Novel Seco Cyclopropa[*c*]pyrrolo[3,2-*e*]indole Bisalkylators Bearing a 3,3′-Arylenebisacryloyl Group as a Linker

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We synthesized the novel seco cyclopropa[*c*]pyrrolo[3,2-*e*]indole (CPI) bisalkylators and evaluated their antitumor activity. Among these derivatives, **11a** (AT-760), in which the two seco 3-methoxycarbonyl-2-trifluoromethyl CPI (MCTFCPI) moieties are connected with a 3,3′-(1,4-phenylene)bisacryloyl group, was found to exhibit more potent cytotoxicity and antitumor activity against HeLaS3 human uterine cervix carcinoma cells and Colon 26 adenocarcinoma cells, respectively, than **8** (bizelesin, U-77,779). It also appeared that compound **11a** exhibits improved in vivo efficacy in the human colon CX-1 model when compared to either compound **8** or mitomycin C (MMC). Efficacious doses for **11a** were found to be 2-fold lower than those for **8**.

Introduction

The antitumor antibiotics **1** (CC-1065),[1] **2** (duocarmycin A),[2] and **3** (duocarmycin SA),[3] carrying a cyclopropa[*c*]pyrrolo[3,2-*e*]indole (CPI) moiety as the common pharmacophore, are isolated from *Streptomyces* sp. The CPI derivatives have been recognized as monoalkylators whose CPI systems are responsible for their potent cytotoxicity through sequence-selective alkylation of double-strand DNA.[4] The seco-type CPI derivatives **5** (carzelesin, U-80,244)[5] and **6** (KW-2189)[6] derived from **1** and **2**, respectively, are presently under clinical trials (Chart 1). Recently, we reported the synthesis and antitumor activity of the novel seco 3-methoxycarbonyl-2-trifluoromethyl CPI (seco MCTFCPI) derivative **7** (AT-3510) showing antitumor activity against human tumor xenografts more potent than that of **5** or **6** or the clinically widely used anticancer agent cisplatin (Chart 2).[7] It has been considered that the seco-type CPI derivatives serve as ring-opened prodrugs of corresponding cytotoxic CPI derivatives.[6b,8a,d]

It is reported that **8** (bizelesin, U-77,779), in which two alkylating moieties are connected with a linker, a 1,3-bis(2-carbonyl-1*H*-indol-5-yl)urea group, behaves as a bisalkylator.[8] The antitumor activity of **8** against L1210 murine leukemia cells is obviously superior to that of other CPI mono- and bisalkylators.[8] The bisalkylator **8** is presently in phase I clinical trials.[8d] More recently, we reported the synthesis and antitumor activity of the novel seco MCTFCPI bisalkylator **9**.[9] In this compound, the two seco MCTFCPI groups are connected with a linker, the 5,5′-bis(2-carbonyl-1*H*-indole) group. We found that **9** shows more potent antitumor activity than does **8** (Chart 3). Based on our studies, it is evident that the length of a linker has a more significant influence on cytotoxicity and antitumor activity rather than does the type of linker.[9] Therefore, with the aim of exploring the novel seco CPI bisalkylators showing even more potent antitumor activity than **8** and **9**, we designed and synthesized the seco MCTFCPI bisalkylator **11a** carrying a 3,3′-(1,4-phenylene)bisacryloyl group whose length is shorter than that in **9**.[10] Taking into account the potent antitumor activity of **11a**, we carried out the synthesis of the various seco CPI bisalkylators **10** bearing the same 3,3′-(1,4-phenylene)-bisacryloyl group as a linker (Chart 4).[10] On the basis of the results of these studies, we next investigated the synthesis and evaluation of the antitumor activity of novel seco MCTFCPI bisalkylators **11b**−**q** to clarify the structure−activity relationships (SARs) of the linker part of the MCTFCPI bisalkylators. Herein, we report on the synthesis and antitumor activity of **11a**−**q**. Among them, **11a** (AT-760) was found to exhibit more potent cytotoxicity and antitumor activity against HeLaS3 human uterine cervix carcinoma cells and Colon 26 adenocarcinoma cells, respectively, than **8** and less toxicity than **9**. It also appeared that, in the human colon CX-1 model, **11a** exhibits more potent activity than does mitomycin C and similar activity to **8**.

Results and Discussion

Chemistry. We synthesized seco MCTFCPI bisalkylators **11b**−**q** following the procedure for synthesizing **11a** reported in our earlier paper.[10] Deprotection of the optically pure **12** under acidic conditions gave the indoline **13** as its hydrochloride. This was immediately coupled with various 3,3′-arylenebisacrylic acids **14b**−**q** in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) to afford the seco MCTFCPI bisalkylators **11b**−**q** (Scheme 1).

