# Diethylaminopropionamido-hydroxy-anthraquinones as Potential Anticancer Agents : Synthesis and Characterization

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A number of new 9,10-anthracenediones were obtained, bearing one or two hydroxyl groups and one positively charged side chain at different positions of the aromatic ring system (compounds **1-5** in Chart 1). These derivatives resemble the anticancer agents mitoxantrone and ametantrone. The synthesis started from dihydroxy- or amino-hydroxy-9,10-anthracenediones, which were converted into the nitro-derivatives. After reduction to the corresponding amines and acylation with 3-chloropropionyl chloride, substitution with diethylamine led to the final diethylaminopropionamido derivatives. The new anthracenediones cause a quite relevant inhibition of cell growth *in vitro* and will be tested as possible anticancer agents.

**Diethylaminopropionamid-hydroxy-anthrachinone mit potentieller Wirkung gegen Krebs: Synthese und Charakterisierung**

Neue 9,10-Anthrachinonderivate mit einem oder zwei Hydroxy- und einem Aminoalkylamido-Substituenten wurden hergestellt. Dihydroxy- und Amino-hydroxy-9,10-anthrachinone wurden zuerst nitriert und dann zu den entspr. Aminen reduziert. Diese wurden acyliert und mit Diethylamin umgesetzt. Die neuen Derivate zeigen deutliche Hemmung der Zellwachstums *in vitro* und sollen auf cytostatische Wirkung geprüft werden.

The anticancer drugs of the anthracycline structural type show very high activity against a number of tumors[1,2]. Unfortunately their efficacy is counterbalanced by a relatively high toxicity and the onset of resistance[3,4]. Studies aimed at developing new derivatives endowed with antineoplastic properties, yet devoid of adverse side-effects, led to the synthesis and investigation of new compounds having the anthraquinone moiety as the basic structure[5-7]. Among them mitoxantrone has shown quite interesting features and is presently utilized in clinical trials[8-10].

In this paper we report on the synthesis and characterization of new mono- and di-hydroxy-9,10-anthracenediones bearing a positively charged side chain at different positions of the aromatic system. Their chemical structures are shown in Chart 1. These compounds contain two relevant features for a possible anticancer action: the tricyclic aromatic intercalating moiety and the amino side chains, which could provide additional electrostatic binding to DNA, the supposed biological target of anthraquinone derivatives[7].

## *Results and Discussion*

The diethylaminopropionamido chains of the products **1-5** were constructed by acylation of the appropriately located aromatic amine with 3-chloropropionyl chloride, followed by nucleophilic substitution of the halogen by diethylamine.

At all stages, synthetic products were identified by spectroscopy ($^1$H-NMR, IR, and MS) and elemental analysis. Mass spectroscopy was used to confirm the identity of the key intermediates, the chloro-derivates, which have a characteristic $[M+2]^{+\cdot}$ signal.

The amino precursors of **1** and **2** (1-amino-4-hydroxy-9,10-anthracenedione and 1-amino-2-methoxy-4-hydroxy-9,10-anthracenedione) were commercial products. The precursor of **3**, compound **6** (2-amino-1,4-dihydroxy-9,10-anthracenedione), was prepared by nitration of 1,4-dihydroxy-9,10-anthracenedione and subsequent reduction of the nitro group. The precursors of **4** and **5**, 1-amino-4,5-dihydroxy-9,10-anthracenedione (**7**) and 2-amino-1,8-dihydroxy-9,10-anthracenedione (**8**), respectively, were also obtained by nitration of 1,8-dihydroxy-9,10-anthracenedione and subsequent reduction of the nitro group, the substituted position of the starting anthraquinone being identified in the nitro-derivatives by $^1$H-NMR spectroscopy.

