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The Synthesis of Anthraquinone Derivatives as Potential Anticancer Agents

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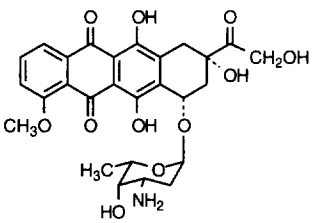
Abstract: The simple anthracycline analogues **3a-c** were synthesized as potential anticancer agents. Anodic oxidation of the phenol derivative **4**, phthalide anion annelation of *p*-quinone monoacetals **5** and selective attachment of the side chain were the three key steps towards these target compounds.

INTRODUCTION

Doxorubicin **1** was discovered several decades ago, but the detailed mechanism of its action has proved elusive.[1] While most anthracyclines are potential DNA intercalators, by nature of their planar quinonoidal chromophore, this property correlates only poorly with their anticancer activity.[2] As a consequence, multimodal mechanisms have been advanced to account for the biological activity of this very significant group of chemotherapeutic agents.[3] Traditionally structure modification has been an important, effective approach both to understand the mechanism of drug action and as a route to better drugs. Anthraquinones, e.g. **2**, have long been viewed as potential simple analogs of anthracyclines.[4]



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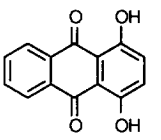
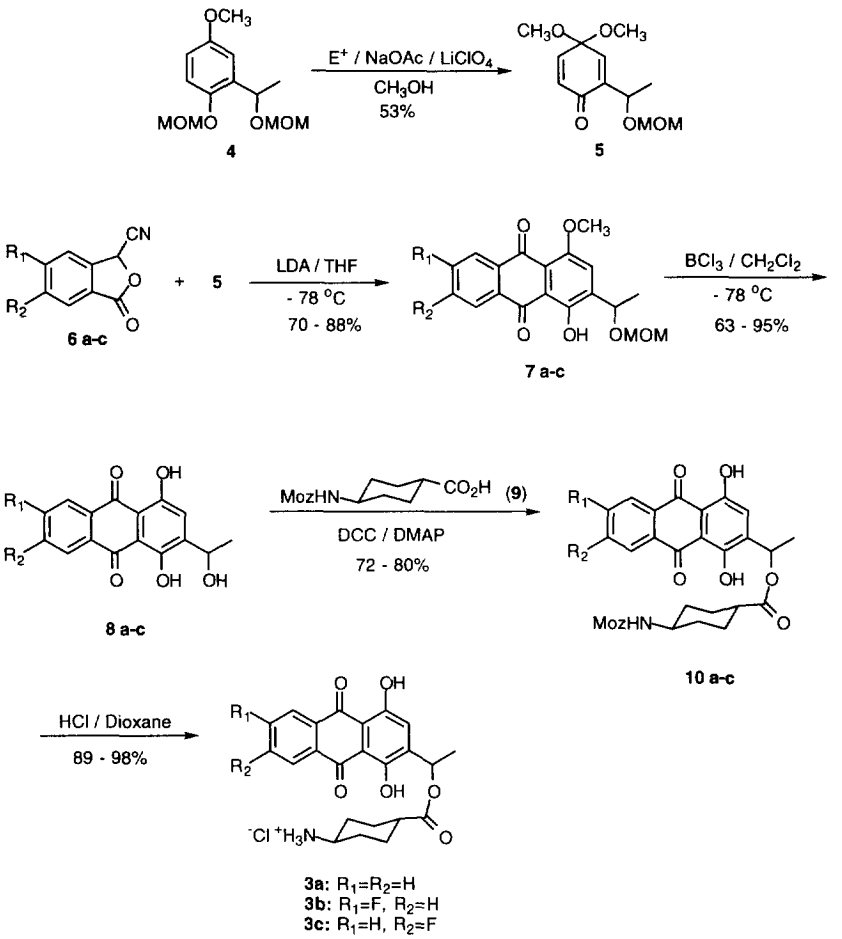


2

However the chromophore **2** itself proved to be biologically inactive, and the presence of a basic side chain, has long been considered essential if the products are to be bioactive.[5] Whilst various sugar derivatives required tedious synthesis, early studies showed that replacement of the daunosamine by simple amino acids resulted in inactive compounds.[6] A significant breakthrough was achieved by Zhang and co-workers who reported that cyclic amino acids such as *trans*-4-amino-1-cyclohexanecarboxylic acid could effectively mimic the sugar moiety of doxorubicin in terms of biological activity.[7] The potential to extend this finding beyond the natural anthracyclines prompted us to examine the synthesis and bio-activity of a series of simple analogues **3a-c**.