While 3,3′-(1,4-phenylene)bisacrylic acid (**14a**) is commercially available, the synthesis of **14c**−**e**,**m**−**q** was accomplished by employing a Heck reaction of various diazonium salts (for **14d**), bistriflates (for **14e**,**m**,**n**,**p**,**q**), or dibromides (for **14c**,**o**) and by employing a Doebner reaction of various dialdehydes (for **14b**,**f**−**l**). Thus, the Heck reaction of 1,2-dibromobenzene **15** with ethyl acrylate provided diethyl ester **16c**. The synthesis of diethyl ester **16d** was achieved from 1,2-diphenylhy-

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Chart 1

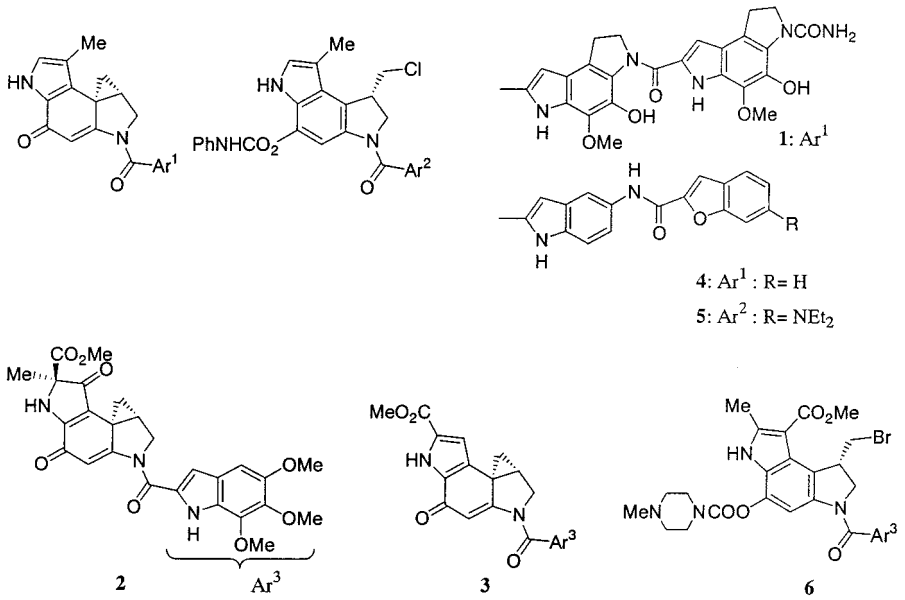

Chart 2

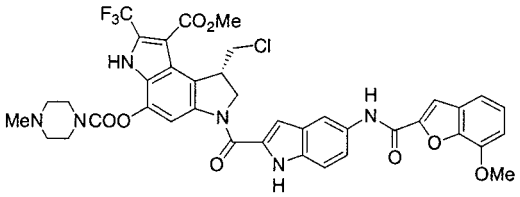

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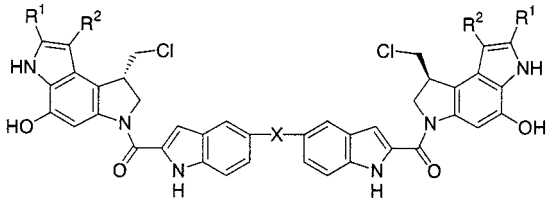
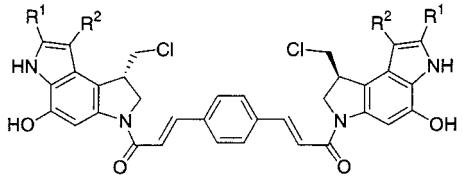
Chart 3