The mononitro-derivatives **9** and **10** were identified by the chemical shifts of their H-3 or H-4 signals with reference to 1,8-dihydroxy-9,10-anthracenedione. In **9** H-3 is meta to the nitro group and ortho to the hydroxyl, while in **10** H-4 is meta to the nitro group and para to the hydroxyl. In 1,8-dihydroxy-9,10-anthracenedione H-2 appears at much higher field than H-4 ($\delta$=7.23 as against $\delta$=7.93) as expected. Since this order should remain unchanged in the nitrated compounds, the upfield doublet appearing at $\delta$=7.51 in the spectrum of **9** was attributed to H-3, and the doublet at lower field ($\delta$=7.76) in the spectrum of **10** to H-4. The assignments for the dinitro-derivative **11** were straightforward, as the shifts corresponded to the theoretical values, the signal at highest field being H-7 coupled to H-6. The spectrum of the other possible dinitro structure, with nitro groups symmetrically located on both rings, would be quite different. This unequivocal identification of **11** confirms structures **9** and **10**, too. In fact one side ring of **11** is identical to the substituted ring of **9** and the other to the substituted ring of **10**. Thus the spectrum of **11** ought to coincide to the superposition of those of **9** and **10**, which was in fact observed. The corresponding coupling constants were practically identical: for **11**, J(H-6-H-7))=9.15 and J(H-3-H-4)=8.35, while for **9** J(H-2-H-3)=8.95 and for **10** J(H-3-H-4)=8.35.

The ability of these compounds to bind to DNA as well as the cytotoxic and genotoxic activity on tumor cells were investigated[7,11,12]. The results indicated that the

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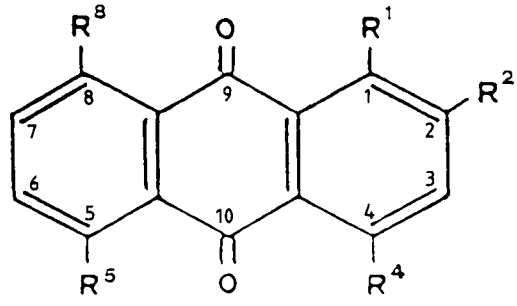
Chart 1- New compounds



| Compound | $R^1$ | $R^2$ | $R^4$ | $R^5$ | $R^8$ |
|---|---|---|---|---|---|
| 1 | X | H | OH | H | H |
| 2 | X | $OCH_3$ | OH | H | H |
| 3 | OH | X | OH | H | H |
| 4 | X | H | OH | OH | H |
| 5 | OH | X | H | H | OH |
| 6 | OH | $NH_2$ | OH | H | H |
| 7 | $NH_2$ | H | OH | OH | H |
| 8 | OH | $NH_2$ | H | H | OH |
| 9 | $NO_2$ | H | OH | OH | H |
| 10 | OH | $NO_2$ | H | H | OH |
| 11 | OH | $NO_2$ | H | $NO_2$ | OH |
| 12 | Z | H | OH | H | H |
| 13 | Z | $OCH_3$ | OH | H | H |
| 14 | OH | $NO_2$ | OH | H | H |
| 15 | OH | Z | OH | H | H |
| 16 | Z | H | OH | OH | H |
| 17 | OH | Z | H | H | OH |

X = $-NH-CO-CH_2-CH_2-N(C_2H_5)_2$

Z = $-NH-CO-CH_2-CH_2-Cl$

physicochemical parameters are directly related to the biological activity *in vitro*. Experiments *in vivo* are now being performed on a number of the above reported compounds. These studies will allow future tailored syntheses of new derivatives of the anthraquinone structural type.

## Experimental Part

Melting points: Büchi 510 apparatus, uncorrected.- IR spectra: Perkin-Elmer mod. 781 spectrometer (KBr discs).- $^1$H-NMR spectra: Varian CFT-20 (80MHz), TMS as int. stand. (chem. shifts in δ values, J in Hz).- Mass spectra: VG micromass 16F at 70 eV.- Microanalyses: Perkin-Elmer 240B instrument (C,H,N).- Chlorine content: method of Schöniger.- Column chromatography: Merck silicagel 60 (70-230 mesh).- Analytical TLC: precoated Merck silicagel 60 F254 (0.25 mm).

