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ORIGINAL PAPER

Synthesis of new Benzo[*f*]isoindole-4,9-diones as anticancer compounds

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Abstract The design and synthesis of monosubstituted and disubstituted azanaphthoquinone annelated pyrroles with anticancer activity are described. N-alkylation with various side chains at the pyrrole ring led to a series of monosubstituted products. For preparation of disubstituted isoindole derivatives, appropriately substituted tosyl methyl isocyanides were used. The biological activity of all the compounds was evaluated against a number of cancer cell lines.

Keywords Anticancer agent · N-Heterocycles · Isoindoles · Alkylating agents

Introduction

Mitoxantrone, an anticancer agent used in the therapy of breast cancer, non-Hodgkin's lymphoma, acute myeloid leukaemia, and hormone refractory prostate cancer, and in various combination regimes, has probably become the most widely used synthetic DNA intercalating agent [1, 2]. The efficacy of this intercalating drug molecule is hampered by the onset of cardiotoxicity, however [3]. Maybe a solution for this severe cardiotoxicity problem has been found by synthesis of BBR 2778 (pixantrone), which is currently in phase III clinical trials in patients with non-Hodgkin's lymphoma. This compound has a better therapeutic index and lower cardiotoxicity than mitoxantrone [4]. It seems that these advantages are based predominantly on the substitution of the 5,8-dihydroxybenzene moiety in mitoxantrone by a pyridine ring (Fig. 1) [5].

The rationale for the reported syntheses is the question whether substitution of the bis-amino-substituted benzene ring in BBR 2778 by a pyrrole ring would also lead to compounds with suitable cytotoxic properties. This seems reasonable, because the π-electron surplus aromatic system of the pyrrole ring would substitute a phenyl ring connected to two amino groups with distinct electron donating effects. In this paper we report the synthesis of derivatives with a [*c*]-annelated pyrrole moiety, thus furnishing a series of naphthoquinone annelated isoindole structures. Moreover it should be emphasized that the isoindole core annelated with a naphthoquinone moiety is found in natural products such as azamonosporascone and bhimamycin C or D, which have distinct biological activity including activity against different cancer cell lines [6–8].

In face of the fact that the main core of the synthesized compounds is a tricyclic system it should allow intercalation, in the same way as mitoxantrone and pixantrone. Intercalation (insertion of the chromophore between base pairs) is driven primarily by stacking and electrostatic interactions [9]. Because intercalation is a reversible binding process to the DNA the side chains attached to the isoindole nucleus were predominantly provided with alkylating groups (oxiranyl, aziridinyl, mesylate) and/or amino groups. As a consequence, alkylation should lead to irreversible connection of drug and DNA. In addition, side chains with amino groups can enhance binding to double-helical DNA by interaction with the phosphate "back-bone" of the DNA.

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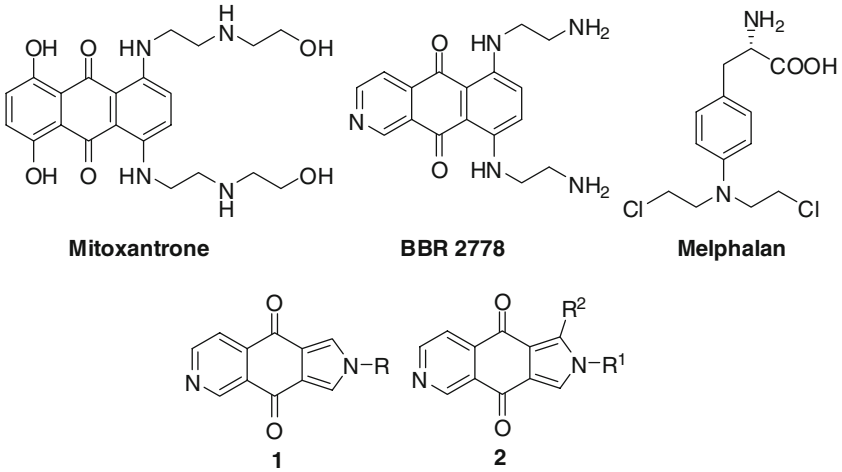


Fig. 1 Structures of mitoxantrone, BBR 2778, and melphalan, monosubstituted (**1**) and disubstituted (**2**) azanaphthoquinone [*c*]-annelated pyrroles

Moreover, to obtain the first information about structure–activity relationships, the side chains contain linkers of different length.

Results and discussion

Synthesis of monosubstituted isoindoles

The synthesis of monosubstituted products was performed as outlined in Scheme 1. Starting from isoindole **3** [10] the epoxy substituted derivatives **4a–4c** were prepared by N-alkylation with oxiranyl halides. In addition, reaction with aziridine gave access to the hydroxy-substituted aziridine derivatives **5a–5c**. The mesylated products **7a–7c** were synthesized by a three-step reaction sequence including N-alkylation with silyloxyalkyl halides, deprotection with tetrabutylammonium fluoride (TBAF), and subsequent mesylation with methanesulfonyl chloride. Finally nucleophilic substitution of mesylates **7a–7c** with aziridine furnished derivatives **8a–8c**.

Alkylation of isoindole **3** with *N*,*N*-dimethylaminoalkyl chlorides led to **11a–11b** (Scheme 2). In addition, the bis(2-chloroethyl)aminophenyl moiety was attached to the pyrrole ring via intermediate **9** to furnish product **10** as an analog of the well known and widely used anticancer drug melphalan [11]. This nitrogen mustard derivative is considered to act predominantly by DNA crosslinking via intermediately built aziridinium cations [12].