8: R^1= H, R^2= Me, X= NHCONH

9: R^1= CF_3, R^2= CO_2Me, X= —

Chart 4



10a-e

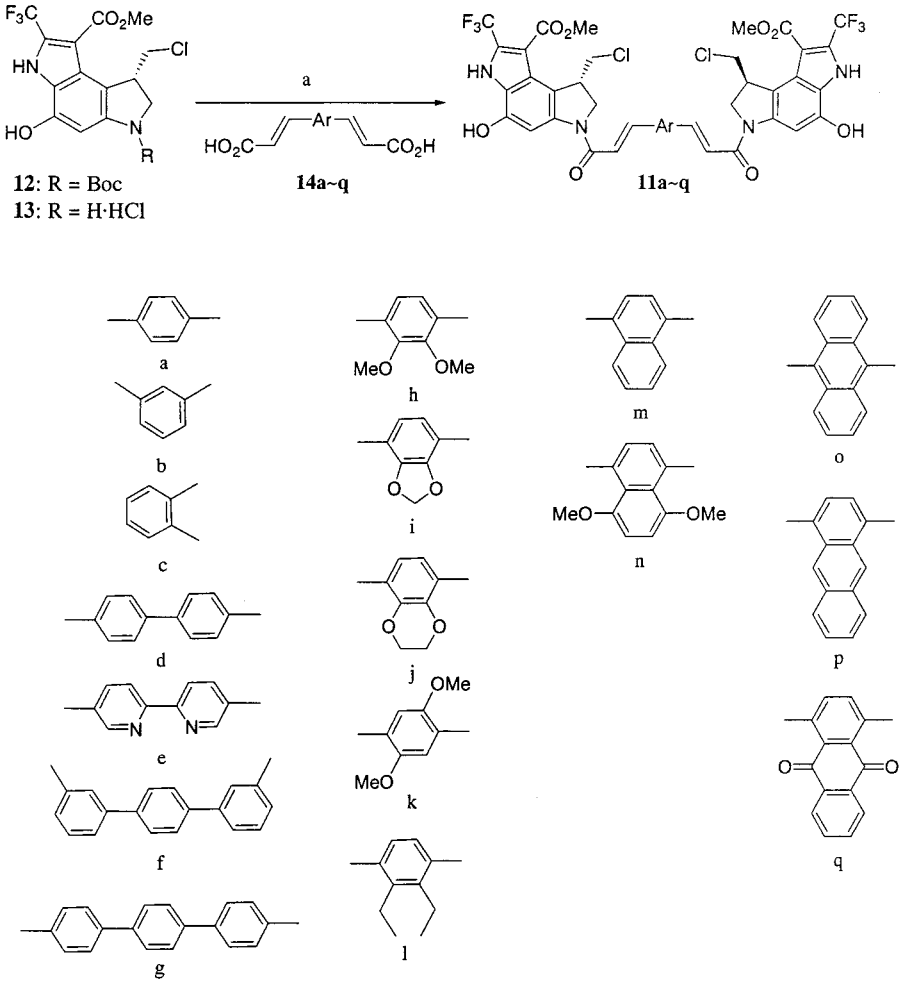
a: R^1= H, R^2= Me; b: R^1= CO_2Me, R^2= H; c: R^1= Me, R^2= CO_2Me;

d: R^1= H, R^2= CO_2Me; e: R^1=R^2= 

drazine (**17**) according to the reported method,[11] with slight modification to avoid the isolation of carcinogenic benzidine. The homo-coupling reaction of the 2-bromopyridine **20**[12] in the presence of $NiBr_2(PPh_3)_2$ cleanly provided the bipyridyl derivative **21**. This was converted to bistriflate **23e** by sequential treatments with 47% HBr and triflic anhydride. Bistriflates **23m**,**n**,**p** were prepared directly from the corresponding 1,4-quinones **24**, **25**, and **29** without isolation of the unstable hydroquinones **26m**,**n**,**p**. The synthesis of bistriflate **23q** was achieved according to the reported method.[13] A Heck reaction of these bistriflates **23e**,**m**,**n**,**p**,**q** with ethyl acrylate smoothly took place to give diethyl esters **16e**,**m**,**n**,**p**,**q**. Unfortunately, a Heck reaction of bistriflate **23o** was found to give 9,10-anthraquinone **28** as the sole product instead of the expected diethyl ester **16o** under these conditions. The Heck reaction of 9,10-dibromoanthrathene (**27**), however, cleanly provided the desired **16o**. The resulting diethyl esters **16c**−**e**,**m**−**q** were hydrolyzed under basic conditions to afford the bisacrylic acids **14c**−**e**,**m**−**q**.The synthesis of dialdehydes **32h**−**j** was achieved by alkylation of dimethyl 2,3-dihydroxyterephthalate (**30**)[14] in the presence of cesium carbonate, followed by reduction with Red-Al/*N*-methylpiperazine reagent. The syntheses of dialdehydes **32f**,**g** and bisacrylic acid **14k** were carried out according to the reported procedure,[15] as was the synthesis of dialdehyde **32l**.[16] Thus, treatment of the bisoxazolidine derivative **34** derived from 2,3-dimethoxyterephthaloyl dichloride (**33**)[17] with ethylmagnesium bromide cleanly produced the diethyl derivative **35**. This was converted to dialdehyde **32l** by alkylation with methyl iodide and subsequent reduction with sodium borohydride. The Doebner reaction of dialdehydes **32b**,**f**−**l** cleanly provided the corresponding 3,3′-arylenebisacrylic acids **14b**,**f**−**l**.

