Synthesis and Cytotoxic Evaluation of Potential Bis-Intercalators: Tetramethylenebis(oxy)- and Hexamethylenebis(oxy)-Linked Assemblies Consisting of Flavone, Xanthone, Anthraquinone, and Dibenzofuran

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In a search for potential inhibitors of solid-tumor growth, certain alkanediylbis(oxy)-linked assemblies were synthesized and evaluated for their cytotoxicity as bis-intercalators. Symmetrical assemblies **1b**–**12b** were synthesized from their respective Aryl-OH and either dibromobutane or dibromohexane, while unsymmetrical ones **13**–**15** were prepared from $Aryl^1$-OH and either $Aryl^2$-O-$(CH_2)_4$Br or $Aryl^2$-O-$(CH_2)_6$Br. These bis-intercalators were inactive against the growth of leukemia cells. However, some of them were active against the growth of certain solid tumors such as HOP-62, HOP-92 (non-small-cell lung cancer), SF-265, SNB-75, U251 (CNS cancer), A498 (renal cancer), and HS578T (breast cancer). Among them, [hexane-1,6-diylbis(oxy)-bis(4,1-phenylene)]bis[4*H*-1-benzopyran] (**6b**) was especially active against the growth of all CNS cancer cell lines and also the growth of A498, HOP-62, and HOP-92 with GI_{50} values of 17.0, 20.0, and 21.8 μM, respectively.

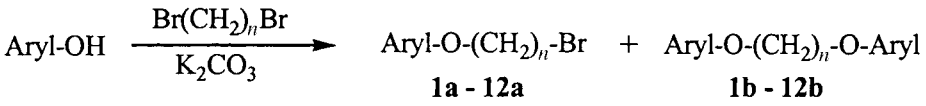
Introduction. – DNA Intercalation, first described in 1961 by *Lerman* [1], is a non-covalent interaction in which a drug is held rigidly perpendicular to the DNA helix axis. This causes the base pairs to separate vertically, thereby distorting the sugar-phosphate backbone and decreasing the pitch of the helix. Although DNA intercalators exhibit a wide range of biological activities, their anticancer properties have attracted the most attention [2–4]. Extensive SAR studies with DNA-intercalating chromophores revealed a positive correlation between the strength of reversible DNA binding and the cytotoxic potency [5–7]. Efforts to identify molecules with a greater affinity for DNA have resulted in the development of hydrophilic bis-intercalators in which two intercalating ligands are linked by a central chain [8–12]. Although many of these compounds did show increased affinity for DNA, their anticancer spectra were usually limited to aqueous leukemia. On the other hand, certain lipophilic dimeric naphthalimides [13][14], imidazoacridones [15], and acridine-4-carboxamides [16] were shown to possess broad-spectrum activity against a variety of human solid-tumor cell lines. Recently, we reported the preparation and evaluation of α-methylidene-γ-butyrolactones, which are linked to coumarins and to potential DNA-intercalating carriers such as flavone, xanthone, carbazole, and dibenzofuran, against 60 human cancer cell lines derived from nine cancer cell types [17]. The results indicated that these compounds inhibit not only leukemia but also certain solid-tumor cancer cell lines. The present report describes the preparation and cytotoxic evaluation of relatively lipophilic, neutral bis-intercalators consisting of flavone, xanthenone, anthraquinone, and dibenzofuran with the aim to develop selective antitumor agents with good inhibitory activities against the growth of solid tumors, especially CNS cancers, which require that the compounds effectively penetrate the blood-brain barrier.

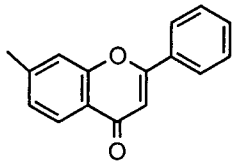
Results and Discussion. – The preparation of tetramethylenebis(oxy)- and hexamethylenebis(oxy)-linked assemblies is illustrated in *Scheme 1*. Reaction of 7-hydroxyflavone (=7-hydroxy-2-phenyl-4*H*-1-benzopyran-4-one) and 1,4-dibromobutane under basic conditions gave mostly the monoalkylated 7-(4-bromobutoxy)flavone (**1a**) in 60% yield along with the desired 7,7′-[butane-1,4-diylbis(oxy)]bis[flavone] (**1b**) as a minor product in 19% yield. Accordingly, monoalkylating products **2a**–**12a** (major) and the desired bis-intercalators **2b**–**12b** (minor) were obtained from their respective Aryl-OHs and dibromoalkanes in fairly good yields. Preparation of the unsymmetrical bis-intercalators is shown in *Scheme 2*. Thus, 2-hydroxyanthraquinone was treated with K_2CO_3 in DMF followed by the addition of 3-[(6-bromohexyl)oxy]-9*H*-xanthen-9-one (**10a**) to give 2-({6-[(9-oxo-9*H*-xanthen-3-yl)oxy]hexyl}oxy)anthracene-9,10-dione (**13**) in 96% yield. Compounds **14** and **15** were synthesized under similar conditions.

