680, 1658, 1607, 1570; δ_H (300 MHz; $CDCl_3$) 3.96 (3H, s), 6.39 (1H, s), 7.47 (1H, dd, *J* = 4.8, 7.7 Hz), 8.11 (1H, d, *J* = 8.2 Hz), 8.54 (2H, m), 8.74 (1H, d, *J* = 3.5 Hz), 9.29 (1H, d, *J* = 1.5 Hz); δ_C (100 MHz; $CDCl_3$) 56.8 (Me), 111.8 (CH), 123.7 (CH), 123.9 (CH), 126.8 (C), 133.2 (C), 135.6 (CH), 136.0 (CH), 147.9 (C), 148.6 (CH), 151.5 (CH), 159.8 (C), 160.2 (C), 179.3 (C), 182.8 (C); *m*/*z* (EI) 266 (M^+, 67%), 209 (11), 177 (19), 149 (100), 71 (15), 57 (22).

3.3.4. 6-Methoxy-2-(4-pyridyl)quinoline-5,8-dione (15). (a) A solution of 2-benzenesulfonyloxy-3-methoxy-6-nitrobenzaldehyde 40 (1.0 g, 3.0 mmol) in THF (40 mL) was hydrogenated over 10% Pd/C (0.5 g). After 2 h the mixture was filtered and the filtrate was used immediately in the Friedländer condensation. To a stirred solution of 4-acetylpyridine (0.5 g, 4.5 mmol) and Triton B (10 drops) was added a solution of the aminoaldehyde in THF under an atmosphere of nitrogen. The solution was stirred at room temperature for 19 h, during which additional Triton B (10 drops) was added. The reaction mixture was neutralized with HCl (1 M) and extracted with chloroform (3×20 mL). The chloroform extract was washed with brine (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. A stirred mixture of the residue and 15% NaOH solution (20 mL) in ethanol (20 mL) was heated under reflux overnight. The solution was cooled, diluted with water, and washed with chloroform (3×10 mL). The aqueous layer was separated, neutralized with dilute HCl, and extracted with chloroform (3×20 mL). The chloroform extract was washed with brine (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (8:2) elution] to give 6-methoxy-2-(4-pyridyl)quinolin-5-ol 44 as a yellow solid (0.05 g, 7%), used directly in the next step.

(b) A solution of the pyridylquinoline **44** (0.05 g, 0.20 mmol) in methanol (27 mL) was added to a stirred solution of Fremy's salt (0.7 g, 2.5 mmol) in dihydrogen phosphate buffer (pH 6, 0.3 M; 27 mL). The solution was stirred at room temperature overnight and diluted with water, and the crystalline solid which precipitated was collected. The solid was recrystallized from dichloromethane to yield the *title compound* **15** as a yellow solid (0.03 g, 64%), mp >260 °C, (Found: M^+, 266.0695. $C_{15}H_{10}N_2O_3$ requires 266.0691); λ_{max} (MeCN)/nm 288 (log ε 3.82), 304 (3.77), 356 (2.85), 428 (1.90); ν_{max}(KBr)/cm^{-1} 3076, 2982, 2945, 2844, 1687, 1651, 1607, 1578; δ_H (400 MHz; $CDCl_3$) 3.97 (3H, s), 6.42 (1H, s), 8.05 (2H, dd, *J* = 1.6, 4.5 Hz), 8.14 (1H, d, *J* = 8.2 Hz), 8.58 (1H, d, *J* = 8.2 Hz), 8.80 (2H, dd, *J* = 1.6, 4.5 Hz); δ_C (100 MHz; $CDCl_3$) 56.8 (Me), 111.0 (CH), 121.6 (CH), 124.1 (CH), 127.5 (C), 136.2 (CH), 144.4 (C), 147.8 (C), 150.7 (CH), 159.7 (C), 160.2 (C), 179.2 (C), 182.6 (C); *m*/*z* (EI) 266 (M^+, 100%), 209 (19), 180 (14), 140 (14).

3.3.5. 2-(2-Hydroxymethyl-1-methylindol-4-yl)-6-methoxyquinoline-5,8-dione (18). (a) Sodium metal (0.97 g, 42.3 mmol) was added to methanol (40 mL), and the mixture was cooled to −30 °C. A solution of 2-bromobenzaldehyde (2.00 g, 11 mmol), methyl azidoacetate (4.87 g, 42.3 mmol) in methanol (10 mL) was added and the mixture was stirred for 3 h at −30 °C and then at 4 °C overnight. Water was added and the solvent was removed in vacuo. The residue was extracted with ethyl acetate, the combined organic phases were washed with water and brine, dried ($MgSO_4$) and concentrated in

vacuo. The product was purified by column chromatography (light petroleum/ethyl acetate (gradient) elution) to give *methyl 2-azido-3-(2-bromophenyl)propenoate* **45** as a yellow solid (1.58 g, 51%), mp 85–86 °C, (Found: M^+, 280.9798. $C_{10}H_8^{79}BrN_3O_2$ requires 280.9800); $\nu_{max}(CHCl_3)/cm^{-1}$ 2130, 1716; δ_H (300 MHz; $CDCl_3$) 3.86 (3H, s), 7.10 (1H, td, $J=7.8$, 1.8 Hz), 7.17 (1H, s), 7.24–7.29 (1H, m), 7.53 (1H, dd, $J=7.8$, 1.8 Hz), 8.03 (1H, dd, $J=7.8$, 1.8 Hz); δ_C (100 MHz; $CDCl_3$) 53.1 (Me), 123.5 (CH), 125.2 (C), 127.1 (CH), 127.2 (C), 130.3 (CH), 131.2 (CH), 132.91 (C), 132.93 (CH), 163.7 (C); *m/z* (EI) 281 (M^+, 2%), 255 (6), 223 (7), 209 (22), 194 (100), 115 (67), 89 (48), 59 (39).

(b) A solution of methyl 2-azido-(2-bromophenyl)propenoate **45** (1.5 g, 5.3 mmol) in dry xylene (45 mL) was added to boiling dry xylene (120 mL) and heating continued for 3 h. After cooling, the xylene was removed in vacuo. The crude product was purified by column chromatography (light petroleum/ethyl acetate (95:5) elution) to give *methyl 4-bromoindole-2-carboxylate* **46** as a colorless solid (1.13 g, 84%), mp 164–165 °C (from ethyl acetate/light petroleum), (Found: C, 47.3; H, 3.0; N, 5.4. $C_{10}H_8BrNO_2$ requires C, 47.3; H, 3.2; N, 5.5%); (Found: M^+, 252.9738. $C_{10}H_8^{79}BrNO_2$ requires 252.9739); ν_{max}(Nujol)/cm^{-1} 3324, 1700, 1567, 1521; δ_H (300 MHz; $CDCl_3$) 3.97 (3H, s), 7.16 (1H, dd, $J=7.5$, 8.1 Hz), 7.27 (1H, dd, $J=2.4$, 0.9 Hz), 7.32 (1H, dd, $J=7.5$, 0.9 Hz), 7.37 (1H, dt, $J=8.1$, 0.9 Hz), 9.33 (1H, br); δ_C (100 MHz; $CDCl_3$) 52.2 (Me), 108.9 (CH), 111.1 (CH), 116.4 (C), 123.7 (CH), 126.1 (CH), 127.4 (C), 128.4 (C), 137.0 (C), 162.3 (C); *m/z* (EI) 253 (M^+, 74%), 221 (100), 195 (8), 169 (15), 114 (63), 88 (9).

(c) A solution of methyl-4-bromoindole-2-carboxylate **46** (1.65 g, 6.5 mmol) in DMF (30 mL) was added to a solution of sodium hydride (0.24 g, 10 mmol) in DMF (80 mL) at 0 °C and the mixture was stirred at room temperature for 45 min. Methyl iodide (1.37 g, 10 mmol) was added at 0 °C and stirring was continued for 2 h at room temperature. Water was added and the mixture was extracted with ether. The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (light petroleum/ethyl acetate (1:1) elution) to give *methyl 4-bromo-1-methylindole-2-carboxylate* **47** as a colorless solid (1.56 g, 90%), mp 86–88 °C (from light petroleum), (Found: C, 49.5; H, 3.6; N, 5.1. $C_{11}H_{10}BrNO_2$ requires C, 49.3; H, 3.8; N, 5.2%); (Found: M^+, 266.9894. $C_{11}H_{10}^{79}BrNO_2$ requires 266.9895); ν_{max} (Nujol)/cm^{-1} 1716, 1552, 1506, 753; δ_H (300 MHz; $CDCl_3$) 3.93 (3H, s), 4.07 (3H, s), 7.19 (1H, t, $J=8.1$ Hz), 7.31–7.33 (3H, m); δ_C (100 MHz; $CDCl_3$) 32.0 (Me), 51.7 (Me), 109.4 (CH), 110.3 (CH), 116.5 (C), 123.4 (CH), 125.6 (CH), 126.7 (C), 128.1 (C), 139.7 (C), 162.2 (C); *m/z* (EI) 267 (M^+, 100%), 254 (15), 236 (35), 209 (18), 188 (23), 169 (23).