Scheme



In these compounds the basic side chain was linked to the anthraquinone aglycone in a manner reminiscent of the natural anthracyclines but without comparable stereochemical constraints. A fluorine atom was also substituted at the positions corresponding to 2 or 3 position of doxorubicin to enhance biological activity [8] and to serve as a probe in studying the interaction of these anthraquinones with DNA or simplified oligonucleotides.[9]

RESULTS AND DISCUSSION

The synthesis of the target compounds **3a-c** can be divided into two parts, namely the aglycone synthesis and the attachment of the side chain (Scheme 1). The key acetal **5** for the construction of the aglycone was itself prepared, in 53% yield, by the regiospecific anodic oxidation[10] of the MOM ether **4**. Typically these reactions were conducted using a platinium anode in a methanolic solution containing

sodium acetate and lithium perchlorate as supporting electrolytes. Subsequent annelation [11] of **5** with the anions derived from phthalides **6a-c**[12] in the presence of lithium diisopropylamide in THF afforded the corresponding anthraquinones **7a-c**. These compounds were subsequently deprotected and demethylated by treatment with boron trichloride in dichloromethane at -78 °C, to yield the required 1,4-dihydroxyanthraquinones **8a-c**.

Trans-4-*p*-(methoxybenzyloxycarbonyl)aminocyclohexane carboxylic acid **9** was synthesized from 4-aminobenzoic acid, by medium pressure hydrogenation followed by protection of the amino group.[7] Selective esterification of the benzylic hydroxy groups of **8a-c,** to afford the monoesters **10a-c,** was achieved by coupling the appropriate alcohol with the acid **10** in the presence of dicyclohexylcarbodiimide(DCC) and 4-dimethylaminopyridine (DMAP). This reaction, although high yielding, required a fourfold excess of acid and a prolonged reaction time. Subsequent removal of the *p*-methoxybenzyloxycarbonyl group from the amide functionality was achieved with hydrogen chloride in dioxane to afford the free amines **3a-c** as their hydrochloride salts.

Preliminary evaluation of the anthraquinone derivatives **3a-c** as inhibitors of the *in vitro* growth of P388 cell line showed that possesed IC50 values in the range 0.2 - 0.4 μM. This activity is approximately one order of magnitude less than that of the daunosaminyl derivatives of racemic daunomycinone measured under identical conditions and is surprising for such a simple analogue. Further studies are in progress to evaluate the activity of each single enantiomer.

EXPERIMENTAL SECTION

Melting points were determined on a Reichert hot-stage microscope, and are uncorrected. Proton and carbon-13 NMR were recorded on Varian Gemini 300 spectrometer and chemical shifts are reported in ppm relative to tetramethylsilane. FT-IR spectra were recorded on Perkin Elmer 1600 FT-IR spectrometer. Solvents and reagents were purchased from Aldrich and Fluka. Chromatographic separations were performed by flash column chromatography on silica gel or by preparative TLC. Buffered silica gel was prepared by washing the commercial product, Merck 60 silica gel, with potassium dihydrogen phosphate/sodium hydroxide buffer (pH 6.8) and drying at 100 °C under vacuum. Anhydrous lithium perchlorate was prepared by dehydrating $LiClO_4.3H_2O$ at 160 °C/1.3kPa. Anhydrous methanol was prepared by distillation from magnesiummethoxide.

1-(4,4-Dimethoxycyclohexa-2,5-dienon-2-yl)-1-methoxymethyloxyethane (5)

Compound **4** (0.5 g, 2 mmol), synthesized by protection of the corresponding phenol,[13] was dissolved in dry methanol (100 ml) containing sodium acetate (0.5 g) and lithium perchlorate (2.0 g) and then anodically oxidized in a divided cell at a controlled anode potential of 1.3V. The completion of the electrolysis was determined by a low cell current and the disappearance of the UV absorption at 287 nm. The solution was then poured into a 50% brine/water. Sodium hydrogen carbonate (5%, 5 ml) was added to keep the solution basic and the resulting mixture was extracted with diethyl ether (50 ml x 3). The combined extracts were washed with water, brine, dried over anhydrous sodium sulfate and filtered. The solvent was removed from the filtrate and the residue was purified by centrifugal layer chromatography (2 mm silica plate, eluting with