Cytotoxicity. The results of cytotoxicity assay of the seco MCTFCPI bisalkylator **11a** and the newly synthesized derivatives **11b**−**q** against HeLaS3 human uterine cervix carcinoma cells are summarized in Table 1. The bisalkylator **11a** bearing a 3,3′-(1,4-phenylene)bisacryloyl group exhibited more potent cytotoxicity than did **8** or **9**. The strong cytotoxicity observed for **11a** disappeared in its positional isomers **11b**,**c**.[10] Cytotoxicity of the bisalkylators **11d**,**f**,**g**, in which one or more phenylene group(s) are added to the linker of **11a**, reduced dramatically. The bipyridyl analogue **11e** showed superior cytotoxicity to the corresponding biphenyl derivative **11d**. Cytotoxicity of **11h**−**j** in which the C-2 and

Scheme 1[a]



[a] (a) (i) 3 M HCl−AcOEt, (ii) EDCI, **14a**−**q**, 46−82% (2 steps).

C-3 positions of the 1,4-phenylene group are substituted by dimethoxy, methylenedioxy, or ethylenedioxy group(s) was comparable to that of **11a**. Interestingly, **11k**, carrying dimethoxy groups at the C-2 and C-5 positions of 1,4-phenylene group, exhibited cytotoxicity 3500 times less than that of **11a**. In contrast to the case of **11h**, the additional methoxy group at the C-5 position of the phenylene ring debilitates cytotoxicity, probably due to its steric hindrance of the interaction in a minor groove of duplex DNA. Although the naphthalene analogues **11m**,**n** turned out to be 3−4 times less cytotoxic than **11a**, the anthracene analogues **11o**−**q** exhibited cytotoxicity about 1000 times less than that of **11a**. From these results, it appeared that cytotoxicity of the bisalkylators depends highly not only on the length but also on the width of the linker. As for **11a**, further cytotoxicity assays were also made against the human cancer cell lines SBC-3 (lung), SBC-3/ADR (lung, adriamycin-resistant), PC-3 (lung), KATO III (gastric), ZR-75-1 (breast), A2780 (ovarian), and DLD-1 (colon). As shown in Table 2, cytotoxicity of **11a** was superior to that of adriamycin (ADR) in all human cancer cell lines tested and **11a** showed different cytotoxic properties compared with those of adriamycin.

In Vivo Antitumor Activity. The seco MCTFCPI bisalkylators **11a**−**q** were subjected to in vivo antitumor activity assay against Colon 26 murine adenocarcinoma cells. The results shown in Table 1 indicate that **11a** shows more potent antitumor activity than **8** and less toxicity than **9** in the murine Colon 26 model. Next, we further evaluated in vivo antitumor activity against human colon CX-1 tumor xenografts for **11a** and **8**. The results are shown in Table 3 and Figure 1. Compound **11a** exhibits improved in vivo efficacy in the human colon CX-1 model when compared to either compound **8** or mitomycin C (MMC). Efficacious doses for **11a** were found to be 2-fold lower than those for **8**.