*1-(3-Chloropropionamido)-4-hydroxy-9,10-anthracenedione* (**12**)

To a solution of 1-amino-4-hydroxy-9,10-anthracenedione (360 mg, 1.51 mmol) in benzene (150 mL), pyridine (0.5 mL, 6.25 mmol) and 3-chloropropionyl chloride (1 mL, 10.5 mmol) were added and the mixture was heated 4 h at 70°C. The solvent was then evaporated *in vacuo* and the solid red-orange residue recrystallized from toluene-ligroin. Yield 430 mg. - M.p. 206°C.- $^1$H-NMR ($CDCl_3$): 3.00 (2H, t, J=6.8, $-CH_2$-CO); 3.93 (2H, t, J=6.8, $-CH_2$-Cl); 7.36 (1H, d, J=9.6, H-3); 7.82 (2H, m, H-6, H-7); 8.31 (2H, m, H-5, H-8); 9.11 (1H, d, J=9.6, H-2); 12.40 (1H, s; NH); 13.27 (1H, s, OH).- $C_{17}H_{12}ClNO_4$ (329.8) Calcd. C 61.9 H 3.64 N 4.2 Cl 10.8 Found C 61.8 H 3.88 N 4.0 Cl 11.0.

*1-(3-Diethylaminopropionamido)-4-hydroxy-9,10-anthracenedione hydrochloride* (**1**)

A mixture of **12** (400 mg, 1.22 mmol) and diethylamine (2 mL, 19.18 mmol) in ethanol (200 mL) was heated 4 h at 70°C. The solvent was then evaporated to dryness and the residue redissolved in ethanol (20 mL). After bubbling of HCl and addition of ethyl ether to incipient precipitation, the mixture was ice-cooled. The red-orange precipitate was washed with ether and recrystallized from ethanol-ligroin. Yield 442 mg.- M.p. 217°C.- $^1$H-NMR ($D_2O$): 1.37 (6H, t, J=7.3, $-CH_3$); 2.95 (2H, t, J=6.3, $-CH_2$-CO); 3.31 (4H, q, J=7.3, $-CH_2-CH_3$); 3.53 (2H, t, J=6.3, $-CH_2$-N); 6.94 (1H, d, J=9.6, H-3); 7.68 (4H, m, H-6, H-7, H-8, H-9); 8.23 (1H, d, J=9.6, H-2).- $C_{21}H_{23}ClN_2O_4$ (402.9) Calcd. C 62.5 H 5.75 N 7.0 Cl 8.8 Found C 62.6 H 5.69 N 6.8 Cl 9.1.

*1-(3-Chloropropionamido)-4-hydroxy-2-methoxy-9,10-anthracenedione* (**13**)

A solution of 1-amino-4-hydroxy-2-methoxy-9,10-anthracenedione (450 mg, 1.67 mmol) in benzene (150 mL), pyridine (0.5 mL, 6.25 mmol) and 3-chloropropionyl chloride (1 mL, 10.5 mmol) was heated 4 h at 70°C. The solvent was then evaporated *in vacuo* and the solid residue was recrystallized from toluene-ligroin to give **13** as yellow needles (400 mg).- M.p. 226°C.- $^1$H-NMR ($CDCl_3$): 2.97 (2H, t, J=6.5, $-CH_2$-CO); 3.89 (2H, t, J=6.5, $-CH_2Cl$); 3.96 (3H, s, $CH_3O$); 6.78 (1H, s, H-3); 7.78 (2H, m, H-6, H-7); 8.24 (2H, m, H-5, H-8); 11.63 (1H, s, NH); 13.59 (1H, s, OH).- MS: m/z (%): 361 [$(M+2)^+$ 33%]; 359 ($M^+$, 14); 269 (M-90, 89); 254 (269 - $CH_3$, 17); 226 (254 - CO, 24); 127 (17); 69 (100).- $C_{18}H_{14}ClNO_5$ (359.8) Calcd. C 60.1 H 3.89 N 3.9 Cl 9.9 Found C 60.3 H 3.55 N 3.9 Cl 10.2.

*1-(3-Diethylaminopropionamido)-4-hydroxy-2-methoxy-9,10-anthracenedione hydrochloride* (**2**)

