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Antitumour indolequinones: synthesis and activity against human pancreatic cancer cells†

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An important determinant of the growth inhibitory activity of indolequinones against pancreatic cancer cells is substitution on the 2-position with 2-unsubstituted derivatives being markedly more potent. A series of indolequinones bearing a range of substituents on nitrogen and at the indolylcarbinyl position was prepared by copper(II)-mediated reaction of bromoquinones and enamines, followed by functional group interconversions. The compounds were then assayed for their ability to inhibit the growth of pancreatic cancer cells. The pK_a of the leaving group at the 3-position was shown to influence growth inhibitory activity that is consistent with the proposed mechanism of action of reduction, loss of leaving group and formation of a reactive iminium species. Substitutions on the indole nitrogen were well tolerated with little influence on growth inhibitory activity while substitutions at the 5- and 6-positions larger than methoxy led to decreased activity. The studies presented define the range of substitutions of 2-unsubstituted indolequinones required for optimal growth inhibitory activity.

Introduction

Compounds containing the indolequinone core structure often possess powerful biological activity. Examples include the well known natural product mitomycin C (MMC) used clinically for the treatment of solid tumours,[1] the synthetic MMC analogue EO9 (apaziquone, EOquin) currently being trialled as a treatment for bladder cancer,[2,3] and the antitumour zyzzyanone B and related pyrroloindolequinone natural products (Fig. 1).[4] Hence indolequinones have attracted considerable interest in the anticancer arena not only as cytotoxins, but also as bioreductively activated prodrugs.[5–8] In continuation of our studies on the synthesis and biology of indolequinones, we investigated a number of relatively simple tri- and tetra-substituted derivatives initially evaluating their cytotoxicity and also their metabolism by quinone reductase enzymes.[9–16]

In terms of cytotoxicity towards cancer cell lines, it became apparent that the 2-unsubstituted indolequinones were the most potent, and therefore we initiated a more detailed study on the 5- and 6-methoxy derivatives **1–4** (Fig. 1).[17,18] All four compounds exhibited potent cytotoxicity against human pancreatic cancer cell lines (PANC-1, Mia PaCa-2 and BxPC-3) and induced caspase-dependent apoptosis. The mechanism of action was shown to involve quinone reduction, followed by loss of the phenoxide leaving group to generate an electrophilic iminium ion leading to irreversible inhibition of thioredoxin reductase (Scheme 1), and represents a potential novel

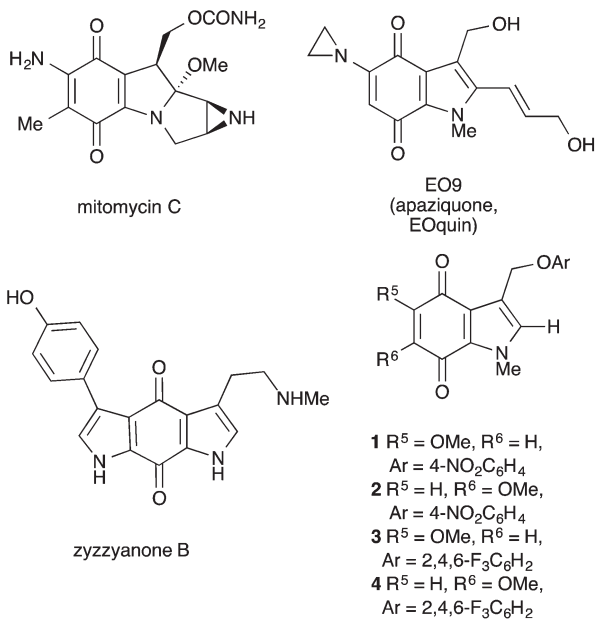

Fig. 1 Indolequinones with antitumour properties.

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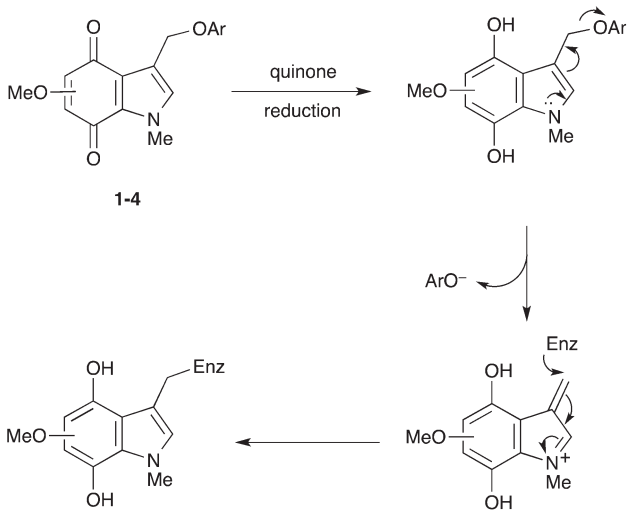
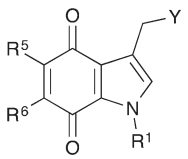


1-4

Scheme 1 Reduction of indolequinones leading to loss of phenoxide and formation of an electrophilic iminium intermediate capable of inactivating an enzyme.



1-25

Fig. 2 Range of 2-unsubstituted indolequinones studied. R^1, R^5, R^6 and Y defined in Table 1.

molecular target in pancreatic cancer.[17] Indolequinone **3** was subsequently studied in more detail and its effect on MAPK signalling pathways investigated.[18] Inhibition of thioredoxin reductase leads to oxidation of thioredoxin, dissociation of free ASK1, phosphorylation of JNK and p38 and subsequent apoptosis.[18]

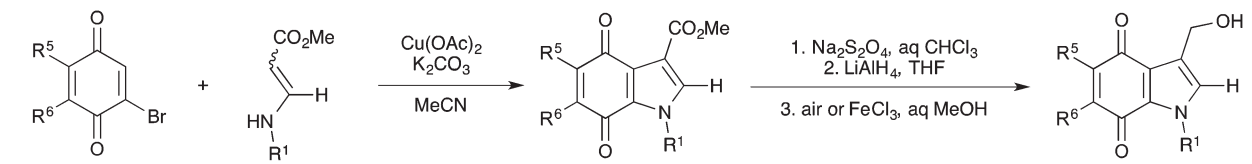
The incidence of pancreatic cancer is increasing and is the fourth leading cause of cancer deaths in Europe and the US. Currently the most viable treatment options are surgery and/or radiation with the value of chemotherapy being described as insignificant. Existing treatments are suboptimal, and the 5 year survival rate is amongst the most dismal of any tumour type at around 5%.[19] Therefore novel therapeutic agents are urgently needed. In view of the biological activity of the indolequinones **1–4**, we now report a study of a much wider range of 2-unsubstituted indolequinones **1–25** (Fig. 2) with details of their synthesis, and structure activity relationships in terms of their cytotoxicity against Mia-PaCa human pancreatic tumour cells.

Results and discussion

Chemistry

The key intermediates in the synthesis of indolequinones **1–25** are the corresponding 3-hydroxymethyl indolequinones **29**. Previously, such indolequinones have been synthesized by us and others *via* the corresponding indole-3-carboxaldehyde or indole-3-carboxylate ester, with the quinone functionality introduced by the classical sequence of nitration, reduction and oxidation of the resulting aniline.[20,21] While these routes are effective, they are unsuited to the synthesis of large compound collections due to their laborious nature and poor functional group tolerance. In order to address this problem, we have recently developed a new route to indolequinones based on the regioselective reaction of bromoquinones with enamines.[22,23] Thus, reaction of bromo-5-methoxy-1,4-benzoquinone **26a** with methyl 3-methylaminoacrylate **27a** gave the indolequinone ester **28a** in 40% yield (Scheme 2). Use of the isomeric 2-bromo-6-methoxy-1,4-benzoquinone **26b** with the same enamine gave the corresponding 6-methoxyindolequinone **28b** in 64% yield.

The reduction of the ester functionality of the resulting indolequinones was found to be problematic; the best results were obtained by prior reduction of the quinone with sodium dithionite in a two phase system, followed by treatment with lithium aluminium hydride and subsequent re-oxidation of the hydroquinone with either air or iron(III)



26a R^5 = OMe, R^6 = H
26b R^5 = H, R^6 = OMe
26c R^5 = H, R^6 = OEt
26d R^5 = OMe, R^6 = Me
26e R^5R^6 = benzo

27a R^1 = Me
27b R^1 = $(CH_2)_2$OPMP
27c R^1 = $(CH_2)_3$OPMP
27d R^1 = $(CH_2)_2NMe_2$
27e R^1 = $(CH_2)_2$Morph

R^1NH_2

CO_2Me

28

28/29a R^1 = Me, R^5 = OMe, R^6 = H
28/29b R^1 = Me, R^5 = H, R^6 = OMe
28/29c R^1 = $(CH_2)_2$OPMP, R^5 = H, R^6 = OMe
28/29d R^1 = $(CH_2)_3$OPMP, R^5 = H, R^6 = OMe
28/29e R^1 = $(CH_2)_2NMe_2$, R^5 = H, R^6 = OMe
28/29f R^1 = $(CH_2)_2$Morph, R^5 = H, R^6 = OMe
28/29g R^1 = $(CH_2)_2$Morph, R^5 = H, R^6 = OEt
28/29h R^1 = $(CH_2)_2$Morph, R^5 = OMe, R^6 = Me
28/29i R^1 = Me, R^5R^6 = benzo

29

Scheme 2 Synthesis of 3-hydroxymethylindolequinones [PMP = 4-methoxyphenyl, Morph = 4-morpholinyl].

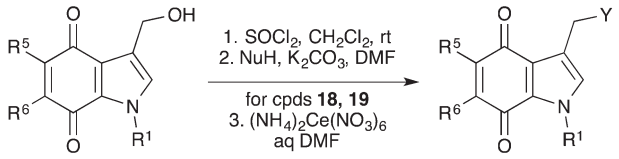
chloride. However, the yield for this sequence remained modest; the 3-hydroxymethyl indolequinones **29a** and **29b** were synthesized in 21% and 60% yield respectively. Most of the remaining material was either over-reduced to the corresponding 3-methylindolequinone or recovered as unreacted methyl ester.

Having developed a convergent route to the key 3-hydroxymethyl indolequinones **29**, a range of compounds was synthesized, particular attention being paid to the substituent on the indole 1-position, where it was hoped that a water-solubilising functionality such as an alcohol or a tertiary amine could be incorporated. Whilst tertiary amines were tolerated by the synthetic route, the hydroxyethyl and hydroxypropyl groups had to be protected as their 4-methoxyphenyl ethers. To effect variation at the 1-position, the requisite enamines **27b–27e** were synthesized by conjugate addition of the corresponding primary amines to methyl propiolate. Additionally, in order to explore variation of the 5- and 6-positions, the bromoquinones **26c–26e** were subjected to our reaction conditions; these were either commercially available or could be easily synthesized from phenolic precursors.

With a range of 3-hydroxymethyl indolequinones **29** in hand, it only remained to convert the hydroxyl group into a better leaving group, since from previous work it is known that this is an essential requirement for biological activity (Scheme 1). Reaction of the 3-hydroxymethyl compounds **29** with thionyl chloride gave the corresponding chloromethyl derivative, which underwent reaction with the appropriate nucleophile in the presence of potassium carbonate to give the products **1–17** and **20–25**. In cases where a PMP-protected alcohol was present, subsequent deprotection under oxidative conditions using cerium(IV) ammonium nitrate in aqueous DMF gave the corresponding alcohols **18** and **19**.

Variations in the 1-position, the leaving group (Y, Scheme 2) and the 5- and 6-positions were studied in turn. Firstly, the leaving group was investigated; in addition to the previously studied 4-nitro- and 2,4,6-trifluoro-phenoxy derivatives **1–4**, we prepared a range of indolequinones **5–9** bearing alternative phenolic leaving groups, including phenoxy itself, 4-methanesulfonylphenoxy, 4-carboxyphenoxy and 4-carboxy-2-fluorophenoxy. We next investigated alternatives to phenolic leaving groups and prepared a series of indolequinones **10–16** containing heterocyclic rings, chosen so that the leaving heterocycles have a pK_a value in the correct range (see below). All these examples were carried out in the 6-methoxyindolequinone series, with some replicated in the 5-methoxyindolequinone series, and the 1-substituent was maintained as a methyl group throughout.

Next, the indolequinones **17–21** were prepared in order to investigate the possibility of improving the water solubility *via* the incorporation of 2-hydroxyethyl, 3-hydroxypropyl, 2-dimethylaminoethyl, and 2-(4-morpholinyl)ethyl groups in the 1-position. Again, these compounds exclusively bear a 6-methoxy group, and used the 2,4,6-trifluorophenoxy leaving group. Finally, some minor variations at the 5- and 6-positions were studied with compounds **22–25** (Scheme 3).



29 **1-25**

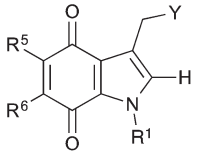
Scheme 3 Functionalization of 3-hydroxymethylindolequinones. R^1, R^5, R^6 and Y defined in Table 1.