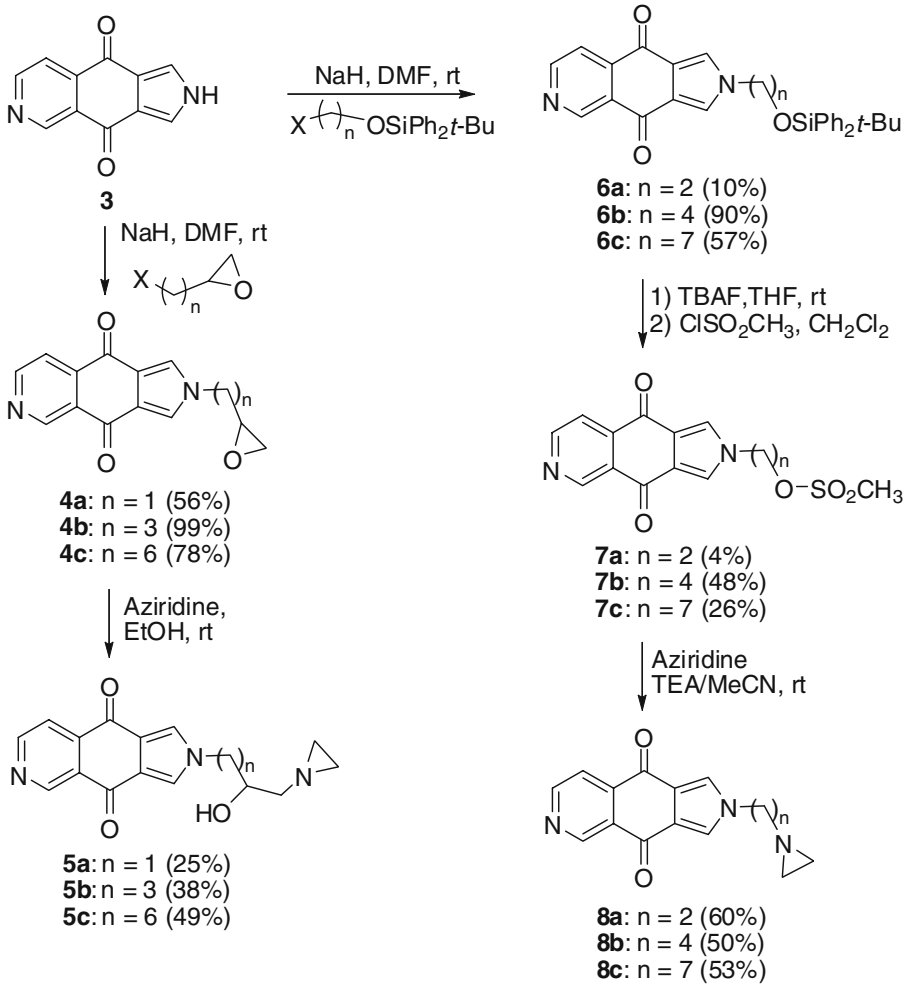
Synthesis of disubstituted isoindoles

The synthesis of disubstituted products was performed as outlined in Scheme 3. Starting from α,β-unsaturated ketone **12** [10] the cyclisation reaction for building up the pyrrole ring was realized in a way similar to that already exploited for preparation of **3** [10]. To achieve the intended substitution pattern, first the appropriately substituted TosMIC derivative **13** had to be synthesized according to Ref. [13]. Ring closure to isoindole **14** occurred smoothly and was followed by N-alkylation with *N*,*N*-dimethylaminopropyl chloride yielding **15**. Cleavage of the ketal function (with PPTS) and deprotection of the THPO-protected alcohol (with *p*-TsOH) led to **16**. Subsequently the HO group was converted via mesylate **17** to aziridine and amine-substituted derivatives **18a–18c**.

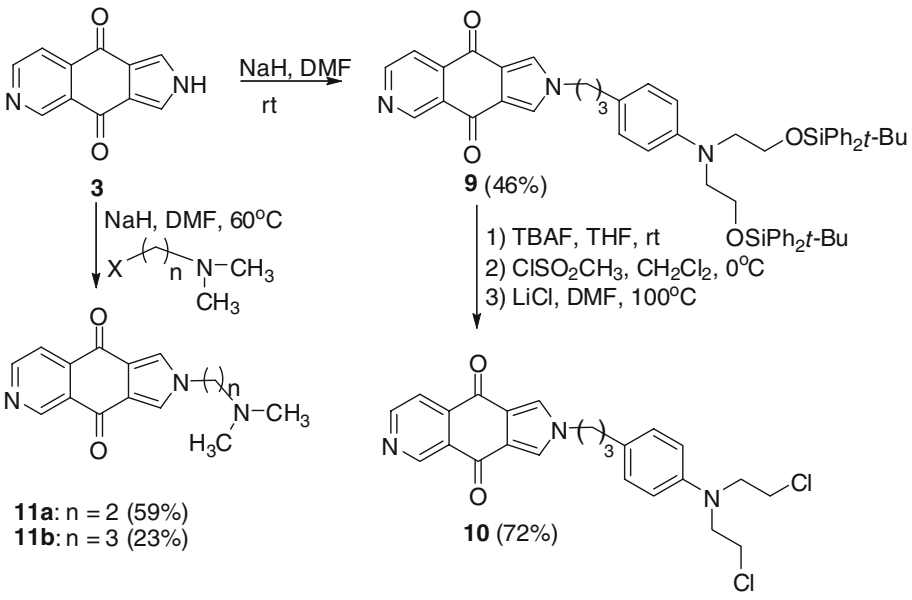
The biological activity of all synthesized target compounds (**4a–5c**, **7a–8c**, **10**, **11a–11 b**, **16**, **17**, **18a–18c**) was tested in vitro at Zentaris, Germany. The cytotoxicity was evaluated on five different cell lines, cervix cancer (KB), ovarian carcinoma (SK-OV-3), brain cancer (SF-268), non-small-cell lung cancer (NCl-H460), and adenocarcinoma colon cancer (RKOP-27) [14, 15]. The first screening was carried out at a predefined concentration of 3.16 μg cm^{-3}. If the compound led to more than 50% inhibition at this concentration it was evaluated for EC_{50} mean values (μM) from at least two experiments on those five different cell lines.

The results showed that only five monosubstituted compounds (**4a**, **5b**, **5c**, **8b**, **8c**) and one disubstituted compound **18c** exhibited moderate activity, as summarized in Table 1. It seems evident that the substitution of the bis-amino substituted benzene ring by a pyrrole ring led to compounds with a poor biological activity. Attachment of side chains with neither basic amino groups nor alkylating groups led to satisfactory activity with EC_{50} values in the nM range. Moreover no structure–activity relationships are noticeable. Further studies will give a clear answer to the question about the effects on cytotoxic impact of different kinds of annelation ([*c*] and [*b*]-annelation) of the pyrrole ring to the azanaphthoquinone nucleus.

Scheme 1



Scheme 2



Scheme 3

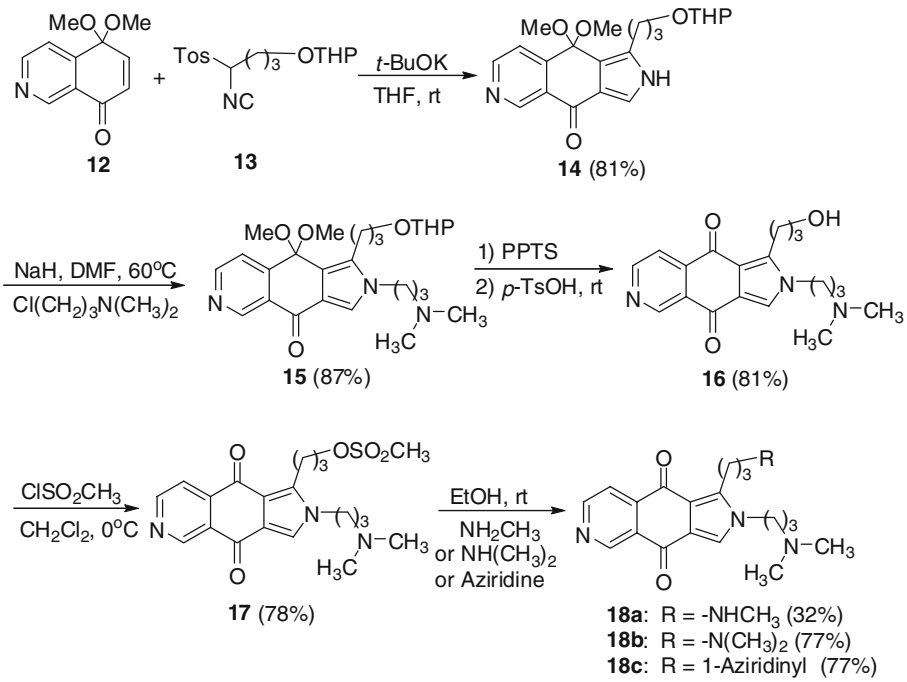


Table 1 Cytotoxic activity of test compounds toward five cancer cell lines

Compound	EC_{50} (μM)				
	KB	SKOV3	SF268	NCIH460	RKOP27
4a	3.269	>12	2.082	>12	6.852
5b	2.192	>12	7.166	4.622	2.604
5c	2.841	>12	8.426	10.410	4.270
8b	2.081	>12	1.446	2.143	1.401
8c	2.833	>12	1.437	>12	1.583
18c	3.727	>12	>12	–	0.808