10% ethyl acetate in light petroleum spirit) to afford the product as colorless oil (250 mg, 53%). ^{1}H NMR ($CDCl_3$) δppm: 1.35 (d, 3H, J = 6.7 Hz, 2-H), 3.38 (d, 6H, J =1 Hz, 2 x OCH_3), 3.39 (s, 3H, OCH_3), 4.62 (d, 1H, J = 15 Hz, C<u>H</u>OCH_3), 4.64 (d, 1H, J = 15 Hz, C<u>H</u>OCH_3), 4.75 (q, 1H, J = 6.7 Hz, 1-H), 6.27 (d, 1H, J = 10.5 Hz, 6'-PhH), 6.82 (dd, 1H, J = 10.5 and 3.3 Hz, 5'-PhH), 6.89 (dd, 1H, J = 3 and 1Hz, 3'-PhH).

General procedure for the synthesis of compounds 7a-c.

To a solution of butyl lithium (1.3 M in hexanes, 0.65 ml, 0.85 mmol) in dry THF (0.5 ml) was added dropwise diisopropylamine (0.12 ml, 0.85 mmol) at 0 °C under nitrogen. After stirring for 10 min, the pale yellow solution was cooled to -78 °C. To this was added a solution of **6** (0.83 mmol) in THF (0.5 ml) to give a dark yellow mixture, then a solution of **5** (203 mg, 0.83 mmol) in THF (0.8 ml) was added. The resulting mixture was stirred for 1 h then gradually warmed to room temperature. The mixture was poured into 50% brine/water (8 ml), and extracted with ethyl acetate (20 ml x 2). The extracts were washed with water (5 ml), brine (5 ml), and dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by column chromatography (silica gel, eluting with 2% methanol in dichloromethane) to afford **7**.

1-(1-Hydroxy-4-methoxyanthracene-9,10-dion-2-yl)-1-methoxymethyloxyethane (7a)

From **6a** (135 mg, 0.83 mmol) and **5** (203 mg, 0.83 mmol), **7a** was obtained as orange crystals (230 mg, 80.2%), mp 98 - 100 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.53 (d, 3H, J = 6.4 Hz, 2-H), 3.24 (s, 3H, OCH_3), 4.02 (s, 3H, PhOCH_3), 4.66 (d, 1H, J = 19 Hz, C<u>H</u>OCH_3), 4.73 (d, 1H, J = 19 Hz, C<u>H</u>OCH_3), 5.30 (q, 1H, J= 6.4 Hz, 1-H), 7.63 (s, 1H, 3'-PhH), 7.74 - 7.85 (m, 2H, 6' and 7'-PhH), 8.27 - 8.32 (m, 2H, 5' and 8'-PhH), 13.42 (s, 1H, PhOH). MS (EI) m/z: 343 (M+1), 342 (M^+). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.67; H, 5.26. Found: C, 66.67; H, 5.29.

1-(1-Hydroxy-6-fluoro-4-methoxyanthracene-9,10-dion-2-yl)-1-methoxymethyloxyethan (7b)

From **6b** (716 mg, 4.05 mmol) and **5** (980 mg, 4.05 mmol), **7b** was obtained as red crystals (1.02 g, 70%), mp 102 - 104 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.50 (d, 3H, J = 6.4 Hz, 2-H), 3.40 (s, 3H, OCH_3), 4.05 (s, 3H, PhOCH_3), 4.63 (d, 1H, J = 19.5 Hz, C<u>H</u>OCH_3), 4.71 (d, 1H, J = 19.5 Hz, C<u>H</u>OCH_3), 5.26 (q, 1H, J = 6.6 Hz, 1-H), 7.41 (dt, 1H, J = 2.5 and 8.7 Hz, 7'-PhH), 7.60 (s, 1H, 3'-PhH), 7.90 (dd, 1H, J = 2.5 and 8.9 Hz, 5'-PhH), 8.31 (dd, 1H, J = 5.3 and 8.7 Hz, 8'-PhH), 13.35 (s, 1H, 1'-PhOH). ^{13}C NMR ($CDCl_3$) δppm: 21.7 (s, C2), 55.6 (s, OCH_3), 56.8 (s, OCH_3), 68.5 (s, C1), 95.2 (s, <u>C</u>H_2OCH_3), 114.0 (d, J = 23.4 Hz, C5'), 115.3 (s, C9'a and C4'a), 119.8 (s, C3'), 120.9 (d, J = 22.7 Hz, C7'), 129.0 (d, J = 3 Hz, C8'a), 130.0 (d, J = 9.3 Hz, C8'), 138.2 (d, J = 8.2 Hz, C10'a), 143.2 (s, C2'), 154.9 (s, C1'), 155.0 (s, C4'), 167.2 (d, J = 257.5 Hz, C7'), 180.4 (s, C10'), 188.3 (s, C9'). MS (EI) m/z: 361 (M+1), 360 (M^+). IR (KBr) cm^{-1}: 3522(m), 2933(s), 1661(s), 1627(s), 1589(s), 1455(s), 1428(s), 1350(s), 1239(s), 1220(s), 1172(s), 1155(s), 1095(s), 1039(s), 1005(s), 727(s). Anal. Calcd for $C_{19}H_{17}FO_6$: C, 63.33; H, 4.72. Found: C, 63.74; H, 4.88.

