Articles

1,4-Disubstituted Anthracene Antitumor Agents

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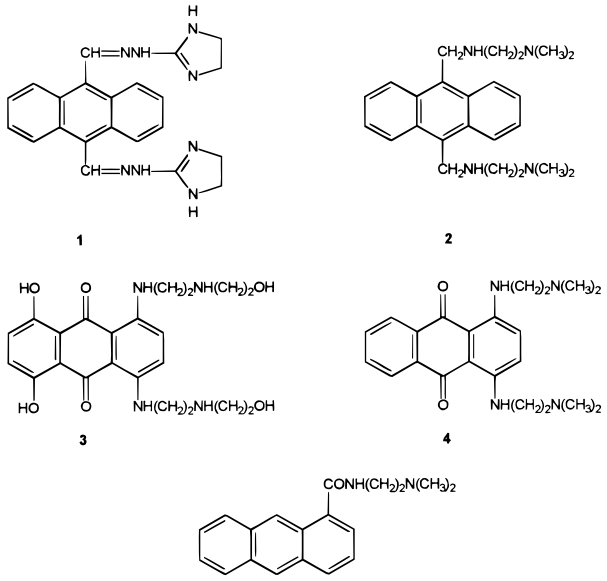
Three different types of 1,4-disubstituted anthracenes were synthesized, and their cytotoxicity in a panel of tumor cells was compared with that of the corresponding 9,10-disubstituted anthracenes. The panel contained human myeloma, melanoma, colon, and lung cancer cells and sensitive and multidrug-resistant murine L1210 leukemia cells. These compounds had [[(dimethylamino)ethyl]amino]methyl, *N*-[(dimethylamino)ethyl]carbamoyl, and carboxaldehyde (4,5-dihydro-1*H*-imidazol-2-yl)hydrazone side chains. The 1,4-diamide was more potent across the tumor panel than the corresponding 9,10-isomer, but the 1,4-diamine and the 1,4-hydrazone were less potent than their 9,10-isomers. Although the 1,4-hydrazone was active against P388 leukemia in mice, it was inactive against L1210 leukemia. Within each pair of compounds, the one with greater average potency against tumor cells gave a greater increase in the transition melt temperature of DNA.

The anthracene nucleus is present in many compounds that have activity against tumor cells. These compounds typically are DNA-intercalating agents, based on the ability of the large, flat anthracene chromophore to bind strongly between the base pairs. They usually have side chains or sugar substituents with basic nitrogens which, upon protonation, further strengthen the DNA binding. Bisantrene (**1**) is one example of a 9,10-disubstituted anthracene antitumor agent,[1] and a related compound (**2**) had good potency against tumor cells in culture, although its activity was only marginal in tumored mice.[2] Examples of 1,4-disubstituted anthracenes with antitumor activity include mitoxantrone (**3**)[3,4] and 1,4-bis[[(dimethylamino)ethyl]amino]anthracene-9,10-dione (**4**).[4] Even some monosubstituted anthracenes, for example, amide derivative **5**, have activity against tumor cells.[5] The very important anthracyclines such as doxorubicin and daunorubicin also may be considered as anthracene derivatives.



1 **2** **3** **4** **5**

Thus far, the 1,4-disubstituted anthracenes studied have been 9,10-anthraquinones. It was of interest to investigate the potential antitumor activity of 1,4-disubstituted anthracenes without the quinone function, particularly in view of the in vivo antitumor activity reported for **5**.[5] Such compounds should not have the toxicity associated with hydroxyl radicals generated by quinone redox processes.[6] Consequently, three different types of 1,4-disubstituted anthracenes were synthesized and evaluated for antitumor activity in comparison with the corresponding 9,10-disubstituted anthracenes.