Experimental

^{1}H NMR spectra were recorded on a Bruker DPX200 spectrometer (^{1}H 200 MHz, ^{13}C 50 MHz). Chemical shifts are reported in ppm using TMS as internal standard. IR spectra were recorded on a Perkin–Elmer 298 or a Perkin–Elmer Spectrum 1000 FT-IR spectrometer. Mass spectra were recorded on Hewlett–Packard GC–MS equipment (GC 5890, MS 5970). Melting points were determined on a Kofler-type Leica Galen III micro hot-stage microscope. Thin-layer chromatography (TLC) was performed on silica gel 60 PF254 plates or aluminum oxide plates from Merck. Column chromatography was performed on silica gel 60 from Merck (70–230 mesh ASTM) or on alumina B (aluminum oxide), activity III from ICN. Unless otherwise noted chemicals were purchased from commercial suppliers and used without further purification.

General procedure I: N-alkylation reactions

NaH (60% suspension in oil) was washed three times with hexane before dissolution in DMF under Ar. The solution was cooled to 0 °C, then starting material was added dropwise. The reaction mixture was stirred for additional 0.5 h at 0 °C. Afterwards the appropriate alkyl halide (dissolved in DMF) was added and the reaction mixture was stirred at room temperature or at 60 °C until completion of the reaction. Afterwards water was added and the mixture was extracted with EtOAc. The combined extracts were dried ($MgSO_4$), filtered, and concentrated and purified by column chromatography.

2-(Oxiran-2-ylmethyl)-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**4a**, $C_{14}H_{10}N_2O_3$)

Following general procedure I, NaH (0.083 g, 2.06 mmol) in DMF (4 cm^3), **3** (0.408 g, 2.06 mmol) in DMF (4 cm^3), and epichlorohydrin (0.24 cm^3, 3.09 mmol) were used. The reaction mixture was stirred at room temperature for 24 h. The crude product was purified by column chromatography (aluminum oxide; EtOAc/light petroleum, 1/1) to obtain 0.295 g (56%) **4a** as an oil. ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.62$ (dd, $J = 4.8$, 2.5 Hz, 1H), 2.84 (dd, $J = 4.5$, 4.5 Hz, 1H), 3.41 (m, 1H), 4.15 (dd, $J = 14.3$, 6.1 Hz, 1H), 4.46 (dd, $J = 14.3$, 3.5 Hz, 1H), 7.76 (d, $J = 1.8$ Hz, 1H), 7.80 (d, $J = 1.8$ Hz, 1H), 7.87 (d, $J = 5.0$ Hz, 1H), 8.99 (d, $J = 5.0$ Hz, 1H), 9.19 (s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 45.1$, 50.3, 51.7, 118.8, 121.4, 121.4, 126.4, 126.8, 127.6, 140.3, 148.2, 154.8, 178.1, 178.7 ppm; IR (KBr): $\bar{\nu} = 1,659$,

1,583, 1,537, 1,240 cm^{-1}; HRMS: calcd. 254.0691, found 254.0687 ± 5 ppm.

2-[3-(Oxiran-2-yl)propyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**4b**, $C_{16}H_{14}N_2O_3$)

Following general procedure I, NaH (0.200 g, 5 mmol) in DMF (5 cm^3), **3** (0.800 g, 4 mmol) in DMF (6 cm^3), and 2-(3-bromopropyl)oxirane (0.729 g, 4.4 mmol) in DMF (8 cm^3) were used. The reaction mixture was stirred at room temperature for 48 h. The crude product was purified by column chromatography (aluminum oxide; EtOAc/light petroleum, 1/1) to obtain 1.140 g (99%) **4b**. M.p.: 162–168 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.30–1.65 (m, 2H), 1.80–2.05 (m, 2H), 2.43 (dd, J = 4.7, 2.7 Hz, 1H), 2.65 (dd, J = 4.7, 4.7 Hz, 1H), 2.80–3.00 (m, 1H), 4.13 (t, J = 7.0 Hz, 2H), 7.84 (s, 1H), 7.86 (s, 1H), 7.88 (d, J = 5.0 Hz, 1H), 8.99 (d, J = 5.0 Hz, 1H), 9.20 (s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ = 26.9, 28.7, 46.0, 49.7, 50.9, 118.8, 121.3, 121.4, 126.1, 126.5, 127.7, 140.4, 148.2, 154.8, 178.1, 178.6 ppm; IR (KBr): $\bar{\nu}$ = 3,113, 1,656, 1,582, 1,538, 1,238, 1,226 cm^{-1}; MS: *m/z* (%) = 282 (M^+, 25), 251 (35), 211 (49), 199 (48), 183 (33), 55 (100).

2-[6-(Oxiran-2-yl)hexyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**4c**, $C_{19}H_{20}N_2O_3$)

Following general procedure I, NaH (0.067 g, 1.7 mmol) in DMF (3 cm^3), **3** (0.300 g, 1.5 mmol) in DMF (4 cm^3), and 2-(6-bromohexyl)oxirane (0.350 g, 1.7 mmol) in DMF (4 cm^3) were used. The reaction mixture was stirred at room temperature for 18 h. The crude product was purified by column chromatography (aluminum oxide; EtOAc/MeOH, 9/1) to give 0.400 g (78%) **4c**. M.p.: 155–156 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.25–1.37 (m, 8H), 1.70–1.85 (m, 2H), 2.34 (dd, J = 5.0, 2.6 Hz, 1H), 2.59 (dd, J = 4.0, 4.0 Hz, 1H), 2.76–2.86 (m, 1H), 4.05 (t, J = 7.0 Hz, 2H), 7.82 (d, J = 1.7 Hz, 1H), 7.86 (d, J = 1.7 Hz, 1H), 7.89 (d, J = 5.0 Hz, 1H), 8.98 (d, J = 5.0 Hz, 1H), 9.20 (s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ = 25.3, 25.6, 28.2, 30.0, 31.8, 46.0, 49.9, 51.5, 118.8, 121.3, 121.3, 126.1, 126.6, 127.7, 140.4, 148.2, 154.8, 178.1, 178.7 ppm; IR (KBr): $\bar{\nu}$ = 3,108, 1,654, 1,583, 1,539, 1,417, 1,402, 1,239 cm^{-1}; MS: *m/z* (%) = 324 (M^+, 19.9), 293 (38), 212 (100), 183 (50).

General procedure II: reaction with aziridine and amines

The appropriate starting material (**4a**–**4c**) was dissolved in absolute EtOH in the presence of 1% triethylamine or acetonitrile/triethylamine (1/1) under Ar. The corresponding amines were added dropwise at room temperature. The reaction mixture was stirred at room temperature or heated under reflux until completion of the reaction. Afterwards, the solvent was removed and the residue was purified by column chromatography (aluminum oxide; EtOAc/MeOH, 9/1).