1-(1-Hydroxy-7-fluoro-4-methoxyanthracene-9,10-dion-2-yl)-1-methoxymethyloxyethane (7c)

From **6c** (716 mg, 4.05 mmol) and **5** (980 mg, 4.05 mmol), **7c** was obtained as red crystals (1.28 g, 88%), mp 136 - 138 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.50 (d, 3H, J = 6.4 Hz, 2-H), 3.39 (s, 3H, OCH_3), 4.03 (s, 3H, PhOCH_3), 4.65 (d, 1H, J = 19 Hz, C<u>H</u>OCH_3), 4.75 (d, 1H, J = 19 Hz, C<u>H</u>OCH_3), 5.30 (q, 1H, J = 6.4 Hz, 1-H), 7.43 (dt, 1H, J = 2.6 and 8.5 Hz, 6'-PhH), 7.87 (dd, 1H, J = 2.6 and 8.5 Hz, 8'-PhH), 8.30 (dd, 1H,

J = 5.3 and 8.5 Hz, 5'-PhH), 13.21 (s, 1H, 1'-PhOH). ^{13}C NMR ($CDCl_3$) δppm: 21.7 (s, C2), 55.6 (s, OCH_3), 56.9 (s, OCH_3), 68.5 (s, C1), 95.2 (s, $\underline{C}H_2OCH_3$), 112.7 (d, J = 23.2 Hz, C8'), 115.8 (s, C4'a), 117.6 (s, C9'a), 120.4 (s, C3'), 122.3 (d, J = 22.7 Hz, C6'), 130.8 (d, J = 8.9 Hz, C5'), 131.9 (d, J = 3 Hz, C10'a), 135.0 (d, 8.1 Hz, C8'a), 142.9 (s, C2'), 154.9 (s, C1'), 154.93 (s, C4'), 166.1 (d, J = 255.8 Hz, C7'), 180.6 (s, C10'), 188.5 (s, C9'). MS (EI) m/z: 361 (M+1), 360 (M^+). IR (KBr) cm^{-1}: 3083(m), 2989(m), 2947(m), 1655(s), 1635(s), 1600(s), 1420(s), 1350(s), 1260(s), 1248(s), 1210(s), 1155(s), 1100(s), 1035(s). Anal. Calcd for $C_{19}H_{17}FO_6$: C, 63.33; H, 4.72. Found: C, 63.25; H, 4.50.

General procedure for the synthesis of compounds 8a-c.

To a solution of **7** (2.44 mmol) in dry dichloromethane (90 ml) was added boron trichloride (1.15 M in dichloromethane, 9.5 ml, 10.9 mmol) at -78 °C under nitrogen. The resulting purple solution was stirred for 20 min before being allowed to warm to room temperature. The stirring was continued for a further hour. Sodium hydrogen carbonate (5%, 60 ml) was then added and the mixture was extracted with dichloromethane (150 ml). The extract was washed with water (10 ml), brine (10 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated and the red residue purified by column chromatography (silica gel, eluting with dichloromethane) to afford **8** as a red solid.

1-(1,4-Dihydroxyanthracene-9,10-dion-2-yl)-1-ethanol (8a)

From **7a** (702 mg, 2.44 mmol) and boron trichloride (1.15 M, 9.5 ml, 10.9 mmol), **8a** was obtained as a red solid (370 mg, 63%), mp 136 - 137 °C (lit. [14] 110 °C). ^1H NMR ($CDCl_3$) δppm: 1.58 (d, 3H, J = 6.5 Hz, 2-H), 1.80 (br, 1H, 1-OH), 5.25 (m, 1H, 1-H), 7.48 (s, 1H, 3'-PhH), 7.85 (m, 2H, 5' and 8'-PhH), 8.35 (m, 2H, 6' and 7'-PhH), 12.95 (s, 1H, 4'-PhOH), 13.50 (s, 1H, 1'-PhOH). Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.61; H, 4.22. Found: C, 67.32; H, 4.26.