Chemistry

The first compound prepared was **13**, which corresponds to **5** with two side chains. The first step in the preparation of **13** was formation of 1,4-dimethylanthraquinone (**8**) (Scheme 1). This compound had been prepared previously by a Diels−Alder condensation of 1,4-naphthoquinone with 2,4-hexadiene followed by air oxidation in alkaline solution.[7] We found it more convenient to prepare **8** by Friedel−Crafts acylation of 1,4-xylene with phthalic anhydride followed by cyclization of the crude intermediate in sulfuric acid. The overall yield was 57.5%. Oxidation of **8** to the corresponding diacid **9** was effected by the known method of nitric acid oxidation at high temperature.[8] Reduction of the quinone carbonyls of **9** was accomplished by the literature procedure involving zinc dust and ammonia,[9] and the resulting anthracene-1,4-dicarboxlyate (**11**) was converted into its dimethyl ester **12** by the known procedure involving HCl in methanol.[10] Diester **12** was then heated with *N*,*N*-dimethylethylenediamine to afford the desired diamide **13**. The corresponding diamide with anthraquinone functionality (**10**) was prepared by converting **9** into a bis(acid chloride), which was then heated with (*N*,*N*-dimethylamino)ethylamine.

The reduction of diester **12** to bis(hydroxymethyl)-anthracene **14** by LAH was reported.[10] We were unable

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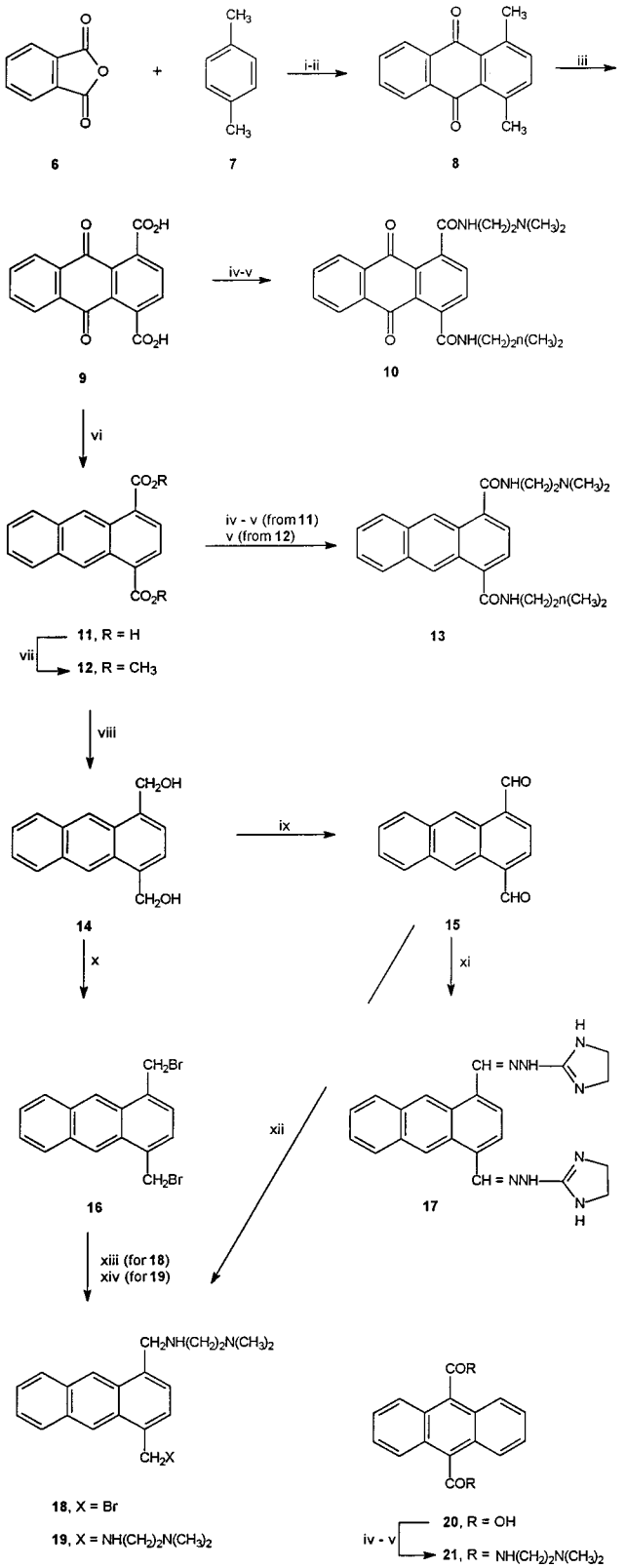
Scheme 1[a]