2-[3-(Aziridin-1-yl)-2-hydroxypropyl]-2H-pyrrolo-3,4-g]isoquinoline-4,9-dione (**5a**, $C_{16}H_{15}N_3O_3$)

Following general procedure II, the reaction mixture **4a** (0.142 g, 0.6 mmol) and aziridine (0.19 cm^3, 3.7 mmol) in EtOH (6 cm^3) was stirred at room temperature for 24 h and worked up as described to give 0.035 g (25%) **5a**. M.p.: 134–136 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.14 (dd, J = 2.7, 1.5 Hz, 2H), 1.61 (dd, J = 2.7, 1.5 Hz, 2H) 2.03 (dd, J = 12.0, 5.7 Hz, 1H), 2.31 (dd, J = 12.0, 5.7 Hz, 1H), 4.08 (dd, J = 13.3, 7.9 Hz, 2H), 4.31 (dd, J = 13.3, 2.7 Hz, 1H), 5.21 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 1.7 Hz, 1H), 7.79 (d, J = 1.7 Hz, 1H), 7.92 (d, J = 5.0 Hz, 1H), 9.02 (d, J = 5.0 Hz, 1H), 9.24 (s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ = 26.5, 26.7, 54.4, 64.3, 69.5, 118.9, 121.0, 121.0, 126.9, 127.4, 127.7, 140.5, 148.3, 154.9, 178.1, 178.7; IR (KBr): $\bar{\nu}$ = 3,241, 3,120, 1,665, 1,585, 1,447, 1,402, 1,239 cm^{-1}.

2-[5-(Aziridin-1-yl)-4-hydroxypentyl]-2H-pyrrolo-[3,4-g]isoquinoline-4,9-dione (**5b**, $C_{18}H_{19}N_3O_3$)

Following general procedure II, the reaction mixture **4b** (0.700 g, 2.5 mmol) and aziridine (0.87 cm^3, 16.9 mmol) in EtOH (26.8 cm^3) was stirred and heated under reflux for 2 h and worked up as described to give 0.310 g (38%) **5b**. M.p.: 150–156 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.90–1.10 (m, 2H), 1.10–1.35 (m, 2H), 1.40–1.60 (m, 2H), 1.70–2.00 (m, 2H), 2.00 (dd, J = 11.8, 6.0 Hz, 1H), 2.13 (dd, J = 11.8, 6.0 Hz, 1H), 3.55 (S_{br}, 1H), 4.11 (t, J = 6.9 Hz, 2H), 4.55 (d, J = 3.5 Hz, 1H), 7.84 (d, J = 1.7 Hz, 1H), 7.88 (d, J = 1.7 Hz, 1H), 7.89 (d, J = 5.0 Hz, 1H), 9.00 (d, J = 5.0 Hz, 1H), 9.22 (s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ = 26.3, 26.6, 26.8, 31.7, 50.2, 67.4, 69.3, 118.9, 121.3, 121.3, 126.2, 126.6, 127.7, 140.4, 148.2, 154.8, 178.1, 178.7 ppm; IR (KBr): $\bar{\nu}$ = 3,392, 3,113, 1,657, 1,585, 1,541, 1,238 cm^{-1}; MS: *m/z* (%) = 325 (M^+, 0.3), 282 (1.7), 269 (6.4), 126 (2.2), 56 (100).

2-[8-(Aziridin-1-yl)-7-hydroxyoctyl]-2H-pyrrolo-[3,4-g]isoquinoline-4,9-dione (**5c**, $C_{21}H_{25}N_3O_3$)

Following general procedure II, the reaction mixture **4c** (0.304 g, 0.9 mmol) and aziridine (0.33 cm^3, 6.3 mmol) in EtOH (10 cm^3) was stirred and heated under reflux for 2 h and worked up as described to give 0.190 g (49%) **5c**. M.p.: 137-138 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00–1.55 (m, 11H), 1.65–2.08 (m, 5H), 2.35–2.50 (m, 1H), 3.55–3.70 (m, 1H), 4.01 (t, J = 7.0 Hz, 2H), 7.43 (s, 2H), 7.97 (d, J = 5.0 Hz, 1H), 8.97 (d, J = 5.0 Hz, 1H), 9.43 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$):

δ = 25.3, 26.3, 26.8, 27.4, 28.9, 30.6, 34.5, 51.1, 67.4, 70.5, 119.1, 122.3, 122.4, 124.6, 124.9, 128.0, 140.8, 149.2, 154.6, 178.8, 179.4 ppm; IR (KBr): $\bar{\nu}$ = 3,109, 1,655, 1,583, 1,539, 1,239 cm^{-1}; MS: *m/z* (%) = 367 (M^+, 1.6), 311 (6.8), 211 (1.4), 56 (100).

2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-2H-pyrrolo-[3,4-g]isoquinoline-4,9-dione (**6a**, $C_{29}H_{28}N_2O_3Si$)
Following general procedure I, the reaction mixture NaH (0.133 g, 5.6 mmol) in DMF (6.8 cm^3), **3** (0.684 g, 3.4 mmol) in DMF (6.8 cm^3), and 2-bromoethoxy(*tert*-butyl)diphenylsilane (1.881 g, 5.2 mmol) in DMF (10.3 cm^3) was stirred at room temperature for 20 h. The crude product was purified by column chromatography (aluminum oxide; DCM) to give 0.157 g (10%) **6a** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 9H), 3.94 (t, *J* = 5.1 Hz, 2H), 4.13 (t, *J* = 5.1 Hz, 2H), 7.27–7.52 (m, 12H), 8.03 (d, *J* = 5.0 Hz, 1H), 9.02 (d, *J* = 5.0 Hz, 1H), 9.50 (s, 1H) ppm; MS: *m/z* (%) = 423 (M^+-57, 100), 345 (35), 197 (17), 105 (23).

2-[4-(tert-Butyldiphenylsilyloxy)butyl]-2H-pyrrolo-[3,4-g]isoquinoline-4,9-dione (**6b**, $C_{31}H_{32}N_2O_3Si$)
Following general procedure I, the reaction mixture NaH (0.080 g, 3.4 mmol) in DMF (5 cm^3), **3** (0.600 g, 3.1 mmol) in DMF (5 cm^3), and 4-chlorobutoxy(*tert*-butyl)diphenylsilane (1.160 g, 3.4 mmol) in DMF (8 cm^3) was stirred and heated under reflux for 4 h. The crude product was purified by column chromatography (aluminum oxide; DCM) to give 1.419 g (90%) **6b**. M.p.: 173–174 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (s, 9H), 1.45–1.70 (m, 2H), 1.85–2.10 (m, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 4.02 (t, *J* = 7.1 Hz, 2H), 7.28–7.50 (m, 8H), 7.55–7.75 (m, 4H), 8.00 (d, *J* = 5.0 Hz, 1H), 8.99 (d, *J* = 5.0 Hz, 1H), 9.47 (s, 1H) ppm; MS: *m/z* (%) = 508 (M^+, 0.07) 493 (0.3), 451 (100), 183 (16), 105 (5).