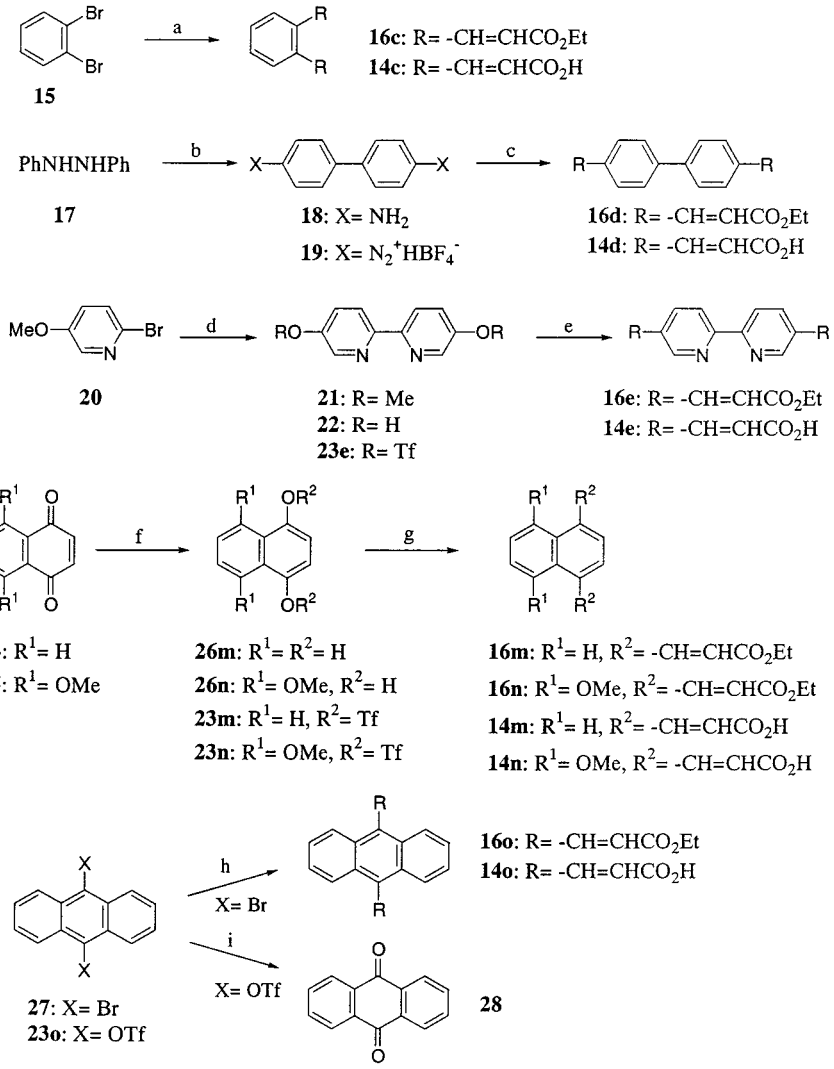
Conclusion

As described above, we have succeeded in the design, synthesis, and evaluation of the novel seco MCTFCPI bisalkylators **11a**−**q** carrying various 3,3′-arylenebisacryloyl groups. We found that the bisalkylator **11a**, bearing a 3,3′-(1,4-phenylene)bisacryloyl group as a linker, exhibited more potent antitumor activity or less toxicity than did the other bisalkylators **11b**−**q** in the Colon 26 model. Moreover, **11a**, much like clinical trial candidate **8**, shows more potent antitumor activity in the human colon CX-1 system xenografts model than the clinically widely used anticancer agent mitomycin C. Further investigation of the pharmacological profiles of **11a** is in progress.

Experimental Section

All melting points were determined with a Yamato MP-500 melting point apparatus and are uncorrected. Measurements of optical rotations were carried out using a JASCODIP-360

Scheme 2[a]



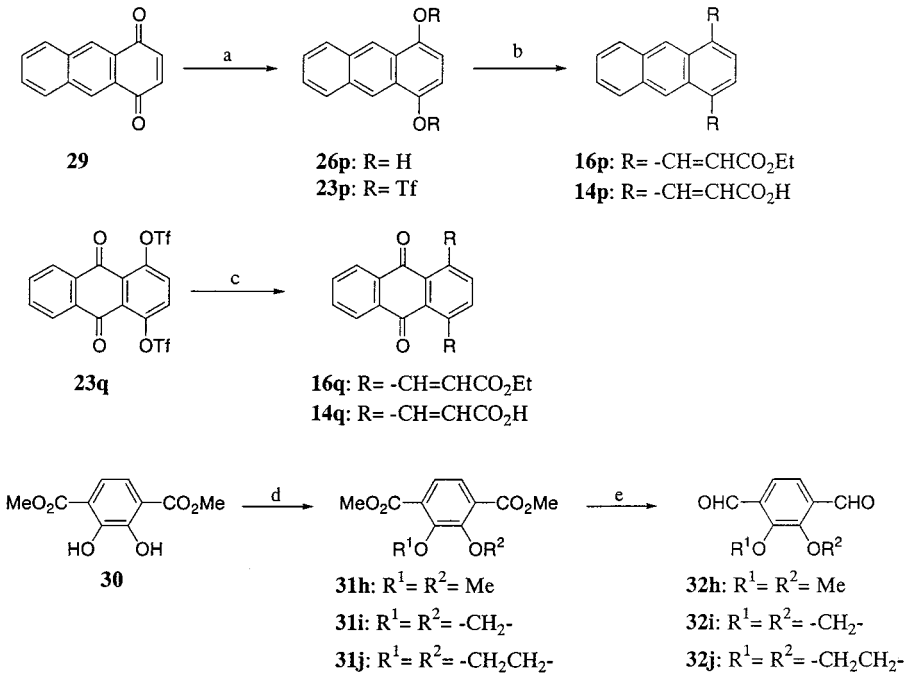
[a] (a) (i) Ethyl acrylate, $Pd(OAc)_2$, DPPP, Et_3N, 31%, (ii) KOH, 91%; (b) (i) 42% HBF_4, (ii) $NaNO_2$, 42% HBF_4; (c) (i) ethyl acrylate, $Pd(OAc)_2$, 29%, (ii) KOH, 83%; (d) (i) $NiBr_2(PPh_3)_2$, Zn, Et_4NI, 87%, (ii) 47% HBr, 84%, (iii) Tf_2O, 2,4,6-collidine, 84%; (e) (i) ethyl acrylate, $Pd(OAc)_2$, DPPP, Et_3N, 86%, (ii) KOH, 89%; (f) (i) 10% Pd−C, H_2, (ii) Tf_2O, 2,4,6-collidine, 84% (for **23m**), Tf_2O, DMAP, 67% (for **23n**); (g) (i) ethyl acrylate, $Pd(OAc)_2$, DPPP, Et_3N, 85% (for **16m**), 92% (for **16n**), (ii) KOH, 96% (for **14m**), 93% (for **14n**); (h) (i) ethyl acrylate, $Pd(OAc)_2$, DPPP, Et_3N, 94% (for **16o**), (ii) KOH, 96%; (i) ethyl acrylate, $Pd(OAc)_2$, DPPP, Et_3N.