[a] (i) $AlCl_3$; (ii) concd H_2SO_4; (iii) HNO_3, 185−190 °C; (iv) $SOCl_2$; (v) $H_2N(CH_2)_2N(CH_3)_2$, toluene; (vi) Zn, NH_4OH; (vii) HCl, CH_3OH; (viii) Red-Al, toluene; (ix) pyridine chlorochromate, CH_2Cl_2; (x) dibromotriphenylphosphorane, CH_3CN; (xi) 2-hydrazino-2-imidazoline·HBr; (xii) $H_2N(CH_2)_2N(CH_3)_2$, $H_2N(CH_2)_2N(CH_3)_2$·HCl, $NaCNBH_4$, ethanol; (xiii) $H_2N(CH_2)_2N(CH_3)_2$, CH_2Cl_2, rt; (xiv) $H_2N(CH_2)_2N(CH_3)_2$, toluene, reflux.

to repeat this conversion, but we found that Red-Al in toluene gave a 49% yield of **14**. Oxidation of **14** with pyridine chlorochromate in dichloromethane provided anthracene-1,4-dicarboxaldehyde (**15**), which was converted into **17**, an isomer of bisantrene (**1**), by condensation with two molecules of 2-hydrazino-2-imidazole hydrobromide (Scheme 1).

Treatment of 1,4-bis(hydroxymethyl)anthracene (**14**) with dibromotriphenylphosphorane in acetonitrile afforded the corresponding bis(bromomethyl)anthracene **16**. This compound could be converted into either the mono- or bis(dimethylamino)ethylamino derivatives **18** and **19**, depending on the reaction conditions. Thus, treatment with (dimethylamino)ethylamine for 1.5 h at room temperature gave **18**, whereas heating a mixture of **16** with (dimethylamino)ethylamine in toluene at reflux afforded **19** (Scheme 1). A better preparation of **19** was obtained by treating dialdehyde **15** with (dimethylamino)ethylamine hydrochloride and sodium cyanoborohydride in ethanol.

Anthracene-9,10-bis[*N*-[(dimethylamino)ethyl]carboxamide] (**21**) was prepared from anthracene-1,9-dicarboxylic acid (**20**) by treatment with thionyl chloride followed by (dimethylamino)ethylamine.

Biology

The potencies of new 1,4-disubstituted anthracenes in a panel of tumor cell lines are compared with those of related 1,9-disubstituted anthracenes in Table 1. The human tumor cell lines include sensitive and 40-fold multidrug-resistant multiple myeloma, two colon carcinomas, and a non-small-cell lung carcinoma. Furthermore, it contains sensitive and 10-fold multidrug-resistant (P-glycoprotein expressing) murine L1210 leukemia cell lines. Also listed in this table are the inhibitory potency to neonatal rat heart myocytes and the effect of drug concentration on increasing the melt transition temperature (ΔT_m) of calf thymus DNA.

It is apparent in Table 1 that the 1,4-diamide **13** is considerably more potent than the corresponding 9,10-diamide **21**. 1,4-Diamide-9,10-dione **10** is active in some tumor cell lines but not in others. Among the diaminoanthracenes, 9,10-diamine **2** is more potent on average than 1,4-diamine **19** by a factor of approximately 2. The corresponding monoamine **18** is less active than diamine **19**. The largest difference between members of paired 1,9- and 1,4-isomers occurs with bisantrene (**1**) and its 1,4-isomer **17**, wherein bisantrene is considerably more potent against most of the tumor cell lines, although its potencies against the resistant strains of 8226 myeloma and L1210 leukemia decrease to surprising degrees.

Compound **17**, the 1,4-isomer of bisantrene, was tested against P388 lymphocytic leukemia in DBA/2J mice according to the standard NCI protocol (10^6 tumor cells).[11] At a dose of 50 mg/kg given on days 1, 5, and 9, it showed an ILS of 32%, but it was toxic at higher doses. It was inactive against L1210 leukemia in mice.