2-[7-(tert-Butyldiphenylsilyloxy)heptyl]-2H-pyrrolo-[3,4-g]isoquinoline-4,9-dione (**6c**, $C_{34}H_{38}N_2O_3Si$)
Following general procedure I, the reaction mixture NaH (0.330 g, 8.3 mmol) in DMF (12 cm^3), **3** (1.500 g, 7.6 mmol) in DMF (15 cm^3), and 7-chloroheptoxy(*tert*-butyl)diphenylsilane (3.610 g, 8.3 mmol) in DMF (20 cm^3) was stirred at room temperature for 18 h. The crude product was purified by column chromatography (aluminum oxide; DCM) to give 2.360 g (57%) **6c**. M.p.: 135–136 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (s, 9H), 1.20–1.40 (m, 6H), 1.45–1.60 (m, 2H), 1.75–1.95 (m, 2H), 3.64 (t, *J* = 6.3 Hz, 2H), 4.00 (t, *J* = 7.1 Hz, 2H), 7.28–7.48 (m, 8H), 7.55–7.73 (m, 4H), 8.00 (d, *J* = 5.0 Hz, 1H), 8.99 (d, *J* = 5.0 Hz, 1H), 9.47 (s, 1H) ppm; MS: *m/z* (%) = 535 (M^+-15, 0.5), 493 (M^+-57, 100), 295 (4), 199 (16), 183 (7).

General procedure III: deprotection of silyl ethers

The starting material was dissolved in absolute THF. Then 1 M tetrabutylammonium fluoride (TBAF) in THF was added and the reaction mixture was stirred at room temperature for an additional 1.5–5 h. Afterwards, water was added and the mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), the solvents were removed by distillation, and the residue was purified by column chromatography.

General procedure IV: reaction with methanesulfonyl chloride

The alcohol obtained was dissolved in DCM in the presence of a small amount (2–3 drops) of triethylamine under Ar. Afterwards the mixture was cooled to 0 to −10 °C. Then methanesulfonyl chloride was added dropwise and the reaction mixture was stirred at this temperature for an additional 0.25–2 h. Afterwards the solvent was removed at room temperature under reduced pressure. The crude product obtained was purified by column chromatography (aluminum oxide; EtOAc/MeOH, 98/2) to give the mesylated products.

2-(4,9-Dihydro-4,9-dioxo-2H-pyrrolo[3,4-g]isoquinolin-2-yl)ethyl methanesulfonate (**7a**, $C_{14}H_{12}N_2O_5S$)
Mesylate **7a** was prepared in a two-step reaction (according to general procedures III and IV).

1. The reaction mixture **6a** (2.085 g, 4.3 mmol) and 1 M TBAF (8.8 cm^3, 8.8 mmol) in THF (29 cm^3) was stirred at room temperature for 5 h. After purification by column chromatography (aluminum oxide; EtOAc) 0.137 g (13%) of the corresponding alcohol was obtained. M.p.: 221–222 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.81 (d, *J* = 4.7 Hz, 2H), 4.21 (d, *J* = 4.7 Hz, 2H), 5.05 (s, 1H), 7.86 (s, 1H), 7.89 (s, 1H), 7.98 (d, *J* = 5.1 Hz, 1H), 9.08 (d, *J* = 5.1 Hz, 1H), 9.30 (s, 1H) ppm; MS: *m/z* (%) = 242 (M^+, 83), 211 (60), 198 (86), 115 (34), 43 (100).

2. The alcohol obtained (0.185 g, 0.8 mmol), methanesulfonyl chloride (0.07 cm^3), and triethylamine (0.16 cm^3) in DCM (7 cm^3) gave 0.120 g (29%) **7a** as an oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.15 (s, 3H), 4.55 (d, *J* = 4.8 Hz, 2H), 4.67 (d, *J* = 4.8 Hz, 2H), 7.89–7.95 (m, 3H), 9.03 (br s, 1H), 9.26 (br s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 36.6, 49.2, 68.7, 119.1, 121.5, 121.5, 126.6, 127.0, 127.9, 140.7, 148.1, 154.6, 178.1, 178.6 ppm; IR (KBr): $\bar{\nu}$ = 3,420, 1,669, 1,584, 1,540, 1,344, 1,242 cm^{-1}; MS: *m/z* (%) = 320 (M^+, 75.3), 224 (64), 211 (100), 183 (29).

4-(4,9-Dihydro-4,9-dioxo-2H-pyrrolo[3,4-g]isoquinolin-2-yl)butyl methanesulfonate (**7b**, $C_{16}H_{16}N_2O_5S$)
Mesylate **7b** was prepared in a two-step reaction (according to general procedures III and IV).

1. The reaction mixture **6b** (2.200 g, 4.3 mmol) and 1 M TBAF (8.7 cm^3, 8.7 mmol) in THF (29 cm^3) was stirred at room temperature for 5 h. After purification by column chromatography (aluminum oxide; EtOAc/MeOH, 9/1) 0.704 g (60%) of the corresponding alcohol was obtained. M.p.: 217–218 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.36$ (quint, $J = 6.7$ Hz, 2H), 1.82 (quint, $J = 6.7$ Hz, 2H), 3.41 (t, $J = 6.0$ Hz, 2H), 4.10 (t, $J = 7.0$ Hz, 2H), 4.47 (t, $J = 5.3$ Hz, 1H), 7.78–7.92 (m, 3H), 8.98 (d, $J = 5.0$ Hz, 1H), 9.19 (s, 1H) ppm; MS: *m/z* (%) = 270 (M^+, 100), 242 (22), 213 (69), 199 (44), 183 (27).

2. The alcohol obtained (0.593 g, 2.8 mmol), methanesulfonyl chloride (0.26 cm^3, 3.4 mmol), and triethylamine (0.59 cm^3) in DCM (26 cm^3) gave 0.780 g (80%) **7b**. M.p.: 135–136 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.50$–1.72 (m, 2H), 1.80–2.00 (m, 2H), 3.16 (s, 3H), 4.05–4.35 (m, 4H), 7.75–8.00 (m, 3H), 9.00 (d, $J = 4.8$ Hz, 1H), 9.22 (s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 25.5$, 26.4, 36.5, 49.4, 69.7, 118.9, 121.4, 121.4, 126.1, 126.6, 127.7, 140.4, 148.2, 154.8, 178.1, 178.7 ppm; IR (KBr): $\bar{\nu} = 3{,}120$, 1,667, 1,583, 1,537, 1,452, 1,353 cm^{-1}; MS: *m/z* (%) = 252 (M^+-SO_3Me, 70), 237 (32), 223 (13), 96 (57), 79 (100).

7-(4,9-Dihydro-4,9-dioxo-2H-pyrrolo[3,4-g]isoquinolin-2-yl)heptyl methanesulfonate (**7c**, $C_{19}H_{22}N_2O_5S$)

Mesylate **7c** was prepared in a two-step reaction (according to general procedures III and IV).

1. The reaction mixture of **6c** (2.300 g, 4.2 mmol) and 1 M TBAF (8.36 cm^3, 8.3 mmol) in THF (28 cm^3) was stirred at room temperature for 3.5 h. After purification by column chromatography (aluminum oxide; EtOAc/MeOH, 9/1) 1.070 g (82%) of the corresponding alcohol was obtained. M.p.: 179–180 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.10$–1.50 (m, 8H), 1.65–1.90 (m, 2H), 3.36 (t, $J = 6.4$ Hz, 2H), 4.09 (t, $J = 7.0$ Hz, 2H), 4.30 (t, $J = 5.1$ Hz, 1H), 7.87 (d, $J = 1.7$ Hz, 1H), 7.90 (d, $J = 1.7$ Hz, 1H), 7.92 (d, $J = 5.0$ Hz, 1H), 9.02 (d, $J = 5.0$ Hz, 1H), 9.25 (s, 1H) ppm; MS: *m/z* (%) = 312 (M^+, 100), 253 (37), 212 (97), 199 (35), 183 (60).