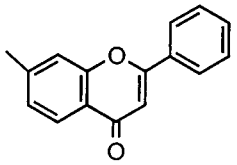
All compounds were evaluated *in vitro* against a three-cell-line panel consisting of MCF 7 (breast), NCI-H460 (lung), and SF-268 (CNS) cells. In this protocol, each cell line was inoculated and preincubated on a microtiter plate. Test agents were then added at a single concentration (100 μM), and the culture was incubated for 48 h. End-point determinations were made with sulforhodamine B, a protein-binding dye. Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds that reduced the growth of any one of the cell lines to 32% or less (negative numbers indicate cell kill) were passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range. The results (*Table 1*) indicated that all compounds, with the exception of **6b**–**8b** and **10b**, are inactive. Therefore, a hexamethylene link is more favorable than a tetramethylene link (**5b** *vs.* **6b**; **9b** *vs.* **10b**). Among the hexamethylene-linked compounds, **12b** is inactive, implying that two O-atoms in each arene moiety is preferred. Among the three bis-flavones **2b**, **4b**, and **6b**, only 4′,4‴-[hexane-1,6-diylbis(oxy)]bis[flavone] (**6b**) is active, indicating that the distance of both chromenone O-atoms from the linker may also play an important role.

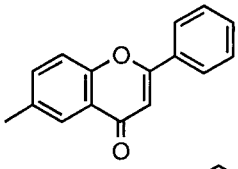
The active compounds were evaluated in the full panel of 60 human tumor cell lines derived from nine cancer-cell types (leukemia, non-small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer). For each compound, dose-response curves for each cell line were measured with five different drug concentrations, and the concentration causing 50% cell-growth inhibition (GI_{50}) compared with the control was calculated (see *Table 2*) [18]. All four bis-intercalators were inactive against the growth of leukemia cells. However, they were active against the growth of certain solid tumors such as HOP-62, HOP-92 (non-small-cell lung cancer), SF-265, SNB-75, U251 (CNS cancer), A498 (renal cancer), and HS578T (breast cancer). Among them, **6b** was the most cytotoxic with a mean GI_{50} of 76.0 μM. Compound **6b** and its xanthone counterpart **10b** were especially active against the growth of CNS cancer cell lines probably due to their highly lipophilic properties. Besides, **6b** was especially active against the growth of A498, HOP-62, and HOP-92 with GI_{50} values of 17.0, 20.0, and 21.8 μM, respectively. Although 2,2′-[hexane-1,6-diylbis(oxy)]anthracene-9,10-dione (**8b**) was relatively inactive with a mean GI_{50} of 92.3 μM, it exhibited a selective cytotoxicity against the growth of SNB-75 and HOP-62 with GI_{50} values of 16.1 and 38.4 μM, respectively.

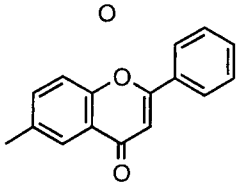
Scheme 1

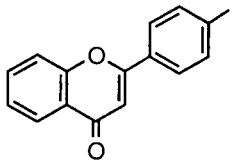


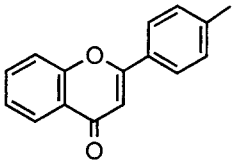
1 $n = 4$, Aryl = 

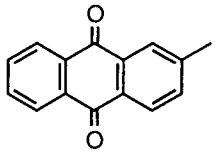
2 $n = 6$, Aryl = 

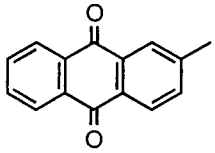
3 $n = 4$, Aryl = 

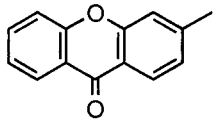
4 $n = 6$, Aryl = 

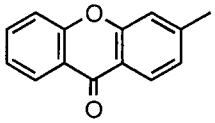
5 $n = 4$, Aryl = 

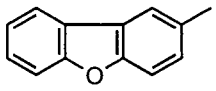
6 $n = 6$, Aryl = 

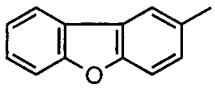
7 $n = 4$, Aryl = 

8 $n = 6$, Aryl = 

9 $n = 4$, Aryl = 

10 $n = 6$, Aryl = 

11 $n = 4$, Aryl = 

12 $n = 6$, Aryl = 

Conclusions. – Certain symmetrical and unsymmetrical bis-intercalators were synthesized and evaluated for their cytotoxicity. The preliminary results indicated that these bis-intercalators were inactive against the growth of leukemia cells. However,