Structure−Activity Relationships

In a large set of DNA-intercalating anthracene derivatives related to amonafide, it was found that within series of compounds that are closely related structurally, there are correlations between the strength of DNA binding, as measured by transition melt temperature (ΔT_m), and the cytotoxicity to tumor cells.[12] It is known that bisantrene (**1**) and 9,10-diamine **2** both intercalate DNA,[13] and probably the other compounds in Table 1

Table 1. Activity of Anthracene Derivatives against Human and Murine Tumor Cells in Culture[a]

	potency against tumor cells: IC_{50} (μM)							
	myeloma 8226		leukemia L1210		colon		lung	
compd	S	R[b]	S	R[c]	SW 480	WiDr	A549	ΔT_m (°C)[d]
10	>10	5.0	63	73	UA[e]	4.5	UA	0.0
13	3.3	5.0	4.2	29	3.2	1.4	0.71	5.2
21	>10	>10	44	140	44	26	99	1.5
19	7.0	4.0	2.8	8.3	19	17	8.1	6.2
2	3.0	3.0	3.3	3.6	5.0	4.0	5.0	13.6
18	12	4	52	188	UA	15	91	
17	5.6	6.7	2.6	13	0.72	1.6	5.0	17
1	0.018	9.1	0.049	3.2	0.09	0.79	0.017	18.9

[a] The murine leukemia and human myeloma experiments utilized the MTT assay (Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinsky, M. J.; Fine, D. L.; Mayo, J. D.; Shoemaker, R. R.; Boyd, M. R. Feasibility of Drug Screening with Panels of Human Tumor Cell Lines Using a Microculture Tetrazolium Assay. *Cancer Res.* **1988**, *48*, 589−601). Determination of cytotoxicity against colon and lung tumors utilized the sulforhodamine B assay (Skehan, P.; Strong, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesh, H.; Kenney, S.; Boyd, M. R. New Colorimetric Assay for Anticancer-Drug Screening. *J. Natl. Cancer Inst.* **1990**, *82*, 1107−1112). [b] A human myeloma 40-fold resistant to doxorubicin (Dalton, W. S.; Durie, B. G. M.; Alberts, D. S.; Gerlach, J. H.; Cress, A. Characterization of a New Drug Resistant Human Myeloma Cell Line Which Expresses P-Glycoprotein. *Cancer Res.* **1986**, *46*, 5125−5130). [c] A multidrug-resistant murine leukemia that expresses high levels of P-glycoprotein (Dorr, R. T.; Liddil, J. D.; Trent, J. M.; Dalton, W. S. Mitomycin C Resistant L1210 Leukemia Cells: Association with Pleiotropic Drug Resistance. *Biochem. Pharmacol.* **1987**, *20*, 33−36). [d] Transition melt temperature increases for calf thymus DNA were determined at 5×10^{-5} M (base pairs) in pH 7.0 buffer solution of 0.01 M NaH_2PO_4 and 0.001 M EDTA. [e] Potency was so low that the IC_{50} was unachievable.

also intercalate. Although it is unlikely that a correlation between ΔT_m and antitumor potency can be found for the compounds in Table 1 as a group, it is interesting to compare the relative ΔT_m values and antitumor potencies for the isomeric pairs. These pairs should be nearly identical in lipophilicity and degree of ionization, which should minimize potential differences in cellular uptake and emphasize the effect of different DNA binding strengths. Inspection of the table shows that 9,10-diamine **2** has a higher ΔT_m value than **19**, bisantrene (**1**) has a higher ΔT_m value than isobisantrene **17,** and 1,4-diamide **13** has a higher ΔT_m value than 9,10-diamide **21**. Thus, there is agreement with the concept that DNA binding strength correlates with antitumor potency within pairs of isomers. It is unclear why the 1,4-diamide **13** is more potent than its 9,10-isomer whereas the opposite relationship occurs for the other two isomer pairs. An attempt to include all of the 1,4-disubstituted anthracenes into a correlation of antitumor potency with ΔT_m was unsuccessful, probably because of the wide diversity in structural types within this family.