1-(1,4-Dihydroxy-6-fluoroanthracene-9,10-dion-2-yl)-1-ethanol (8b)

From **7b** (108 mg, 0.3 mmol) and boron trichloride in dichloromethane (1.0 M, 1.2 ml, 1.2 mmol), **8b** was obtained as maroon solid (86 mg, 95%), mp 178 - 180 °C. ^1H NMR ($CDCl_3$) δppm: 1.55 (d, 3H, J = 6.5 Hz, 2-H), 5.20 (m, 1H, 1-H), 7.50 (s, 1H, 3'-PhH), 7.50 (m, 1H, 7'-PhH), 7.98 (dd, 1H, J = 2.5 and 8.8 Hz, 5'-PhH), 8.84 (dd, 1H, J = 5.3 and 8.7 Hz, 8'-PhH), 12.79 (s, 1H, 4'-PhOH), 13.45 (s, 1H, 1'-PhOH). Anal. Calcd for $C_{16}H_{11}FO_5$: C, 63.57; H, 3.64. Found: C, 63.54; H, 4.07.

1-(1,4-Dihydroxy-7-fluoroanthracene-9,10-dion-2-yl)-1-ethanol (8c)

From **7c** (108 mg, 0.3 mmol) and boron trichloride in dichloromethane (1.0 M, 1.2 ml, 1.2 mmol), **8c** was obtained as maroon solid (82 mg, 91%), mp 163 - 165 °C. ^1H NMR ($CDCl_3$) δppm: 1.55 (d, 3H, J = 6.5 Hz, 2-H), 2.40 (d, 1H, 1-OH), 5.20 (m, 1H, 1-H), 7.50 (s, 1H, 3'-PhH), 7.50 (m, 1H, 6'-PhH), 7.98 (dd, 1H, J = 2.5 and 8.7 Hz, 8'-PhH), 8.40 (dd, 1H, J = 5.4 and 8.6 Hz, 5'-PhH), 12.90 (s, 1H, 4'-PhOH), 13.30 (s, 1H, 1'-PhOH). Anal. Calcd for $C_{16}H_{11}FO_5$: C, 63.57; H, 3.64. Found: C, 63.38; H, 4.04.

General procedure for the synthesis of compounds 8a-c.

To a solution of DCC (100 mg, 0.5 mmol) in dry dichloromethane (4 ml) was added **9** (125 mg, 0.4 mmol) at room temperature. The resulting mixture was stirred for 10 min. 4-dimethylaminopyridine (50 mg, 0.4 mmol)

and **8** (0.1 mmol) were then added. The resulting mixture was stirred for 4 days. The solid was removed by filtration and the filtrate was evaporated to dryness. The red residue was purified by column chromatography (silica gel, eluting with dichloromethane) to afford **10** as red crystals.

1-(1,4-Dihydroxyanthracene-9,10-dion-2-yl)-1-[trans-4-(N-p-methoxybenzyloxy-carbonyl)amino]-cyclohexylcarbonyloxyethane (10a)