(d) Dichloro[1,1′-bis(diphenylphosphino)ferrocene]-palladium (II) (32 mg, 0.04 mmol), diphenylphosphinoferrocene (24 mg, 0.04 mmol), potassium acetate (0.4 g, 4 mmol) and bis(pinacolato)diboron (0.38g, 1.5 mmol) in a flask was flushed with nitrogen. A solution of methyl 4-bromo-1-methylindole-2-carboxylate **47** (0.38 g, 1.4 mmol) in dioxane (20 mL) was added and the mixture was heated to 80 °C for 18 h. After cooling the mixture was diluted with ether and washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (light petroleum/ethyl acetate (95:5) elution) to give the *boronate ester of methyl 4-bromo-1-methylindole-2-carboxylate* **48** as a colorless solid (0.24 g, 54%), mp 161–162 °C (from light petroleum), (Found: C, 65.0; H,7.3; N, 4.3. $C_{17}H_{22}BNO_4$ requires C, 64.8; H, 7.0; N, 4.4%); (Found: M^+, 315.1643. $C_{17}H_{22}BNO_4$ requires 315.1642); ν_{max}(Nujol)/cm^{-1} 1710, 1562, 1506, 1367, 1234; δ_H (300 MHz; $CDCl_3$) 1.39 (12H, s), 3.92 (3H, s), 4.07 (3H, s), 7.35 (1H, dd, $J=8.4$, 6.9 Hz), 7.47 (1H, d, $J=8.4$ Hz), 7.66 (1H, dd, $J=6.9$, 0.9 Hz), 7.72 (1H, d, $J=0.9$ Hz); δ_C (100 MHz; $CDCl_3$) 24.9 (Me), 31.5 (Me), 51.5 (Me), 83.6 (C), 112.1 (CH), 113.0 (CH), 124.3 (CH), 127.9 (C), 128.8 (CH), 130.1 (C), 139.1 (C), 162.9 (C); one C unobserved; *m/z* (EI) 315 (M^+, 100%), 269 (34), 242 (25), 215 (37), 198 (17).

(e) A flask was charged with 2-chloro-6-methoxy-5-nitroquinoline **35** (0.57 g, 2.4 mmol), dichloro[1,1′-bis-(diphenylphosphino)ferrocene]palladium(II) (114 mg, 0.14 mmol) and potassium phosphate (3.1 g, 15 mmol) and was flushed with nitrogen. A solution of the indole boronate **48** (0.7 g, 2.2 mmol) in dioxane (70 mL) was added and the mixture was heated to 80 °C for 24 h. After cooling the mixture was diluted with ether and was washed with brine. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (light petroleum/ethyl acetate(gradient) elution) to give *methyl 4-(6-methoxy-5-nitroquinolin-2-yl)-1-methylindole-2-carboxylate* **49** as a pale yellow solid (0.37 g, 44%), mp 189–191 °C (from ethyl acetate/light petroleum), (Found: C, 64.7; H, 4.4; N, 10.4. $C_{21}H_{17}N_3O_5$ requires C, 64.4; H, 4.4; N, 10.7%); (Found: M^+, 391.1164. $C_{21}H_{17}N_3O_5$ requires 391.1168); ν_{max} (Nujol)/cm^{-1} 1721, 1618, 1593, 1516, 1352; δ_H (300 MHz; $CDCl_3$) 3.92 (3H, s), 4.10 (3H, s), 4.13 (3H, s), 7.48–7.50 (2H, m), 7.58 (1H, d, $J=9.6$ Hz), 7.67 (1H, dd, $J=6.0$, 2.4 Hz), 7.90 (1H, s), 8.03 (1H, d, $J=9.0$ Hz), 8.15 (1H, dd, $J=9.0$, 0.6 Hz), 8.37 (1H, dd, $J=9.6$, 0.6 Hz); δ_C (100 MHz; $CDCl_3$) 31.8 (Me), 51.6 (Me), 57.2 (Me), 110.6 (CH), 111.7 (CH), 116.3 (CH), 120.0 (C), 121.4 (CH), 123.6 (CH), 124.1 (C), 125.0 (CH), 128.8 (C), 129.6 (CH), 133.1 (C), 134.3 (CH), 134.9 (C), 140.5 (C), 142.5 (C), 149.1 (C), 157.5 (C), 162.5 (C); *m/z* (EI) 391 (M^+, 100%), 346 (23), 318 (20), 285 (51), 257 (30), 256 (55), 255 (35).

(f) Tin powder (0.83 g) and HCl (3 M; 17 mL) were added to a solution of methyl 4-(6-methoxy-5-nitroquinolin-2-yl)-1-methylindole-2-carboxylate 49 (0.46 g, 1.2 mmol) in ethanol (35 mL) and the mixture was heated under reflux for 30 min. After cooling the mixture was decanted from the excess tin and neutralized with saturated $NaHCO_3$ solution. An equal volume of water was added and the mixture was stirred in dichloromethane for 2 h. The layers were separated and the organic phase was dried (Na_2SO_4) and concentrated in vacuo.

The residue was purified by column chromatography (dichloromethane/ethyl acetate (98:2) elution) to give methyl 4-(5-amino-6-methoxyquinolin-2-yl)-1-methylindole-2-carboxylate 50 as an orange sticky solid (0.11 g, 26%), ν_{max} (Nujol)/cm^{-1} 3457, 3365, 1751, 1613, 1557; δ_H (300 MHz; $CDCl_3$) 3.93 (3H, s), 4.02 (3H, s), 4.14 (3H, s), 7.47–7.49 (3H, m), 7.67 (1H, dd, $J=6.0$, 2.4 Hz), 7.74 (1H, dd, $J=9.0$, 0.6 Hz), 7.84 (1H, d, $J=8.7$ Hz), 7.92 (1H, s), 8.24 (1H, dd, $J=9.0$, 0.6 Hz); NH_2 not observed; δ_C (100 MHz; $CDCl_3$) 31.7 (Me), 51.5 (Me), 56.7 (Me), 110.9 (CH), 111.0 (CH), 116.5 (CH), 117.4 (C), 119.7 (CH), 120.1 (CH), 121.0 (CH), 124.3 (C), 125.1 (CH), 128.4 (C), 129.3 (C), 129.4 (CH), 134.5 (C), 140.5 (C), 142.7 (C), 144.0 (C), 155.9 (C), 162.7 (C); *m/z* (EI) 361 (M^+, 48%), 346 (60), 217 (35), 216 (34), 59 (88), 52 (47), 45 (100).

(g) A solution of the methyl 4-(5-amino-6-methoxyquinolin-2-yl)-1-methylindole-2-carboxylate **50** (0.11 g, 0.4 mmol) in THF (15 mL) was added to a solution of lithium aluminium hydride (15 mg, 1.4 mmol) in THF (10 mL) at 0 °C. The mixture was warmed and stirred at room temperature for 30 min. The mixture was cooled to 0 °C and water (1 mL) was added followed by NaOH solution (1 M; 1 mL) and flash silica. The mixture was filtered through Celite, and the filtrate was dried (Na_2SO_4) and concentrated in vacuo to give 4-(5-amino-6-methoxyquinolin-2-yl)-1-methylindole-2-methanol **51** as a yellow oily solid (88 mg, 75%), which was used without purification or characterisation, δ_H (300 MHz; $CDCl_3$) 3.82 (3H, s), 4.01 (3H, s), 4.82 (2H, s), 7.01 (1H, s), 7.36 (2H, m), 7.44 (1H, d, $J=9.0$ Hz), 7.58 (1H, dd, $J=6.0$, 2.4 Hz), 7.71 (1H, d, $J=9.0$ Hz), 7.79 (1H, d, $J=8.7$ Hz), 8.17 (1H, d, $J=8.7$ Hz).

(h) A solution of Fremy's salt (36 mg, 0.12 mmol) in sodium dihydrogen phosphate buffer (0.3 M; 5 mL) was added to a solution of 4-(5-amino-6-methoxyquinolin-2-yl)-1-methylindole-2-methanol **51** (26 mg, 0.08 mmol) in acetone (10 mL) and the mixture was stirred at room temperature for 1.5 h. A further solution of Fremy's salt (36 mg, 0.12 mmol) in the buffer (0.3 M; 5 mL) was added and the mixture was stirred for a further 1.5 h. The mixture was extracted with dichloromethane, and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (dichloromethane/ethyl acetate (3:1) elution) to give the *title compound* **18** as a pink/red solid (19 mg, 69%), mp 261 °C (from chloroform/methanol), (Found: C, 66.4; H, 4.4; N, 7.6. $C_{20}H_{16}N_2O_4.0.7H_2O$ requires C, 66.5; H, 4.9; N, 7.8%); (Found: M^+, 348.1120. $C_{20}H_{16}N_2O_4$ requires 348.1110); λ_{max} (MeOH)/nm 242 (log ε 4.28), 278 (4.17), 352 (3.96), 454 (3.45); ν_{max} (Nujol)/cm^{-1} 3472, 1675, 1644, 1603, 1572; δ_H (300 MHz; $CDCl_3$) 3.86 (3H, s), 4.01 (3H, s), 4.89 (2H, d, $J=3.9$ Hz), 6.36 (1H, s), 7.33–7.38 (2H, m), 7.48 (1H, d, $J=8.1$ Hz), 7.72 (1H, d, $J=8.1$ Hz), 8.17 (1H, d, $J=8.4$ Hz), 8.48 (1H, d, $J=8.4$ Hz); OH not observed; δ_C (100 MHz; $CDCl_3$) 29.9 (Me), 56.6 (Me), 56.7 (CH_2), 101.8 (CH), 110.2 (CH), 111.9 (CH), 120.6 (CH), 121.5 (CH), 125.52 (C), 125.58 (CH), 125.8 (C), 129.5 (C), 135.0 (CH), 138.9 (C), 141.3 (C), 147.3 (C), 160.3 (C), 164.2 (C) 179.5 (C), 183.6 (C); *m/z* (CI) 349 (MH^+, 3%), 335 (2), 146 (47), 132 (33), 110 (47), 108 (55), 96 (52), 72 (49), 69 (40), 58 (100).