Scheme 2

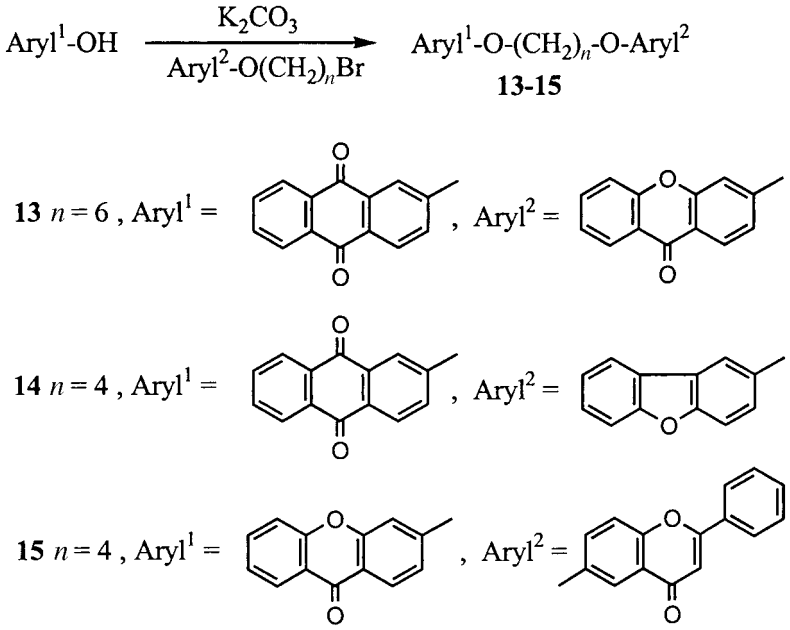


Table 1. *Primary Anticancer Assay of Bis-Intercalators*

	Growth percentages			
	NCI-H460 (Lung)	MCF 7 (Breast)	SF-268 (CNS)	Activity
1b	102	88	103	inactive
2b	100	88	103	inactive
3b	101	89	102	inactive
4b	95	77	103	inactive
5b	105	88	108	inactive
6b	97	87	16	active
7b	94	87	−2	active
8b	98	87	14	active
9b	125	54	99	inactive
10b	86	85	3	active
11b	72	86	95	inactive
12b	124	76	100	inactive
13	97	75	38	inactive
14	99	90	103	inactive
15	104	97	50	inactive

some of them were active against the growth of certain solid tumors such as HOP-62, HOP-92 (non-small-cell lung cancer), SF-265, SNB-75, U251 (CNS cancer), A498 (renal cancer), and HS578T (breast cancer). Among them, bis-flavolone **6b** and its bis-xanthenone counterpart **10b** are especially active against the growth of CNS cancer cell lines, probably due to their highly lipophilic properties. Further, hexamethylene-linked

Table 2. *Inhibition* (GI_{50} [μM])[a]) *of* in vitro *Cancer Cell Lines by Bis-Intercalators*

Cell Line	**6b**	**7b**	**8b**	**10b**
Leukemia: CCRF-CEM	> 100	> 100	> 100	> 100
HL-60(TB)	> 100	> 100	> 100	> 100
SR	> 100	> 100	> 100	> 100
Non-small-cell lung cancer: HOP-62	20.0	30.0	38.4	23.3
HOP-92	21.8	73.2	> 100	91.7
NCI-H460	> 100	> 100	> 100	> 100
CNS cancer: SF-268	64.1	> 100	> 100	39.1
SF-295	29.4	48.1	55.2	50.4
SF-539	64.2	> 100	> 100	> 100
SNB-19	27.8	69.0	> 100	46.6
SNB-75	n.d.[b])	n.d.[b])	16.1	13.5
U251	23.0	64.3	> 100	50.5
Renal cancer: 786-0	52.4	77.4	> 100	76.3
A498	17.0	26.0	73.3	> 100
TK-10	40.3	99.8	> 100	47.0
Breast cancer: MCF7	> 100	> 100	> 100	> 100
MDA-MB-231/ATCC	49.9	> 100	> 100	> 100
HS578T	52.1	98.6	> 100	45.4
Mean[c])	76.0	91.7	92.3	84.5

[a]) Data obtained from *NCI*'s *in vitro* disease-oriented tumor-cell screen [18]. GI_{50} = drug molar concentration causing 50% cell-growth inhibition. [b]) Not determined. [c]) Mean values over all cell lines tested. Theses cell lines are: leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); non-small-cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); renal cancer (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); prostate cancer (PC-3 and DU-145); and breast cancer (MCF7, MCF7/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, MDA-N, and T-47D).

bis-intercalators are more active than their tetramethylene-linked counterparts (**5b** *vs.* **6b**; **9b** *vs.* **10b**).

Experimental Part

General. CC = Column chromatography. TLC: precoated (0.2 mm) silica gel *60* F_{254} plates from *EM Laboratories, Inc.*; detection by UV light (254 nm). M.p.: *Electrothermal IA9100* digital melting-point apparatus; uncorrected. ^{1}H-NMR Spectra: *Varian Unity-400* spectrometer at 400 MHz or *Varian Gemini-200* spectrometer at 200 MHz; chemical shifts δ in ppm with $SiMe_4$ as an internal standard (= 0 ppm), coupling constants J in Hz. Elemental analyses were carried out on a *Heraeus CHN-O-Rapid* elemental analyzer, and results were within ± 0.4% of calc. values.