A mixture of **13** (200 mg, 0.56 mmol) and diethylamine (2 mL, 19.18 mmol) in ethanol (80 mL) was refluxed for 1 h. The solvent was then evaporated to dryness and the residue redissolved in ethanol (15 mL). After bubbling of HCl and addition of ethyl ether to incipient precipitation, the mixture was ice-cooled. The precipitate was separated and crystallized from ethanol-ligroin as red-orange crystals. Yield 180 mg.- M.p. 235°C.- $^1$H-NMR ($D_2O$): 1.32 (6H, t, J=7.2, $-CH_3$); 2.97 (2H, t, J=6.7, $-CH_2$-CO); 3.28 (4H, q, J=7.2, $-CH_2-CH_3$); 3.50 (2H, t, J=6.7, $-CH_2$-N); 3.74 (3H, s, $CH_3O$); 6.42 (1H, s, H-3); 7.50 (4H, m, H-6, H-7, H-8, H-9).- IR(base): 3400(OH); 3280(NH); 2960 and 2920; 1670(CO, ketone); 1625(amide I); 1590(C=C); 1520(amide II); 1395; 1270; 1140; 980; 960; 795 and 725 $cm^{-1}$.- $C_{22}H_{25}ClN_2O_5$ (432.9) Calcd. C 61.0 H 5.77 N 6.4 Cl 8.2 Found C 60.7 H 5.72 N 6.6 Cl 8.3.

*1,4-Dihydroxy-2-nitro-9,10-anthracenedione* (**14**)

A solution of 1,4-dihydroxy-9,10-anthracenedione (1g, 4.17 mmol) in acetic acid (100 mL) at 50°C was treated with nitric acid (1 mL, 22.22 mmol). The mixture was left overnight at room temp. Water (400 mL) was added, upon which a solid separated, which was purified on a silicagel

column using toluene. Subsequent crystallization from toluene yielded 533 mg of the pure red-brown **14**.- M.p. 233-234°C.- $^1$H-NMR ($D_6$-DMSO): 8.04 (2H, m, H-6, H-7); 8.08 (1H, s, H-3); 8.28 (2H, m, H-5, H-8); 12.32 and 13.09 (2H, s, -OH).- $C_{14}H_7NO_6$ (285.2) Calcd. C 59.0 H 2.72 N 4.9 Found C 59.2 H 2.38 N 5.2.

*2-Amino-1,4-dihydroxy-9,10-anthracenedione* (**6**)

To a solution of **14** (500 mg, 1.75 mmol) in ethanol (100 mL) Sn (3g, 25.27 mmol), $SnCl_2$ (3g, 13.30 mmol) and conc. HCl (15 mL, 180 mmol) were added. The mixture was stirred 24 h at room temp. and then poured into water (50 mL). A solid precipitated, which was purified on a silicagel column with benzene/ethyl acetate (1:1). The product was recrystallized from toluene-ethyl acetate. Yield 295 mg.- M.p.>300°C.- $^1$H-NMR ($D_6$-DMSO): 6.32 (1H, s, H-3); 7.10 (2H, s, $NH_2$); 7.90 (2H, m, H-6, H-7); 8.25 (2H, m, H-6, H-7); 8.25 (2H, m, H-5, H-8); 13.63 and 14.05 (2H, s, -OH).- $C_{14}H_9NO_4$ (255.2) Calcd. C 65.9 H 3.55 N 5.5 Found C 65.9 H 3.38 N 5.4.

*2-(3-Chloropropionamido)-1,4-dihydroxy-9,10-anthracenedione* (**15**)

A solution of **6** (200 mg, 0.78 mmol) in benzene (100 mL), pyridine (0.5 mL, 6.25 mmol), and 3-chloropropionyl chloride (1.2 mL, 12.5 mmol) was heated 1 h at 70°C. The solvent was then evaporated *in vacuo* and the solid residue purified on a silicagel column with benzene/ethyl acetate (3:1). Subsequent crystallization from toluene-ligroin yielded pure red-brown **15** (40 mg).- M.p. 239-240°C.- $^1$H-NMR ($CDCl_3$): 2.95 (2H, t, J=6.4, -$CH_2$-CO); 3.91 (2H, t, J=6.4, -$CH_2$-Cl); 7.82 (2H, m, H-6, H-7); 8.35 (2H, m, H-5, H-8); 8.43 (1H, s, H-3); 13.09 and 13.73 (2H, 2s, OH).- MS: m/z (%): 347 [$(M+2)^+$, 34%]; 345 ($M^+$, 19); 255 (M-90, 100).- $C_{17}H_{12}ClNO_5$ (345.8) Calcd. C 59.0 H 3.50 N 4.0 Cl 10.2 Found C 59.1 H 3.40 N 3.9 Cl 10.6.