From DCC (100 mg, 0.5 mmol), **9** (125 mg, 0.4 mmol), 4-dimethylaminopyridine (50 mg, 0.4 mmol) and **8a** (30 mg, 0.1 mmol), **10a** was obtained as red crystals (48 mg, 80%), mp 187 - 188 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.10 - 2.20 (m, 8H, cyclohexyl), 1.53 (d, 3H, J = 6.5 Hz, 2-H), 2.30 (m, 1H, 1-H cyclohexyl), 3.50 (m, 1H, 4-H cyclohexyl), 3.80 (s, 3H, $PhOCH_3$), 4.55 (m, 1H, NH), 5.00 (s, 2H, OCH_2), 6.22 (q, 1H, J = 6.5 Hz, 1-H), 6.87 (d, 2H, J = 8.7 Hz, 3 and 5-PhH in Moz-), 7.28 (d, 2H, J = 8.7 Hz, 2 and 6-PhH in Moz-), 7.31 (s, 1H, 3'-PhH), 7.83 (m, 2H, 5' and 8'-PhH), 8.33 (m, 2H, 6' and 7'-PhH), 12.89 (s, 1H, 4'-PhOH), 13.31 (s, 1H, 1'-PhOH). ^{13}C NMR ($CDCl_3$) δppm: 20.38 (C2), 27.50 (C2, C6 in cyclohexyl), 32.21 (C3, C5 in cyclohexyl), 42.22 (C1 in cyclohexyl), 49.27 (C4 in cyclohexyl), 55.19 (OCH_3), 66.36 (C1 and OCH_2-), 112.22 (C4'a), 112.78 (C9'a), 114.04 (C3, C5 in Moz-), 124.67 (C3'), 127.19, 127.28 (C5', C8'), 128.82 (C1 in Moz-), 130.19 (C2, C6 in Moz-), 133.63 (C10'a, C8'a), 134.71, 134.79 (C6', C7'), 143.87 (C2'), 155.15 (C1'), 155.88 (C4 in Moz-), 157.88 (C4'), 159.85 (CONH), 174.35 (-CO_2-), 187.02 (C10'), 187.62 (C9'). IR (KBr) cm^{-1} 3339(m), 2947(s), 1733(s), 1686(s), 1625(s), 1590(s), 1529(s), 1407(m), 1253(s). Anal. Calcd for $C_{32}H_{31}NO_9$: C, 67.01; H, 5.41; N, 2.44. Found: C, 66.91; H, 5.37; N, 2.39.

1-(1,4-Dihydroxy-6-fluoroanthracene-9,10-dion-2-yl)-1-[trans-4-(N-p-methoxybenzyl-oxycarbonyl)-amino]cyclohexylcarbonyloxyethane (10b)

From DCC (100 mg, 0.5 mmol), **9** (120 mg, 0.4 mmol), 4-dimethylaminopyridine (50 mg, 0.4 mmol) and **8b** (30 mg, 0.1 mmol), **10b** was obtained as orange crystals (42 mg, 72%), mp 192 - 194 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.10 - 2.20 (m, 8H, cyclohexyl), 1.50 (d, 3H, J = 6.5 Hz, 2-H), 2.30 (m, 1H, 1-H cyclohexyl), 3.50 (m, 1H, 4-H cyclohexyl), 3.80 (s, 3H, $PhOCH_3$), 4.55 (m, 1H, NH), 5.00 (s, 2H, OCH_2), 6.21 (q, 1H, J = 6.3 Hz, 1-H), 6.87 (d, 2H, J = 8.7 Hz, 3 and 5-PhH in Moz-), 7.29 (d, 2H, J = 8.7 Hz, 2 and 6-PhH in Moz-), 7.31 (s, 1H, 3'-PhH), 7.49 (dt, 1H, J = 2.6 and 8.6 Hz, 7'-PhH), 7.97 (dd, 1H, J = 2.6 and 8.6 Hz, 5'-PhH), 8.39 (dd, 1H, J = 5.3 and 8.6 Hz, 8'-PhH), 12.75 (s, 1H, 4'-PhOH), 13.29 (s, 1H, 1'-PhOH). ^{13}C NMR ($CDCl_3$) δppm: 20.36 (s,C2), 27.50 (s, C2, C6 in cyclohexyl), 32.22 (s, C3, C5 in cyclohexyl), 42.20 (s, C1 in cyclohexyl), 49.27 (s, C4 in cyclohexyl), 55.19 (s, OCH_3), 66.35 (s, C1 and OCH_2-), 112.27 (s, C4'a), 112.38 (s, C9'a), 113.75 (d, J = 23.4 Hz, C5'), 114.06 (s, C3, C5 in Moz-), 122.05 (d, J = 22.4 Hz, C7'), 124.63 (s, C3'), 128.82 (s, C1 in Moz-), 130.21 (s, C2, C6 in Moz-), 130.66 (d, J = 9.1 Hz, C8'), 136.5 (m, C10'a, C8'a), 144.51 (s, C2'), 155.38 (s, C1'), 155.88 (s, -CONH-), 158.19 (s, C4'), 159.86 (s, C4 in Moz-), 166.95 (d, J = 258.4 Hz, C6'), 174.34 (-CO2-), 185.73 (d, J = 2.3 Hz, C10'), 186.36 (s, C9'). IR (KBr) cm^{-1} 3329(m), 1936(s), 1733(s), 1684(s), 1620(s), 1592(s), 1532(s), 1430(s), 1408(s), 1258(s). Anal. Calcd for $C_{32}H_{30}FNO_9$: C, 64.97; H, 5.07; N, 2.37. Found: C, 64.70; H, 5.15; N, 2.36.