*7-(4-Bromobutoxy)-2-phenyl-4*H*-1-benzopyran-4-one* (**1a**) *and 7,7′-[Butane-1,4-diylbis(oxy)]bis[2-phenyl-4*H*-1-benzopyran-4-one]* (**1b**). At r.t. 7-hydroxyflavone (2.38 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol), and dry DMF (50 ml) were stirred for 30 min. To this soln. was added 1,4-dibromobutane (2.16 g, 10 mmol) in dry DMF (10 ml) in one portion. The resulting mixture was stirred at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 ml). The yellow solid thus obtained was collected and purified by CC (silica gel, CH_2Cl_2/MeOH 20:1) followed by crystallization from Et_2O and CH_2Cl_2 **1a** (1.12 g, 60%) and **1b** (0.51 g, 19%).

Data of **1a**: M.p. 137–138°. ^{1}H-NMR ($CDCl_3$): 2.00–2.14 (*m*, 2 CH_2); 3.52 (*t*, *J* = 6.3, CH_2Br); 4.13 (*t*, *J* = 5.8, CH_2O); 6.79 (*s*, H–C(3)); 6.96–8.16 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 27.62, 29.27 (CH_2); 33.13

(CH_2Br); 67.58 (CH_2O); 100.93, 107.47, 114.69, 117.80, 126.16, 127.08, 129.00, 131.43, 131.82, 157.97, 163.08, 164.33 (arom. C); 177.82 (C(4)). Anal. calc. for $C_{19}H_{17}BrO_3$: C 61.14, H 4.59; found: C 61.12, H 4.66.

Data of **1b**: M.p. 215–216°. ^{1}H-NMR ($CDCl_3$): 2.11 (*s*, 2 CH_2); 4.21 (*s*, 2 CH_2O); 6.83 (*s*, 2 H, H–C(3)); 6.98–8.16 (*m*, 16 arom. H). Anal. calc. for $C_{34}H_{26}O_6$: C 76.97, H 4.94; found: C 76.70, H 5.00.

Bis-intercalators **2b**–**12b** *and Monoalkylated Products* **2a**–**12a**. As described for **1a**/**1b**, **2a**/**2b** to **12a**/**12b** were obtained from the corresponding Aryl-OH.

*7-[(6-Bromohexyl)oxy]-2-phenyl-4*H*-1-benzopyran-4-one* (**2a**): Yield 70%. M.p. 115–116°. ^{1}H-NMR ($CDCl_3$): 1.53–1.95 (*m*, 4 CH_2); 3.44 (*t*, *J* = 6.8, CH_2Br); 4.08 (*t*, *J* = 6.4, CH_2O); 6.77 (*s*, H–C(3)); 6.95–8.13 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 25.17, 27.80, 28.77, 32.55 (CH_2); 33.65 (CH_2Br); 68.41 (CH_2O); 100.84, 107.42, 114.73, 117.63, 126.11, 126.96, 128.95, 131.36, 131.84, 157.96, 163.00, 163.65 (arom. C); 177.81 (C(4)). Anal. calc. for $C_{21}H_{21}BrO_3$: C 62.85, H 5.27; found: C 62.87, H 5.27.

*7,7′-[Hexane-1,6-diylbis(oxy)]bis[2-phenyl-4*H*-1-benzopyran-4-one]* (**2b**): Yield 19%. M.p. 237–238°. ^{1}H-NMR ($CDCl_3$): 2.08–2.13 (*m*, 4 CH_2); 4.11 (*t*, *J* = 6.3, 2 CH_2O); 6.82 (*s*, 2 H, H–C(3)); 6.97–8.16 (*m*, 16 arom. H). Anal. calc. for $C_{36}H_{30}O_6 \cdot 0.25\ H_2O$: C 76.78, H 5.46; found: C 76.76, H 5.46.

*6-(4-Bromobutoxy)-2-phenyl-4*H*-1-benzopyran-4-one* (**3a**): Yield 59%. M.p. 108–109°. ^{1}H-NMR ($CDCl_3$): 1.99–2.10 (*m*, 2 CH_2); 3.51 (*t*, *J* = 6.4, CH_2Br); 4.11 (*t*, *J* = 6.0, CH_2O); 6.82 (*s*, H–C(3)); 7.28–7.94 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 27.77, 29.42 (CH_2); 33.24 (CH_2Br); 67.61 (CH_2O); 105.57, 106.84, 119.51, 123.99, 124.55, 126.22, 129.01, 131.48, 131.88, 151.07, 156.24, 163.18 (arom. C); 178.26 (C(4)). Anal. calc. for $C_{19}H_{17}BrO_3$: C 61.14, H 4.59; found: C 61.19, H 4.65.