2. The alcohol obtained (0.621 g, 2.0 mmol), methanesulfonyl chloride (0.19 cm^3), and triethylamine (0.42 cm^3) in DCM (18.6 cm^3) gave 0.720 g (93%) **7c**. M.p.: 129–130 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.10$–1.40 (m, 6H), 1.50–1.70 (m, 2H), 1.70–1.90 (m, 2H), 3.13 (s, 3H), 3.95–4.24 (m, 4H), 7.83 (d, $J = 1.7$ Hz, 1H), 7.86 (d, $J = 1.7$ Hz, 1H), 7.89 (d, $J = 5.0$ Hz, 1H), 8.99 (d, $J = 5.0$ Hz, 1H), 9.21 (s, 1H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 24.7$, 25.6, 27.8, 28.3, 30.0, 36.5, 49.9, 70.3, 118.8, 121.3, 121.3, 126.1, 126.5, 127.7, 140.4, 148.2, 154.8, 178.1, 178.6 ppm; IR (KBr):$\bar{\nu} = 3{,}113$, 1,655, 1,544, 1,533, 1,338, 1,240 cm^{-1}; MS: *m/z* (%) = 390 (M^+, 4), 294 (5), 91 (100).

2-[2-(Aziridin-1-yl)ethyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**8a**, $C_{15}H_{13}N_3O_2$)

Following general procedure II, treatment of **7a** (0.060 g, 0.19 mmol) and aziridine (0.4 cm^3, 7.2 mmol) in acetonitrile/triethylamine (0.8/1 cm^3) at room temperature for 48 h and subsequent purification with column chromatography (aluminum oxide; EtOAc) gave 0.030 g (60%) **8a**. M.p.: 194–196 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.07$–1.08 (m, 2H), 1.75–1.76 (m, 2H), 2.62 (t, $J = 5.6$ Hz, 2H), 4.21 (t, $J = 5.6$ Hz, 2H), 7.55 (s, 2H), 7.99 (d, $J = 5.1$ Hz, 1H), 8.99 (d, $J = 5.1$ Hz, 1H), 9.45 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 27.2$, 51.0, 61.1, 119.1, 122.5, 122.6, 125.2, 125.6, 128.1, 140.8, 149.3, 154.7, 178.9, 179.5 ppm; IR (KBr): $\bar{\nu} = 3{,}100$, 1,660, 1,584, 1,537, 1,239 cm^{-1}; MS: *m/z* (%) = 267 (M^+, 5), 78 (3), 57 (4), 56 (100).

2-[4-(Aziridin-1-yl)butyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**8b**, $C_{17}H_{17}N_3O_2$)

Following general procedure II, treatment of **7b** (0.069 g, 0.24 mmol) and aziridine (0.5 cm^3, 9.6 mmol) in acetonitrile/triethylamine (1/1, 2 cm^3) at room temperature for 48 h and subsequent purification by column chromatography (aluminum oxide; EtOAc) gave 0.035 g (50%) **8b**. M.p.: 158–160 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.03$ (dd, $J = 4.2$, 2.3 Hz, 2H), 1.53 (quint, $J = 7.0$ Hz, 2H), 1.67 (dd, $J = 4.2$, 2.3 Hz, 2H), 1.98 (quint, $J = 7.0$ Hz, 2H), 2.18 (t, $J = 6.6$ Hz, 2H), 4.07 (t, $J = 7.1$ Hz, 2H), 7.44 (s, 2H), 7.95 (d, $J = 5.0$ Hz, 1H), 8.95 (d, $J = 5.0$ Hz, 1H), 9.40 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 26.5$, 27.2, 27.2, 28.7, 51.0, 60.8, 119.0, 122.3, 122.4, 124.6, 124.9, 128.0, 140.7, 149.2, 154.5, 178.8, 179.3 ppm; IR (KBr): $\bar{\nu} = 3{,}109$, 1,654, 1,582, 1,539, 1,240 cm^{-1}; MS: *m/z* (%) = 295 (M^+, 3.4), 211 (7.8), 97 (56), 56 (100).

2-[7-(Aziridin-1-yl)heptyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**8c**, $C_{20}H_{23}N_3O_2$)

Following general procedure II, treatment of **7c** (0.300 g, 0.77 mmol) and aziridine (1.6 cm^3, 30 mmol) in acetonitrile/triethylamine (1/1, 6 cm^3) at room temperature for 48 h and subsequent purification by column chromatography (aluminum oxide; EtOAc/MeOH, 98/2) gave 0.140 g (53%) **8c**. M.p.: 142–146 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.99$ (d, $J = 4.3$ Hz, 2H), 1.15–1.55 (m, 8H), 1.63 (d, $J = 4.3$ Hz, 2H), 1.70–1.90 (m, 2H), 2.09 (t, $J = 6.8$ Hz, 2H), 3.99 (t, $J = 7.0$ Hz, 2H), 7.41 (s, 2H), 7.94 (d, $J = 5.0$ Hz, 1H), 8.94 (d, $J = 5.0$ Hz, 1H), 9.39 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 26.2$, 27.1, 27.1, 28.9, 29.5, 30.6, 51.0, 61.7, 119.0, 122.3, 122.4, 124.5, 124.8, 127.9, 140.7, 149.2, 154.5, 178.7, 179.3 ppm; IR (KBr): $\bar{\nu} = 3{,}109$, 1,655, 1,582, 1,539, 1,239 cm^{-1}; MS: *m/z* (%) = 337 (M^+, 28), 253 (28), 84 (18), 56 (100).

2-[3-[4-[Bis(2-chloroethyl)amino]phenyl]propyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**10**, $C_{24}H_{23}Cl_2N_3O_2$)

1. Following general procedure I, NaH (0.125 g, 3.3 mmol) in DMF (4.8 cm^3), **3** (0.413 g, 2.0 mmol) in DMF (3.7 cm^3), and 4-(3-bromopropyl)-*N,N*-bis[2-[(*tert*-butyl)diphenylsilyloxy]ethyl]benzenamine [14] (2.44 g, 3.1 mmol) in DMF (5.2 cm^3) were used. Column chromatography (silica gel; EtOAc/light petroleum, 4/6) furnished 0.821 g **9** as the crude product.

2. According to general procedure III, the reaction mixture **9** (0.821 g, 0.9 mmol) and 1 M TBAF/THF (3.66 cm^3, 3.7 mmol) in THF (6.4 cm^3) was stirred at room temperature for 1.5 h. After purification by column chromatography (silica gel; EtOAc) 0.322 g (83%) of the corresponding alcohol was obtained.

3. Following general procedure IV, the reaction mixture of the obtained alcohol (0.150 g, 0.4 mmol), methanesulfonyl chloride (0.06 cm^3, 0.8 mmol), and triethylamine (1.1 cm^3) in DCM (1.7 cm^3) was stirred at 0 °C for 0.25 h. The solvent was removed under vacuum.