1-(1,4-Dihydroxy-7-fluoroanthracene-9,10-dion-2-yl)-1-[trans-4-(N-p-methoxybenzyloxycarbonyl)-amino]cyclohexylcarbonyloxyethane (10c)

From DCC (50 mg, 0.25 mmol), **9** (60 mg, 0.2 mmol), 4-dimethylaminopyridine (25 mg, 0.2 mmol)

and **8c** (10 mg, 0.03 mmol), **10c** was obtained as red solid (16 mg, 72%), mp 216 - 218 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.10 - 2.15 (m, 8H, cyclohexyl), 1.50 (d, 3H, J = 6.5 Hz, 2-H), 2.30 (m, 1H, 1-H cyclohexyl), 3.50 (m, 1H, 4-H cyclohexyl), 3.79 (s, 3H, $PhOCH_3$), 4.55 (m, 1H, NH), 5.01 (s, 2H, OCH_2), 6.21 (q, 1H, J = 6.5 Hz, 1-H), 6.87 (d, 2H, J = 8.7 Hz, 3 and 5-PhH in Moz-), 7.29 (d, 2H, J = 8.7 Hz, 2 and 6-PhH in Moz-), 7.32 (s, 1H, 3'-PhH), 7.49 (dt, 1H, J = 2.6 and 8.4 Hz, 6'-PhH), 7.98 (dd, 1H, J = 2.6 and 8.6 Hz, 8'-PhH), 8.38 (dd, 1H, J = 5.3 and 8.6 Hz, 5'-PhH), 12.87 (s, 1H, 4'-PhOH), 13.17 (s, 1H, 1'-PhOH). ^{13}C NMR ($CDCl_3$) δppm: 20.38 (s, C2), 27.51 (s, C2, C6 in cyclohexyl), 32.22 (s, C3, C5 in cyclohexyl), 42.22 (s, C1 in cyclohexyl), 49.28 (s, C4 in cyclohexyl), 55.21 (s, OCH_3), 66.31 (s, -OCH_2-), 66.39 (s, C1), 111.82 (s, C4'a), 112.87 (s, C9'a), 113.85 (d, J = 23.6 Hz, C8'), 114.07 (s, C3, C5 in Moz-), 122.15 (d, J = 22.5 Hz, C6'), 125.20 (s, C3'), 128.83 (s, C1 in Moz-), 130.22 (s, C2, C6 in Moz-), 130.56 (d, J = 9.1 Hz, C5'), 136.5 (d, J = 7.9 Hz, C8'a), 136.6 (s, C10'a), 143.95 (s, C2'), 155.46 (s, C1'), 155.90 (s, -CONH-), 158.12 (s, C4'), 159.88 (s, C4 in Moz-), 166.89 (d, J = 258.4 Hz, C7'), 174.35 (-CO2-), 185.77 (d, J = 2.3 Hz, C9'), 186.40 (s, C10'). IR (KBr) cm^{-1} 3326(m), 1739(s), 1696(s), 1598(s), 1544(s), 1527(s), 1253(s).

General procedure for the synthesis of compounds 3a-c.

To a solution of **10** (0.3 mmol) in dry dichloromethane (3 ml) was added hydrogen chloride in dioxane (1.3 M, 2.5 ml) at room temperature. The resulting red solution was stirred for 2 h. The red crystals were separated, washed thoroughly with dry dioxane (0.5 ml) and diethyl ether (1 ml) to give **3**.

1-(1,4-Dihydroxyanthracene-9,10-dion-2-yl)-1-(trans-4-aminocyclohexylcarbonyl)oxyethane hydrochloride (3a)