Conclusion

Three different types of 1,4-disubstituted anthracenes were synthesized and their activities against tumor cells in culture were compared with those of the corresponding 9,10-disubstituted anthracenes. The 1,4-disubstituted anthracenes had significant cytotoxicity in these assays but showed no advantages in potency over the 9,10-disubstituted anthracenes. In particular, bisantrene was much more potent than its 1,4-isomer. These results are in contrast to the outstanding antitumor potency shown by 1,4-disubstituted anthracene-9,10-diones such as mitoxantrone. Within matched pairs of 1,4- and 9,10-disubstituted anthracenes, the isomer with greater DNA binding strength had greater cytotoxicity to tumor cells in culture; however, the large potency differences among the types of pairs limit the ability of transition melt increase studies to correlate or predict structure−activity relationships for disubstituted anthracenes.

Experimental Section

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Infrared spectra were taken on a Beckman IR 33 spectrophotometer with samples prepared as KBr pellets, and absorbances are reported in cm^{-1}. ^1H NMR spectra were recorded on either a Brucker WM-250 MHz or a JEOL FXQ 90 MHz spectrometer using deuteriochloroform as solvent (unless stated otherwise) and tetramethylsilane as the internal standard. NMR shift values (δ) are expressed in ppm. Mass spectra were obtained on a Varian-MAT311 spectrometer in electron impact mode. Elemental analyses were performed by Desert Analytics, Inc., Tucson, AZ.

Preparation of 1,4-Dimethylanthracene-9,10-dione (8). To an ice-cooled mixture of phthalic anhydride (**6**; 18 g, 0.12 mol) and *p*-xylene (**7**; 125 mL) was added aluminum chloride (36 g, 0.33 mol) in three portions over a period of 30 min keeping the mixture well stirred. After another 30 min of stirring at 0−5 °C the mixture was allowed to warm to room temperature, and then the mixture was stirred at reflux overnight. The dark brown residue was cooled and carefully poured onto 1 kg of crushed ice containing 50 mL of concentrated HCl. The resulting mixture was stirred for 40 min and then filtered. The yellow solid was washed with deionized water (2 × 100 mL) and dried under vacuum. It had mp 144−148 °C.

Without further purification, the yellow product was heated with 150 mL of concentrated H_2SO_4 in a sealed tube at 50−55 °C for 1 h. The dark product was cooled and carefully poured into 1.75 L of crushed ice. After stirring for 45 min, the mixture was filtered, and the yellow solid was washed with deionized water and then dissolved in ethyl acetate. This solution was washed with 5% sodium bicarbonate solution (2 × 200 mL) and water (2 × 200 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. This procedure gave 16.5 g (57.5%) of **8** as a pale yellow solid: mp 138−140 °C (lit.[7] mp 141−142 °C); ^1H NMR 2.59 (s, 6), 7.40 (br s, 2), 7.73 (br s, 2), 8.13 (br s, 2); IR 3000−3600, 1650, 1310, 1240 cm^{-1}; MS 236 (M^+).

Preparation of 9,10-Dioxoanthracene-1,4-dicarboxylic Acid (9). This compound was prepared by the procedure described in the literature, except that the reaction was run in a Parr type T316 stainless steel pressure vessel at 185−190 °C in an oil bath for 2 h. The yield of **9** was 8.0 g (80%): mp 310−314 °C (lit.[8] mp >300 °C); ^1H NMR 7.88 (s, 2), 7.96 (2d, 2), 8.17 (2d, 2); IR 3000−3600, 1700, 1665, 1300, 1250 cm^{-1}; MS 252 ($M^+ - CO$), 208 ($M^+ - 2\ CO$).