Biology

The indolequinones were assayed for their effect on the growth of human pancreatic cancer cells using the MTT assay in the Mia Paca-2 cell line. Cell growth was measured after 4 and 72 hour treatment using previously described methods,[17] and the results are shown in Table 1. For comparison data for gemcitabine, one of the current standard chemotherapeutic treatments for pancreatic cancer, are also presented. The data, which include the previously described compounds **1–4** for completeness, enable a number of conclusions about the structural requirements for cytotoxicity to be made. Firstly, as previously established for indolequinones **1–4**, the location of the methoxy group at C-5 or C-6 makes little difference to the cytotoxicity towards Mia Paca-2 cells (entries 1 *vs.* 2, 3 *vs.* 4, 6 *vs.* 7), although the pair of *N*-hydroxysuccinimide derivatives (entries 11 and 12) appear to be an exception. Secondly in terms of the substituent Y, the ability of the group to act as a leaving group upon reductive activation of the quinone is clearly an important factor. 4-Nitrophenol and 2,4,6-trifluorophenol have similar pK_a values (7.2 and 7.5 respectively) and in the 5- and 6-methoxy indolequinones, compounds containing these leaving groups are generally among the most cytotoxic (entries 1–4, 18–23). A poorer leaving group such as phenol itself (pK_a 9.9) results in a less cytotoxic compound (entry 5) whereas use of a 4-methanesulfonylphenol leaving group (pK_a 7.5) restores biological activity (entries 6 and 7). The indolequinones **8** and **9**, incorporating phenolic substituents (pK_a 8.3 and 7.1 respectively) designed to increase solubility, are somewhat less active. As alternatives to phenolic leaving groups, the indolequinones **10–16** containing heterocyclic rings were next studied. Incorporation of succinimide (pK_a 9.6), 1,2,3-triazole (pK_a 8.7), and tetrazole (pK_a 4.7) as potential leaving groups resulted in non-toxic compounds (entries 10, 13–16), whereas use of *N*-hydroxysuccinimide (pK_a 7.8) in the 6-methoxyindolequinone series (entry 12) resulted in a highly cytotoxic compound. Hence, although the pK_a of the leaving group is clearly an important factor, there is not a simple linear relationship between pK_a and potency of the indolequinone.

The substituent on the indolequinone nitrogen appears to have little effect on biological activity, and a range of groups containing substituents likely to increase aqueous solubility are well tolerated. Thus the indolequinones containing *N*-hydroxyalkyl or -aminoalkyl groups **18–21** are all highly cytotoxic. Less well tolerated are changes to the indolequinone 5- and 6-positions. Replacement of methoxy by ethoxy or

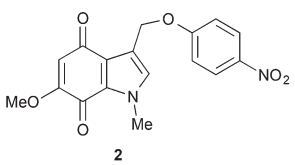
Table 1 Cytotoxicity of 2-unsubstituted indolequinones towards Mia PaCa-2 tumour cells after 4 and 72 hours exposure



Entry	Cpd	R^1 [a]	Y [b]	R^5	R^6	IC_{50} [c] 4 h/nM	IC_{50} [c] 72 h/nM
1	**1**	Me	O(4-$NO_2C_6H_4$)	OMe	H	39 ± 13	24 ± 6
2	**2**	Me	O(4-$NO_2C_6H_4$)	H	OMe	32 ± 9	18 ± 5
3	**3**	Me	OAr	OMe	H	34 ± 9	18 ± 6
4	**4**	Me	OAr	H	OMe	26 ± 7	19 ± 4
5	**5**	Me	OPh	H	OMe	276 ± 26	122 ± 18
6	**6**	Me	O(4-$MeSO_2C_6H_4$)	OMe	H	31 ± 6	24 ± 4
7	**7**	Me	O(4-$MeSO_2C_6H_4$)	H	OMe	29 ± 8	31 ± 6
8	**8**	Me	O(4-$HO_2CC_6H_4$)	H	OMe	110 ± 15	50 ± 10
9	**9**	Me	O(2-F-4-$HO_2CC_6H_4$)	H	OMe	198 ± 16	56 ± 5
10	**10**	Me	*N*-Succinimidyl	H	OMe	NT	NT
11	**11**	Me	O-*N*-Succinimidyl	OMe	H	178 ± 30	127 ± 18
12	**12**	Me	O-*N*-Succinimidyl	H	OMe	42 ± 13	26 ± 4
13	**13**	Me	1,2,3-Triazol-1-yl	H	OMe	NT	NT
14	**14**	Me	1,2,3-Triazol-2-yl	H	OMe	NT	NT
15	**15**	Me	1-Tetrazolyl	H	OMe	NT	NT
16	**16**	Me	2-Tetrazolyl	H	OMe	NT	NT
17	**17**	$(CH_2)_2$OPMP	OAr	H	OMe	68 ± 8	27 ± 3
18	**18**	$(CH_2)_2$OH	OAr	H	OMe	64 ± 9	34 ± 5
19	**19**	$(CH_2)_3$OH	OAr	H	OMe	64 ± 9	34 ± 7
20	**20**	$(CH_2)_2NMe_2$	OAr	H	OMe	51 ± 9	35 ± 7
21	**21**	$(CH_2)_2$Morpholinyl	OAr	H	OMe	35 ± 3	17 ± 2
22	**22**	$(CH_2)_2$Morpholinyl	OAr	H	OEt	242 ± 36	137 ± 22
23	**23**	$(CH_2)_2$Morpholinyl	OAr	OMe	Me	120 ± 32	65 ± 15
24	**24**	Me	O-*N*-Succinimidyl	Benzo		NT	NT
25	**25**	Me	O(4-$MeSO_2C_6H_4$)	Benzo		NT	NT
26	Gemcitabine		—	—		359 ± 45	25 ± 4

Compounds **1–4** also described in ref. 17. [a] PMP = 4-methoxyphenyl, Morph = 4-morpholinyl. [b] Ar = 2,4,6-trifluorophenyl unless otherwise stated. [c] NT = non toxic (IC_{50} > 5 μM).

Table 2 Cytotoxicity of indolequinones **2** and **3** towards tumour cells after 4 and 72 hours exposure



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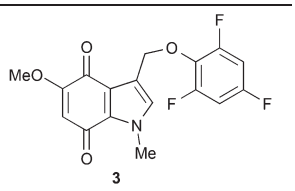

3

		Compound **2** IC_{50} (nM)		Compound **3** IC_{50} (nM)	
Entry	Cell line	4 h	72 h	4 h	72 h
1	Panc1	49 ± 4	24 ± 3		
2	BxPC-3	126 ± 14	58 ± 8	100 ± 11	43 ± 10
3	Jurkat	328 ± 14			
4	KG1A	804 ± 6			
5	MDA468	244 ± 26			
6	SKMEL-5			96 ± 4	46 ± 5

inclusion of an additional methyl group results in lower toxicity (entries 22 and 23), while fusion of an additional benzene ring results in non-toxic quinones (entries 24 and 25).

The more potent compounds (Table 1, entries 1–4, 6, 7, 17–21) are all more potent than gemcitabine at the 4 hour treatment point, and equipotent at the 72 hour point suggesting this series of indolequinones is worthy of further investigation. Therefore two of the more potent compounds, **2** and **3**, were tested against a small range of other tumour cell lines (Table 2). High potency was retained against other human pancreatic cell lines (entries 1 and 2), and also observed, for compound **3**, against a melanoma line (entry 6). On the other hand, compound **2** was less potent against leukaemia and breast lines (entries 3–5). These data are similar to previously published results obtained with indolequinones in the National Cancer Institute's 60-cell line screen which showed that breast cancer and leukaemia cell lines were relatively resistant to these agents.[17]

Conclusions

The reaction of bromoquinones with enamines provides a convenient route to indolequinone-3-carboxylates, converted into novel indolequinones containing a range of substituents on the indolic nitrogen and leaving groups at the 3-indolylmethyl

position. Subsequently they were tested for their ability to inhibit the growth of human pancreatic cancer cells. A number of potent inhibitors have been identified, and the key structural features for biological activity delineated. More detailed biological evaluation of key compounds is in progress.

Experimental section

General experimental details

Commercially available reagents were used throughout without purification unless otherwise stated. All anhydrous solvents were used as supplied, except tetrahydrofuran and dichloromethane that were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless otherwise stated, and all glassware was flame-dried before use. Light petroleum refers to the fraction with bp 40–60 °C. Ether refers to diethyl ether.

Analytical thin layer chromatography was carried out on aluminium backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm and/or by chemical staining. Flash chromatography was carried out using silica gel, with the eluent specified.

Infrared spectra were recorded using an FT-IR spectrometer over the range 4000–600 cm^{-1}. NMR spectra were recorded at 400 or 500 MHz (^1H frequency, 100 or 125 MHz ^{13}C frequency). Chemical shifts are quoted in parts per million (ppm), and are referenced to residual H in the deuterated solvent as the internal standard. Coupling constants, *J*, are quoted in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from the DEPT spectra all others are C. Mass spectra were recorded on a time-of-flight mass spectrometer using electrospray ionization (ESI), or an EI magnetic sector instrument.

General procedure 1: copper(II) acetate mediated synthesis of indolequinone-3-esters

A solution of enamine (1.0–4.0 mol equiv.) in acetonitrile (5–10 mL $mmol^{-1}$) was added to a mixture of bromoquinone (1.0 mol equiv.), copper(II) acetate monohydrate (2.0 mol equiv.) and potassium carbonate (3.0 mol equiv.). The resulting mixture was stirred at reflux for the indicated time, cooled to room temperature and diluted with dichloromethane (20 mL $mmol^{-1}$), filtered through Celite and concentrated *in vacuo*. Column chromatography of the residue gave the indolequinone.

General procedure 2: synthesis of indolequinone-3-carbinols

A solution of sodium dithionite (5 mol equiv.) in water (10 mL $mmol^{-1}$) was added to a solution of the indolequinone-3-ester in chloroform (10 mL $mmol^{-1}$), and the resulting mixture was stirred at room temperature under argon for 2 h, then extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered and concentrated, and dried under vacuum for ~1 h. The residue was dissolved in THF (10–20 mL $mmol^{-1}$), and lithium aluminium hydride (5 mol equiv.) was added portionwise. The resulting mixture was stirred at room temperature for 2 h and quenched by sequential slow addition of ethyl acetate (~5 mL $mmol^{-1}$), water (~1 mL $mmol^{-1}$), aqueous sodium hydroxide solution (1 M; ~1 mL $mmol^{-1}$) and silica gel (~100 mg $mmol^{-1}$). The quenched mixture was stirred under air for 30 min, filtered and concentrated. Column chromatography gave the alcohol product.

In cases where the aerobic oxidation of the hydroquinone was slow, the quenched mixture was immediately filtered and concentrated, and dissolved in methanol (10 mL $mmol^{-1}$). A solution of iron(III) chloride hexahydrate (5 mol equiv.) in water (10 mL $mmol^{-1}$) was added, and the mixture was stirred at room temperature for 1 h, concentrated to half its volume and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue gave the product.

General procedure 3: synthesis of 3-indolequinonylmethyl ethers

Thionyl chloride (10 mol equiv.) was added to a stirred solution of the alcohol in dichloromethane (10 mL $mmol^{-1}$), and the resulting mixture was stirred at room temperature for 3–7 h, concentrated and azeotroped with two further portions of dichloromethane. The residue was dissolved in DMF (10 mL $mmol^{-1}$) and the appropriate nucleophile (5 mol equiv.) was added. When this had dissolved, potassium carbonate (5 mol equiv.) was added, and the mixture was stirred for 14–18 h, diluted with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue gave the product.

2-Bromo-5-methoxy-1,4-benzoquinone 26a. Prepared as previously described.[23]

2-Bromo-6-methoxy-1,4-benzoquinone 26b. Prepared as previously described.[23]

2,4-Dibromo-6-ethoxyphenol. A solution of bromine (6.56 g, 41 mmol) in dichloromethane (20 mL) was added over 40 min to a stirred solution of 2-ethoxyphenol (2.76 g, 20 mmol) in dichloromethane (80 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, washed with saturated aqueous sodium thiosulfate solution (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated to give the *title compound* as a colourless solid (5.74 g, 97%), mp 89–91 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3538, 2987, 1494, 1565; δ_H (400 MHz; $CDCl_3$) 7.20 (1H, s, ArH), 7.07 (1H, s, ArH), 5.65 (1H, br s, OH), 4.11 (2H, q, *J* 7.0, CH_2), 1.48 (3H, t, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$) 145.7, 124.0, 119.1 (CH), 116.1 (CH), 115.3, 113.7, 65.1 (CH_2), 14.7 (Me).