3.3.6. 6-(Pyrrolidin-1-yl)quinoline-5,8-dione (19). Pyrrolidine (0.4 mL, 5.3 mmol) was added to a solution of 6-methoxyquinoline-5,8-dione **2** (50 mg, 0.3 mmol) in DMF (5 mL) and the mixture was stirred at room temperature for 3 days. The mixture was diluted with dichloromethane and washed with water (×5). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The product was purified by column chromatography (ethyl acetate elution) to give the *title compound* **19** as a red solid (42 mg, 71%), mp 196–197 °C (from ethyl acetate/light petroleum), (Found: M^+, 228.0901. $C_{13}H_{12}N_2O_2$ requires 228.0898); λ_{max} (MeOH)/nm 232 (log ε 4.34), 268 (4.11), 310 (3.90), 472 (3.73); ν_{max} (Nujol)/cm^{-1} 1680, 1618, 1577, 1552; δ_H (300 MHz; $CDCl_3$) 1.99–2.04 (4H, m), 3.38 (2H, br), 3.98 (2H, br), 5.94 (1H, s), 7.54 (1H, dd, $J=7.8$, 4.5 Hz), 8.32 (1H, dd, $J=7.8$, 1.8 Hz), 8.97 (1H, dd, $J=4.5$, 1.8 Hz); δ_C (100 MHz; $CDCl_3$) 25.2 (br, CH_2), 51.1 (br, CH_2), 106.0 (CH), 125.8 (CH), 128.2 (C), 134.2 (CH), 148.3 (C), 148.8 (C) 154.5 (CH), 180.5 (C), 182.7 (C); *m/z* (EI) 228 (M^+, 26%), 209 (30), 114 (17), 83 (33), 70 (100), 57 (77).

3.3.7. 2-Phenyl-6-(pyrrolidin-1-yl)-quinoline-5,8-dione (20). Pyrrolidine (0.5 mL, 4.20 mmol) was added to a solution of 6-methoxy-2-phenylquinoline-5,8-dione **5** (21 mg, 0.08 mmol) in DMF (2 mL) and the mixture was stirred at room temperature for 3 days. The mixture was diluted with dichloromethane and washed with water (3×5 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate elution) to give the *title compound* **20** as a red solid (24 mg, 100%), mp 202–203 °C (from ethyl acetate), (Found: MH^+, 305.1290. $C_{19}H_{16}N_2O_2+H$ requires 305.1290); λ_{max} (MeOH)/nm 300 (log ε 4.11), 316 (4.09), 336 (4.05), 480 (3.61); ν_{max}(KBr)/cm^{-1} 3047, 2955, 2868, 1680, 1567, 1552; δ_H (400 MHz; $CDCl_3$, −20 °C) 2.00–2.05 (4H, m), 3.40 (2H, t, $J=6.0$ Hz), 4.01 (2H, t, $J=6.0$ Hz), 6.01 (1H, s), 7.49–7.52 (3H, m), 8.00 (1H, d, $J=8.4$ Hz), 8.18 (2H, d, $J=1.6$ Hz), 8.38 (1H, d, $J=8.4$ Hz); δ_C (100 MHz; $CDCl_3$, −20 °C) 23.9 (CH_2), 26.8 (CH_2), 51.0 (CH_2), 51.9 (CH_2), 105.6 (CH), 122.7 (CH), 126.6 (C), 127.9 (CH), 129.0 (CH), 130.6 (CH), 135.6 (CH), 137.6 (C), 148.5 (C), 148.9 (C), 161.9 (C), 181.0 (C), 182.5 (C); *m/z* (EI) 304 (M^+, 9%), 178 (9), 154 (20), 102 (34), 77 (35), 53 (60), 49 (47), 41 (100).

3.3.8. 6-(Morpholin-4-yl)-2-phenylquinoline-5,8-dione (21). Morpholine (1 mL, 11 mmol) was added to a solution of 6-methoxy-2-phenylquinoline-5,8-dione **5** (23 mg, 0.10 mmol) in DMF (2 mL) and the mixture was stirred at room temperature for 3 days. The mixture was diluted with dichloromethane and washed with water (3×5 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate elution) to give the *title compound* **21** as a red solid (33 mg, 100%), mp 203–204 °C (from ethyl acetate), (Found: MH^+, 321.1233. $C_{19}H_{16}N_2O_3+H$ requires 321.1239); ν_{max}(KBr)/cm^{-1} 3057, 2945, 2919, 2852, 1675, 1572; δ_H (400 MHz;

$CDCl_3$) 3.56 (4H, t, $J=4.8$ Hz), 3.87 (4H, t, $J=4.8$ Hz), 6.20 (1H, s), 7.49 (3H, m), 7.99 (1H, d, $J=8.3$ Hz), 8.17 (2H, d, $J=7.9$ Hz), 8.36 (1H, d, $J=8.3$ Hz); δ_C (100 MHz; $CDCl_3$) 49.2 (CH_2), 66.4 (CH_2), 112.4 (CH), 122.9 (CH), 127.78 (C), 127.82 (CH), 128.9 (CH), 130.6 (CH), 135.6 (CH), 137.6 (C), 147.9 (C), 152.7 (C), 162.0 (C), 182.2 (C), 182.3 (C); *m*/*z* (EI) 320 (M^+, 75%), 264 (84), 263 (100), 223 (55), 179 (81).

3.3.9. 2-Phenylquinoline-5,8-dione (22). (a) A solution of 8-benzyloxy-2(1*H*)-quinolone **52**[70] (1.00 g, 4.0 mmol) in phosphorus oxychloride (110 mL) was heated under reflux for 4 h. The phosphorus oxychloride was removed in vacuo. The residue was poured into ice water and neutralized with saturated K_2CO_3 solution. This mixture was extracted with dichloromethane, the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallized from ethyl acetate/light petroleum to give *8-benzyloxy-2-chloroquinoline* **53** as a colorless solid (0.91 g, 85%), mp 96–97 °C, (Found: C, 70.9; H, 4.3; N, 5.1. $C_{16}H_{12}ClNO$ requires C, 71.2; H, 4.5; N, 5.2%); (Found: M^+, 269.0609. $C_{16}H_{12}^{35}ClNO$ requires 269.0607); ν_{max}(Nujol)/cm^{-1} 1591, 1564, 847; δ_H (300 MHz; $CDCl_3$) 5.43 (2H, s), 7.07 (1H, dd, $J=6.0$, 3.0 Hz), 7.28–7.42 (6H, m), 7.50 (2H, d, $J=7.2$ Hz), 8.06 (1H, d, $J=8.7$ Hz); δ_C (100 MHz; $CDCl_3$) 70.9 (CH_2), 111.7 (CH), 119.6 (CH), 122.9 (CH), 126.9 (CH), 127.0 (CH), 127.8 (CH), 128.1 (C), 128.5 (CH), 136.8 (C), 138.7 (CH), 139.9 (C), 149.8 (C), 153.6 (C); *m*/*z* (EI) 269 (M^+, 19%), 163 (7), 91 (100).

(b) A solution of 8-benzyloxy-2-chloroquinoline **53** (1.1 g, 4.0 mmol) in 1,2-dimethoxyethane (71 mL) was degassed under reduced pressure and flushed with nitrogen. $Pd(PPh_3)_4$ (0.24 g) was added and the mixture was degassed further. The mixture was stirred for 10 min then Na_2CO_3 solution (2 M; 8.1 mmol) was added followed by phenylboronic acid (0.71 g, 5.9 mmol). The mixture was heated under reflux for 18 h. After cooling the mixture was poured into dichloromethane and washed with water, the organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (light petroleum/ethyl acetate (gradient) elution) to give *8-benzyloxy-2-phenylquinoline* **54** as a colorless solid (0.96 g, 78%), mp 90–91 °C (from ethyl acetate/light petroleum), (Found: C, 84.2; H, 5.3; N, 4.4. $C_{22}H_{17}NO.0.1H_2O$ requires C, 84.4; H, 5.5; N, 4.5%); (Found: M^+, 311.1310. $C_{22}H_{17}NO$ requires 311.1310); ν_{max}(Nujol)/cm^{-1} 1597, 1558, 1255, 1104; δ_H (300 MHz, $CDCl_3$) 5.45 (2H, s), 7.12 (1H, dd, $J=7.2$, 1.8 Hz), 7.31–7.46 (6H, m), 7.48–7.53 (2H, m), 7.60 (2H, d, $J=7.2$ Hz), 7.92 (1H, d, $J=8.7$ Hz), 8.18 (1H, d, $J=8.7$ Hz), 8.22–8.25 (2H, m); δ_C (100 MHz; $CDCl_3$) 71.3 (CH_2), 111.6 (CH), 119.1 (CH), 120.0 (CH), 126.3 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 136.7 (CH), 137.4 (C), 139.7 (C), 140.7 (C), 154.8 (C), 155.9 (C); one C unobserved; *m*/*z* (EI) 311 (M^+, 34%), 234 (25), 205 (39), 191 (39), 91 (100).