*2-(3-Diethylaminopropionamido)-1,4-dihydroxy-9,10-anthracenedione hydrochloride* (**3**)

A mixture of **15** (100 mg, 0.29 mmol) and diethylamine (1 mL, 9.59 mmol) in ethanol (40 mL) was refluxed for 15 min. The solvent was then evaporated to dryness and the residue redissolved in ethanol (10 mL). After bubbling of HCl and addition of ethyl ether to incipient precipitation, the mixture was ice-cooled. The orange-yellow precipitate was washed with ether. Yield 82 mg. - M.p. 248°C.- $^1$H-NMR ($D_2O$): 1.20 (6H, t, J=7.3, -$CH_3$); 2.76 (2H, m, -$CH_2$-CO); 3.12 (4H, q, J=7.3, -$CH_2$-$CH_3$); 3.28 (2H, m, -$CH_2$-N); 7.05 (1H, s, H-3); 7.41 (4H, m, H-5, H-6, H-7, H-8).- IR: 3400(OH); 3375(NH); 2980-2900; 2700-2400(NH, salts); 1710(CO ketone); 1625(amide I); 1585; 1445 and 1405(C=C); 1525(amide II); 1355; 1250; 1200; 1165; 880; 750 and 630 $cm^{-1}$.- $C_{21}H_{23}ClN_2O_5$ (418.9) Calcd. C 60.2 H 5.54 N 6.7 Cl 8.5 Found C 59.8 H 5.41 N 6.5 Cl 9.2.

*Nitration of 1,8-dihydroxy-9,10-anthracenedione*

A mixture of 1,8-dihydroxy-9,10-anthracenedione (5 g, 22.32 mmol), $KNO_3$ (3.2 g, 31.68 mmol) and acetic acid (400 mL) was refluxed for 15 min. The mixture was left overnight at room temp.. Water (250 mL) was poured in, and a yellow solid precipitated (4.95 g) which was separated and then fractionated on a silicagel column using a benzene/ethyl acetate gradient (up to 50% ethyl acetate). The obtained products are described following the order of elution:

*4,5-dihydroxy-1-nitro-9,10-anthracenedione* (**9**)

Recrystallization from toluene (900 mg).- M.p. 244°C.- $^1$H-NMR ($D_6$-DMSO): 7.41 (1H, dd, J=1.4 and 8.0, H-6); 7.51 (1H, d, J=9.0, H-3); 7.60 (1H, dd, J=1.4 and 8.0, H-8); 7.80 (1H, "t", J=8.0, H-7); 8.06 (1H, d, J=9.0, H-2).- IR: 1450(OH); 3095; 1680 and 1630(CO); 1570 and 1460(C=C); 1545 and 1370(NO); 1278; 1195; 1160; 1090; 840; 775; 735 and 660 $cm^{-1}$.- $C_{14}H_7NO_6$ (285.2) Calcd. C 58.9 H 2.47 N 4.9 Found C 59.1 H 2.33 N 4.7.

*1,8-dihydroxy-2-nitro-9,10-anthracenedione* (**10**)

Recrystallization from acetic acid (1218 mg).- M.p. 232°C.- $^1$H-NMR ($D_6$-DMSO); 7.41 (1H, dd, J=1.9 and 7.6, H-7); 7.72 (1H, dd, J=1.9 and 7.6, H-5); 7.76 (1H, d, J=8.4, H-4); 7.80 (1H, "t", J=7.6, H-6); 8.36 (1H, d, J=8.4, H-3).- IR: 3450(OH); 3230; 3085; 1680 and 1630(CO); 1605; 1445 and 1425(C=C); 1530 and 1350(NO); 1270; 1200; 1160; 1005; 860; 800; 745 and 690 $cm^{-1}$.- $C_{14}H_7NO_6$ (285.2) Calcd. C 58.9 H 2.47 N 4.9 Found C 58.6 H 2.38 N 5.1.

*1,8-dihydroxy-2,5-dinitro-9,10-anthracenedione* (**11**)

Recrystallization from toluene-ligroin (350 mg).- M.p. 272°C.- $^1$H-NMR ($D_6$-DMSO): 7.57 (1H, d, J=9.1, H-7); 7.70 (1H, d, J=8.3, H-4); 8.11 (1H, d, J=9.1, H-6); 8.37 (1H, d, J=8.3, H-3).- IR: 3450(OH); 3095; 2970 and 2940(CH); 1730; 1685 and 1630(CO); 1600; 1450 and 1415(C=C); 1545 and 1350(NO); 1285; 1265; 1190; 1080; 860; 745 and 645 $cm^{-1}$.- $C_{14}H_6N_2O_8$ (330.2) Calcd. C 50.9 H 1.83 N 8.5 Found C 51.1 H 1.75 N 8.3.