*6,6′-[Butane-1,4-diylbis(oxy)]bis[2-phenyl-4*H*-1-benzopyran-4-one]* (**3b**): Yield 20%. M.p. 242–243°. ^{1}H-NMR ($CDCl_3$): 2.06 (*s*, 2 CH_2); 4.18 (*s*, 2 CH_2O); 6.82 (*s*, 2 H, H–C(3)); 7.29–7.94 (*m*, 16 arom. H). Anal. calc. for $C_{34}H_{26}O_6 \cdot 0.5\ H_2O$: C 75.68, H 5.04; found: C 75.52, H 4.94.

*6-[(6-Bromohexyl)oxy]-2-phenyl-4*H*-1-benzopyran-4-one* (**4a**): Yield 60%. M.p. 96–97°. ^{1}H-NMR ($CDCl_3$): 1.50–1.91 (*m*, 4 CH_2); 3.43 (*t*, *J* = 6.8, CH_2Br); 4.07 (*t*, *J* = 6.3, CH_2O); 6.85 (*s*, H–C(3)); 7.27–7.95 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 25.23, 27.87, 28.90, 32.65 (CH_2); 33.68 (CH_2Br); 68.47 (CH_2O); 105.49, 106.74, 119.44, 124.13, 124.46, 126.24, 129.00, 131.48, 131.85, 151.00, 156.46, 163.23 (arom. C); 178.31 (C(4)). Anal. calc. for $C_{21}H_{21}BrO_3$: C 62.85, H 5.27; found: C 62.82, H 5.30.

*6,6′-[Hexane-1,6-diylbis(oxy)]bis[2-phenyl-4*H*-1-benzopyran-4-one]* (**4b**): Yield 21%. M.p. 234–235°. ^{1}H-NMR ($CDCl_3$): 1.57–1.89 (*m*, 4 CH_2); 4.09 (*t*, *J* = 6.4, 2 CH_2O); 6.85 (*s*, 2 H, H–C(3)); 7.29–7.95 (*m*, 16 arom. H). Anal. calc. for $C_{36}H_{30}O_6 \cdot 0.25\ H_2O$: C 76.78, H 5.46; found: C 76.50, H 5.44.

*2-[4-(4-Bromobutoxy)phenyl]-4*H*-1-benzopyran-4-one* (**5a**): Yield 50%: M.p. 130–131°. ^{1}H-NMR ($CDCl_3$): 1.97–2.13 (*m*, 2 CH_2); 3.51 (*t*, *J* = 6.8, CH_2Br); 4.09 (*t*, *J* = 6.0, CH_2O); 6.82 (*s*, H–C(3)); 7.00–8.24 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 27.72, 29.31 (CH_2); 33.20 (CH_2Br); 67.15 (CH_2O); 105.93, 114.92, 117.94, 123.67, 123.90, 125.17, 125.63, 128.12, 133.70, 156.19, 161.81, 163.68 (arom. C); 178.31 (C(4)). Anal. calc. for $C_{19}H_{17}BrO_3$: C 61.14, H 4.59; found: C 61.16, H 4.60.

*2,2′-[Butane-1,4-diylbis(oxy)bis(4,1-phenylene)]bis[4*H*-1-benzopyran-4-one]* (**5b**): Yield 11%. M.p. 246–247°. ^{1}H-NMR ($CDCl_3$): 2.05 (*m*, 2 CH_2); 4.15 (*t*, *J* = 5.1, 2 CH_2O); 6.80 (*s*, 2 H, H–C(3)); 7.01–8.25 (*m*, 16 arom. H). Anal. calc. for $C_{34}H_{26}O_6$: C 76.97, H 4.94; found: C 76.60, H 5.02.

*2-[4-[(6-Bromohexyl)oxy]phenyl]-4*H*-1-benzopyran-4-one* (**6a**): Yield 66%. M.p. 121–122°. ^{1}H-NMR ($CDCl_3$): 1.49–1.91 (*m*, 4 CH_2); 3.44 (*t*, *J* = 6.8, CH_2Br); 4.05 (*t*, *J* = 6.4, CH_2O); 6.84 (*s*, H–C(3)); 7.00–8.24 (*m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$): 25.20, 27.84, 28.90, 32.59 (CH_2); 33.67 (CH_2Br); 68.02 (CH_2O); 105.83, 114.95, 117.94, 123.67, 125.19, 125.63, 128.12, 133.70, 156.19, 162.09, 163.83 (arom. C); 178.31 (C(4)). Anal. calc. for $C_{21}H_{21}BrO_3$: C 62.85, H 5.27; found: C 62.76, H 5.30.

*2,2′-[Hexane-1,6-diylbis(oxy)bis(4,1-phenylene)]bis[4*H*-1-benzopyran]* (**6b**): Yield 15%. M.p. 205–206°. ^{1}H-NMR ($CDCl_3$): 1.58–1.88 (*m*, 4 CH_2); 4.07 (*t*, *J* = 6.4, 2 CH_2O); 6.75 (*s*, 2 H, H–C(3)); 6.99–8.25 (*m*, 16 arom. H). Anal. calc. for $C_{36}H_{30}O_6$: C 77.40, H 5.41; found: C 77.10, H 5.47.