(c) Boron trichloride dimethyl sulfide complex (2.0M; 10 mL, 20 mmol) was added to a solution of 8-benzyloxy-2-phenylquinoline **54** (0.3g, 1.0 mmol) in dichloromethane (10 mL) and the mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated $NaHCO_3$ solution. The resulting mixture was extracted with dichloromethane, the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography [light petroleum/ethyl acetate (7:3) elution] to give 2-phenylquinolin-8-ol **55** as a colorless oil (0.18 g, 84%) (lit.,[71] mp 55 °C), ν_{max} ($CHCl_3$)/cm^{-1} 3411 (OH), 1598, 1562; δ_H (300 MHz; $CDCl_3$) 7.19 (1H, dd, $J=7.2$, 1.2 Hz), 7.33 (1H, dd, $J=8.1$, 1.2 Hz), 7.42 (1H, d, $J=7.2$ Hz), 7.46–7.56 (3H, m), 7.91 (1H, d, $J=8.7$ Hz), 8.14–8.17 (2H, m), 8.21 (1H, d, $J=8.7$ Hz); δ_C (100 MHz; $CDCl_3$) 110.1 (CH), 117.6 (CH), 119.5 (CH), 127.3 (CH), 127.5 (CH), 128.7 (CH), 128.8 (CH), 129.5 (CH), 136.9 (CH), 138.0 (C), 138.8 (C), 152.3 (C), 154.9 (C).

(d) To a solution of 2-phenylquinolin-8-ol **55** (0.17 g, 0.75 mmol) in acetone (30 mL) was added a solution of Fremy's salt (0.35 g, 1.3 mmol) in sodium dihydrogen phosphate buffer (0.3 M; 30 mL) and the mixture was stirred at room temperature for 1 h. A further solution of Fremy's salt (0.35 g, 1.3 mmol) in the buffer (0.3 M; 30 mL) was added and stirring was continued for 1 h. The acetone was removed in vacuo. The residue was extracted with dichloromethane and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (dichloromethane elution) to give the *title compound* **22** as a yellow/brown solid (0.10 g, 58%), mp 139–141 °C (lit.,[72] mp 121–123 °C), λ_{max} (MeOH)/nm 230 (log ε 4.26), 266 (4.39), 302 (4.06), 354 (3.52); ν_{max} ($CHCl_3$)/cm^{-1} 1685, 1669, 1582; δ_H (300 MHz; $CDCl_3$) 7.06 (1H, d, $J=10.2$ Hz), 7.16 (1H, d, $J=10.2$ Hz), 7.51–7.53 (3H, m), 8.11 (1H, d, $J=8.1$ Hz), 8.16–8.19 (2H, m), 8.45 (1H, d, $J=8.1$ Hz); δ_C (100 MHz; $CDCl_3$) 124.1 (CH), 127.5, 127.8 (CH), 129.0 (CH), 130.8 (CH), 135.3 (CH), 137.3, 137.9 (CH), 139.1 (CH), 147.4, 162.1, 183.2 (C), 184.5 (C).

3.3.10. 3-Hydroxymethylquinoline-5,8-dione (23). (a) Phosphorus oxychloride (7.0 mL, 72 mmol) was added to DMF (2 mL, 26 mmol) at 0 °C, *N*-(2′,5′-dimethoxyphenyl)acetamide 56 (2.0 g, 10.3 mmol) was added and the mixture was stirred for 5 min at 0 °C and was then heated under reflux for 2 h. After cooling the mixture was poured into ice water. The mixture was extracted with dichloromethane, the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (light petroleum/ethyl acetate (7:3) elution) to give 2-chloro-5,8-dimethoxyquinoline-3-carbaldehyde **57** as an orange solid (1.1 g, 41%), mp 157–159 °C (lit.,[73] mp 159 °C), δ_H (300 MHz; $CDCl_3$) 3.99 (3H, s), 4.05 (3H, s), 6.84 (1H, d, $J=8.7$ Hz), 7.14 (1H, d, $J=8.7$ Hz), 9.15 (1H, s), 10.56 (1H, s).

(b) A solution of 5,8-dimethoxy-2-chloroquinoline-3-carbaldehyde **57** (1.0 g, 3.9 mmol) in THF (120 mL) was added to a solution of lithium aluminium hydride (0.6 g, 16 mmol) in THF (80 mL) at −60 °C. The mixture was stirred at −60 °C for 1 h. Water (8 mL) was added followed by NaOH (1M; 8 mL) and silica (1 g), and the

mixture was then filtered through Celite. The filtrate was dried (Na_2SO_4) and concentrated in vacuo. The residue was recrystallized from dichloromethane/light petroleum to give *2-chloro-5,8-dimethoxyquinoline-3-methanol* 58 as a colorless solid (1.0 g, 100%), mp 151–154 °C, (Found: C, 54.1; H, 4.6; N, 5.2. $C_{12}H_{12}ClNO_3.0.7H_2O$ requires C, 54.1; H, 5.0; N, 5.3%); (Found: M^+, 253.0505. $C_{12}H_{12}^{35}ClNO_3$ requires 253.0506); ν_{max} (Nujol)/cm^{-1} 3416, 3318, 1613, 1598, 725; δ_H (300 MHz; $CDCl_3$) 2.38 (1H, t, $J=5.7$ Hz), 3.94 (3H, s), 4.01 (3H, s), 4.91 (2H, d, $J=5.7$ Hz), 6.76 (1H, d, $J=8.4$ Hz), 6.94 (1H, d, $J=8.4$ Hz), 8.62 (1H, s); δ_C (100 MHz; $CDCl_3$) 55.8 (Me), 56.1 (Me), 62.2 (CH_2), 104.5 (CH), 108.1 (CH), 120.7, 131.5 (CH), 132.1, 139.0, 148.5, 148.6, 148.9; *m/z* (EI) 253 (M^+, 40%), 238 (100), 224 (29), 160 (8), 116 (8), 75 (10), 63 (10).

(c) Tin (0.45 g) and HCl (3M; 7 mL) was added to a solution of 2-chloro-5,8-dimethoxyquinoline-3-methanol **58** (0.17 g, 0.7 mmol) in ethanol (20 mL) and the mixture was heated under reflux for 2 h. After cooling the mixture was decanted from the excess tin. The mixture was neutralized with saturated $NaHCO_3$ solution, an equal volume of water was added and the mixture was stirred in dichloromethane for 1 h. The mixture was filtered through Celite and the layers were separated, the organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (gradient) elution) to give 5,8-dimethoxyquinoline-3-methanol **59** as a colorless oily solid (80 mg, 55%), (Found: M^+, 219.0905. $C_{12}H_{13}NO_3$ requires 219.0895); ν_{max} ($CHCl_3$)/cm^{-1} 3385 (OH), 1629, 1506; δ_H (300 MHz; $CDCl_3$) 3.94 (3H, s), 4.02 (3H, s), 4.90 (2H, s), 6.74 (1H, d, $J=8.4$ Hz), 6.90 (1H, d, $J=8.4$ Hz), 8.49–8.50 (1H, m), 8.89 (1H, d, $J=2.1$ Hz); OH not observed; δ_C (100 MHz, $CDCl_3$) 55.7 (Me), 56.0 (Me), 63.1 (CH_2), 104.0 (CH), 106.7 (CH), 121.2, 128.6 (CH), 133.3, 139.8, 148.6, 149.2 (CH), 149.4; *m/z* (EI) 219 (M^+, 39%), 211 (21), 204 (100), 190 (21), 91 (84), 57 (47).

(d) Cerium(IV) ammonium nitrate (0.47 g, 0.8 mmol) was added to a solution of 5,8-dimethoxyquinoline-3-methanol **59** (80 mg, 0.4 mmol) in acetonitrile (20 mL) and water (7 mL) and the mixture was stirred at room temperature for 3 h. The mixture was diluted with water and was extracted with dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (dichloromethane elution) to give the *title compound* **23** as a pale pink solid (66 mg, 87%), mp 144–146 °C (from ethyl acetate/light petroleum), (Found: C, 62.7; H, 3.6; N, 7.2. $C_{10}H_7NO_3.0.1{\cdot}H_2O$ requires C, 62.9; H, 3.8; N, 7.3%); (Found: M^+, 189.0424. $C_{10}H_7NO_3$ requires 189.0426); λ_{max} (MeOH)/nm 242 (log ε 4.36), 320 (3.12); ν_{max} (Nujol)/cm^{-1} 3354, 1680, 1660, 1588; δ_H (300 MHz; $CDCl_3$) 2.39 (1H, br), 4.96 (2H, br), 7.06 (1H, d, $J=10.5$ Hz), 7.15 (1H, d, $J=10.5$ Hz), 8.43–8.44 (1H, m), 9.03 (1H, d, $J=2.1$ Hz); δ_C (100 MHz; $CDCl_3$) 60.9 (CH_2), 128.0, 132.0 (CH), 138.1 (CH), 139.1 (CH), 143.1, 146.1, 153.0 (CH), 183.3 (C), 185.8 (C); *m/z* (EI) 189 (M^+, 100%), 160 (60), 133 (51), 104 (16), 91 (63).