2-Bromo-6-ethoxy-1,4-benzoquinone 26c. A solution of chromium(VI) oxide (2.107 g, 21.1 mmol) in water (10 mL) was added to a stirred solution of 2,4-dibromo-6-ethoxyphenol (5.67 g, 19.2 mmol) in acetic acid (20 mL), acetonitrile (10 mL) and water (5 mL), and the resulting mixture was stirred at 60 °C for 1.5 h, cooled to room temperature, diluted with water (150 mL) and extracted with chloroform (4 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and

concentrated. Column chromatography eluting with dichloromethane and light petroleum (1 : 1 then 2 : 1) gave the *title compound* as an orange solid (2.07 g, 47%), mp 82–84 °C; (Found: M + Na^+, 252.9487. $C_8H_7{}^{79}BrO_3Na$ requires 252.9471); ν_{max} ($CHCl_3$)/cm^{-1} 2992, 1680, 1656, 1586, 1182; δ_H (400 MHz; $CDCl_3$) 7.20 (1H, s, CH), 5.95 (1H, s, CH), 4.05 (2H, q, *J* 7.0, CH_2), 1.51 (3H, t, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$) 184.9, 174.6, 157.5, 138.4 (CH), 134.3, 107.9 (CH), 65.9 (CH_2), 13.8 (Me); *m*/*z* (ESI) 253 (M + Na^+, 88%), 413 (100).

4,6-Dibromo-3-methoxy-2-methylphenol. A solution of bromine (2.797 g, 17.48 mmol) in dichloromethane (8 mL) was added over 15 min to a stirred solution of 2-methyl-3-methoxyphenol (1.206 g, 8.74 mmol) in dichloromethane (13 mL). The mixture was stirred at room temperature for 1.5 h, washed with saturated sodium thiosulfate solution (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give the *title compound* as a colourless solid (2.417 g, 93%), mp 64–66 °C; (Found: M − H^-, 292.8821. $C_8H_7O_2{}^{79}Br_2Na$ requires 292.8818); ν_{max} ($CHCl_3$)/cm^{-1} 3519, 3007, 2940, 1601, 1459, 1439; δ_H (400 MHz; $CDCl_3$) 7.54 (1H, s, CH), 5.56 (1H, br s, OH), 3.81 (3H, s, Me), 2.30 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 155.8, 150.8, 131.3 (CH), 121.0, 107.9, 105.3, 60.5 (Me), 10.6 (Me); *m*/*z* (ESI) 293/295/297 (M − H^-, 52/100/60%).

5-Bromo-2-methoxy-3-methyl-1,4-benzoquinone 26d. A solution of chromium(VI) oxide (0.892 g, 8.92 mmol) in water (4 mL) was added to a stirred solution of 4,6-dibromo-3-methoxy-2-methylphenol (2.40 g, 8.11 mmol) in acetic acid (12 mL), acetonitrile (12 mL) and water (8 mL), and the resulting mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the mixture was diluted with water (100 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with dichloromethane and light petroleum (1 : 1) gave the *title compound* as an orange solid (1.12 g, 60%), mp 52–54 °C; (Found: M + Na^+, 252.9443. $C_8H_7O_3{}^{79}BrNa$ requires 252.9476); ν_{max} ($CHCl_3$)/cm^{-1} 2951, 1667, 1590, 1323; δ_H (400 MHz; $CDCl_3$) 7.14 (1H, s CH), 4.08 (3H, s, Me), 2.05 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 180.9, 180.3, 155.6, 137.6, 135.9 (CH), 128.5, 61.1 (Me), 9.8 (Me); *m*/*z* (ESI) 253/255 (M + Na^+, 33/34%), 413 (100).

Methyl 3-(methylamino)acrylate 27a. Prepared as previously described.[23]

***tert*-Butyl (2-bromoethyl)carbamate.**[24] Triethylamine (20 mL) was added as a single portion to a stirred suspension of 2-bromoethylamine hydrobromide (8.20 g, 40 mmol) and di-*tert*-butyl dicarbonate (8.72 g, 40 mmol) in dichloromethane (200 mL), and the mixture was stirred at room temperature for 15 h, washed with water (100 mL), dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ether and light petroleum (1 : 4) gave the *title compound* as a colourless oil (6.92 g, 77%); δ_H (400 MHz; $CDCl_3$) 5.00 (1H, br s, NH), 3.55 (2H, dt, *J* 5.6, 5.4, CH_2N), 3.47 (2H, t, *J* 5.6, CH_2), 1.47 (9H, s, *t*Bu); δ_C (75 MHz; $CDCl_3$) 156.2, 79.9, 42.4 (CH_2), 32.9 (CH_2), 28.4 (Me). NMR data matches literature values.[24]

2-(4-Methoxyphenoxy)ethylamine. Potassium carbonate (8.223 g, 59.6 mmol) was added to a stirred solution of *tert*-butyl (2-bromoethyl)carbamate (4.449 g, 19.9 mmol) and 4-methoxyphenol (7.389 g, 59.6 mmol) in DMF (50 mL), and the resulting mixture was stirred at 50 °C for 15 h. Water (350 mL) was added, and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1 : 7) gave an inseparable mixture of 4-methoxyphenol and the 4-methoxyphenyl ether. This mixture was dissolved in dichloromethane (100 mL) and trifluoroacetic acid (20 mL) was added. The mixture was stirred at room temperature for 4 h and extracted with water (3 × 150 mL). The combined aqueous phases were basified to pH 14 with sodium hydroxide pellets at 0 °C and extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the *title compound* as a colourless solid (2.200 g, 81%), mp 37–39 °C; (Found: M + H^+, 168.1033. $C_9H_{14}NO_2$ requires 168.1019); ν_{max} ($CHCl_3$)/cm^{-1} 3443, 3011, 2653, 1686, 1602, 1509; δ_H (400 MHz; $CDCl_3$) 6.87 (2H, d, *J* 9.2, ArH), 6.84 (2H, d, *J* 9.2, ArH), 3.95 (2H, t, *J* 5.2, CH_2), 3.78 (3H, s, Me), 3.07 (2H, t, *J* 5.2, CH_2), 1.44 (2H, br s, NH_2); δ_C (75 MHz; $CDCl_3$) 153.9, 153.1, 115.5 (CH), 114.7 (CH), 70.9 (CH_2), 55.7 (Me), 41.7 (CH_2); *m*/*z* (ESI) 168 (M + H^+, 9%), 218 (100).

Methyl 3-[2-(4-methoxyphenoxy)ethylamino]acrylate 27b. 2-(4-Methoxyphenoxy)ethylamine (2.200 g, 13.2 mmol) was added over 5 min to a stirred solution of methyl propiolate (1.107 g, 13.2 mmol) in dichloromethane (26 mL), and the mixture was stirred at room temperature for 20 h and concentrated to give the *title compound* as an off-white solid (3.19 g, 96%), 2 : 1 *cis* : *trans*; mp 85–87 °C; (Found: M + Na^+, 274.1022. $C_{13}H_{17}NO_4Na$ requires 274.1050); ν_{max} ($CHCl_3$)/cm^{-1} 3447, 3010, 2951, 1685, 1621, 1508; δ_H (400 MHz; $CDCl_3$) major isomer: 8.03 (1H, br s, NH), 6.86 (4H, s, ArH), 6.73 (1H, dd, *J* 13.2, 8.0, CH), 4.55 (1H, d, *J* 8.0, CH), 4.00 (2H, t, *J* 5.5, CH_2O), 3.79 (3H, s, Me), 3.67 (3H, s, Me), 3.54 (2H, q, *J* 5.5, CH_2); minor isomer: 7.58 (1H, dd, *J* 13.0, 8.2, CH), 6.86 (4H, s, ArH), 4.88 (1H, br s, NH), 4.83 (1H, d, *J* 13.0, CH), 4.08 (2H, t, *J* 5.2, CH_2), 3.79 (3H, s, Me), 3.70 (3H, s, Me), 3.44 (2H, q, *J* 5.2, CH_2); δ_C (75 MHz; $CDCl_3$) mixture: 171.1, 169.8, 154.3, 154.2, 152.6, 152.4 (CH), 152.3, 149.1 (CH), 116.0 (CH), 115.6 (CH), 114.8 (CH), 114.6 (CH), 86.3 (CH), 82.4 (CH), 68.7 (CH_2), 66.4 (CH_2), 55.7 (Me), 50.6 (Me), 50.2 (Me), 47.9 (Me); *m*/*z* (ESI) 274 (M + Na^+, 100%).

***tert*-Butyl (3-bromopropyl)carbamate.**[25] Triethylamine (15 mL) was added over 1 min to a stirred suspension of 3-bromopropylamine hydrobromide (6.57 g, 30 mmol) and di-*tert*-butyl dicarbonate (6.54 g, 30 mmol) in dichloromethane (150 mL). The mixture was stirred at room temperature for 17 h, washed with water (100 mL), dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ether and light petroleum (1 : 4) gave the *title compound* as a colourless oil (6.205 g, 87%); ν_{max} ($CHCl_3$)/cm^{-1} 3449, 3251, 1703, 1490; δ_H (400 MHz; $CDCl_3$) 4.72 (1H, br s, NH), 3.45 (2H, t, *J* 6.5, CH_2), 3.28 (q, *J* 6.5, CH_2), 2.06 (2H, pent, *J* 6.5, CH_2), 1.45 (9H, s, *t*Bu); δ_C (75 MHz; $CDCl_3$) 156.0, 79.4, 32.7 (CH_2), 30.8 (CH_2), 28.4 (Me), 27.4 (CH_2).

3-(4-Methoxyphenoxy)propyl-1-amine. Potassium carbonate (6.21 g, 45 mmol) was added to a stirred solution of *tert*-butyl (3-bromopropyl)carbamate (3.57 g, 15 mmol) and 4-methoxyphenol (5.58 g, 45 mmol) in DMF (60 mL) at room temperature. The resulting mixture was stirred at 50 °C for 17 h, diluted with water (350 mL) and extracted with ethyl acetate (4 × 75 mL). The combined organic phases were washed with water (100 mL), dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ether and light petroleum (1 : 3) gave an inseparable mixture of 4-methoxyphenol and the intermediate.

This mixture was dissolved in dichloromethane (75 mL), and trifluoroacetic acid (15 mL) was added as a single portion. The resulting mixture was stirred at room temperature for 3 h and extracted with water (3 × 50 mL). The combined aqueous extracts were basified to pH 14 with sodium hydroxide pellets at 0 °C and extracted with dichloromethane (4 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to give the *title compound* as an off-white solid (2.359 g, 87%), mp 42–44 °C; (Found: M + Na^+, 182.1175. $C_{10}H_{16}NO_2Na$ requires 182.1176); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2952, 1591, 1509, 1468; δ_H (400 MHz; $CDCl_3$) 6.85 (4H, s, ArH), 4.05 (2H, t, *J* 6.2, CH_2), 3.78 (3H, s, Me), 2.92 (2H, t, *J* 6.8, CH_2), 1.92 (2H, tt, *J* 6.8, 6.2, CH_2); δ_C (75 MHz; $CDCl_3$) 153.8, 153.1, 115.4 (CH), 114.6 (CH), 66.5 (CH_2), 55.7 (Me), 39.3 (CH_2), 33.2 (CH_2); *m*/*z* (ESI) 182 (M + H^+, 100%).

Methyl 3-[3-(4-methoxyphenoxy)propylamino]acrylate 27c. Methyl propiolate (1.510 g, 18 mmol) was added over 3 min to a stirred solution of 3-(4-methoxyphenoxy)propyl-1-amine (3.254 g, 18 mmol) in acetonitrile (20 mL) at room temperature. The resulting mixture was stirred at room temperature for 14 h and concentrated to give the *title compound* as a pale yellow oil (4.721 g, 99%), 1.5 : 1 *cis* : *trans*; (Found: M + Na^+, 288.1186. $C_{14}H_{19}NO_4Na$ requires 288.1212); ν_{max} ($CHCl_3$)/cm^{-1} 3446, 3010, 2953, 1719, 1665, 1617, 1509, 1441; δ_H (400 MHz; $CDCl_3$) major isomer: 7.91 (1H, br s, NH), 6.87–6.84 (4H, m, ArH), 6.65 (1H, dd, *J* 13.1, 8.0, CH), 4.49 (1H, d, *J* 8.0, CH), 4.03–3.98 (2H, m, CH_2), 3.80 (3H, s, Me), 3.67 (3H, s, Me), 3.42 (2H, dt, *J* 6.5, 6.4, CH_2), 2.00 (2H, tt, *J* 6.4, 6.0, CH_2); minor isomer: 7.54 (1H, dd, *J* 13.3, 8.2, CH), 6.87–6.84 (4H, m, ArH), 4.86 (1H, br s, NH), 4.79 (1H, d, *J* 13.3, CH), 4.03–3.98 (2H, m, CH_2), 3.80 (3H, s, Me), 3.69 (3H, s, Me), 3.30 (2H, dt, *J* 6.4, 6.0, CH_2), 2.05 (2H, tt, *J* 6.4, 6.1, CH_2); δ_C (75 MHz; $CDCl_3$) mixture: 171.2, 170.0, 154.1, 154.0, 152.8, 152.6, 152.5 (CH), 116.0 (CH), 115.5 (CH), 115.4 (CH), 114.8 (CH), 114.7 (CH), 114.6 9 (CH), 81.6 (CH), 66.6 (CH_2), 65.2 (CH_2), 55.7 (Me), 50.6 (Me), 50.2 (Me), 45.5 (CH_2), 31.0 (CH_2); *m*/*z* (ESI) 288 (M + Na^+, 49%), 302 (100).