2-(4-Bromobutoxy)anthracene-9,10-dione (**7a**): Yield 56%. M.p. 132–133°. ^{1}H-NMR ($CDCl_3$): 2.04–2.09 (*m*, 2 CH_2); 3.52 (*t*, *J* = 6.3, CH_2Br); 4.20 (*t*, *J* = 5.7, CH_2O); 7.26 (*dd*, *J* = 8.6, 2.6, H–C(3)); 7.71 (*d*, *J* = 2.6, H–C(1)); 8.26 (*d*, *J* = 8.6, H–C(4)); 7.76–8.32 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 27.70, 29.30 (CH_2); 33.12 (CH_2Br); 67.71 (CH_2O); 110.50, 121.43, 127.16, 129.80, 133.59, 133.68, 134.18, 135.61, 163.64 (arom. C); 182.14, 183.26 (C(9), C(10)). Anal. calc. for $C_{18}H_{15}BrO_3$: C 60.18, H 4.21; found: C 60.07, H 4.20.

2,2′-[Butane-1,4-diylbis(oxy)]anthracene-9,10-dione (**7b**): Yield 12%. M.p. 261–262°. ^{1}H-NMR ($CDCl_3$): 2.11 (*s*, 2 CH_2); 4.27 (*s*, 2 CH_2O); 7.27 (*dd*, *J* = 8.7, 2.7, 2 H, H–C(3)); 7.73 (*d*, *J* = 2.7, 2 H, H–C(1)); 8.27 (*d*, *J* = 8.7, 2 H, H–C(4)); 7.75–8.32 (*m*, 8 arom. H). Anal. calc. for $C_{32}H_{22}O_6 \cdot 0.2\ H_2O$: C 75.94, H 4.46; found: C 75.85, H 4.53.

2-([(6-Bromohexyl)oxy]anthracene-9,10-dione (**8a**): Yield 52%. M.p. 91–92°. ^{1}H-NMR ($CDCl_3$): 1.52–1.91 (*m*, 4 CH_2); 3.44 (*t*, *J* = 6.7, CH_2Br); 4.15 (*t*, *J* = 6.3, CH_2O); 7.25 (*dd*, *J* = 8.7, 2.5, H–C(3)); 7.70 (*d*, *J* = 2.5, H–C(1)); 8.24 (*d*, *J* = 8.8, H–C(4)); 7.74–8.30 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 25.21, 27.87, 28.85, 29.70 (CH_2); 33.65 (CH_2Br); 68.55 (CH_2O); 110.50, 121.43, 126.99, 127.11, 129.74, 133.61, 133.70, 134.12, 135.58, 163.85 (arom. C); 182.12, 183.28 (C(9), C(10)). Anal. calc. for $C_{20}H_{19}BrO_3$: C 62.03, H 4.95; found: C 62.01, H 4.97.

2,2′-[Hexane-1,6-diylbis(oxy)]anthracene-9,10-dione (**8b**): Yield 9%. M.p. 200–201°. ^{1}H-NMR ($CDCl_3$): 1.60–1.93 (*m*, 4 CH_2); 4.19 (*t*, *J* = 6.3, 2 CH_2O); 7.27 (*dd*, *J* = 8.6, 2.6, 2 H, H–C(3)); 7.72 (*d*, *J* = 2.6, 2 H, H–C(1)); 8.26 (*d*, *J* = 8.7, 2 H, H–C(4)); 7.76–8.31 (*m*, 8 arom. H). Anal. calc. for $C_{34}H_{26}O_6 \cdot 2\,H_2O$: C 72.07, H 5.34; found: C 72.06, H 4.95.

*3-(4-Bromobutoxy)-9*H*-xanthen-9-one* (**9a**): Yield 56%. M.p. 117–118°. ^{1}H-NMR ($CDCl_3$): 1.99–2.15 (*m*, 2 CH_2); 3.51 (*t*, *J* = 6.4, CH_2Br); 4.12 (*t*, *J* = 5.6, CH_2O); 6.86 (*d*, *J* = 2.4, H–C(4)); 6.93 (*dd*, *J* = 8.8, 2.4, H–C(2)); 8.24 (*d*, *J* = 9.2, H–C(1)); 7.35–8.34 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 27.64, 29.29 (CH_2); 33.13 (CH_2Br); 67.54 (CH_2O); 100.68, 113.46, 115.83, 117.66, 121.96, 123.85, 126.64, 128.29, 134.26, 156.18, 158.01, 164.29 (arom. C); 176.23 (C(9)). Anal. calc. for $C_{17}H_{15}BrO_3$: C 58.81, H 4.35; found: C 58.82, H 4.39.