3.3.11. 3-Hydroxymethyl-2-phenylquinoline-5,8-dione (24). (a) A solution of 2-chloro-5,8-dimethoxyquinoline-3-carbaldehyde **57** (1.0 g, 3.9 mmol) in 1,2-dimethoxyethane (70 mL) was degassed under reduced pressure. $Pd(PPh_3)_4$ (0.44 g) was added followed by further degassing. The mixture was stirred under a nitrogen atmosphere for 10 min. Na_2CO_3 solution (2 M; 10 mL) was added followed by phenylboronic acid (0.7 g, 5.7 mmol). The mixture was heated under reflux for 18 h. After cooling the mixture was poured into dichloromethane and washed with brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (dichloromethane elution) to give *5,8-dimethoxy-2-phenylquinoline-3-carbaldehyde* **60** as a yellow solid (0.8 g, 71%), mp 219–221 °C (from ethyl acetate), (Found: M^+, 293.1060. $C_{18}H_{15}NO_3$ requires 293.1052); ν_{max} (Nujol)/cm^{-1} 1690, 1608, 1572; δ_H (300 MHz; $CDCl_3$) 4.00 (3H, s), 4.03 (3H, s), 6.80 (1H, d, $J=8.4$ Hz), 7.09 (1H, d, $J=8.4$ Hz), 7.49–7.55 (3H, m), 7.68–7.72 (2H, m), 9.23 (1H, s), 10.17 (1H, s); δ_C (100 MHz; $CDCl_3$) 55.9 (Me), 56.4 (Me), 104.3 (CH), 110.8 (CH), 120.0 (C), 127.1 (C), 128.5 (CH), 129.2 (CH), 130.6 (CH), 133.4 (CH), 137.9 (C), 141.5 (C), 149.3 (C), 150.0 (C), 159.6 (C), 191.5 (CH); *m/z* (EI) 293 (M^+, 56%), 292 (32), 278 (91), 264 (20), 85 (65), 83 (100).

(b) Sodium borohydride (0.01 g, 0.34 mmol) was added to a solution of 5,8-dimethoxy-2-phenylquinoline-3-carbaldehyde **60** (0.2 g, 0.7 mmol) in 1,2-dimethoxyethane (30 mL) and the mixture was heated under reflux for 2 h. After cooling water was added followed by HCl (2 M). The mixture was extracted with ether and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (gradient) elution) to give *5,8-dimethoxy-2-phenylquinoline-3-methanol* **61** as a colorless solid (0.11 g, 55%), mp 170–172 °C (from dichloromethane/light petroleum), (Found: C, 72.5; H, 5.7; N, 4.6. $C_{18}H_{17}NO_3.0.2H_2O$ requires C, 72.3; H, 5.9; N, 4.7%); (Found: M^+, 295.1203. $C_{18}H_{17}NO_3$ requires 295.1208); ν_{max} (Nujol)/cm^{-1} 3457, 1618, 1593; δ_H (300 MHz; $CDCl_3$) 3.99 (3H, s), 4.01 (3H, s), 4.82 (2H, br), 6.77 (1H, d, $J=8.4$ Hz), 6.94 (1H, d, $J=8.4$ Hz), 7.42–7.49 (3H, m), 7.64–7.67 (2H, m), 8.73 (1H, s); OH not observed; δ_C (100 MHz; $CDCl_3$) 55.8 (Me), 56.1 (Me), 62.8 (CH_2), 103.8 (CH), 107.2 (CH), 120.7 (C), 128.2 (CH), 128.4 (CH), 129.1 (CH), 130.5 (CH), 131.8 (C), 139.5 (C), 140.0 (C), 148.6 (C), 149.5 (C), 158.1 (C); *m/z* (EI) 295 (M^+, 60%), 280 (100), 266 (29), 139 (16), 83 (61).

(c) Cerium(IV) ammonium nitrate (0.4 g, 0.8 mmol) was added to a solution of 5,8-dimethoxy-3-hydroxymethyl-2-phenylquinoline **61** (0.1 g, 0.34 mmol) in acetonitrile (10 mL) and water (6 mL). The mixture was stirred at room temperature for 1.5 h. The mixture was diluted with water and extracted with dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (gradient) elution) to give the *title compound* **24**

as a pale yellow solid (51 mg, 57%), mp 185–187 °C (from ethyl acetate/light petroleum), (Found: M^+, 265.0741. $C_{16}H_{11}NO_3$ requires 265.0739); λ_{max} (MeOH)/nm 252 (log ε 4.38), 344 (3.30); ν_{max} (Nujol)/cm^{-1} 3308, 1675, 1669, 1582; δ_H (400 MHz; DMSO) 4.62 (2H, d, $J=4.4$ Hz), 7.14 (1H, d, $J=10.4$ Hz), 7.18 (1H, d, $J=10.4$ Hz), 7.52–7.53 (3H, m), 7.60–7.62 (2H, m), 8.53 (1H, s); OH not observed; δ_C (100 MHz; DMSO) 60.4 (CH_2), 128.0 (C), 128.7 (CH), 129.4 (CH), 129.7 (CH), 133.6 (CH), 138.3 (CH), 138.5 (C), 139.8 (CH), 140.9 (C), 145.8 (C), 161.2 (C), 183.5 (C), 185.4 (C); *m*/*z* (EI) 265 (M^+, 86%), 264 (68), 133 (42), 91 (100).

3.3.12. 3-Hydroxymethyl-2-(thien-2-yl)quinoline-5,8-dione (25). (a) A solution of 2-chloro-5,8-dimethoxyquinoline-3-carbaldehyde **57** (0.1 g, 0.40 mmol) in 1,2-dimethoxyethane (10 mL) was degassed under reduced pressure and flushed with nitrogen. $Pd(PPh_3)_4$ (50 mg, 0.05 mmol) was added and the system was degassed again. The mixture was stirred for 10 min. Sodium carbonate solution (2 M; 1 mL) was added followed by thiophene-2-boronic acid (0.06 g, 0.50 mmol) and the mixture was heated under reflux for 19 h. After cooling, the mixture was poured into dichloromethane (10 mL) and washed with water (3×5 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane elution) to give 5,8-dimethoxy-2-(thien-2-yl)quinoline-3-carbaldehyde **62** as a yellow solid (0.08 g, 69%), used without further purification, ν_{max}(KBr)/cm^{-1} 1670, 1608, 1567; δ_H (300 MHz; $CDCl_3$) 3.98 (3H, s), 4.04 (3H, s), 6.75 (1H, d, $J=8.5$ Hz), 7.06 (1H, d, $J=8.5$ Hz), 7.19 (1H, dd, $J=5.2$, 3.6 Hz), 7.36 (1H, dd, $J=3.6$, 1.1 Hz), 7.59 (1H, dd, $J=5.2$, 1.1 Hz), 9.15 (1H, s), 10.45 (1H, s), δ_C (100 MHz; $CDCl_3$) 55.9 (Me), 56.5 (Me), 104.4 (CH), 111.2 (CH), 119.7 (C), 126.8 (C), 128.0 (CH), 129.7 (CH), 130.9 (CH), 134.0 (CH), 141.4 (C), 141.5 (C), 149.0 (C), 149.9 (C), 152.4 (C), 191.2 (CH).

(b) Sodium borohydride (4 mg, 0.10 mmol) was added to a solution of 5,8-dimethoxy-2-(thien-2-yl)quinoline-3-carbaldehyde **62** (77 mg, 0.26 mmol) in 1,2-dimethoxyethane (15 mL) and the mixture was heated to reflux for 2 h. After cooling, water was added followed by HCl (2 M). The mixture was extracted with ether (3×5 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (gradient) elution) to give 5,8-dimethoxy-2-(thien-2-yl)quinoline-3-methanol **63** as a colorless solid (62 mg, 79%), used without further purification, δ_H (300 MHz; $CDCl_3$) 2.66 (1H, br), 3.90 (3H, s), 4.02 (3H, s), 4.95 (2H, s), 6.64 (1H, d, $J=8.5$ Hz), 6.87 (1H, d, $J=8.5$ Hz), 7.11 (1H, dd, $J=5.2$, 3.8 Hz), 7.47 (1H, dd, $J=5.2$, 1.1 Hz), 7.60 (1H, dd, $J=3.8$, 1.1 Hz), 8.54 (1H, s).