Methyl 3-(2-dimethylaminoethylamino)acrylate 27d. *N*,*N*-Dimethylethylenediamine (1.76 g, 20 mmol) was added over 5 min to a stirred solution of methyl propiolate (1.68 g, 20 mmol) in acetonitrile (10 mL), and the resulting mixture was stirred at room temperature for 14 h and concentrated to give the *title compound* as a pale yellow oil (3.42 g, 99%), 1 : 2.5 *cis* : *trans*; (Found: M + H^+, 173.1296. $C_8H_{17}N_2O_2$ requires 173.1285); ν_{max} ($CHCl_3$)/cm^{-1} 3401, 3011, 2951, 1665, 1615, 1438; δ_H (400 MHz; $CDCl_3$) major isomer: 7.57 (1H, dd, *J* 13.2, 7.8, CH), 5.19 (1H, br s, NH), 4.71 (1H, d, *J* 13.2, CH), 3.68 (3H, s, Me), 3.08 (2H, dt, *J* 6.1, 5.3, CH_2), 2.51 (2H, t, *J* 6.1, CH_2), 2.25 (6H, s, Me); minor isomer: 7.90 (1H, br s, NH), 6.66 (1H, dd, *J* 13.3, 8.1, CH), 4.50 (1H, d, *J* 8.1, CH), 3.66 (3H, s, Me), 3.27 (2H, dt, *J* 6.5, 6.2, CH_2), 2.46 (2H, *J* 6.5, CH_2), 2.28 (6H, s, Me); δ_C (75 MHz; $CDCl_3$) mixture: 171.0, 170.0, 152.1 (CH), 149.0 (CH), 85.3 (CH), 81.7 (CH), 59.9 (CH_2), 57.7 (CH_2), 50.5 (Me), 50.2 (Me), 48.0 (CH_2), 46.5 (CH_2), 45.6 (Me), 44.9 (Me); *m*/*z* (ESI) 173 (M + H^+, 59%), 225 (90), 257 (100).

Methyl 3-[(2-morpholinoethyl)amino]acrylate 27e. 1-(2-Aminoethyl)morpholine (2.60 g, 20 mmol) was added over 5 min to a stirred solution of methyl propiolate (1.68 g, 20 mmol) in acetonitrile (10 mL), and the resulting mixture was stirred at room temperature for 15 h and concentrated to give the *title compound* as a pale yellow oil (4.28 g, 100%), 1 : 2 *cis* : *trans*; (Found: M + H^+, 215.1388. $C_{10}H_{19}N_2O_3$ requires 215.1396); ν_{max} ($CHCl_3$)/cm^{-1} 3412, 3011, 2949, 2820, 1671, 1618; δ_H (400 MHz; $CDCl_3$) major isomer: 6.66 (1H, dd, *J* 13.2, 8.0, CH), 5.12 (1H, br s, NH), 4.50 (1H, d, *J* 8.0, CH), 3.75–3.71 (4H, m, CH_2), 3.67 (3H, s, Me), 3.30 (2H, dt, *J* 6.3, 6.2, CH_2), 2.53 (2H, t, *J* 6.3, CH_2), 2.50–2.45 (4H, m, CH_2); minor isomer: 7.90 (1H, br s, NH), 7.58 (1H, dd, *J* 7.8, 13.3, CH), 4.73 (1H, d, *J* 13.3, CH), 3.75–3.71 (4H, m, CH_2O), 3.69 (3H, s, Me), 3.10 (2H, dt, *J* 5.9, 5.4, CH_2), 2.59 (2H, t, *J* 5.9, CH_2), 2.50–2.45 (4H, m, CH_2); δ_C (75 MHz; $CDCl_3$) mixture: 171.0, 169.9, 152.0 (CH), 148.9 (CH), 85.6 (CH), 81.8 (CH), 67.0 (CH_2), 59.1 (CH_2), 56.0 (CH_2), 53.7 (CH_2), 53.1 (CH_2), 50.6 (Me), 50.2 (Me), 45.5 (CH_2); *m*/*z* (ESI) 215 (M + H^+, 100%), 237 (M + Na^+, 67), 451 (2M + Na^+, 64).

Methyl 5-methoxy-1-methyl-4,7-dioxo-1*H*-indole-3-carboxylate 28a. Prepared by general procedure 1 from methyl 3-(methylamino)acrylate **27a** (4.24 g, 36.9 mmol), 2-bromo-5-methoxy-1,4-benzoquinone **26a** (4.00 g, 18.4 mmol), copper(II) acetate monohydrate (5.52 g, 27.7 mmol) and potassium carbonate (7.64 g, 55.3 mmol), stirred at reflux in acetonitrile (180 mL). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 19) gave the *title compound* as a yellow-orange solid (1.83 g, 40%); mp 212–214 °C; (Found: M + Na^+, 272.0521. $C_{12}H_{11}NO_5Na$ requires 272.0529); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1733, 1688, 1650, 1606, 1268, 1239, 1027; δ_H (400 MHz; $CDCl_3$) 7.39 (1H, s, CH), 5.72 (1H, s, CH), 4.00 (3H, s, Me), 3.88 (3H, s, Me), 3.84 (3H, s, CO_2Me); δ_C (100 MHz; $CDCl_3$) 179.3, 175.0, 162.8, 160.9, 134.6 (CH), 131.2, 121.9, 114.7, 105.8 (CH), 56.7 (Me), 51.9 (Me), 37.0 (Me).

Methyl 6-methoxy-1-methyl-4,7-dioxo-1*H*-indole-3-carboxylate 28b. Prepared as previously described.[23]

Methyl 6-methoxy-1-[2-(4-methoxyphenoxy)ethyl]-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate 28c. Prepared by general procedure 1 from methyl 3-([2-(4-methoxyphenoxy)ethyl]-amino)acrylate **27b** (2.51 g, 10 mmol), 2-bromo-6-methoxy-1,4-benzoquinone **26b** (2.17 g, 10 mmol), copper(II) acetate monohydrate (3.99 g, 20 mmol) and potassium carbonate (4.14 g, 30 mmol) stirred at reflux in acetonitrile (100 mL) for 15 h. Column chromatography eluting with ethyl acetate and dichloromethane (1 : 9) gave the *title compound* as a yellow

solid (1.607 g, 42%), mp 123–125 °C; (Found: M + Na^+, 408.1054. $C_{20}H_{19}NO_7Na$ requires 408.1054); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2954, 1737, 1677, 1602, 1538, 1509; δ_H (400 MHz; $CDCl_3$) 7.67 (1H, s, CH), 6.83 (2H, d, *J* 9.3, ArH), 6.78 (2H, d, *J* 9.3, ArH), 5.84 (1H, s, CH), 4.76 (2H, t, *J* 4.8, CH_2), 4.27 (2H, t, *J* 4.8, CH_2), 3.92 (3H, s, Me), 3.85 (3H, s, Me), 3.78 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 180.8, 173.2, 162.7, 158.3, 154.4, 152.0, 136.6 (CH), 128.7, 125.5, 115.6 (CH), 114.8 (CH), 114.6, 108.6 (CH), 67.0 (CH_2), 56.7 (Me), 55.7 (Me), 52.0 (Me), 49.5 (CH_2); *m*/*z* (ESI) 408 (M + Na^+, 76%), 793 (2M + Na^+, 100).

Methyl 6-methoxy-1-[3-(4-methoxyphenoxy)propyl]-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate 28d. Prepared by general procedure 1 from methyl 3-([3-(4-methoxyphenoxy)propyl]-amino)acrylate **27c** (1.060 g, 4.0 mmol), 2-bromo-6-methoxy-1,4-benzoquinone **26b** (0.868 g, 4.0 mmol), copper(II) acetate monohydrate (1.596 g, 8.0 mmol) and potassium carbonate (1.656 g, 12.0 mmol) stirred at reflux in acetonitrile (40 mL) for 14 h. Column chromatography eluting with ethyl acetate and dichloromethane (1 : 11) gave the *title compound* as a yellow solid (0.899 g, 56%), mp 80–82 °C; (Found: M + Na^+, 422.1219. $C_{21}H_{21}NO_7Na$ requires 422.1210); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1734, 1671, 1656, 1610, 1509; δ_H (400 MHz; $CDCl_3$) 7.50 (1H, s, CH), 6.83–6.82 (4H, m, ArH), 5.82 (1H, s, CH), 4.58 (2H, t, *J* 6.7, CH_2), 3.92 (2H, t, *J* 5.7, CH_2), 3.86 (3H, s, Me), 3.83 (3H, s, Me), 3.78 (3H, s, Me), 2.27 (2H, tt, *J* 6.7, 5.7, CH_2); δ_C (75 MHz; $CDCl_3$) 180.9, 172.8, 162.6, 158.4, 154.1, 152.4, 165.6 (CH), 129.0, 125.4, 115.4 (CH), 114.7 (CH), 114.5, 108.5 (CH), 64.8 (CH_2), 56.6 (Me), 55.7 (Me), 51.9 (Me), 47.2 (CH_2), 30.0 (CH_2); *m*/*z* (ESI) 422 (M + Na^+, 100%).

Methyl 1-[2-(dimethylamino)ethyl]-6-methoxy-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate 28e. Prepared by general procedure 1 from methyl 3-([2-(dimethylamino)ethyl]amino)acrylate **27d** (0.516 g, 3.0 mmol), 2-bromo-6-methoxy-1,4-benzoquinone **26b** (0.651 g, 3.0 mmol), copper(II) acetate monohydrate (1.197 g, 6.0 mmol) and potassium carbonate (1.242 g, 9 mmol) stirred at reflux in acetonitrile (30 mL) for 15 h. Column chromatography eluting with methanol, ethyl acetate and triethylamine (1 : 19 : 0.1) gave the *title compound* as a red solid (0.688 g, 75%), mp 108–110 °C; (Found: M + H^+, 323.1227. $C_{15}H_{18}N_2O_7$ requires 323.1238); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2952, 1733, 1670, 1655, 1610, 1536, 1243; δ_H (400 MHz; $CDCl_3$) 7.56 (1H, s, CH), 5.83 (1H, s, CH), 4.47 (2H, t, *J* 6.5, CH_2), 3.90 (3H, s, Me), 3.85 (3H, s, Me), 2.69 (2H, t, *J* 6.5, CH_2), 2.31 (6H, s, Me); δ_C (75 MHz; $CDCl_3$) 181.0, 172.9, 162.7, 158.3, 135.7 (CH), 129.0, 125.2, 114.6, 108.5 (CH), 59.1 (CH_2), 56.6 (Me), 52.0 (Me), 47.6 (CH_2), 45.5 (Me); *m*/*z* (ESI) 323 (M + Na^+, 33%), 307 (100).

Methyl 6-methoxy-1-(2-morpholinoethyl)-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate 28f. Prepared by general procedure 1 from methyl 3-[(2-morpholinoethyl)amino]acrylate **27e** (0.856 g, 4.0 mmol), 2-bromo-6-methoxy-1,4-benzoquinone **26b** (0.868 g, 4.0 mmol), copper(II) acetate monohydrate (1.596 g, 8.0 mmol) and potassium carbonate (1.656 g, 12 mmol) stirred at reflux in acetonitrile (40 mL) for 4 h. Column chromatography eluting with methanol and ethyl acetate (1 : 9) gave the *title compound* as an orange-brown solid (0.976 g, 80%), mp 156–158 °C; (Found: M + Na^+, 371.1203. $C_{17}H_{20}N_2O_5Na$ requires 371.1214); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2953, 1734, 1670, 1656, 1610, 1536; δ_H (400 MHz; $CDCl_3$) 7.55 (1H, s, CH), 5.85 (1H, s, CH), 4.50 (2H, t, *J* 6.5, CH_2), 3.92 (3H, s, Me), 3.86 (3H, s, Me), 3.69 (4H, t, *J* 4.6, CH_2O), 2.75 (2H, t, *J* 6.5, CH_2), 2.53 (4H, t, *J* 4.6, CH_2); δ_C (75 MHz; $CDCl_3$) 181.0, 173.0, 162.7, 158.4, 135.7 (CH), 129.1, 125.2, 114.6, 108.5 (CH), 66.9 (CH_2), 58.4 (CH_2), 56.7 (Me), 53.7 (CH_2), 52.0 (Me), 46.8 (CH_2); *m*/*z* (ESI) 371 (M + Na^+, 100%).