automatic digital polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-5300 spectrometer. ^{1}H NMR spectra were measured with a JEOL JNM-EX-400 (400 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane, using tetramethylsilane ($\delta = 0$) and/or residual solvents such as chloroform ($\delta = 7.26$) and benzene ($\delta = 7.20$) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Measurements of mass spectra were performed with a Hitachi M-2000 mass spectrometer. Data for elemental analysis are within ±0.3% of theoretical values and were determined by a Yanaco CHN corder MT-5. Unless otherwise noted, all the experiments were carried out using anhydrous solvents under an atmosphere of dry argon. Tetrahydrofuran and diethyl ether (ether) were distilled from sodium benzophenone ketyl. Throughout this work, Merck precoated thin layer chromatographic (TLC) plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) were used for TLC analyses. Wako Gel C-200 and C-300 were used as an adsorbent for flash column chromatography. To minimize the health risks posed by these potent cytotoxic compounds to analytical service personnel of our laboratory and to allow preparation of only the very limited quantities needed for testing, infrared spectra and combustion elemental analyses were not obtained for the final analogues.[4c]

Diethyl 3,3′-(1,2-Phenylene)bisacrylate (16c). A mixture of 1,2-dibromobenzene (500 mg, 2.1 mmol), ethyl acrylate (4.6 mL, 42 mmol), triethylamine (1.2 mL, 8.6 mmol), 1,3-(diphenylphosphino)propane (87 mg, 0.21 mmol), and palladium(II) acetate (48 mg, 0.21 mmol) in DMF (100 mL) was stirred at 100 °C for 18 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2. The dichloromethane solution was washed with water, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2) of the residue gave **16c** as yellow crystals (181 mg, 31%). Mp: 75−76 °C. ^{1}H NMR ($CDCl_3$): δ 1.35 (t, $J = 7.3$ Hz, 6H), 4.29 (q, $J = 7.3$ Hz, 4H), 6.35 (d, $J = 15.6$ Hz, 2H), 7.40 (dd, $J = 5.9$ Hz, 3.4 Hz, 2H), 7.57 (dd, $J = 5.9$ Hz, 3.4 Hz, 2H), 8.04 (d, $J = 15.6$ Hz, 2H). IR (KBr): 1709, 1637, 1626, 1314, 1186 cm^{-1}. MS (EI) m/z: 274 (M^+). Anal. ($C_{16}H_{18}O_4$) C, H, N.