(c) Cerium(IV) ammonium nitrate (0.2 g, 0.49 mmol) was added to a solution of 5,8-dimethoxy-2-(thien-2-yl)quinoline-3-methanol **63** (0.06 g, 0.21 mmol) in acetonitrile (6 mL) and water (4 mL). The mixture was stirred at room temperature for 1.5 h. The mixture was diluted with water and extracted with dichloromethane (3×5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (gradient) elution) to give the *title compound* **25** as a yellow solid (0.05 g, 94%), mp 148–149 °C, (Found; M^+, 271.0312. $C_{14}H_9NO_3S$ requires 271.0303); λ_{max} (MeOH)/nm 292 (log ε 4.02), 324 (3.99), 388 (3.48); ν_{max}(KBr)/cm^{-1} 3426, 1669, 1665, 1608, 1577; δ_H (400 MHz; DMSO-d_6) 4.87 (2H, d, $J=5.4$ Hz), 5.87 (1H, t, $J=5.4$ Hz), 7.11 (1H, d, $J=10.4$ Hz), 7.16 (1H, d, $J=10.4$ Hz), 7.25 (1H, dd, $J=5.1$, 3.8 Hz), 7.73 (1H, dd, $J=3.8$, 1.0 Hz), 7.86 (1H, dd, $J=5.1$, 1.0 Hz), 8.53 (1H, s); δ_C (100 MHz; DMSO-d_6) 61.0 (CH_2), 127.1 (C), 129.3 (CH), 130.6 (CH), 131.9 (CH), 133.9 (CH), 138.4 (CH), 138.9 (C), 139.7 (CH), 143.0 (C), 145.8 (C), 153.6 (C), 183.2 (C), 185.1 (C); *m*/*z* (EI) 271 (M^+, 100%), 242 (32), 238 (31), 210 (31).

3.3.13. 2-(Benzofuran-2-yl)-3-hydroxymethylquinoline-5,8-dione (26). (a) A solution of 2-chloro-5,8-dimethoxyquinoline-3-carbaldehyde **57** (0.1 g, 0.40 mmol) in 1,2-dimethoxyethane (15 mL) was degassed under reduced pressure and flushed with nitrogen. $Pd(PPh_3)_4$ (47 mg, 0.05 mmol) was added and the system was degassed again. The mixture was stirred for 10 min. Sodium carbonate solution (2 M; 1 mL) was added followed by benzofuran-2-boronic acid (0.08 g, 0.50 mmol) and the mixture was heated under reflux for 19 h. After cooling, the mixture was poured into dichloromethane (10 mL) and washed with water (3×10 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane elution) to give 2-(benzofuran-2-yl)-5,8-dimethoxyquinoline-3-carbaldehyde **64** as a yellow solid (113 mg, 85%), used without further purification, ν_{max}(KBr)/cm^{-1} 1680, 1613, 1577; δ_H (300 MHz; $CDCl_3$) 4.00 (3H, s), 4.08 (3H, s), 6.80 (1H, d, $J=8.5$ Hz), 7.10 (1H, d, $J=8.5$ Hz), 7.32 (1H, ddd, $J=7.7$, 7.4, 0.8 Hz), 7.41 (1H, ddd, $J=8.2$, 7.4, 1.4 Hz), 7.62 (1H, dd, $J=8.2$, 0.8 Hz), 7.68 (1H, d, $J=0.8$ Hz), 7.73 (1H, dd, $J=7.7$, 0.8 Hz), 9.23 (1H, s), 10.88 (1H, s); δ_C (100 MHz; $CDCl_3$) 55.8 (Me), 56.3 (Me), 104.8 (CH), 110.2 (CH), 110.8 (CH), 111.8 (CH), 120.0 (C), 122.1 (CH), 123.5 (CH), 125.9 (CH), 127.1 (C), 128.2 (C), 133.8 (CH), 141.3 (C), 147.7 (C), 149.0 (C), 149.8 (C), 154.0 (C), 155.9 (C), 191.5 (CH).

(b) Sodium borohydride (0.007 g, 0.19 mmol) was added to a solution of 2-benzofuran-2-yl-5,8-dimethoxyquinoline-3-carbaldehyde **64** (0.1 g, 0.34 mmol) in 1,2-dimethoxyethane (20 mL) and the mixture was heated to reflux for 2 h. After cooling water was added followed by HCl (2 M). The mixture was extracted with ether (3×10 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (gradient) elution] to give 2-(benzofuran-2-yl)-5,8-dimethoxyquinoline-3-methanol **65** as a colorless solid (0.1 g, 92%), used without further purification, ν_{max}(KBr)/cm^{-1} 3400, 1598, 1557; δ_H (300 MHz; $CDCl_3$) 3.00 (1H, br), 3.88 (3H, s), 4.04 (3H,

s), 5.11 (2H, s), 6.65 (1H, d, $J=8.5$ Hz), 6.87 (1H, d, $J=8.5$ Hz), 7.26 (1H, ddd, $J=7.4$, 7.1, 1.1 Hz), 7.34 (1H, ddd, $J=8.2$, 7.1, 1.1 Hz), 7.56 (1H, dd, $J=8.2$, 0.8 Hz), 7.61 (1H, d, $J=0.8$ Hz), 7.65 (1H, dd, $J=7.4$, 0.8 Hz), 8.61 (1H, s); δ_C (100 MHz; $CDCl_3$) 55.6 (Me), 56.1 (Me), 63.1 (CH_2), 104.0 (CH), 107.2 (CH), 108.9 (CH), 111.7 (CH), 120.5 (C), 122.8 (CH), 123.2 (CH), 125.4 (CH), 128.4 (C), 131.2 (CH), 131.5 (C), 139.2 (C), 146.5 (C), 148.4 (C), 149.0 (C), 154.7 (C), 155.2 (C). No further characterisation was carried out, and the compound was used directly in the next step.

(c) Cerium(IV) ammonium nitrate (0.4 g, 0.73 mmol) was added to a solution of 2-(benzofuran-2-yl)-5,8-dimethoxyquinoline-3-methanol **65** (0.1 g, 0.31 mmol) in acetonitrile (10 mL) and water (6 mL). The mixture was stirred at room temperature for 1.5 h and then diluted with water and extracted with dichloromethane (3×10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate (9:1) elution) to give the *title compound* **26** as a yellow solid (0.04 g, 39%), mp 197–198 °C (Found; M^+, 305.0689. $C_{18}H_{11}NO_4$ requires 305.0688); λ_{max} (MeOH)/nm 300 (log ε 4.09), 338 (4.04), 390 (3.61); ν_{max}(KBr)/cm^{-1} 3472, 1680, 1654, 1577; δ_H (400 MHz; DMSO-d_6) 5.07 (2H, d, $J=4.9$ Hz), 5.86 (1H, t, $J=5.5$ Hz), 7.15 (1H, d, $J=10.4$ Hz), 7.20 (1H, d, $J=10.4$ Hz), 7.21 (1H, ddd, $J=7.4$, 7.1, 1.1 Hz), 7.34 (1H, ddd, $J=8.2$, 7.1, 1.1 Hz), 7.74–7.76 (2H, m), 7.81 (1H, dd, $J=7.4$, 0.8 Hz), 8.61 (1H, s); δ_C (100 MHz; DMSO-d_6) 60.4 (CH_2), 111.2 (CH), 112.2 (CH), 122.9 (CH), 124.2 (CH), 126.9 (CH), 127.9 (C), 128.2 (C), 133.4 (CH), 138.5 (CH), 139.8 (CH), 140.7 (C), 146.1 (C), 149.1 (C), 153.8 (C), 155.4 (C), 183.2 (C), 185.0 (C); *m/z* (FI) 305 (M^+, 100%).

3.3.14. 3-Acetoxymethyl-2-phenylquinoline-5,8-dione (27). (a) DMAP (a few crystals) was added to a solution of 5,8-dimethoxy-2-phenylquinoline-3-methanol **61** (50 mg, 0.17 mmol) in pyridine (1 mL, 12 mmol) and acetic anhydride (1 mL, 10 mmol). The reaction mixture was stirred at room temperature for 3 days. Water was added and the mixture was extracted with ethyl acetate (3×3 mL). The combined organic phases were washed with $CuSO_4$ (10% solution), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (9:1) elution] to yield *3-acetoxymethyl-5,8-dimethoxy-2-phenylquinoline* **66** as a yellow solid (50 mg, 87%), mp 152–153 °C, (Found: MH^+, 338.1396. $C_{20}H_{19}NO_4+H$ requires 338.1392); ν_{max}(KBr)/cm^{-1} 1738, 1607, 1469; δ_H (300 MHz; $CDCl_3$) 2.11 (3H, s), 4.00 (3H, s), 4.03 (3H, s), 5.24 (2H, s), 6.79 (1H, d, $J=8.5$ Hz), 6.98 (1H, d, $J=8.5$ Hz), 7.45–7.47 (3H, m), 7.62–7.65 (2H, m), 8.67 (1H, d, $J=0.5$ Hz); δ_C (75 MHz; $CDCl_3$) 21.0 (Me), 55.8 (Me), 56.2 (Me), 64.1 (CH_2), 103.9 (CH), 107.7 (CH), 120.4 (C), 127.1 (C), 128.3 (CH), 128.6 (CH), 129.2 (CH), 132.3 (CH), 139.3 (C), 148.6 (C), 149.5 (C), 158.8 (C), 170.6 (C); one C unobserved; *m/z* (EI) 338 (MH^+, 32%), 322 (20), 280 (28), 264 (22), 174 (20), 105 (50), 91 (100).