Preparation of 9,10-Dioxoanthracene-1,4-bis[*N*-[2-(dimethylamino)ethyl]carboxamide] Dihydrochloride (10). A solution of 9,10-dioxoanthracene-1,4-dicarboxylic acid (**9**; 1.0 g, 3.3 mmol) in 10 mL of thionyl chloride was heated at reflux under N_2 for 5 h, cooled, and concentrated on a rotary

evaporator. The residue was dried by adding 10 mL of dry toluene and concentrating on a rotary evaporator. It was then heated with 30 mL of dry toluene under N_2 and treated with *N*,*N*-dimethylethylenediamine (1 mL, 9 mmol) in dry toluene. The dark red mixture was heated at reflux under N_2 for 3 h, cooled, and stirred at room temperature overnight. The solvent was then removed on a rotary evaporator, and the residue was stirred with 50 mL of absolute ethanol and then filtered. The residue was washed with ice-cold ethanol (2 × 5 mL) and dried under vacuum to give 471 mg (32%) of **10** as the dihydrochloride: mp 240−245 °C dec; ^{1}H NMR 3.15 (s, 12), 3.63 (t, 4), 3.93 (t, 4), 7.7−7.8 (m, 2), 7.9 (s, 2), 8.1−8.2 (m, 2). Anal. ($C_{24}H_{28}N_4O_4$·2HCl·0.5H_2O) C, H; N: calcd, 10.80; found, 10.35.

Synthesis of Anthracene-1,4-bis[*N*-[2-(dimethylamino)ethyl]carboxamide] (13). Method A. A mixture of dimethyl anthracene-1,4-dicarboxylate[10] (**12**; 500 mg, 1.7 mmol) and *N*,*N*-dimethylethylenediamine (5 mL, 4.5 mmol) in 20 mL of *p*-xylene was heated at reflux for 24 h, cooled, and concentrated on a rotary evaporator. The oily residue was stirred with 125 mL of diethyl ether and filtered, and the solids were washed with diethyl ether (2 × 10 mL) and dried. This procedure gave 67 mg (9%) of **13**: mp 190−195 °C; ^{1}H NMR 2.29 (s, 12), 2.6 (t, 4), 3.67 (q, 4), 6.76 (t, 2, NH), 7.5 (dd, 2, J = 6.5, 3.5 Hz), 7.6 (s, 2), 8.0 (dd, 2, J = 6.5, 3.5 Hz), 8.9 (s, 2); HRMS calcd for $C_{24}H_{30}N_4O_2$ 406.236 850, found 406.234 600.

Method B. A mixture of anthracene-1,4-dicarboxylic acid[9] (**11**; 0.5 g) and 5 mL of thionyl chloride was heated at reflux under N_2 for 5 h, cooled, and concentrated on a rotary evaporator. The residue was dried by treatment with 5 mL of dry toluene and concentrated on a rotary evaporator, and then the yellow residue was heated with 15 mL of dry toluene under N_2 and treated with a solution of 0.45 mL of *N*,*N*-diethylethylenediamine. The resulting mixture was heated at reflux for 3 h under N_2, cooled, and stirred overnight at room temperature. It was then concentrated on a rotary evaporator, and the residue was stirred with 15 mL of absolute ethanol for 1 h. The solid was washed with absolute ethanol (2 × 5 mL) and dried to give 66 mg (8%) of **13** as the dihydrochloride with mp 235−240 °C. A small sample of this product was converted into the free base by treatment with NaOH in CH_3-OH. The free base was identical with **13** prepared by method A according to TLC.

Preparation of 1,4-Bis(hydroxymethyl)anthracene (14). A solution of dimethyl anthracene-1,4-dicarboxylate (**12**; 5.0 g, 0.017 mol) in 120 mL of freshly distilled toluene was cooled in an ice bath and treated with 12 mL of a 3.4 M solution of Red-Al in toluene under a nitrogen atmosphere. The mixture was stirred well for 1 h, and then excess reducing agent was destroyed by adding 10 mL of ice-cold 10% HCl. After being stirred for 30 min, the mixture was filtered, and the solid was washed with ice-cold water (2 × 100 mL) and dried under vacuum. This procedure gave 2.0 g (49%) of **14**: mp 155−158 °C (lit.[9] mp 160 °C); ^{1}H NMR (DMSO-d_6) 4.5 (d, 4), 4.7 (t, 2); MS 238 (M^+), 220 ($M^+ - H_2O$), 202 ($M^+ - 2\ H_2O$).