*1-Amino-4,5-dihydroxy-9,10-anthracenedione* (**7**)

To a solution of **9** (500 mg, 1.86 mmol) in ethanol (50 mL); Sn (1.7 g, 14.32 mmol), $SnCl_2$ (1.7 g, 7.54 mmol) and conc. HCl (10 mL, 120 mmol) were added. The mixture was stirred 24 h at room temp. and then poured into water (100 mL). A solid precipitated which was purified on a silicagel column using benzene. The product was recrystallized from ligroin. Yield 366 mg.- M.p. 268°C.- $^1$H-NMR ($D_6$-DMSO): 7.14-7.30 (3H, m, H-2, H-3, H-6); 7.66-7.80 (2H, m, H-7, H-8); 8.35 (2H, s, $NH_2$); 12.46 (2H, s, 2(OH)).- $C_{14}H_9NO_4$ (255.2) Calcd. C 65.9 H 3.55 N 5.5 Found C 65.7 H 3.42 N 5.7.

*1-(3-Chloropropionamido)-4,5-dihydroxy-9,10-anthracenedione* (**16**)

A solution of the amino compound **7** (360 mg, 1.41 mmol) in benzene (150 mL), pyridine (0.5 mL, 6.25 mmol), and 3-chloropropionyl chloride (1.3 mL, 13.61 mmol) was heated 3 h at 70°C. The solvent was then evaporated *in vacuo* and the solid residue purified on a silicagel column with benzene. The product was recrystallized from toluene. Yield 350 mg.- M.p. 232°C.- $^1$H-NMR ($D_6$-DMSO): 3.01 (2H, t, J=6.1, -$CH_2$-CO); 3.93 (2H, t, J=6.1, -$CH_2$-Cl); 7.38 (1H, dd, J=2.4 and 7.3, H-6); 7.46 (1H, d, J=9.4, H-3); 7.66-7.94 (2H, m, H-7, H-8); 8.86 (1H, d, J=9.4, H-2); 11.80 (1H, s, OH); 12.04 (1H, s, NH); 12.49 (1H, s, OH).- IR: 3380(OH); 3130; 2930; 1690(CO ketone); 1620(amide I); 1600, 1490 and 1460(C=C); 1575(amide II); 1280; 1160; 775 and 720 $cm^{-1}$.- $C_{17}H_{12}ClNO_5$ (345.8) Calcd. C 59.3 H 3.49 N 4.0 Cl 10.2 Found C 59.3 H 3.66 N 4.2 Cl 10.1.

*1-(3-Diethylaminopropionamido)-4,5-dihydroxy-9,10-anthracenedione hydrochloride* (**4**)

A solution of **16** (100 mg, 0.29 mmol) and diethylamine (1 mL, 9.59 mmol) in ethanol (30 mL) was refluxed for 15 min. The solvent was then evaporated to dryness and the residue redissolved in ethanol (10 mL). After bubbling of HCl and addition of ethyl ether to incipient precipitation, the mixture was ice-cooled. A red solid precipitated which was washed with ether. Yield 84 mg.- M.p. 238°C.- $^1$H-NMR ($D_2O$): 1.19 (6H, t, J=7.2, -$CH_3$); 2.76 (2H, m, -$CH_2$-CO); 3.15 (4H, q, J=7.2, -$CH_2$-$CH_3$); 3.34 (2H, m, -$CH_2$-N); 6.68-7.31 (4H, m, H-3, H-6, H-7, H-8); 8.06 (1H, d, J=10.0, H-2).- IR: 3420(OH); 3120-3100(NH); 2930; 2640-2470(NH, salts); 1695(CO); 1612(amide I); 1590, 1500 and 1450(C=C); 1560(amide II); 1245, 1160; 1085; 830; 770 and 730 $cm^{-1}$.- $C_{21}H_{23}ClN_2O_5$ (418.9) Calcd. C 60.2 H 5.36 N 6.7 Cl 8.5 Found C 60.3 H 5.55 N 6.4 Cl. 8.7.