*3,3′-[Butane-1,4-diylbis(oxy)]bis[9*H*-xanthen-9-one]* (**9b**): Yield 13%. M.p. 218–219°. ^{1}H-NMR ($CDCl_3$): 2.08–2.11 (*m*, 2 CH_2); 4.20 (*t*, *J* = 5.2, 2 CH_2O); 6.88 (*d*, *J* = 2.4, 2 H, H–C(4)); 6.95 (*dd*, *J* = 8.8, 2.4, 2 H, H–C(2)); 8.26 (*d*, *J* = 8.8, 2 H, H–C(1)); 7.26–8.35 (*m*, 8 arom. H). Anal. calc. for $C_{30}H_{22}O_6$: C 75.30, H 4.63; found: C 75.13, H 4.66.

*3-[(6-Bromohexyl)oxy]-9*H*-xanthen-9-one* (**10a**): Yield 43%. M.p. 94–95°. ^{1}H-NMR ($CDCl_3$): 1.52–1.92 (*m*, 4 CH_2); 3.44 (*t*, *J* = 6.7, CH_2Br); 4.08 (*t*, *J* = 6.4, CH_2O); 6.86 (*d*, *J* = 2.3, H–C(4)); 6.93 (*dd*, *J* = 8.8, 2.4, H–C(2)); 8.24 (*d*, *J* = 8.8, H–C(1)); 7.35–8.35 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 25.22, 27.84, 28.81, 32.59 (CH_2); 33.71 (CH_2Br); 68.41 (CH_2O); 100.61, 113.56, 115.67, 117.65, 121.95, 123.82, 126.63, 128.22, 134.23, 156.19, 158.04, 164.54 (arom. C); 176.26 (C(9)). Anal. calc. for $C_{19}H_{19}BrO_3$: C 60.81, H 5.10; found: C 60.80, H 5.17.

*3,3′-[Hexane-1,6-diylbis(oxy)]bis[9*H*-xanthen-9-one]* (**10b**): Yield 17%. M.p. 197–198°. ^{1}H-NMR ($CDCl_3$): 1.60–1.95 (*m*, 4 CH_2); 4.11 (*t*, *J* = 6.3, 2 CH_2O); 6.87 (*d*, *J* = 2.3, 2 H, H–C(4)); 6.94 (*dd*, *J* = 8.9, 2.3, 2 H, H–C(2)); 8.25 (*d*, *J* = 8.8, 2 H, H–C(1)); 7.32–8.35 (*m*, 8 arom. H). Anal. calc. for $C_{32}H_{26}O_6 \cdot 0.25\,H_2O$: C 75.21, H 5.23; found: C 75.21, H 5.22.

2-(4-Bromobutoxy)dibenzofuran (**11a**): Yield 44%. M.p. 57–58°. ^{1}H-NMR ($CDCl_3$): 1.96–2.15 (*m*, 2 CH_2); 3.52 (*t*, *J* = 6.8, CH_2Br); 4.08 (*t*, *J* = 6.0, CH_2O); 7.02 (*dd*, *J* = 8.8, 2.8, H–C(3)); 7.40 (*d*, *J* = 2.8, H–C(1)); 7.45 (*d*, *J* = 8.8, H–C(4)); 7.29–7.91 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 27.99, 29.51 (CH_2); 33.46 (CH_2Br); 67.81 (CH_2O); 104.69, 111.72, 112.08, 115.60, 120.52, 122.41, 124.41, 124.69, 127.10, 150.94, 155.06, 156.90 (arom. C). Anal. calc. for $C_{16}H_{15}BrO_2$: C 60.21, H 4.74; found: C 60.55, H 4.80.

2,2′-[Butane-1,4-diylbis(oxy)]bis[dibenzofuran] (**11b**): Yield 12%. M.p. 152–153°. ^{1}H-NMR ($CDCl_3$): 2.08–2.11 (*m*, 2 CH_2); 4.18 (*m*, 2 CH_2O); 7.06 (*dd*, *J* = 8.8, 2.4, 2 H, H–C(3)); 7.44 (*d*, *J* = 2.4, 2 H, H–C(1)); 7.46 (*d*, *J* = 8.8, 2 H, H–C(4)); 7.29–7.90 (*m*, 8 arom. H). Anal. calc. for $C_{28}H_{22}O_4$: C 79.60, H 5.5.25; found: C 79.33, H 5.32.

2-[(6-Bromohexyl)oxy]dibenzofuran (**12a**): Yield 52%. M.p. 38–39°. ^{1}H-NMR ($CDCl_3$): 1.52–1.95 (*m*, 4 CH_2); 3.43 (*t*, *J* = 6.4, CH_2Br); 4.05 (*t*, *J* = 6.4, CH_2O); 7.03 (*dd*, *J* = 8.8, 2.8, H–C(3)); 7.41 (*d*, *J* = 2.4, H–C(1)); 7.45 (*d*, *J* = 8.8, H–C(4)); 7.29–7.91 (*m*, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 25.35, 27.95, 29.22, 29.51 (CH_2); 33.77 (CH_2Br); 68.72 (CH_2O); 104.71, 111.72, 112.05, 115.68, 120.52, 122.38, 124.49, 124.67, 127.05, 150.88, 155.28, 156.90 (arom. C). Anal. calc. for $C_{18}H_{19}BrO_2$: C 62.26, H 5.52; found: C 62.10, H 5.50.