(b) Cerium(IV) ammonium nitrate (90 mg, 0.18 mmol) was added to a solution of 3-acetoxymethyl-5,8-dimethoxy-2-phenylquinoline **66** (27 mg, 0.08 mmol) in acetonitrile (2.3 mL) and water (1.4 mL). The reaction mixture was stirred for 1.5 h, diluted with water and extracted with dichloromethane (3×3 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (9:1) elution] to give the *title compound* **27** as a yellow solid (24 mg, 98%), mp 141–143 °C, (Found: MH^+, 308.0922. $C_{18}H_{13}NO_4+H$ requires 308.0923); λ_{max} (MeCN)/nm 265 (log ε 4.20), 348 (3.44); ν_{max}(KBr)/cm^{-1} 1730, 1665, 1585, 1432; δ_H (300 MHz; $CDCl_3$) 2.17 (3H, s), 5.31 (2H, s), 7.10 (1H, d, $J=10.4$ Hz), 7.19 (1H, d, $J=10.4$ Hz), 7.49–7.54 (3H, m), 7.57–7.61 (2H, m), 8.55 (1H, s); δ_C (75 MHz; $CDCl_3$) 20.8 (Me), 62.7 (CH_2), 127.5 (C), 128.7 (CH), 129.0 (CH), 130.0 (CH), 134.8 (C), 134.9 (CH), 137.7 (C), 138.0 (CH), 139.3 (CH), 146.2 (C), 163.4 (C), 170.3 (C), 182.9 (C), 184.4 (C); *m/z* (ESI) 330 ($[M+Na]^+$, 100%), 308 (MH^+, 58%), 271 (12), 239 (48), 151 (27).

3.3.15. 3-Acetoxymethyl-2-(thien-2-yl)quinoline-5,8-dione (28). (a) DMAP (a few crystals) was added to a solution of the alcohol (51 mg, 0.17 mmol) in pyridine (1 mL, 12 mmol) and acetic anhydride (1 mL, 10 mmol). The reaction mixture was stirred at room temperature for 3 days. Water was added and the mixture was extracted with ethyl acetate (3×3 mL). The combined organic phases were washed with $CuSO_4$ (10% solution), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (9:1) elution] to yield *3-acetoxymethyl-5,8-dimethoxy-2-(thien-2-yl)quinoline* **67** as a yellow solid (54 mg, 92%), mp 116–117 °C, (Found: MH^+, 344.0962. $C_{18}H_{17}NO_4S+H$ requires 344.0956); ν_{max}(KBr)/cm^{-1} 1723, 1600, 1571; δ_H (300 MHz; $CDCl_3$) 2.18 (3H, s), 3.97 (3H, s), 4.04 (3H, s), 5.46 (2H, s), 6.73 (1H, d, $J=8.5$ Hz), 6.94 (1H, d, $J=8.5$ Hz), 7.14–7.17 (1H, m), 7.49–7.56 (2H, m), 8.67 (1H, d, $J=0.5$ Hz); δ_C (75 MHz; $CDCl_3$) 21.1 (Me), 55.8 (Me), 56.5 (Me), 64.4 (CH_2), 103.9 (CH), 108.4 (CH), 120.0 (C), 125.6 (C), 127.80 (CH), 127.83 (CH), 128.8 (CH), 133.5 (CH), 139.8 (C), 143.7 (C), 148.6 (C), 149.2 (C), 151.4 (C), 170.7 (C); *m/z* (EI) 344 (MH^+, 52%), 328 (32), 286 (100), 270 (90), 256 (35), 84 (63), 60 (100).

(b) Cerium(IV) ammonium nitrate (90 mg, 0.18 mmol) was added to a solution of 3-acetoxymethyl-5,8-dimethoxy-2-(thien-2-yl)quinoline 67 (27 mg, 0.08 mmol) in acetonitrile (2.3 mL) and water (1.4 mL). The reaction mixture was stirred for 1.5 h, diluted with water and extracted with dichloromethane (3×3 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (9:1) elution] to give the *title compound* **28** as a yellow solid (24 mg, 95%), mp 147–148 °C, (Found: M^+, 313.0409. $C_{16}H_{11}NO_4S$ requires 313.0409); λ_{max} (MeCN)/nm 320 (log ε 3.98), 376 (3.59); ν_{max}(KBr)/cm^{-1} 1745, 1724, 1665, 1578, 1418; δ_H (400 MHz; $CDCl_3$) 2.21 (3H, s), 5.46 (2H, s), 7.06 (1H, d, $J=10.4$

Hz), 7.14 (1H, d, $J=10.4$ Hz), 7.20 (1H, dd, $J=3.8$, 5.1 Hz), 7.59 (1H, dd, $J=0.8$, 3.8 Hz), 7.63 (1H, dd, $J=0.8$, 5.1 Hz), 8.52 (1H, s); δ_C (100 MHz; $CDCl_3$) 20.9 (Me), 63.0 (CH_2), 126.6 (C), 128.5 (CH), 129.7 (CH), 131.5 (CH), 132.2 (C), 135.4 (CH), 138.1 (CH), 139.1 (CH), 141.9 (C), 146.1 (C), 155.6 (C), 170.4 (C), 182.5 (C), 184.1 (C); *m/z* (EI) 313 (M^+, 53%), 271 (47), 255 (77), 254 (100).

3.3.16. 3-Acetoxymethyl-2-(benzofuran-2-yl)quinoline-5,8-dione (29). (a) DMAP (a few crystals) was added to a solution of the alcohol (57 mg, 0.17 mmol) in pyridine (1 mL, 12 mmol) and acetic anhydride (1 mL, 10 mmol). The reaction mixture was stirred at room temperature for 3 days. Water was added and the mixture was extracted with ethyl acetate (3×3 mL). The combined organic phases were washed with $CuSO_4$ (10% solution), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (9:1) elution] to yield *3-acetoxymethyl-2-(benzofuran-2-yl)-5,8-dimethoxyquinoline* **68** as a yellow solid (47 mg, 74%), mp 157–158 °C, (Found: MH^+, 378.1342. $C_{22}H_{19}NO_5+H$ requires 378.1341); ν_{max}(KBr)/cm^{-1} 1723, 1593, 1461; δ_H (300 MHz; $CDCl_3$) 2.19 (3H, s), 4.01 (3H, s), 4.09 (3H, s), 5.71 (2H, s), 6.81 (1H, d, $J=8.5$ Hz), 6.99 (1H, d, $J=8.5$ Hz), 7.27–7.30 (2H, m), 7.32–7.42 (1H, m), 7.63 (1H, d, $J=6.5$ Hz), 7.71 (1H, d, $J=6.5$ Hz), 8.71 (1H, s); δ_C (75 MHz; $CDCl_3$) 21.1 (Me), 55.8 (Me), 56.2 (Me), 64.3 (CH_2), 104.5 (CH), 107.8 (CH), 108.8 (CH), 111.9 (CH), 120.4 (C), 121.8 (CH), 123.2 (CH), 125.4 (CH), 126.4 (C), 128.4 (C), 132.9 (CH), 139.7 (C), 147.0 (C), 148.5 (C), 149.3 (C), 154.5 (C), 155.5 (C), 170.8 (C); *m/z* (EI) 377 (M^+, 72%), 362 (100), 304 (42), 91 (58), 84 (72).

(b) Cerium (IV) ammonium nitrate (90 mg, 0.18 mmol) was added to a solution of 3-acetoxymethyl-2-(benzofuran-2-yl)-5,8-dimethoxyquinoline **68** (30 mg, 0.08 mmol) in acetonitrile (2.3 mL) and water (1.4 mL). The reaction mixture was stirred for 1.5 h, diluted with water and extracted with dichloromethane (3×3 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (9:1) elution] to give the *title compound* **29** as a yellow solid (26 mg, 93%), mp 224 °C, (Found: M^+, 347.0802. $C_{20}H_{13}NO_5$ requires 347.0794); λ_{max} (MeCN)/nm 348 (log ε 4.27), 390 (3.99); ν_{max}(KBr)/cm^{-1} 1738, 1665, 1600, 1563; δ_H (400 MHz; $CDCl_3$) 2.23 (3H, s), 5.77 (2H, s), 7.08 (1H, d, $J=10.4$ Hz), 7.17 (1H, d, $J=10.4$ Hz), 7.32–7.34 (1H, m), 7.40–7.44 (1H, m), 7.59 (1H, d, $J=8.0$ Hz), 7.72 (1H, d, $J=8.0$ Hz), 7.89 (1H, s), 8.52 (1H, s); δ_C (100 MHz; $CDCl_3$) 21.0 (Me), 62.9 (CH_2), 111.9 (CH), 112.1 (CH), 122.5 (CH), 123.9 (CH), 126.7 (CH), 127.1 (C), 127.7 (C), 133.4 (C), 134.8 (CH), 138.3 (CH), 139.1 (CH), 146.3 (C), 150.8 (C), 153.7 (C), 156.0 (C), 170.5 (C), 182.6 (C), 183.9 (C); *m/z* (EI) 347 (M^+, 19%), 289 (100), 260 (44), 207 (27).