*2-Amino-1,8-dihydroxy-9,10-anthracenedione* (**8**)

To a solution of **10** (500 mg, 1.86 mmol) in ethanol (50 mL); Sn (1.7 mg, 14.32 mmol), $SnCl_2$ (1.7 mg, 7.54 mmol) and conc. HCl (10 mL,

120 mmol) were added. The mixture was stirred 24 h at room temp. and then poured into water (50 mL). A solid precipitated which was purified on a silicagel column using benzene/ethyl acetate (9:1). The dark brown product was recrystallized from toluene. Yield 200 mg.- M.p. 272-273°C.- $^1$H-NMR ($D_6$-DMSO): 6.46 (2H, s, $NH_2$); 6.94 (1H, d, J=8.4, H-3); 7.28 (1H, dd, J=2.0 and 7.3, H-7); 7.59 (1H, d, J=8.4, H-4); 7.63 (1H, dd, J=2.0 and 7.3, H-5); 7.78 (1H, t, J=7.3, H-6).- $C_{14}H_9NO_4$ (255.2) Calcd. C 65.9 H 3.55 N 5.5 Found C 66.2 H 3.48 N 5.5.

*2-(3-Chloropropionamido)-1,8-dihydroxy-9,10-anthracenedione* (**17**)

A solution of **8** (400 mg, 1.57 mmol) in benzene (200 mL), pyridine (0.5 mL, 6.25 mmol), and 3-chloropropionyl chloride (2 mL, 21 mmol) was heated 3 h at 70°C. The solvent was then evaporated *in vacuo* and the solid residue purified on a silicagel column using a benzene/ethyl acetate gradient (up to 30% ethyl acetate). The yellow product was recrystallized from toluene. Yield 112 mg.- M.p. 262°C.- $^1$H-NMR ($D_6$-DMSO): 3.07 (2H, t, J=6.2, -$CH_2$-CO); 3.89 (2H, t, J=6.2, -$CH_2$-Cl); 7.39 (1H, dd, J=2.3 and 7.4, H-7); 7.69-7.90 (3H, m, H-4, H-5, H-6); 8.59 (1H, d, J=8.4, H-3); 9.95 (1H, s, NH); 11.80 and 12.61 (2H, 2s, 2(OH)).- IR: 3400; 2980-2920; 1700(CO); 1620(amide I); 1590, 1460 and 1445(C=C); 1540 (amide II); 1270; 870; 780 and 745 cm$^{-1}$.- MS: m/z (%): 347 [$(M+2)^+$, 33%]; 345 ($M^+$, 12); 309 (M-HCl, 11)$^+$; 255(M-90, 100).- $C_{17}H_{12}ClNO_5$ (345.8) Calcd. C 59.3 H 3.49 N 4.0 Found C 59.5 H 3.83 N 4.2.

*2-(3-Diethylaminopropionamido)-1,8-dihydroxy-9,10-anthracenedione hydrochloride* (**5**)

A solution of **17** (140 mg, 0.40 mmol) and diethylamine (1.6 mL, 15.37 mmol) in ethanol (50 mL) was refluxed for 15 min. The solvent was then evaporated to dryness and the residue redissolved in ethanol (15 mL). After bubbling of HCl and addition of ethyl ether, the mixture was ice-cooled. The orange-yellow precipitate was washed with ether. Yield 130 mg.- M.p. 259°C.- $^1$H-NMR ($D_2O$): 1.20 (6H, t, J=7.2, -$CH_3$); 2.82 (2H, m, -$CH_2$-CO); 3.14 (4H, q, J=7.2, -$CH_2$-$CH_3$); 3.34 (2H, m, -$CH_2$-N); 6.80-7.75 (5H, m, H-3, H-4, H-5, H-6, H-7).- IR: 3400(OH); 3300-3250(NH); 2980-2920; 2700-2450(NH, salts); 1695(CO); 1620(amide I); 1600, 1470 and 1430(C=C); 1530(amide II); 1360; 1290; 1245; 1205; 1180; 1070; 865; 820; 760 and 740 cm$^{-1}$.- $C_{21}H_{23}ClN_2O_5$ (418.9) Calcd. C 60.2 H 5.36 N 6.7 Cl 8.5 Found C 60.1 H 5.36 N 6.4 Cl 8.4.

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