2,2′-[Hexane-1,6-diylbis(oxy)]bis[dibenzofuran] (**12b**): Yield 38%. M.p. 126–127°. ^{1}H-NMR ($CDCl_3$): 1.61–1.92 (*m*, 4 CH_2); 4.09 (*t*, *J* = 6.4, 2 CH_2O); 7.05 (*dd*, *J* = 8.8, 2.8, 2 H, H–C(3)); 7.42 (*d*, *J* = 2.8, 2 H, H–C(1)); 7.45 (*d*, *J* = 8.8, 2 H, H–C(4)); 7.29–7.91 (*m*, 8 arom. H). Anal. calc. for $C_{30}H_{26}O_4$: C 79.98, H 5.82; found: C 79.69, H 5.90.

*2-({6-[(9-Oxo-9*H*-xanthen-3-yl)oxy]hexyl}oxy)anthracene-9,10-dione* (**13**). At r.t. 2-hydroxyanthracene-9,10-dione (0.45 g, 2 mmol), K_2CO_3 (0.28 g, 2 mmol), and dry DMF (50 ml) were stirred for 30 min. To this soln., **10a** (0.75 g, 2 mmol) was added in dry DMF (10 ml) in one portion. The resulting mixture was stirred at r.t. for 24 h (TLC monitoring) and then poured into ice-water (100 ml). The yellow solid thus obtained was collected and purified by CC (silica gel, hexane/CH_2Cl_2 1:1) followed by crystallization from Et_2O: **13** (0.99 g, 96%). M.p. 161–162°. ^{1}H-NMR ($CDCl_3$): 1.60–1.93 (*m*, 4 CH_2); 4.10 (*t*, *J* = 8.0, 1 CH_2O); 4.17 (*t*, *J* = 8.4, 1 CH_2O); 6.86 (*d*, *J* = 2.4, H–C(4′)); 6.94 (*dd*, *J* = 9.2, 2.4, H–C(2′)); 8.23 (*d*, *J* = 8.8, H–C(1′)); 7.25 (*dd*, *J* = 8.8, 2.4, H–C(3)); 7.70 (*d*, *J* = 2.4, H–C(1)); 8.24 (*d*, *J* = 8.8, H–C(4)); 7.34–8.32 (*m*, 8 arom. H). Anal. calc. for $C_{33}H_{26}BrO_3$: C 76.43, H 5.05; found: C 76.20, H 5.09.

Bis-Intercalators **14** *and* **15**. As described for **13**, **11a** was converted to **14** and **3a** to **15**.

2-[4-(Dibenzofuran-2-yloxy)butoxy]anthracene-9,10-dione (**14**): Yield 66%. M.p. 133–134°. ^{1}H-NMR ($CDCl_3$): 2.07–2.19 (*m*, 2 CH_2); 4.17 (*t*, *J* = 6.0, 1 CH_2O); 4.27 (*t*, *J* = 6.0, 1 CH_2O); 7.05 (*dd*, *J* = 8.8, 2.8, H–C(3′)); 7.42 (*d*, *J* = 2.4, H–C(1′)); 7.46 (*d*, *J* = 8.8, H–C(4′)); 7.27 (*dd*, *J* = 8.8, 2.8, H–C(3)); 7.73 (*d*, *J* = 2.8, H–C(1)); 8.25 (*d*, *J* = 8.8, H–C(4)); 7.30–8.31 (*m*, 8 arom. H). Anal. calc. for $C_{30}H_{22}O_5$: C 77.91, H 4.79; found: C 77.54, H 4.85.

*3-[4-[(4-Oxo-2-phenyl-4*H*-1-benzopyran-6-yl)oxy]butoxy]-9*H*-xanthen-9-one* (**15**): Yield 87%. M.p. 193–194°. ^{1}H-NMR ($CDCl_3$): 2.08–2.10 (*m*, 2 CH_2); 4.18–4.22 (*m*, 2 CH_2O); 6.89 (*d*, *J* = 2.4, H–C(4)); 6.95 (*dd*, *J* = 8.8, 2.4, H–C(2)); 8.25 (*d*, *J* = 8.8, H–C(1)); 6.90 (*s*, H–C(3′)); 7.32–8.34 (*m*, 12 arom. H). Anal. calc. for $C_{32}H_{24}O_6$: C 76.18, H 4.79; found: C 76.16, H 4.88.

Financial support of this work by the *National Science Council of the Republic of China* is gratefully acknowledged. We also thank the *National Cancer Institute* (*NCI*) of the United States for the anticancer screenings and the *National Center for High-Performance Computing* for providing computer resources and chemical database services.

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Received November 27, 2001