Preparation of Anthracene-1,4-dicarboxaldehyde (15). A solution of 1,4- bis(hydroxymethyl)anthracene (**14**; 200 mg, 0.84 mmol) in 250 mL of dry dichloromethane was treated with pyridine chlorochromate (500 mg, 2.32 mmol) at room temperature for 2 h. The mixture was filtered through a Florisil bed which was washed with dichloromethane until the washings became colorless. The combined filtrate and washings were concentrated to dryness under reduced pressure and the residue was chromatographed on a silica gel column with dichloromethane as eluant. The fast moving pale yellow fraction was collected and evaporated under reduced pressure to afford 96 mg (49%) of **15**: mp 166−169 °C; ^{1}H NMR 7.63−7.66 (m, 2), 8.14−8.18 (m, 2), 8.15 (s, 2), 9.92 (s, 2), 10.56 (s, 2); IR 3010 (very weak), 1690 cm^{-1}; MS 234 (M^+). Anal. ($C_{10}H_{10}O_2$·0.0.1H_2O) C, H.

Preparation of 1,4-Bis(bromomethyl)anthracene (16). A solution of 1,4-bis(hydroxymethyl)anthracene (**14**; 500 mg, 2.1 mmol) in 150 mL of dry acetonitrile was treated with dibromotriphenylphosphorane (1.8 g, 4.3 mmol), and the mixture was heated at reflux overnight and then filtered through Florisil. The filtrate was evaporated under reduced pressure to give a crude solid that was chromatographed on silica gel with dichloromethane as eluant. The fast-moving pale yellow fraction was evaporated to give 300 mg (40%) of **16**, which was recrystallized from toluene−petroleum ether: mp >300 °C dec (lit.[10] mp >300 °C); ^{1}H NMR 5.06 (s, 4), 7.49 (s, 2), 7.57 (2d, 2), 8.1 (2d, 2), 8.76 (s, 2); MS (EI) 3.64 (M^+), 366 (M + 2).

Preparation of Anthracene-1,4-dicarboxaldehyde Bis-[(4,5-dihydro-1*H*-imidazol-2-yl)hydrazone] (17). A mixture of anthracene-1,4-dicarboxaldehyde (**15**; 50 mg, 0.213 mmol) and 2-hydrazino-2-imidazoline hydrobromide (105 mg, 0.058 mmol) in 5 mL of ethanol was heated at reflux for 5 h. The resulting orange precipitate was filtered hot, washed with hot ethanol (2 × 5 mL), and dried to give 52.5 mg (44%) of **17**: mp 330−340 °C dec; ^{1}H NMR 3.8 (s, 8), 6.7 (br s, 2), 8.24 (s, 4), 8.5−9.0 (br s, NH), 9.16 (s, 2), 9.26 (s, 2); MS (EI) 398 (M^+), 313 (M − aminoimidazole), 228 (M − 2 aminoimidazole). Anal. ($C_{22}H_{22}N_8$·2HBr·0.5H_2O) C, H, N.

Preparation of 4-(Bromomethyl)-1-[[[2-(dimethylamino)ethyl]amino]methyl]anthracene (18). A solution of 1,4-bis(bromomethyl)anthracene (**16**; 100 mg, 0.27 mmol) and *N*,*N*-dimethylethylenediamine (0.8 mL, excess) in 15 mL of dry dichloromethane was stirred for 1.5 h at room temperature. The yellow precipitate that formed was collected, washed with dichloromethane, and dried under vacuum. This procedure gave 50 mg (41%) of **18**: mp 195−205 °C dec; ^{1}H NMR 3.06 (s, 6), 3.01−3.36 (m, 2), 3.49 (t, 2), 4.02 (s, 2), 5.2 (s, 2), 7.65 (br s, 2), 7.9 (br s, 1), 8.15 (d, 2), 8.25 (br s, 1), 9.15 (s, 1), 9.30 (s, 1). Anal. ($C_{20}H_{23}N_2$Br·HBr) C, H, N.