Methyl 6-ethoxy-1-(2-morpholinoethyl)-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate 28g. Prepared by general procedure 1 from 2-bromo-6-ethoxy-1,4-benzoquinone **26c** (0.924 g, 4.0 mmol), methyl 3-[(2-morpholinoethyl)amino]acrylate **27e** (0.856 g, 4.0 mmol, copper acetate monohydrate (1.596 g, 8.0 mmol) and potassium carbonate (1.656 g, 12.0 mmol) stirred at reflux in acetonitrile (40 mL) for 15 h. Column chromatography eluting with ethyl acetate gave the *title compound* as a red oil (0.512 g, 37%); (Found: M + H^+, 363.1245. $C_{18}H_{23}N_2O_6$ requires 363.1551); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2953, 1732, 1688, 1643, 1603; δ_H (400 MHz; $CDCl_3$) 7.51 (1H, s, CH), 5.69 (1H, s, CH), 4.51 (2H, t, *J* 6.4, CH_2), 4.04 (2H, q, *J* 7.0, CH_2), 3.91 (3H, s, Me), 3.69 (4H, t, *J* 4.6, CH_2), 2.74 (2H, t, *J* 7.0, CH_2), 2.52 (4H, t, *J* 4.6, CH_2), 1.52 (3H, t, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$) 179.5, 175.3, 163.2, 159.9, 134.3 (CH), 130.6, 122.0, 114.8, 106.2 (CH), 66.9 (CH_2), 65.6 (CH_2), 58.5 (CH_2), 53.7 (CH_2), 51.9 (Me), 46.5 (CH_2), 13.9 (Me); *m*/*z* (ESI) 363 (M + H^+, 100%).

Methyl 5-methoxy-6-methyl-1-(2-morpholinoethyl)-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate 28h. Prepared by general procedure 1 from 5-bromo-2-methoxy-3-methyl-1,4-benzoquinone **26d** (0.693 g, 3.0 mmol), methyl 3-[(2-morpholinoethyl)-amino]acrylate **27e** (0.552 g, 3.0 mmol, copper acetate monohydrate (1.197 g, 6.0 mmol) and potassium carbonate (1.242 g, 9.0 mmol) stirred at reflux in acetonitrile for 16 h. Column chromatography eluting with ethyl acetate and methanol (49 : 1) gave the *title compound* as a red oil (0.468 g, 43%); (Found: M + H^+, 363.1537. $C_{18}H_{23}N_2O_6$ requires 363.1551); ν_{max} ($CHCl_3$)/cm^{-1} 3006, 1731, 1602; δ_H (400 MHz; $CDCl_3$) 7.48 (1H, s, CH), 4.49 (2H, t, *J* 6.4, CH_2), 4.10 (3H, s, Me), 3.91 (3H, s, Me), 3.69 (4H, t, *J* 4.5, CH_2), 2.73 (2H, t, *J* 6.4, CH_2), 2.52 (4H, t, *J* 4.5, CH_2), 1.97 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 180.0, 177.0, 162.8, 157.3, 134.5 (CH), 130.6, 126.9, 122.6, 114.3, 66.8 (CH_2), 61.3 (Me), 58.4 (CH_2), 53.6 (CH_2), 51.9 (Me), 46.6 (CH_2), 8.5 (Me); *m*/*z* (ESI) 363 (M + H^+, 100%).

Methyl 1-methyl-4,9-dioxo-1*H*-benz[*f*]indole-3-carboxylate 28i. Prepared by general procedure 1 from methyl 3-(methylamino)acrylate **27a** (49.0 mg, 0.422 mmol), 2-bromo-1,4-naphthoquinone **26e** (100 mg, 0.422 mmol), copper(II) acetate monohydrate (126 mg, 0.633 mmol) and potassium carbonate (175 mg, 1.27 mmol) stirred at reflux in acetonitrile (5 mL). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 19) gave the *title compound* as a yellow-orange solid (58.0 mg, 51%); mp 195–197 °C; (Found: M + Na^+, 292.0580. $C_{15}H_{11}NO_4Na$ requires 292.0580); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1737, 1664, 1601, 1272, 1106, 930; δ_H (400 MHz; $CDCl_3$) 8.23–8.21 (1H, m, ArH), 8.15–8.13 (1H, m, ArH), 7.74–7.67 (2H,

m, ArH), 7.51 (1H, s, CH), 4.13 (3H, s, Me), 3.93 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 179.0, 177.1, 162.9, 136.0 (CH), 134.3, 133.7 (CH), 133.0 (CH), 132.6, 132.3, 127.2 (CH), 126.1 (CH), 125.9, 115.0, 52.0 (Me), 37.6 (Me).

3-Hydroxymethyl-5-methoxy-1-methyl-1*H*-indole-4,7-dione 29a. Prepared by general procedure 2 from methyl 5-methoxy-1-methyl-4,7-dioxo-1*H*-indole-3-carboxylate **28a** (43.8 mg, 0.176 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 9) gave the *title compound* as an orange solid (8.00 mg, 21%); mp 185–187 °C (lit.,[26] mp 186–187 °C); (Found: M + Na^+, 244.0572. $C_{11}H_{11}NO_4Na$ requires 244.0580); ν_{max} ($CHCl_3$)/cm^{-1} 3692, 3009, 1645, 1600, 1509, 1177, 1036, 1017; δ_H (400 MHz; $CDCl_3$) 6.71 (1H, s, CH), 5.68 (1H, s, CH), 4.64 (2H, d, *J* 5.8, CH_2), 3.93 (3H, s, Me), 3.84 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 178.8, 178.7, 160.3, 130.4, 127.4 (CH), 125.9, 122.1, 107.0 (CH), 56.8 (CH_2), 56.6 (Me), 36.1 (Me).

3-Hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione 29b. Prepared by general procedure 2 from methyl 6-methoxy-1-methyl-4,7-dioxo-1*H*-indole-3-carboxylate **28b** (1.00 g, 4.01 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (2 : 3) gave the *title compound* as an orange solid (0.528 g, 60%); mp 228–230 °C; (Found: M + Na^+, 244.0578. $C_{11}H_{11}NO_4Na$ requires 244.0580); ν_{max} ($CHCl_3$)/cm^{-1} 3416, 1670, 1629, 1601, 1337, 1035; δ_H (400 MHz; DMSO-d_6) 7.19 (1H, s, CH), 5.74 (1H, s, CH), 5.00 (1H, t, *J* 5.5, OH), 4.57 (2H, d, *J* 5.5, CH_2), 3.87 (3H, s, Me), 3.85 (3H, s, Me); δ_C (100 MHz; DMSO-d_6) 184.0, 171.5, 160.2, 131.1 (CH), 127.8, 126.7, 122.8, 107.3 (CH), 57.0 (Me), 56.3 (CH_2), 36.5 (Me).

3-Hydroxymethyl-6-methoxy-1-[2-(4-methoxyphenoxy)ethyl]-1*H*-indole-4,7-dione 29c. Prepared by general procedure 2 from methyl 6-methoxy-1-[2-(4-methoxyphenoxy)ethyl]-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate **28c** (1.600 g, 4.16 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 5) gave recovered methyl ester (0.207 g, 13%) and the *title compound* as an orange solid (0.813 g, 56%; 64% brsm), mp 178–180 °C; (Found: M + Na^+, 380.1101. $C_{19}H_{19}NO_6Na$ requires 380.1105); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1667, 1631, 1601, 1508; δ_H (400 MHz; $CDCl_3$) 7.02 (1H, s, CH), 6.83 (2H, d, *J* 9.1, ArH), 6.79 (2H, d, *J* 9.1, ArH), 5.78 (1H, s, CH), 4.68 (2H, t, *J* 5.0, CH_2), 4.65 (2H, d, *J* 6.9, CH_2), 4.26 (1H, t, *J* 6.9, OH), 4.25 (2H, t, *J* 5.0, CH_2), 3.87 (3H, s, Me), 3.77 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 185.1, 171.8, 160.3, 154.3, 152.1, 130.0 (CH), 127.7, 125.9, 125.6, 115.5 (CH), 114.7 (CH), 106.8 (CH), 67.2 (CH_2), 56.9 (CH_2), 56.8 (Me), 55.7 (Me), 48.7 (CH_2); *m*/*z* (ESI) 380 (M + Na^+, 100%).

3-Hydroxymethyl-6-methoxy-1-[3-(4-methoxyphenoxy)propyl]-1*H*-indole-4,7-dione 29d. Prepared by general procedure 2 from methyl 6-methoxy-1-[3-(4-methoxyphenoxy)propyl]-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate **28d** (0.890 g, 2.2 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 5) gave the *title compound* as an orange solid (0.284 g, 34%), mp 121–123 °C; (Found: M + Na^+, 394.1260. $C_{20}H_{21}NO_6Na$ requires 394.1261); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3011, 1669, 1630, 1602, 1508; δ_H (400 MHz; $CDCl_3$) 6.87–6.82 (5H, m, ArH + CH), 5.78 (1H, s, CH), 4.61 (2H, d, *J* 6.9, CH_2), 4.52 (2H, t, *J* 6.8, CH_2), 4.29 (1H, t, *J* 6.9, OH), 3.93 (2H, t, *J* 5.6, CH_2), 3.87 (3H, s, Me), 3.80 (3H, s, Me), 2.26 (2H, tt, *J* 6.8, 5.6, CH_2); δ_C (75 MHz; $CDCl_3$) 185.1, 171.5, 160.3, 154.1, 152.5, 129.1 (CH), 128.0, 125.9, 125.5, 115.4 (CH), 114.7 (CH), 106.8 (CH), 64.7 (CH_2), 56.9 (CH_2), 56.8 (Me), 55.7 (Me), 46.4 (CH_2), 30.1 (CH_2); *m*/*z* (ESI) 394 (M + Na^+, 100%).

1-[2-(Dimethylamino)ethyl]-3-hydroxymethyl-6-methoxy-1*H*-indole-4,7-dione 29e. Prepared by general procedure 2 from methyl 1-[2-(dimethylamino)ethyl]-6-methoxy-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate **28e** (1.031 g, 3.37 mmol). Column chromatography eluting with methanol, ethyl acetate and triethylamine (8 : 1 : 0.01) gave the *title compound* as an orange oil (0.210 g, 22%); (Found: M + Na^+, 301.1157. $C_{14}H_{18}N_2O_4Na$ requires 301.1159); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1668, 1630, 1602, 1505; δ_H (400 MHz; $CDCl_3$) 6.93 (1H, s, CH), 5.75 (1H, s, CH), 4.63 (2H, s, CH_2), 4.40 (2H, t, *J* 6.6, CH_2), 3.85 (3H, s, Me), 2.66 (2H, t, *J* 6.6, CH_2), 2.29 (6H, s, Me); δ_C (75 MHz; $CDCl_3$) 185.1, 171.5, 160.3, 129.0 (CH), 127.9, 126.0, 125.2, 106.7 (CH), 60.5 (CH_2), 56.9 (CH_2), 56.8 (Me), 46.9 (CH_2), 45.4 (Me); *m*/*z* (ESI) 279 (M + H^+, 100%).

3-Hydroxymethyl-6-methoxy-1-(2-morpholinoethyl)-1*H*-indole-4,7-dione 29f. Prepared by general procedure 2 from methyl 6-methoxy-1-(2-morpholinoethyl)-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate **28f** (0.560 g, 1.61 mmol). Column chromatography eluting with methanol, ethyl acetate and triethylamine (1 : 14 : 0.1) gave the *title compound* as a yellow solid (0.211 g, 41%), mp 128–130 °C; (Found: M + Na^+, 321.1445. $C_{16}H_{21}N_2O_5$ requires 321.1445); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2968, 1668, 1630, 1601, 1505; δ_H (400 MHz; $CDCl_3$) 6.92 (1H, s, CH), 5.79 (1H, s, CH), 4.65 (2H, d, *J* 6.9, CH_2), 4.44 (2H, t, *J* 6.6, CH_2), 4.28 (1H, t, *J* 6.9, OH), 3.88 (3H, s, Me), 3.70 (4H, t, *J* 4.6, CH_2O), 2.73 (2H, t, *J* 6.6, CH_2), 2.55 (4H, t, *J* 4.6, CH_2); δ_C (75 MHz; $CDCl_3$) 185.1, 171.6, 160.3, 128.8 (CH), 128.1, 126.0, 125.3, 106.8 (CH), 67.0 (CH_2), 58.7 (CH_2), 56.9 (CH_2), 56.8 (Me), 53.7 (CH_2), 46.2 (CH_2); *m*/*z* (ESI) 321 (M + H^+, 100%), 343 (M + Na^+, 62).

6-Ethoxy-3-hydroxymethyl-1-(2-morpholinoethyl)-1*H*-indole-4,7-dione 29g. Prepared by general procedure 2 from methyl 6-ethoxy-1-(2-morpholinoethyl)-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate **28g** (0.503 g, 1.45 mmol). Column chromatography eluting with ethyl acetate and methanol (49 : 1) gave the *title compound* as an orange oil (0.183 g, 38%); (Found: M + H^+, 335.1583. $C_{17}H_{23}N_2O_5$ requires 335.1601); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3011, 1663, 1639, 1598, 1506; δ_H (400 MHz; $CDCl_3$) 6.83 (1H, s, CH), 5.65 (1H, s, CH), 4.65 (2H, s, CH_2), 4.43 (2H, t, *J* 6.5, CH_2), 4.03 (2H, q, *J* 7.0, CH_2), 3.69 (4H, t, *J* 4.6, CH_2), 2.71 (2H, t, *J* 6.5, CH_2), 2.52 (4H, t, *J* 4.6, CH_2), 1.52 (3H, t, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$) 179.0, 159.4, 130.0, 128.8, 126.8, 126.0 (CH), 122.3, 107.5 (CH), 66.9 (CH_2), 65.5 (CH_2), 58.7 (CH_2), 56.9 (CH_2), 53.7 (CH_2), 45.7 (CH_2), 13.9 (Me); *m*/*z* (ESI) 335 (M + H^+, 100%).