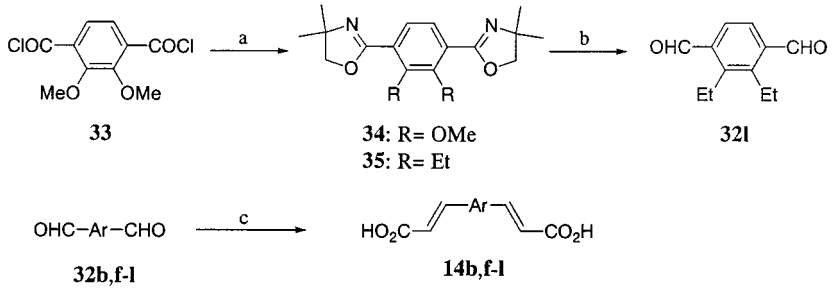
3,3′-(1,2-Phenylene)bisacrylic Acid (14c). A suspension of **16c** (98 mg, 0.36 mmol) and KOH (202 mg, 3.6 mmol) in EtOH (2 mL) was heated at reflux for 2 h. After cooling, the mixture was adjusted to pH 1 by the addition of 1 N HCl solution. The resulting precipitates were collected by filtration, washed with water, and then dried in vacuo to give **14c** as colorless crystals (71 mg, 91%). Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.44 (d, $J = 15.7$ Hz, 2H), 7.47 (dd, $J = 5.9$ Hz, 3.9 Hz, 2H), 7.77 (dd, $J = 5.9$ Hz, 3.9 Hz, 2H), 7.90 (d, $J = 15.7$ Hz, 2H), 12.60 (br, 2H). IR (KBr): 2976, 2828, 1690, 1624,

Scheme 3[a]



[a] (a) (i) $Na_2S_2O_4$, (ii) Tf_2O, 2,4,6-collidine, 66%; (b) (i) ethyl acrylate, $Pd(OAc)_2$, DPPP, Et_3N, 90%, (ii) KOH, 90%; (c) (i) ethyl acrylate, $Pd(OAc)_2$, DPPP, Et_3N, 90%, (ii) KOH, 90%; (d) Cs_2CO_3, MeI, 99% (for **31h**), $BrCH_2Cl$, 98% (for **31i**), $BrCH_2CH_2Br$, 99% (for **31j**); (e) $NaAlH_2(OCH_2CH_2OMe)_2$, *N*-methylpiperazine, 80% (for **32h**), 66% (for **32i**), 68% (for **32j**).

Scheme 4[a]



[a] (a) (i) 2-Amino-2-methyl-1-propanol, 100%, (ii) $SOCl_2$, 47%, (iii) EtMgBr, 100%; (b) (i) MeI, 76%, (ii) $NaBH_4$, 13%; (c) malonic acid, pyridine, piperidine, 91% (for **14b**), 95% (for **14f**), 93% (for **14g**), 93% (for **14h**), 95% (for **14i**), 95% (for **14j**), 61% (for **14k**), 74% (for **14l**).

1292 cm^{-1}. MS (EI) *m/z*: 218 (M^+). Anal. ($C_{12}H_{10}O_4 \cdot 1/10H_2O$) C, H, N.

Diethyl 3,3′-(1,1′-Diphenyl-4,4′-diyl)bisacrylate (16d). To a solution of 42% HBF_4 (12.5 g, 58 mmol) was added **17** (2.15 g, 12 mmol) at room temperature, and the mixture was stirred at the same temperature for 2.5 h. After the addition of more 42% HBF_4 solution (10 mL), $NaNO_2$ (1.64 g, 24 mmol) in water (4 mL) was added to the mixture at 0 °C, and the whole mixture was stirred at the same temperature for 1.5 h. MeOH (0.7 mL), ethyl acrylate (3.5 mL, 32 mmol), and $Pd(OAc)_2$ (49 mg, 0.22 mmol) were added to the resulting solution. The mixture was stirred at 55−60 °C for 1 h and then extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2:benzene = 1:1) of the residue gave **16d** as colorless crystals (1.17 g, 29%). Mp: 147−149 °C. ^1H NMR ($CDCl_3$): δ 1.35 (t, J = 7.3 Hz, 6H), 4.28 (q, J = 7.3 Hz, 4H), 6.49 (d, J = 15.6 Hz, 2H), 7.60 (d, J = 8.3 Hz, 4H), 7.65 (d, J = 8.3 Hz, 4H), 7.72 (d, J = 15.6 Hz, 2H). IR (KBr): 1705, 1631, 1306, 1208, 1182 cm^{-1}. MS (EI) *m/z*: 350 (M^+). Anal. ($C_{22}H_{22}O_4$) C, H, N.

3,3′-(1,1′-Diphenyl-4,4′-diyl)bisacrylic Acid (14d). A suspension of **16d** (200 mg, 0.57 mmol) and KOH (377 mg, 6.7 mmol) in EtOH (3 mL) was heated at reflux for 1 h. After concentration in vacuo, the resulting residue was dissolved in water. The aqueous solution was adjusted to pH 2−3 by the addition of 1 N HCl solution. The resulting precipitates were collected by filtration, washed with water, and then dried in vacuo to give **14d** as colorless crystals (140 mg, 83%). Mp: >300 °C. ^1H NMR (DMSO-d_6): δ 6.60 (d, J = 15.7 Hz, 2H), 7.64 (d, J = 15.7 Hz, 2H), 7.80 (s, 8H), 12.48 (brs, 2H). IR (KBr): 2970, 1680, 1624, 1316, 1215 cm^{-1}. MS (EI) *m/z*: 294 (M^+). Anal. ($C_{18}H_{14}O_4 \cdot 1/5H_2O$) C, H, N.