From **10a** (177 mg, 0.31 mmol) and hydrogen chloride in dioxane (1.3 M, 2.5 ml), **3a** was obtained as red crystals (128 mg, 93%), mp 256 - 257 °C. ^{1}H NMR (DMSO-d_6) δppm: 1.30 - 2.10 (m, 8H, cyclohexyl), 1.50 (d, 3H, J = 6.6 Hz, 2-H), 2.42 (m, 1H, 1-H in cyclohexyl), 3.00 (m, 1H, 4-H in cyclohexyl), 6.06 (q, 1H, J = 6.6 Hz, 1-H), 7.38 (s, 1H, 3'-PhH), 7.98 (m, 2H, 5' and 8'-PhH), 8.02 (brs, 3H, $NH3^+$), 8.25 (m, 2H, 6' and 7'-PhH), 12.67 (s, 1H, 4'-PhOH), 13.18 (s, 1H, 1'-PhOH). ^{13}C NMR (DMSO-d_6) δppm: 20.05 (C2), 26.30 and 26.35 (C2, C6 in cylcohexyl), 29.12 (C3, C5 in cyclohexyl), 40.90 (C1 in cyclohexyl), 65.84 (C1), 112.42 (C4'a), 113.00 (C9'a), 124.34 (C3'), 127.00, 127.07 (C5', C8'), 133.18, 133.25 (C10'a, C8'a), 135.46, 135.59 (C6', C7'), 142.99 (C2'), 153.92 (C1'), 156.77 (C4'), 173.82 (-CO_2-), 186.9 (C10'), 187.70 (C9'). IR (KBr) cm^{-1}: 3431(m), 2935(s), 1732(s), 1621(s), 1585(s), 1422(s), 104(s), 1253(s), 1071(m). MS (FAB) m/z: 410 (M+1). Anal. Calcd for $C_{23}H_{24}ClNO_6$: C, 61.95; H, 5.39; N, 3.14. Found: C, 61.81; H, 5.33; N, 3.03.

1-(1,4-Dihydroxy-6-fluoroanthracene-9,10-dion-2-yl)-1-(trans-4-aminocyclohexyl-carbonyl)oxyethane hydrochloride (3b)

From **10b** (80 mg, 0.14 mmol) and hydrogen chloride in dioxane (1.3 M, 2 ml), **3b** was obtained as red crystals (62 mg, 98%), mp 254 °C (dec.). ^{1}H NMR (CD_3OD) δppm: 1.45 - 1.65 (m, 4H, cyclohexyl), 1.54 (d, 3H, J = 6.6 Hz, 2-H), 2.15 (m, 4H, cyclohexyl), 2.5 (m, 1H, 1-H in cyclohexyl), 3.15 (m, 1H, 4-H in cyclohexyl), 6.1 (q, 1H, J = 6.6 Hz, 1-H), 7.28 (s, 1H, 3'-PhH), 7.61 (dt, 1H, J = 2.5 and 8.3 Hz, 7'-PhH), 7.80 (dd, 1H, J = 2.5 and 8.9 Hz, 5'-PhH), 8.23 (dd, 1H, J = 5.1 and 8.6 Hz, 8'-PhH). IR (KBr) cm^{-1}: 3347(s), ß2947(s), 1733(s), 1624(s), 1592(s), 1427(s), 1410(s), 1326(s), 1260(s). MS (EI) m/z: 427 (M^+). MS (FAB)

m/z: 428 (M+1). Anal. Calcd for $C_{23}H_{23}ClFNO_6$: C, 59.55; H, 4.96; N, 3.02. Found: C, 59.31; H, 4.87; N, 2.90.

1-(1,4-Dihydroxy-7-fluoroanthracene-9,10-dion-2-yl)-1-(trans-4-aminocyclohexyl-carbonyl)oxyethane hydrochloride (3c)

From **10c** (80 mg, 0.14 mmol) and hydrogen chloride in dioxane (1.3 M, 2 ml), **3c** was obtained as red crystals (56 mg, 89%), mp 269 - 271 °C (dec.). ^1H NMR (CD_3OD) δppm: 1.40 - 1.60 (m, 4H, cyclohexyl), 1.55 (d, 3H, J = 6.5 Hz, 2-H), 2.10 - 2.20 (m, 4H, cyclohexyl), 2.5 (m, 1H, 1-H in cyclohexyl), 3.10 (m, 1H, 4-H in cyclohexyl), 6.15 (q, 1H, J = 6.5 Hz, 1-H), 7.30 (s, 1H, 3'-PhH), 7.64 (dt, 1H, J = 2.6 and 8.5 Hz, 6'-PhH), 7.89 (dd, 1H, J = 2.6 and 8.9 Hz, 8'-PhH), 8.31 (dd, 1H, J = 5.3 and 8.8 Hz, 5'-PhH). IR (KBr) cm^{-1}: 2942(s), 1735(s), 1624(s), 1594(s), 1425(m), 1408(s), 1259(s), 1183(s). MS (EI) m/z: 427 (M^+). MS (FAB) m/z: 428 (M+1). Anal. Calcd for $C_{23}H_{23}ClFNO_6$: C, 59.55; H, 4.96; N, 3.02. Found: C, 59.28; H, 4.98; N, 2.81.

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