3-Hydroxymethyl-5-methoxy-6-methyl-1-(2-morpholinoethyl)-1*H*-indole-4,7-dione 29h. Prepared by general procedure 2 from methyl 5-methoxy-6-methyl-1-(2-morpholinoethyl)-4,7-dioxo-4,7-dihydro-1*H*-indole-3-carboxylate **28h** (0.461 g, 1.27 mmol). Column chromatography eluting with ethyl

acetate and methanol (19 : 1) gave the *title compound* as an orange oil (0.233 g, 55%); (Found: M + H^+, 335.1597. $C_{17}H_{23}N_2O_5$ requires 335.1601); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2965, 1640, 1509; δ_H (400 MHz; $CDCl_3$) 6.81 (1H, s, CH), 4.63 (2H, s, CH_2), 4.40 (2H, t, *J* 6.6, CH_2), 4.01 (3H, s, Me), 3.68 (4H, t, *J* 4.6, CH_2), 2.69 (2H, t, *J* 6.6, CH_2), 2.51 (4H, t, *J* 4.6, CH_2), 1.97 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 180.6, 179.1, 156.6, 129.7, 129.6, 127.2 (CH), 125.7, 122.7, 66.9 (CH_2), 61.2 (Me), 58.6 (CH_2), 56.9 (CH_2), 53.7 (CH_2), 45.9 (CH_2), 8.8 (Me); *m*/*z* (ESI) 335 (M + H^+, 100%).

3-Hydroxymethyl-1-methyl-1*H*-benz[*f*]indole-4,9-dione 29i. Prepared by general procedure 2 from methyl 1-methyl-4,9-dioxo-1*H*-benz[*f*]indole-3-carboxylate **28i** (0.461 g, 1.71 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 4) gave the *title compound* as a yellow solid (0.151 g, 37%); mp 219–221 °C; (Found: M + Na^+, 264.0633. $C_{14}H_{11}NO_3Na$ requires 264.0631); ν_{max} ($CHCl_3$)/cm^{-1} 3007, 1650, 1593, 1506, 1260, 929; δ_H (400 MHz; $CDCl_3$) 8.18–8.14 (2H, m, ArH), 7.72–7.69 (2H, m, ArH), 6.85 (1H, s, CH), 4.72 (2H, d, *J* 6.9, CH_2), 4.36 (1H, t, *J* 6.9, OH), 4.07 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 182.8, 176.2, 133.7, 133.6, 133.4 (CH), 133.3 (CH), 131.6, 129.1 (CH), 126.6 (CH), 126.5 (CH), 126.1, 125.9, 56.9 (CH_2), 36.6 (Me).

5-Methoxy-1-methyl-3-(4-nitrophenoxy)methyl-1*H*-indole-4,7-dione 1. Prepared from 3-hydroxymethyl-5-methoxy-1-methyl-1*H*-indole-4,7-dione **29a** as previously described.[27]

6-Methoxy-1-methyl-3-(4-nitrophenoxy)methyl-1*H*-indole-4,7-dione 2. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (111 mg, 0.50 mmol) and 4-nitrophenol (348 mg, 2.50 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 49) gave the *title compound* as a yellow solid (151 mg, 89%); mp 225–227 °C; (Found: M + Na^+, 365.0750. $C_{17}H_{14}N_2O_6Na$ requires 365.0744); ν_{max} ($CHCl_3$)/cm^{-1} 2360, 1671, 1644, 1596, 1515, 1343; δ_H (400 MHz; $CDCl_3$) 8.22 (2H, d, *J* 7.1, ArH), 7.06 (2H, d, *J* 7.1, ArH), 6.99 (1H, s, CH), 5.77 (1H, s, CH), 5.41 (2H, s, CH_2), 4.00 (3H, s, Me), 3.86 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 183.8, 172.0, 163.4, 160.0, 141.8, 130.2 (CH), 128.2, 126.0 (CH), 123.6, 119.7, 114.8 (CH), 107.3 (CH), 63.1 (CH_2), 56.7 (Me), 36.7 (Me); *m*/*z* (ESI) 365 (M + Na^+, 100%); HPLC: purity (AUC) 100%.

5-Methoxy-1-methyl-3-(2,4,6-trifluorophenoxy)methyl-1*H*-indole-4,7-dione 3. Prepared by general procedure 3 from 3-hydroxymethyl-5-methoxy-1-methyl-1*H*-indole-4,7-dione **29a** (145 mg, 0.66 mmol) 2,4,6-trifluorophenol (485 mg, 3.28 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 24) gave the *title compound* as a yellow solid (195 mg, 85%); mp 182–184 °C; (Found: M + Na^+, 374.0617. $C_{17}H_{12}NO_4F_3Na$ requires 374.0611); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1676, 1645, 1601, 1509; δ_H (400 MHz; $CDCl_3$) 6.99 (1H, s, CH), 6.70 (2H, t, *J* 8.4, ArH), 5.69 (1H, s, CH), 5.33 (2H, s, CH_2), 3.99 (3H, s, Me), 3.84 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 179.1, 177.4, 160.3, 157.3 (dt, *J* 244, 14), 156.2 (ddd, *J* 250, 15, 8), 132.2 (dt, *J* 15, 5), 129.8, 129.0 (CH), 121.1, 120.7, 106.8 (CH), 100.7 (ddd, *J* 28, 27, 8, CH), 68.5 (CH_2), 56.5 (Me), 36.3 (Me); *m*/*z* (ESI) 374 (M + Na^+, 100%); HPLC: purity (AUC) 99.7%.

6-Methoxy-1-methyl-3-(2,4,6-trifluorophenoxy)methyl-1*H*-indole-4,7-dione 4. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (96 mg, 0.43 mmol) and 2,4,6-trifluorophenol (321 mg, 2.17 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 39) gave the *title compound* as a yellow solid (136 mg, 89%); mp 188–190 °C; (Found: M + Na^+, 374.0623. $C_{17}H_{12}NO_4F_3Na$ requires 374.0611); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 1670, 1645, 1602, 1510; δ_H (400 MHz; $CDCl_3$) 7.09 (1H, s, CH), 6.71 (2H, t, *J* 8.4, ArH), 5.72 (1H, s, CH), 5.34 (2H, s, CH_2), 4.02 (3H, s, Me), 3.84 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 183.5, 172.1, 159.8, 157.3 (dt, *J* 245, 15), 156.2 (ddd, *J* 250, 15, 8), 132.2 (dt, *J* 15, 5), 130.7 (CH), 128.1, 123.7, 120.6, 107.2 (CH), 100.7 (ddd, *J* 28, 27, 8, CH), 68.7 (CH_2), 56.6 (Me), 36.3 (Me); *m*/*z* (ESI) 374 (M + Na^+, 100%); HPLC: purity (AUC) 90.3%.

6-Methoxy-1-methyl-3-phenoxymethyl-1*H*-indole-4,7-dione 5. Prepared by a variation of general procedure 2 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (50 mg, 0.23 mmol), phenol (106 mg, 1.13 mmol) and sodium hydride (60% in mineral oil; 45 mg, 1.13 mmol) in place of potassium carbonate. Column chromatography eluting with ethyl acetate and dichloromethane (1 : 9) gave the *title compound* as a yellow solid (21 mg, 31%); mp 147–149 °C; (Found: M + Na^+, 320.0891. $C_{17}H_{15}NO_4Na$ requires 320.0893); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 1669, 1643, 1600, 1240, 1032; δ_H (400 MHz; $CDCl_3$) 7.31–7.26 (2H, m, ArH), 7.01–6.98 (1H, m, CH), 6.97–6.94 (3H, m, ArH), 5.72 (1H, s, CH), 5.30–5.28 (2H, m, CH_2), 3.95 (3H, s, Me), 3.82 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 183.8, 171.9, 159.9, 158.4, 130.2 (CH), 129.5 (CH), 128.0, 123.4, 121.6, 121.0 (CH), 114.7 (CH), 107.2 (CH), 62.5 (CH_2), 56.6 (Me), 36.5 (Me); HPLC: purity (AUC) 100%.

5-Methoxy-1-methyl-3-(4-methylsulfonylphenoxy)methyl-1*H*-indole-4,7-dione 6. Prepared by general procedure 3 from 3-hydroxymethyl-5-methoxy-1-methyl-1*H*-indole-4,7-dione **29a** (50 mg, 0.23 mmol) and 4-methylsulfonylphenol (272 mg, 1.58 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (2 : 3) gave the *title compound* as a yellow solid (61 mg, 72%); mp 196–198 °C; (Found: M + Na^+, 398.0655. $C_{18}H_{17}NO_6SNa$ requires 398.0669); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 1674, 1646, 1599, 1318, 1147; δ_H (400 MHz; $CDCl_3$) 7.88–7.86 (2H, m, ArH), 7.12–7.09 (2H, m, ArH), 6.87 (1H, s, CH), 5.71 (1H, s, CH), 5.36 (2H, s, CH_2), 3.96 (3H, s, Me), 3.84 (3H, s, Me), 3.04 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 178.9, 177.7, 162.5, 160.3, 132.6, 129.9, 129.6 (CH), 128.5 (CH), 121.0, 120.1, 115.3 (CH), 106.9 (CH), 62.8 (CH_2), 56.6 (Me), 44.8 (Me), 36.4 (Me); HPLC: purity (AUC) 93.5%.

6-Methoxy-1-methyl-3-(4-methylsulfonylphenoxy)methyl-1*H*-indole-4,7-dione 7. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (50.0 mg, 0.226 mmol) and 4-methylsulfonylphenol (195 mg, 1.13 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 9) gave the *title compound* as a yellow solid (20 mg, 24%); mp 240–242 °C; (Found: M + Na^+, 398.0669. $C_{18}H_{17}NO_6SNa$ requires 398.0669); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 1671, 1644, 1599, 1340, 1146; δ_H (400 MHz; $CDCl_3$)

7.89–7.86 (2H, m, ArH), 7.13–7.09 (2H, m, ArH), 6.97 (1H, s, CH), 5.75 (1H, s, CH), 5.37 (2H, s, CH_2), 3.99 (3H, s, Me), 3.84 (3H, s, Me), 3.04 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 183.8, 172.0, 162.5, 160.0, 132.6, 130.2 (CH), 129.6 (CH), 128.1, 123.5, 119.9, 115.2 (CH), 107.2 (CH), 62.8 (CH_2), 56.7 (Me), 44.8 (Me), 36.7 (Me); HPLC: purity (AUC) 90.6%.

4-[(6-Methoxy-1-methyl-4,7-dioxo-1*H*-indol-3-yl)methoxy]benzoic acid 8. Prepared by a variation of general procedure 3 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (50 mg, 0.23 mmol), 4-hydroxybenzoic acid (31 mg, 0.23 mmol) and sodium hydride (60% in mineral oil; 45 mg, 1.13 mmol) in place of potassium carbonate. Column chromatography eluting with methanol and dichloromethane (3 : 97) gave the *title compound* as a yellow solid (28 mg, 36%); mp 198–200 °C; (Found: M + Na^+, 364.0782. $C_{18}H_{15}NO_6Na$ requires 364.0792); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3601, 3011, 1708, 1669, 1645, 1602, 1512, 1270, 1165, 1037, 909; δ_H (400 MHz; DMSO-d_6) 10.34 (1H, br s, CO_2H), 7.83 (2H, d, *J* 8.8, ArH), 7.43 (1H, s, CH), 6.84 (2H, d, *J* 8.8, ArH), 5.82 (1H, s, CH), 5.33 (2H, s, CH_2), 3.90 (3H, s, Me), 3.77 (3H, s, Me); δ_C (100 MHz; DMSO-d_6) 183.3, 171.3, 165.4, 162.1, 159.8, 131.9 (CH), 131.6 (CH), 127.7, 123.1, 120.2, 118.5, 115.4 (CH), 107.1 (CH), 58.0 (CH_2), 56.7 (Me), 36.2 (Me); HPLC: purity (AUC) 94.6%.

3-Fluoro-4-[(6-methoxy-1-methyl-4,7-dioxo-1*H*-indol-3-yl)-methoxy]benzoic acid 9. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (20 mg, 0.09 mmol) and 3-fluoro-4-hydroxybenzoic acid (71 mg, 0.45 mmol). Column chromatography eluting with methanol and dichloromethane (1 : 19) gave the *title compound* as a yellow solid (14.0 mg, 43%); mp 220–222 °C; (Found: M + Na^+, 382.0682. $C_{18}H_{14}{}^{19}FNO_6Na$ requires 382.0697); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3572, 3002, 1714, 1670, 1646, 1602, 1514, 1340, 1286, 1037, 909; δ_H (400 MHz; DMSO-d_6) 10.88 (1H, br s, CO_2H), 7.69–7.66 (2H, m, ArH), 7.47 (1H, s, CH), 7.07–7.02 (1H, m, ArH), 5.83 (1H, s, CH), 5.35 (2H, s, CH_2), 3.90 (3H, s, Me), 3.77 (3H, s, Me); δ_C (100 MHz; DMSO-d_6) 183.7, 171.7, 165.0, 160.2, 150.9 (d, *J* 242), 150.4 (d, *J* 12), 132.3 (CH), 128.2, 127.3 (CH), 123.5, 121.1 (d, *J* 7), 118.6, 118.0 (CH), 117.5 (d, *J* 20, CH), 107.5 (CH), 58.9 (CH_2), 57.1 (Me), 36.6 (Me); HPLC: purity (AUC) 94.8%.