4. The crude product from the previous step was dissolved in DMF (1.5 cm^3). Then LiCl (0.377 g, 8.9 mmol) was added and the mixture was heated at 100 °C for 5 min. After addition of water the mixture was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was recrystallized (EtOAc) to give 0.160 g (72%) **10**. M.p.: 150–151 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.02$–2.28 (m, 2H), 2.57 (t, $J = 7.1$ Hz, 2H), 3.50–3.75 (m, 8H), 4.20 (t, $J = 7.0$ Hz, 2H), 6.63 (d, $J = 8.6$ Hz, 2H), 7.03 (d, $J = 8.6$ Hz, 2H), 7.43 (s, 2H), 7.99 (d, $J = 5.0$ Hz, 1H), 8.99 (d, $J = 5.0$ Hz, 1H), 9.46 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 31.1$, 32.1, 40.4, 40.4, 50.2, 53.5, 53.5, 112.2, 119.1, 122.5, 122.6, 124.6, 124.9, 128.1, 128.4, 129.5, 140.8, 144.7, 149.3, 154.7, 178.9, 179.4 ppm; IR (KBr): $\bar{\nu} = 3{,}114$, 1,657, 1,579, 1,236 cm^{-1}; MS: *m/z* (%) = 456 (M^+, 3.7), 406 (100), 357 (48), 214 (77), 118 (80).

2-[2-(Dimethylamino)ethyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**11a**, $C_{15}H_{15}N_3O_2$)

According to general procedure I the reaction mixture NaH (0.525 g, 12.9 mmol) in DMF (10 cm^3), **3** (0.972 g, 4.9 mmol) in DMF (15 cm^3), and 2-chloro-*N,N*-dimethylethylamine hydrochloride (1.083 g, 7.4 mmol) in DMF (15 cm^3) was stirred at 60 °C for 4 h. The crude product was purified by column chromatography (aluminum oxide; EtOAc/light petroleum, 9/1) to give 0.774 g (59%) **11a**. M.p.: 180–181 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.28$ (s, 6H), 2.71 (t, $J = 6.1$ Hz, 2H), 4.09 (t, $J = 6.1$ Hz, 2H), 7.53 (d, $J = 1.8$ Hz, 1H), 7.55 (d, $J = 1.8$ Hz, 1H), 8.01 (d, $J = 5.0$ Hz, 1H), 9.00 (d, $J = 5.0$ Hz, 1H), 9.47 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 45.2$, 48.7, 59.2, 118.9, 122.1, 122.2, 125.0, 125.4, 127.9, 140.7, 149.1, 154.4, 178.8, 179.3 ppm; IR (KBr): $\bar{\nu} = 3{,}111$, 1,657, 1,539, 1,238 cm^{-1}; MS: *m/z* (%) = 270 (M^++1, 0.9), 225 (2.1), 211 (2.3), 58 (100).

2-[3-(Dimethylamino)propyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**11b**, $C_{16}H_{17}N_3O_2$)

According to general procedure I the reaction mixture NaH (0.106 g, 2.7 mmol) in DMF (2.2 cm^3), **3** (0.200 g, 1.0 mmol) in DMF (1.8 cm^3), and 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0.240 g, 1.5 mmol) in DMF (2.5 cm^3) was stirred at 60 °C for 2 h. The crude product was purified by column chromatography (aluminum oxide; EtOAc) to give 0.067 g (23%) **11b**. M.p.: 125–126 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.97$ (quint, $J = 6.7$ Hz, 2H), 2.21 (s, 6H), 2.10–2.35 (m, 2H), 4.13 (t, $J = 6.7$ Hz, 2H), 7.47 (s, 2H), 8.00 (d, $J = 5.0$ Hz, 1H), 8.99 (d, $J = 5.0$ Hz, 1H), 9.46 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 28.6$, 45.3, 48.5, 55.2, 119.1, 122.5, 122.5, 124.9, 125.3, 128.1, 140.9, 149.4, 154.6, 178.9, 179.5 ppm; IR (KBr): $\bar{\nu} = 1{,}662$, 1,536, 1,230 cm^{-1}; MS: *m/z* (%) = 283 (M^+, 59), 227 (11), 212 (41), 183 (13), 58 (100).

9,9-Dimethoxy-1-[3-(tetrahydro-2H-pyran-2-yloxy)-propyl]-2H-pyrrolo[3,4-g]isoquinolin-4(9H)-one (**14**, $C_{21}H_{26}N_2O_5$)

To a vigorously stirred mixture of ketone **12** (1.038 g, 5 mmol) and **13** (1.693 g, 5 mmol) in dry THF (10 cm^3) under Ar, *tert*-BuOK (0.720 g, 6.15 mmol) in absolute THF (5 cm^3) was added. The reaction mixture was stirred at room temperature for 18 h. After dilution with water the mixture was exhaustively extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel; EtOAc) to give 1.567 g (81%) **14** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.40$–1.62 (m, 4H), 1.68–2.10 (m, 4H), 2.86 (s, 3H), 2.89 (s, 3H), 3.03 (t, $J = 7.6$ Hz, 2H), 3.46–3.60 (m, 2H), 3.74–3.94 (m, 2H), 4.45–4.60 (m, 1H), 7.51 (d, $J = 3.0$ Hz, 1H), 7.67 (d, $J = 5.2$ Hz, 1H), 8.81 (d, $J = 5.2$ Hz, 1H), 9.36 (s, 1H) ppm; MS: *m/z* (%) = 387 (M^++1, 0.4), 356 (2), 341 (53), 270 (34), 226 (70).

2-[3-(Dimethylamino)propyl]-9,9-dimethoxy-1-[3-(tetrahydro-2H-pyran-2-yloxy)propyl]-2H-pyrrolo[3,4-g]isoquinolin-4(9H)-one (**15**, $C_{26}H_{37}N_3O_5$)

According to general procedure I, the reaction mixture NaH (0.390 g, 9.7 mmol), **14** (1.303 g, 3.38 mmol), and 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0.816 g, 5.07 mmol) in DMF (24 cm^3) was heated for 18 h at 60 °C to give 1.384 g (87%) **15** as the crude product. The compound was submitted to the next reaction step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$):

δ = 1.40–1.62 (m, 4H), 1.68–2.00 (m, 6H), 2.15 and 2.19 (s, 6H), 2.25 (t, J = 6.7 Hz, 2H), 2.89 (s, 6H), 2.80–3.00 (m, 2H), 3.40–3.58 (m, 2H), 3.75–3.92 (m, 2H), 4.04 (t, J = 7.1 Hz, 2H), 4.59 (br s, 1H), 7.49 (s, 1H), 7.68 (d, J = 5.2 Hz, 1H), 8.84 (d, J = 5.2 Hz, 1H), 9.39 (s, 1H) ppm; MS: *m/z* (%) = 472 (M^++1, 0.6), 315 (43), 285 (89), 226 (86).