3.3.17. 6-Methoxy-1-phenylisoquinoline-5,8-dione (30). (a) A stirred mixture of *N*-[2-(3-methoxy-2-benzyloxyphenyl)-2-methoxyethyl]amine **69**[61] (1.6 g, 5.6 mmol) in dichloromethane (30 mL) was treated dropwise with benzoyl chloride (1.0 mL, 8.4 mmol). After 5 h, triethylamine (0.8 mL, 5.6 mmol) was added and stirring was continued for another 1.5 h, additional triethylamine (0.4 mL, 2.8 mmol) was then added. After 1 h, water (20 mL) was added and the mixture was extracted with ether (3×20 mL), washed with HCl (1 M) and saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane elution) to give *N-[2-(3-methoxy-2-benzyloxyphenyl)-2-methoxyethyl]benzamide* **70** as a yellow oil (1.0 g, 43%), (Found: M^+, 391.1801. $C_{24}H_{25}NO_4$ requires 391.1783); ν_{max}(film)/cm^{-1} 3345, 3061, 3032, 2930, 2829, 1709, 1658, 1520; δ_H (300 MHz; $CDCl_3$) 3.15 (3H, s), 3.49 (1H, ddd, $J=4.1$, 7.5, 11.7 Hz), 3.79–3.90 (1H, m), 3.92 (3H, s), 4.70 (1H, dd, $J=4.5$, 7.5 Hz), 5.11 (2H, d, $J=2.4$ Hz), 6.63 (1H, br), 6.92 (1H, dd, $J=1.5$, 7.9 Hz), 6.98 (1H, dd, $J=1.3$, 7.9 Hz), 7.11 (1H, dd, $J=7.9$, 7.9 Hz), 7.26–7.75 (9H, m), 8.09–8.13 (1H, m); δ_C (100 MHz; $CDCl_3$) 45.7 (CH), 56.2 (CH_2), 57.0 (Me), 57.2 (Me), 75.4 (OCH_2), 112.4 (CH), 119.0 (CH), 124.9 (CH), 127.3 (CH), 127.4 (CH), 128.5 (CH), 128.7 (C), 128.8 (CH), 128.9 (CH), 128.94 (C), 128.97 (C), 129.0 (CH), 130.5 (CH), 131.63 (C), 133.9 (C), 137.9 (CH), 146.1 (CH), 153.1 (CH), 167.7 (C); *m/z* (EI) 391 (M^+, 17%), 362 (53), 361 (36), 360 (100), 257 (52), 239 (15).

(b) $POCl_3$ (4 mL) was added slowly to a solution of *N*-[2-(3-methoxy-2-benzyloxyphenyl)-2-methoxyethyl]benzamide **70** (0.9 g, 2.3 mmol) in toluene (15 mL) and the mixture was heated to 90 °C. After 6 h, ice was added and the mixture was stirred for 0.5 h. The mixture was extracted with ether (3×10 mL). The aqueous layer was basified with NaOH solution (2 M) to pH 10 and extracted with chloroform (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo to give a mixture of 5-benzyloxy-6-methoxy-1-phenylisoquinoline and 6-methoxy-1-phenylisoquinolin-5-ol **71**. The mixture was used without further purification. The mixture (0.2 g) was dissolved in MeOH–HCl (6 M; 5 mL) and heated to reflux overnight. After cooling, the mixture was neutralized with NaOH solution (2 M), extracted with chloroform (3×10 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (8:2) elution] to give *6-methoxy-1-phenylisoquinolin-5-ol* **71** as a yellow solid (0.06 g, 11%), δ_H (300 MHz; $CDCl_3$) 3.95 (3H, s), 7.18 (1H, d, $J=9.2$ Hz), 7.39–7.46 (3H, m), 7.57–7.62 (3H, m), 7.86 (1H, d, $J=5.8$ Hz), 8.45 (1H, d, $J=5.8$ Hz).

(c) A solution of 6-methoxy-1-phenylisoquinolin-5-ol **71** (0.06 g, 0.25 mmol) in methanol (30 mL) was added to a stirred solution of Fremy's salt (0.9 g, 3.2 mmol) in dihydrogen phosphate buffer (pH 6, 0.3 M; 30 mL). The solution was stirred at room temperature overnight and diluted with water and filtered. The filtrate was extracted with chloroform (3×15 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography [dichloromethane/ethyl acetate (9:1) elution] to give the *title compound* **30** as a yellow solid (0.02 g, 35%), mp 220–221 °C, (Found:

$M-H^+$, 264.0658. $C_{16}H_{11}NO_3$-H requires 264.0661); λ_{max} (MeCN)/nm 280 (log ε 3.95), 335 (3.60); ν_{max}(KBr)/cm^{-1} 3432, 3062, 1694, 1650, 1614, 1546; δ_H (300 MHz; $CDCl_3$) 3.91 (3H, s), 6.12 (1H, d, $J=4.9$ Hz), 7.46 (5H, s), 7.97 (1H, d, $J=4.9$ Hz), 9.03 (1H, d, $J=4.9$ Hz); δ_C (100 MHz; $CDCl_3$) 56.5 (Me), 111.8 (CH), 118.0 (CH), 122.9 (C), 128.0 (CH), 128.7 (CH), 128.8 (CH), 138.4 (C), 140.1 (C), 153.3 (CH), 159.0 (C), 160.5 (C), 179.7 (C), 184.1 (C); *m/z* (EI) 264 ($M-H^+$, 56%), 236 (64), 222 (47), 166 (24), 139 (34), 126 (38), 77 (45), 69 (100).

3.4. Electrochemical measurements

Tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) (Aldrich, 99%) was dried under vacuum at 70 °C. Ferrocene (Aldrich, 97%) was resublimed. DMF (Aldrich, 99.8%) was used as solvent.

For each of the quinolinequinones studied, cyclic voltammograms were recorded over a range of potential sweep rates from 50 to 500 mV s^{-1}, using a BAS 100B Electrochemical Analyzer. A three-electrode cell was employed, with a platinum counter electrode and a Ag/AgCl in 3 M NaCl reference electrode (BAS). This reference was separated from the main compartment of the cell by a salt bridge containing DMF solvent and Bu_4NBF_4 supporting electrolyte. The reference, plus bridge, was calibrated by voltammetry relative to $E_{1/2}$ for ferrocene ($Fc^{+/0}$) in DMF/Bu_4NBF_4, to allow the measured $E_{1/2}$ values for the quinolinequinones to be quoted relative to $Fc^{+/0}$. The working electrode was a 3 mm diameter platinum disc (BAS), pretreated by polishing with 1 μm diamond paste, followed by voltammetric cycling in 0.1 M H_2SO_4 until the characteristic voltammogram for polycrystalline platinum was achieved, before finally rinsing in distilled water and drying. Solutions for voltammetry were all 1 mM in quinolinequinone and 0.1 M in Bu_4NBF_4 in DMF. Oxygen was removed from the solutions by purging with nitrogen. All measurements were performed at room temperature.

3.5. Biology

3.5.1. Cell culture. BE-WT and BE-NQ cells were a gift from David Ross (University of Colorado Health Sciences Center, Denver, CO). Cell culture components were obtained from Invitrogen (Carlsbad, CA) unless otherwise noted. Cells were grown in minimum essential medium (MEM) with Earle's salts, non-essential amino acids, L-glutamine, penicillin/streptomycin and supplemented with 10% fetal bovine serum (HyClone Laboratories, Logan, UT). The cells were incubated at 37 °C under a humidified atmosphere containing 5% CO_2.

3.5.2. Spectrophotometric analysis of quinolinequinone reduction. Quinolinequinone reduction by recombinant human NQO1 (gift from David Ross, University of Colorado Health Sciences Center, Denver, CO; specific activity using 2,6-dichlorophenolindophenol as electron acceptor: 314 ±24 μmol min^{-1} mg^{-1} NQO1) was quantified using a modification of an assay that uses cytochrome *c* as the terminal electron acceptor.[21] Reaction mixtures contained 1 mM NADH (Sigma), 25 μM quinolinequinone, 70 μM cytochrome *c* (Sigma) and 0.1–3.0 μg/mL hNQO1 in 25 mM Tris–HCl (pH 7.4) with 0.07% BSA and 0.1% Tween-20. Reactions were run at least in triplicate at 22 °C in a Beckman DU 7500 spectrophotometer at 550 nm (molar absorptivity 21.1 mM^{-1} cm^{-1} for cytochrome *c*). Initial reduction rates (μmol cytochrome *c* reduced/min/mg NQO1) were calculated from the linear portion (0–30 s) of the reaction curves.

3.5.3. Cytotoxicity assay. Cytotoxicity was determined using a MTT colorimetric assay. Cells were plated in 96-well plates at a density of $1–2\times10^4$ cells/mL and allowed to attach overnight (16 h). Quinolinequinone solutions were applied in medium for 2 h. Quinolinequinone solutions were removed and replaced with medium alone, and the 96-well plates were incubated for 5–7 days. MTT (Sigma) was added to each well (50 μg), and the cells were incubated for another 4 h. Medium/MTT solutions were removed carefully by aspiration, the MTT formazan crystals were dissolved in 100 μL DMSO and absorbance was determined on a plate reader at 550 nm. Each compound was run in triplicate, and IC_{50} values (concentration at which cell survival equals 50% of control) were determined from plots of percent of control versus concentration.[74]

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