3-(2,5-Dioxopyrrolidin-1-yl)methyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione 10. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (50.0 mg, 0.226 mmol) and succinimide (112 mg, 1.13 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (2 : 3) gave the *title compound* as a yellow solid (26.0 mg, 40%); mp 275–277 °C; (Found: M + Na^+, 325.0785. $C_{15}H_{14}N_2O_5Na$ requires 325.0795); ν_{max} ($CHCl_3$)/cm^{-1} 1707, 1669, 1645, 1602, 909; δ_H (400 MHz; $CDCl_3$) 6.75 (1H, s, CH), 5.70 (1H, s, CH), 4.90 (2H, s, CH_2), 3.92 (3H, s, Me), 3.81 (3H, s, Me), 2.76 (4H, s, CH_2); δ_C (100 MHz; $CDCl_3$) 183.5, 176.8, 172.1, 159.6, 130.6 (CH), 128.1, 123.8, 119.0, 107.5 (CH), 56.6 (Me), 36.6 (Me), 33.9 (CH_2), 28.2 (CH_2); HPLC: purity (AUC) 96.9%.

3-(2,5-Dioxopyrrolidin-1-yloxy)methyl-5-methoxy-1-methyl-1*H*-indole-4,7-dione 11. Prepared by general procedure 3 from 3-hydroxymethyl-5-methoxy-1-methyl-1*H*-indole-4,7-dione **29a** (50 mg, 0.23 mmol) and *N*-hydroxysuccinimide (130 mg, 1.13 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 4) gave the *title compound* as a yellow solid (24 mg, 34%); mp 194–196 °C; (Found: M + Na^+, 341.0737. $C_{15}H_{14}N_2O_6Na$ requires 341.0744); ν_{max} ($CHCl_3$)/cm^{-1} 1729, 1673, 1646, 1602, 1512, 1192; δ_H (400 MHz; $CDCl_3$) 7.02 (1H, s, CH), 5.66 (1H, s, CH), 5.27 (2H, s, CH_2), 3.96 (3H, s, Me), 3.81 (3H, s, Me), 2.68 (4H, s, CH_2); δ_C (100 MHz; $CDCl_3$) 178.9, 177.8, 171.3, 160.2, 130.8 (CH), 130.1, 121.6, 117.8, 106.8 (CH), 69.6 (CH_2), 56.6 (Me), 36.4 (Me), 25.5 (CH_2); HPLC: purity (AUC) 94.5%.

3-(2,5-Dioxopyrrolidin-1-yloxy)methyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione 12. Prepared by general procedure 4 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (50 mg, 0.23 mmol) and *N*-hydroxysuccinimide (130 mg, 1.13 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (2 : 3) gave the *title compound* as a yellow solid (60 mg, 83%); mp 255–257 °C; (Found: M + Na^+, 341.0731. $C_{15}H_{14}N_2O_6Na$ requires 341.0744); ν_{max} ($CHCl_3$)/cm^{-1} 1729, 1671, 1644, 1603, 909; δ_H (400 MHz; $CDCl_3$) 7.11 (1H, s, CH), 5.67 (1H, s, CH), 5.28 (2H, s, CH_2), 3.99 (3H, s, Me), 3.82 (3H, s, Me), 2.67 (4H, s, CH_2); δ_C (100 MHz; $CDCl_3$) 183.8, 172.1, 171.3, 159.8, 132.6 (CH), 128.3, 124.4, 117.6, 107.2 (CH), 69.4 (CH_2), 56.6 (Me), 36.7 (Me), 25.5 (CH_2); HPLC: purity (AUC) 99.0%.

3-(2*H*-1,2,3-Triazol-2-yl)methyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione 14 and 3-(1*H*-1,2,3-triazol-1-yl)methyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione 13. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (20 mg, 0.09 mmol) and 1,2,3-triazole (0.03 mL, 0.45 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (2 : 3) gave the *title compounds* **14** and **13** as yellow solids (8 mg, 33%; 11 mg, 45% respectively); **14**: mp 210–212 °C; (Found: M + Na^+, 295.0793. $C_{13}H_{12}N_4O_3Na$ requires 295.0802); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1670, 1645, 1601, 1189, 1036; δ_H (400 MHz; $CDCl_3$) 7.65 (2H, s, triazole-H), 6.61 (1H, s, CH), 5.86 (2H, s, CH_2), 5.74 (1H, s, CH), 3.92 (3H, s, Me), 3.83 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 183.6, 172.1, 159.8, 134.4 (CH), 130.5 (CH), 128.1, 123.6, 118.9, 107.4 (CH), 56.6 (Me), 49.8 (CH_2), 36.6 (Me); HPLC: purity (AUC) 93.9%. **13**: mp 268–270 °C; (Found: M + Na^+, 295.0789. $C_{13}H_{12}N_4O_3Na$ requires 295.0802); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1672, 1644, 1602, 1192, 1036; δ_H (400 MHz; $CDCl_3$) 7.83 (1H, d, *J* 0.8, triazole-H), 7.67 (1H, d, *J* 0.8, triazole-H), 6.91 (1H, s, CH), 5.74 (1H, s, CH), 5.72 (2H, s, CH_2), 3.94 (3H, s, Me), 3.84 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 184.0, 172.0, 160.0, 143.4, 133.8 (CH), 131.5 (CH), 128.0, 124.2 (CH), 118.3, 107.3 (CH), 56.7 (Me), 44.3 (CH_2), 36.7 (Me); HPLC: purity (AUC) 97.7%.

3-(2*H*-Tetrazol-2-yl)methyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione 16 and 3-(1*H*-tetrazol-1-yl)methyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione 15. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-methyl-1*H*-indole-4,7-dione **29b** (74.0 mg, 0.34 mmol) and tetrazole (0.45 M in acetonitrile; 6 mL, 2.68 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 4) gave the *title compounds* **16**

and **15** were obtained as yellow solids (20 mg, 22%; 33 mg, 36% respectively); **16**: mp 198–200 °C; (Found: M + Na^+, 296.0745. $C_{12}H_{11}N_5O_3Na$ requires 296.0754); ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2931, 2872, 2337, 1710, 1673, 1646, 1602, 1515, 1195, 1036; δ_H (400 MHz; $CDCl_3$) 8.51 (1H, s, N=C*H*N), 6.78 (1H, s, CH), 6.05 (2H, s, CH_2), 5.74 (1H, s, CH), 3.94 (3H, s, Me), 3.82 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 183.4, 172.1, 159.8, 152.9 (CH), 130.9 (CH), 128.2, 123.6, 116.1, 107.3 (CH), 56.7 (Me), 47.7 (CH_2), 36.6 (Me); HPLC: purity (AUC) 90.0%. **15**: mp 230–232 °C; (Found: M + Na^+, 296.0748. $C_{12}H_{11}N_5O_3Na$ requires 296.0754); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 2929, 2873, 2361, 2342, 1733, 1675, 1643, 1602, 1459, 1036; δ_H (400 MHz; $CDCl_3$) 8.93 (1H, s, NC*H*=N), 7.03 (1H, s, CH), 5.75 (1H, s, CH), 5.72 (2H, s, CH_2), 3.98 (3H, s, Me), 3.85 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 183.9, 172.0, 160.1, 143.0 (CH), 131.6 (CH), 126.2, 123.5, 116.2, 107.2 (CH), 56.8 (Me), 42.4 (CH_2), 36.7 (Me); HPLC: purity (AUC) 98.8%.

6-Methoxy-1-(2-(4-methoxyphenoxy)ethyl)-3-(2,4,6-trifluorophenoxy)methyl-1*H*-indole-4,7-dione 17. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-(2-(4-methoxyphenoxy)ethyl)-1*H*-indole-4,7-dione **29c** (0.801 g, 2.24 mmol) and 2,4,6-trifluorophenol (1.658 g, 11.20 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 24) gave the *title compound* as a yellow solid (0.966 g, 93%), mp 134–136 °C; (Found: M + Na^+, 510.1128. $C_{25}H_{20}NO_5F_3Na$ requires 510.1135); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1645, 1602, 1509; δ_H (400 MHz; $CDCl_3$) 7.29 (1H, s, CH), 6.84 (2H, d, *J* 9.1, ArH), 6.80 (2H, d, *J* 9.1, ArH), 6.66 (2H, t, *J* 8.4, ArH), 5.71 (1H, s, CH), 5.35 (2H, s, CH_2), 4.72 (2H, t, *J* 5.0, CH_2), 4.26 (2H, t, *J* 5.0, CH_2), 3.84 (3H, s, Me), 3.78 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 183.5, 172.1, 159.8, 157.3 (dt, *J* 245, 14, CF), 156.3 (ddd, *J* 250, 15, 8, CF) 154.3, 152.1, 132.2 (dt, *J* 15, 5, C) 131.6 (CH), 127.2, 124.3, 120.6, 115.6 (CH), 114.7 (CH), 107.2 (CH), 100.7 (ddd, *J* 27, 26, 8, CH), 68.6 (CH_2), 67.2 (CH_2), 56.7 (Me), 55.7 (Me), 48.9 (CH_2); *m*/*z* (ESI) 510 (M + Na^+, 100%); HPLC: purity (AUC) 100%.

1-(2-Hydroxyethyl)-6-methoxy-3-(2,4,6-trifluorophenoxy)methyl-1*H*-indole-4,7-dione 18. A solution of cerium(IV) ammonium nitrate (2.74 g, 5.0 mmol) in water (10 mL) was added as a single portion to a stirred solution of 6-methoxy-1-(2-(4-methoxyphenoxy)ethyl)-3-((2,4,6-trifluorophenoxy)methyl)-1*H*-indole-4,7-dione **17** (0.924 g, 2.0 mmol) in DMF (20 mL), and the resulting mixture was stirred at room temperature for 15 h. Water (150 mL) was added, and the mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were washed with water (50 mL), dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ethyl acetate and dichloromethane (1 : 3) gave the *title compound* as a yellow-orange solid (0.732 g, 96%), mp 143–145 °C; (Found: M + Na^+, 404.0717. $C_{18}H_{14}F_3NO_5Na$ requires 404.0716); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1644, 1602, 1510; δ_H (400 MHz; $CDCl_3$) 7.24 (1H, s, CH), 6.69 (2H, t, *J* 8.3, ArH), 5.68 (1H, s, CH), 5.31 (2H, s, CH_2), 4.51 (2H, t, *J* 5.1, CH_2), 4.00 (2H, t, *J* 5.1, CH_2), 3.83 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 183.5, 172.2, 159.9, 157.4 (dt, *J* 246, 14), 156.2 (ddd, *J* 250, 15, 7), 132.3 (dt, *J* 15, 5), 131.3 (CH), 127.5, 124.2, 120.7, 107.2 (CH), 100.7 (ddd, *J* 27, 26, 8, CH), 68.6 (CH_2), 61.9 (CH_2), 56.7 (Me), 51.6 (CH_2); *m*/*z* (ESI) 404 (M + Na^+, 100%); HPLC: purity (AUC) 97.6%.

6-Methoxy-1-(3-(4-methoxyphenoxy)propyl)-3-(2,4,6-trifluorophenoxy)methyl-1*H*-indole-4,7-dione. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-(3-(4-methoxyphenoxy)propyl)-1*H*-indole-4,7-dione **29d** (0.266 g, 0.72 mmol) and 2,4,6-trifluorophenol (0.531 g, 3.58 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (1 : 49) gave the *title compound* as a yellow solid (0.316 g, 88%), mp 138–140 °C; (Found: M + Na^+, 524.1280. $C_{26}H_{22}F_3NO_6Na$ requires 524.1291); ν_{max} ($CHCl_3$)/cm^{-1} 3009, 2938, 1668, 1644, 1602, 1509; δ_H (400 MHz; $CDCl_3$) 7.15 (1H, s, CH), 6.84 (4H, s, ArH), 6.67 (2H, t, *J* 8.4, ArH), 5.71 (1H, s, CH), 5.32 (2H, s, CH_2), 4.56 (2H, t, *J* 6.7, CH_2), 3.93 (2H, t, *J* 5.9, CH_2), 3.84 (3H, s, Me), 3.79 (3H, s, Me), 2.28 (2H, tt, *J* 6.7, 5.9, CH_2); δ_C (75 MHz; $CDCl_3$) 183.6, 171.8, 159.9, 157.4 (dt, *J* 245, 14), 156.6 (ddd, *J* 250, 15, 8), 154.1, 152.6, 132.0 (dt, *J* 15, 5) 130.7 (CH), 127.5, 124.2, 120.6, 115.5 (CH), 114.7 (CH), 107.1 (CH), 100.7 (ddd, *J* 27, 26, 8, CH), 68.5 (CH_2), 64.8 (CH_2), 56.6 (Me), 55.7 (Me), 46.6 (CH_2), 30.2 (CH_2); *m*/*z* (ESI) 524 (M + Na^+, 100%).