Preparation of 1,4-Bis[[[2-(dimethylamino)ethyl]amino]methyl]anthracene (19). Method A. A solution of anthracene-1,4-dicarboxaldehyde (**15**; 80 mg, 0.34 mmol), *N*,*N*-dimethylethylenediamine (185 mg, 2.09 mmol), and *N*,*N*-dimethylethylenediamine hydrochloride (240 mg, 1.5 mmol) in 20 mL of absolute ethanol was stirred for 3 h at room temperature and then treated with 50 mg of sodium cyanoborohydride. The mixture was stirred at room temperature for 24 h, cooled to 0 °C, and treated with 5 mL of 1 N HCl, and the ethanol was removed on a rotary evaporator. The residue was made basic with 5% NaOH and extracted with $CHCl_3$. The organic layer was washed with water (2 × 5 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to give 47 mg (37%) of **19** as a dark brown crystalline solid: ^{1}H NMR 2.2 (s, 6), 2.5 (t, 2, J = 6.0 Hz), 2.88 (t, 2, J = 6 Hz, NCH_2), 4.4 (s, 4, CH_2), 7.42 (s, 2, H2, H3), 7.45−7.50 (m, 2, H6, H7), 8.03 (2d, 2, J = 6.3, 3.3 Hz), 8.69 (s, 2, H9, H10). The hydrochloride salt of **19**, prepared with dry HCl gas in methanol, had mp >300 °C. Anal. ($C_{24}H_{34}N_4$·2HCl) C, H.

Method B. A solution of 1,4-bis(bromomethyl)anthracene (**16**; 50 mg, 0.14 mmol) and *N*,*N*-dimethylethylenediamine (20 mg, 0.34 mmol) in 15 mL of dry toluene was heated at reflux temperature for 6 h, cooled, and concentrated to dryness. The residue was extracted with 15 mL of diethyl ether, filtered, and dried. This procedure gave 8.9 mg (12%) of **19** as the dihydrobromide salt: MS (CI) 379 (MH^+). A small sample of this product was converted into the free base, which was identical in TLC with a sample prepared by method A.

Preparation of Anthracene-9,10-bis[*N*-[(dimethylamino)ethyl]carboxamide] Hydrochloride (21). A solution of anthracene-9,10-dicarboxylic acid (**20**; 514.7 mg) in 15 mL of toluene was stirred under N_2 and treated with 3 mL of thionyl chloride. The mixture was stirred for 3 days at room temperature and concentrated on a rotary evaporator. The residue was treated with 18 mL of *(N*,*N*-dimethylamino)ethylamine, and the mixture was stirred overnight at room temperature. After removal of excess amine on a rotary evaporator, the residue was treated with a small amount of toluene and reconcentrated. The residue was dissolved in methanol and treated with sodium bicarbonate solution. The resulting solution was concentrated on a rotary evaporator, and the residue was purified by chromatography on silica gel with CH_3-OH−$CHCl_3$ (6:10) as solvent. Four bands appeared, and the slowest-moving one was collected, concentrated on a rotary evaporator, and dried under high vacuum to afford 302 mg (38.4%) of **21** as the free base. A 139-mg portion of this product was dissolved in 9 mL of absolute ethanol into which HCl gas

had been bubbled. Dilution of the resulting solution with ether gave the hydrochloride salt, which was collected and dried under vacuum to furnish 228 mg of **21** as a cream-colored solid: mp 296−301 °C; ^{1}H NMR (DMSO-d_6 + TFA) 3.0 (s, 12), 3.6 (br s, 4), 4.1 (br s, 4), 7.65−7.80 (m, 4), 8.05−8.2 (m, 4), 9.25 (br s, 2), 10.6 (br s, 2). Anal. (C_{24} $H_{30}N_4O_4$·1.70HCl) C, H; N: calcd, 11.23; found, 11.86.

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