2-[3-(Dimethylamino)propyl]-1-(3-hydroxypropyl)-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**16**, $C_{19}H_{23}N_3O_3$)
After dissolving compound **15** (1.381 g, 2.93 mmol) in acetone/H_2O (60/6 cm^3/cm^3) 0.677 g (2.64 mmol) pyridinium *p*-toluenesulfonate (PPTS) and *p*-toluenesulfonic acid monohydrate (0.230 g, 1.21 mmol) were added. The reaction mixture was stirred at room temperature for 18 h. Afterwards the solvents were removed in vacuo and the crude product was dissolved in MeOH (20 cm^3). *p*-Toluenesulfonic acid monohydrate (0.915 g, 4.81 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. Afterwards the solvent was removed in vacuo and the crude product was purified by column chromatography (aluminum oxide; EtOAc/MeOH, 8/2) to furnish 0.812 g (81%) **16** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.82–2.10 (m, 5H), 2.22 (s, 6H) 2.29 (t, J = 6.2 Hz, 2H), 3.26 (t, J = 7.0 Hz, 2H), 3.58 (t, J = 5.5 Hz, 2H), 4.11 (t, J = 7.0 Hz), 7.45 (s, 1H), 8.00 (d, J = 5.0 Hz, 1H), 8.99 (d, J = 5.0 Hz, 1H), 9.45 (s, 1H) ppm; MS: *m/z* (%) = 341 (M^+, 2.4), 323 (1), 270 (15), 226 (70).

3-[2-[3-(Dimethylamino)propyl]-4,9-dihydro-4,9-dioxo-2H-pyrrolo[3,4-g]isoquinolin-1-yl]propyl methanesulfonate (**17**, $C_{20}H_{25}N_3O_5S$)
Following general procedure IV, the reaction mixture **16** (0.150 g, 0.44 mmol), methanesulfonyl chloride (0.1 cm^3, 1 mmol), and triethylamine (0.1 cm^3) in DCM (5 cm^3) was stirred at 0 °C for 1 h. The crude product was purified by column chromatography (aluminum oxide; EtOAc/MeOH, 95/5) to give 0.143 g (78%) **17**. M.p.: 208–210 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.83–2.03 (m, 2H), 2.10–2.32 (m, 4H), 2.22 (s, 6H), 3.06 (s, 3H), 3.24 (t, J = 7.6 Hz, 2H), 4.09 (t, J = 7.0 Hz, 2H), 4.35 (t, J = 5.9 Hz, 2H), 7.45 (s, 1H), 7.98 (d, J = 5.0 Hz, 1H), 9.00 (d, J = 5.0 Hz, 1H), 9.46 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4, 28.5, 28.6, 37.5, 44.8, 45.2, 55.2, 69.2, 118.3, 119.0, 121.6, 124.4, 128.0, 140.3, 141.3, 149.3, 154.6, 179.1, 179.3 ppm; IR (KBr): $\bar{\nu}$ = 1,663, 1,539, 1,243, 1,058 cm^{-1}; MS: *m/z* (%) = 420 (M^++1, 0.4), 225 (10.4), 211 (10.3), 58 (100).

2-[3-(Dimethylamino)propyl]-1-[3-(methylamino)propyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione
(**18a**, $C_{20}H_{26}N_4O_2$)
Following general procedure II, the reaction mixture **17** (0.143 g, 0.34 mmol) in 33% methylamine in absolute EtOH (3.6 cm^3) and DMF (1.5 cm^3) was stirred at room temperature under Ar for 22 h. The crude product was purified by column chromatography (aluminum oxide; EtOAc/MeOH, 8/2) to give 0.038 g (32%) **18a**. M.p.: 97–100 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72–2.00 (m, 4H), 2.10–2.38 (m, 2H), 2.19 (s, 6H), 2.43 (s, 3H), 2.65 (t, J = 6.8 Hz, 2H), 3.14 (t, J = 7.7 Hz, 2H), 4.07 (t, J = 6.9 Hz, 2H), 7.41 (s, 1H), 7.98 (d, J = 5.0 Hz, 1H), 8.96 (d, J = 5.0 Hz, 1H), 9.42 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4, 28.4, 28.7, 36.1, 44.4, 44.9, 50.7, 55.1, 117.6, 118.7, 121.2, 123.9, 127.7, 141.2, 142.0, 148.8, 154.2, 178.7, 178.7 ppm; IR (KBr): $\bar{\nu}$ = 3,425, 1,662, 1,539, 1,258, 1,066 cm^{-1}; MS: *m/z* (%) = 354 (M^+, 2.3), 297 (4.2), 252 (11.5), 240 (15.1), 226 (23.4), 58 (100).

1,2-Bis[3-(dimethylamino)propyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione (**18b**, $C_{21}H_{28}N_4O_2$)
Following general procedure II, the reaction mixture **17** (0.143 g, 0.34 mmol) and 40% dimethylamine in H_2O (2.0 cm^3, 2 mmol) in EtOH (5.5 cm^3) was stirred at room temperature for 18 h. The stirring was continued for a further 48 h at 30–35 °C. The crude product was purified by column chromatography (aluminum oxide; EtOAc/MeOH, 95/5) to give 0.077 g (77%) **18b**. M.p.: 100–102 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.75–2.05 (m, 4H), 2.22 (s, 6H), 2.24 (s, 6H), 2.24 (t, J = 7.0 Hz, 2H), 2.37 (t, J = 7.0 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H), 4.10 (t, J = 7.0 Hz, 2H), 7.42 (s, 1H), 8.00 (d, J = 5.0 Hz, 1H), 8.98 (d, J = 5.0 Hz, 1H), 9.44 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.0, 26.9, 28.7, 44.8, 45.3, 45.4, 55.5, 58.8, 117.9, 119.1, 121.5, 124.2, 128.1, 141.6, 142.5, 149.2, 154.5, 178.9, 179.7 ppm; IR (KBr): $\bar{\nu}$ = 1,663, 1,643, 1,539, 1,257, 1,038 cm^{-1}; MS: *m/z* (%) = 368 (M^+, 5.6), 297 (10.1), 252 (6.2), 240 (15.8), 226 (22.8), 58 (100).

1-[3-(1-Aziridinyl)propyl]-2-[3-(dimethylamino)propyl]-2H-pyrrolo[3,4-g]isoquinoline-4,9-dione
(**18c**, $C_{21}H_{26}N_4O_2$)
Following general procedure II, a mixture of **17** (0.194 g, 0.46 mmol), aziridine (0.82 cm^3, 11.56 mmol), and triethylamine (2.2 cm^3) in acetonitrile (2.2 cm^3) was stirred at room temperature for 52 h. The crude product was purified by column chromatography (aluminum oxide; EtOAc) to give 0.130 g (77%) **18c**. M.p.: 107–109 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.14 (dd, J = 4.2, 2.1 Hz, 2H), 1.75 (dd, J = 4.2, 2.1 Hz, 2H), 1.80–2.05 (m, 4H), 2.17–2.38 (m, 4H), 2.22 (s, 6H), 3.21 (t, J = 7.8 Hz, 2H), 4.12 (t, J = 7.0 Hz, 2H), 7.43 (s, 1H), 7.99 (d, J = 4.8 Hz, 1H), 8.98 (d, J = 4.8 Hz, 1H), 9.45 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.0, 27.2, 28.7, 29.0, 44.8, 45.3, 55.5, 60.9, 117.9, 119.0, 121.5, 124.2, 128.1, 141.6, 142.4, 149.2, 154.5, 179.0, 179.7 ppm; IR (KBr): $\bar{\nu}$ = 1,657, 1,533, 1,225, 1,072 cm^{-1}; MS: *m/z* (%) = 366 (M^+, 7.5), 323 (8.8), 297 (9.0), 282 (8.1), 265 (8.9), 252 (18.2), 58 (100).

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