1-(3-Hydroxypropyl)-6-methoxy-3-(2,4,6-trifluorophenoxy)methyl-1*H*-indole-4,7-dione 19. A solution of cerium(IV) ammonium nitrate (0.785 g, 1.43 mmol) in water (15 mL) was added to a stirred solution of 6-methoxy-1-(3-(4-methoxyphenoxy)propyl)-3-((2,4,6-trifluorophenoxy)methyl)-1*H*-indole-4,7-dione (0.287 g, 0.57 mmol) in DMF (15 mL), and the resulting mixture was stirred at room temperature for 1.5 h. Water (100 mL) was added and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with water (25 mL), dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with ethyl acetate and dichloromethane (1 : 6) gave the *title compound* as a yellow solid (0.206 g, 92%), mp 129–131 °C; (Found: M + Na^+, 418.088. $C_{19}H_{16}F_3NO_5Na$ requires 418.0873); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3011, 1644, 1602, 1510; δ_H (400 MHz; $CDCl_3$) 7.19 (1H, s, CH), 6.70 (2H, t, *J* 8.6, ArH), 5.72 (1H, s, CH), 5.34 (2H, s, CH_2), 4.50 (2H, t, *J* 6.6, NCH_2), 3.84 (3H, s, OMe), 3.65 (2H, t, *J* 5.6, CH_2OH), 2.07 (2H, m, CH_2), 1.90 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 183.5, 172.1, 159.9, 157.4 (dt, *J* 246, 14), 156.3 (ddd, *J* 250, 15, 8), 132.2 (dt, *J* 15, 5), 131.7 (CH), 127.6, 124.1, 121.0, 107.1 (CH), 100.7 (ddd, *J* 27, 26, 8, CH), 68.6 (CH_2), 58.7 (CH_2), 56.7 (Me), 45.9 (CH_2), 33.4 (CH_2); *m*/*z* (ESI) 418 (M + Na^+, 100%); HPLC: purity (AUC) 99.2%.

1-(2-(Dimethylamino)ethyl)-6-methoxy-3-(2,4,6-trifluorophenoxy)methyl-1*H*-indole-4,7-dione 20. Prepared by general procedure 3 from 1-(2-(dimethylamino)ethyl)-3-hydroxymethyl-6-methoxy-1*H*-indole-4,7-dione **29e** (0.182 g, 0.65 mmol) and 2,4,6-trifluorophenol (0.484 g, 3.27 mmol). Column chromatography eluting with methanol and ethyl acetate (19 : 1) gave the *title compound* as an orange solid (0.142 g, 54%), mp 76–78 °C; (Found: M + Na^+, 409.1369. $C_{20}H_{20}F_3N_2O_4Na$ requires 409.1370); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2957, 1644, 1602, 1510; δ_H (400 MHz; $CDCl_3$) 7.19 (1H, s, CH), 6.69 (2H, t, *J* 8.4, ArH), 5.71 (1H, s, CH), 5.34 (2H, s, CH_2O), 4.46 (2H, t, *J* 6.8, CH_2), 3.84 (3H, s, OMe), 2.71 (2H, t, *J* 6.8, CH_2), 2.33 (6H, s, Me); δ_C

(75 MHz; $CDCl_3$) 183.6, 171.9, 159.9, 157.3 (dt, *J* 246, 14), 156.2 (ddd, *J* 250, 15, 7), 132.2 (dt, *J* 15, 5), 130.5 (CH), 127.4, 124.0, 120.7, 107.1 (CH), 100.7 (td, *J* 27, 8, CH), 68.6 (CH_2), 59.3 (CH_2), 56.6 (Me), 47.0 (CH_2), 45.5 (Me); *m*/*z* (ESI) 409 (M + H^+, 100%); HPLC: purity (AUC) 97.0%.

6-Methoxy-1-(2-morpholinoethyl)-3-(2,4,6-trifluorophenoxy)-methyl-1*H*-indole-4,7-dione 21. Prepared by general procedure 3 from 3-hydroxymethyl-6-methoxy-1-(2-morpholinoethyl)-1*H*-indole-4,7-dione **29f** (0.208 g, 0.65 mmol) and 2,4,6-trifluorophenol (0.481 g, 3.25 mmol). Column chromatography eluting with ethyl acetate gave the *title compound* as a yellow solid (0.166 g, 57%), mp 101–103 °C; (Found: M + H^+, 451.1496. $C_{22}H_{22}N_2O_5F_3$ requires 451.1475); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1668, 1644, 1602, 1507; δ_H (400 MHz; $CDCl_3$) 7.20 (1H, s, CH), 6.70 (2H, t, *J* 8.4, ArH), 5.72 (1H, s, CH), 5.35 (2H, s, CH_2), 4.48 (2H, t, *J* 6.6, NCH_2), 3.84 (3H, s, OMe), 3.470 (4H, t, *J* 4.7, OCH_2), 2.75 (2H, t, *J* 6.6, CH_2N), 2.55 (4H, t, *J* 4.7, NCH_2); δ_C (75 MHz; $CDCl_3$) 183.6, 171.9, 159.9, 157.3 (dt, *J* 246, 14), 156.2 (ddd, *J* 250, 15, 7), 132.3 (dt, *J* 15, 5), 130.4 (CH), 127.5, 123.9, 120.8, 107.1 (CH), 100.7 (ddd, *J* 27, 26, 9, CH), 68.8 (CH_2), 66.9 (CH_2), 58.6 (CH_2), 56.7 (Me), 53.7 (CH_2), 46.4 (CH_2); *m*/*z* (ESI) 451 (M + H^+, 100%); HPLC: purity (AUC) 99.0%.

6-Ethoxy-1-(2-morpholinoethyl)-3-(2,4,6-trifluorophenoxy)-methyl-1*H*-indole-4,7-dione 22. Prepared by general procedure 3 from 6-ethoxy-3-hydroxymethyl-1-(2-morpholinoethyl)-1*H*-indole-4,7-dione **29g** (0.172 g, 0.51 mmol) and 2,4,6-trifluorophenol (0.381 g, 2.57 mmol). Column chromatography eluting with ethyl acetate gave the *title compound* as an orange oil (0.162 g, 68%); (Found: M + H^+, 565.1645. $C_{23}H_{24}N_2O_5F_3$ requires 465.1632); ν_{max} ($CHCl_3$)/cm^{-1} 3045, 2999, 1674, 1639, 1599, 1509; δ_H (400 MHz; $CDCl_3$) 7.09 (1H, s, CH), 6.69 (2H, t, *J* 8.4, ArH), 5.63 (1H, s, CH), 5.33 (2H, s, CH_2), 4.487 (2H, t, *J* 6.6, CH_2), 4.00 (2H, q, *J* 7.0, CH_2), 3.70 (4H, t, *J* 4.6, CH_2), 2.73 (2H, t, *J* 6.6, CH_2), 2.53 (4H, t, *J* 4.6, CH_2), 1.49 (3H, t, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$) 179.2, 177.7, 159.4, 157.3 (dt, *J* 246, 15), 156.2 (ddd, *J* 250, 15, 8), 132.3 (dt, *J* 15, 5), 129.2, 128.4 (CH), 121.3, 120.8, 107.2 (CH), 100.7 (ddd, *J* 27, 26, 5), 68.6 (CH_2), 66.9 (CH_2), 65.3 (CH_2), 58.7 (CH_2), 53.7 (CH_2), 45.9 (CH_2), 13.9 (Me); *m*/*z* (ESI) 465 (M + H^+, 100%); HPLC: purity (AUC) 98.0%.

5-Methoxy-6-methyl-1-(2-morpholinoethyl)-3-(2,4,6-trifluorophenoxy)methyl-1*H*-indole-4,7-dione 23. Prepared by general procedure 3 from 3-hydroxymethyl-5-methoxy-6-methyl-1-(2-morpholinoethyl)-1*H*-indole-4,7-dione **29h** (0.218 g, 0.65 mmol) and 2,4,6-trifluorophenol (0.483 g, 3.26 mmol). Column chromatography eluting with ethyl acetate and dichloromethane (2 : 1) gave the *title compound* as a yellow solid (0.200 g, 66%), mp 94–96 °C; (Found: M + H^+, 465.1642. $C_{23}H_{24}N_2O_5F_3$ requires 465.4417); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1642, 1602, 1509; δ_H (400 MHz; $CDCl_3$) 7.07 (1H, s, CH), 6.69 (2H, t, *J* 8.4, ArH), 5.33 (2H, s, CH_2), 4.45 (2H, t, *J* 6.5, CH_2), 4.01 (3H, s, Me), 3.70 (4H, t, *J* 4.6, CH_2), 2.72 (2H, t, *J* 6.5, CH_2), 2.54 (4H, t, *J* 4.6, CH_2), 1.97 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 179.4, 179.3, 157.3 (dt, *J* 231, 14), 156.6, 156.2 (ddd, *J* 250, 15, 7), 132.2 (td, *J* 15, 5), 129.1, 128.8 (CH), 121.6, 120.3, 100.7 (ddd, *J* 27, 26, 8, CH), 68.5 (CH_2), 66.9 (CH_2), 61.1 (Me), 58.6 (CH_2), 53.7 (CH_2), 46.1 (CH_2), 8.73 (Me); one carbon unobserved; *m*/*z* (ESI) 465 (M + H^+, 100%); HPLC: purity (AUC) 97.7%.

3-(2,5-Dioxopyrrolidin-1-yloxy)methyl-1-methyl-1*H*-benz[*f*]-indole-4,9-dione 24. Prepared by general procedure 3 from 3-hydroxymethyl-1-methyl-1*H*-benz[*f*]indole-4,9-dione **29i** (50.0 mg, 0.207 mmol) and *N*-hydroxysuccinimide (167 mg, 1.45 mmol). Column chromatography eluting with ethyl acetate–dichloromethane (2 : 8) gave the *title compound* as a yellow solid (56.0 mg, 80%); mp 223–225 °C; (Found: M + Na^+, 361.0784. $C_{18}H_{14}N_2O_5Na$ requires 361.0795); λ_{max} (acetonitrile)/nm 253 (log ε 4.47), 279 (4.18), 327 (3.75), 387 (3.50); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 1729, 1658, 1257; δ_H (400 MHz; $CDCl_3$) 8.16–8.11 (2H, m, H-5, H-8), 7.71–7.66 (2H, m, H-6, H-7), 7.18 (1H, s, H-2), 5.41 (2H, s, CH_2), 4.10 (3H, s, Me), 2.66 (4H, s, CH_2); δ_C (100 MHz; $CDCl_3$) 181.7, 176.4, 171.4, 133.8, 133.6, 133.3 (CH), 132.7 (CH), 131.2, 126.43 (CH), 126.36 (CH), 125.5, 118.0, 69.5 (CH_2), 37.0 (Me), 25.5 (CH_2); HPLC: purity (AUC) 98.4%.

1-Methyl-3-(4-methylsulfonylphenoxy)methyl-1*H*-benz[*f*]-indole-4,9-dione 25. Prepared by general procedure 3 from 3-hydroxymethyl-1-methyl-1*H*-benz[*f*]indole-4,9-dione **29i** (50.0 mg, 0.207 mmol) and 4-methylsulfonylphenol (250 mg, 1.45 mmol). Column chromatography eluting with ethyl acetate–dichloromethane (1 : 9) gave the *title compound* as a yellow solid (58.0 mg, 71%); mp 210–212 °C; (Found: M + Na^+, 418.0719. $C_{21}H_{17}NO_5SNa$ requires 418.0720); λ_{max} (acetonitrile)/nm 246 (log ε 4.47), 278 (4.09), 326 (3.64), 388 (3.43); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 1657, 1595, 1319, 1257, 1147; δ_H (400 MHz; $CDCl_3$) 8.19–8.13 (2H, m, H-5, H-8), 7.91–7.87 (2H, m, H-6, H-7), 7.73–7.69 (2H, m, ArH), 7.16–7.13 (2H, m, ArH), 7.02 (1 H, s, H-2), 5.49 (2H, s, CH_2), 4.09 (3H, s, NMe), 3.05 (3H, s, SO_2Me); δ_C (100 MHz; $CDCl_3$) 181.7, 176.3, 162.6, 133.8, 133.7, 133.28 (CH), 133.26 (CH), 132.6, 131.1, 130.1 (CH), 129.6 (CH), 126.5 (CH), 126.4 (CH), 124.6, 120.4, 115.2 (CH), 63.2 (CH_2), 44.8 (Me), 36.9 (Me); HPLC: purity (AUC) 98.2%.

Cancer growth inhibition assay

All human cancer cell lines were obtained from ATCC. The ability of indolequinones to induce growth inhibition in human cancer cell lines was measured using the MTT assay as previously described.[16,17]

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