5,5′-Dimethoxy-2,2′-bipyridyl (21). To a suspension of zinc dust (2.22 g, 34 mmol), bis(triphenylphosphine)nickel(II) bromide (5.07 g, 6.8 mmol), and tetraethylammonium iodide (5.82 g, 23 mmol) in THF (45 mL) was added a solution of **20** (4.26 g, 23 mmol) in THF (22 mL) at 50 °C. The mixture was stirred at the same temperature for 8 h, and then added to 2 M ammonia solution. The resulting solution was extracted with ether−benzene (1:1). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2:AcOEt = 1:1) of the residue gave **21** as colorless crystals (2.14 g, 87%). Mp: 130−133 °C (cyclohexane). ^1H NMR ($CDCl_3$): δ 3.91 (s, 6H), 7.30 (dd, J = 8.8 Hz, 2.9 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H), 8.33 (d, J = 2.9 Hz, 2H). IR (KBr): 1562, 1467, 1289, 1258, 1227 cm^{-1}. MS (EI) *m/z*: 216 (M^+). HRMS (EI) for $C_{12}H_{12}N_2O_2$ (M^+): calcd, 216.0899; found, 216.0903.

5,5′-Dihydroxy-2,2′-bipyridyl (22). A mixture of **21** (395 mg, 1.8 mmol) in acetic acid (7 mL) and 47% HBr solution (7

Table 1. Cytotoxicity against HeLaS3 Human Uterine Cervix Carcinoma Cells and in Vivo Antitumor Activity against Colon 26 Murine Adenocarcinoma Cells of the MCTFCPI Bisalkylators Bearing 3,3′-Aryldiacryloyl Linkers

compd	IC_{50} (ng/mL)[a]	max; TGI% (μg/kg)[b]	body wt change (%)	MTD[c]/TGI_{50}
11a	0.00274	89 (1.95)	−5	30.7
11b	54.6	91 (4000)	−5	nt
11c	87.6	70 (4000)	−6	nt
11d	0.141	83 (15.6)	4	3.7
11e	0.0198	88 (3.91)	4	3.6
11f	>100	nt	nt	nt
11g	48.3	84 (4000)	−11	nt
11h	0.00158	89 (0.977)	−1	4.6
11i	0.00595	90 (1.95)	−2	13.3
11j	0.00276	91 (0.488)	3	9.0
11k	9.71	81 (2000)	3	>6.5
11l	0.00318	nt	nt	nt
11m	0.011	85 (0.977)	3	7.4
11n	0.00934	nt	nt	nt
11o	1.51	75 (4000)	−18	nt
11p	3.25	82 (15.6)	−6	3.5
11q	0.523	84 (15.6)	−4	6.6
8	0.060	90 (15.6)	−3	8.4
9	0.0049	84 (0.977)	1	3.3

[a] Drug concentration required to inhibit the growth of HeLaS3 human uterine cervix carcinoma cells by 50%. [b] The percentage tumor growth inhibition as compared with the untreated group. [c] Maximum dose within 10% body weight loss. nt, not tested.

Table 2. Cytotoxicity of **11a** and Adriamycin against Human Cancer Cell Lines

	IC_{50} (ng/mL)[a]						
compd	SBC-3	SBC-3/ ADR	PC-3	KATO III	ZR-75-1	A2780	DLD-1
11a	0.00122	0.00349	0.148	0.816	0.00463	0.000397	0.0149
ADR	11.2	129	275	905	6.39	12.1	136

[a] Drug concentration required to inhibit the growth of HeLaS3 human uterine cervix carcinoma cells by 50%.

Table 3. Antitumor Activity of the Bisalkylators **8** and **11a** Evaluated Using Athymic Mice on Which Human Colon CX-1 Tumor Xenografts Were Implanted

compd	dose (μg/kg)[a]	TGI%[b]
11a	3.91	77
	7.81	83
8	7.81	53
	15.6	56
MMC	9180	65

[a] Tumor fragments of human colon CX-1 were implanted sc on day 0. Drugs were administered iv on day 19. [b] The percentage tumor growth inhibition as compared with the untreated group.

mL) was heated at reflux for 37 h. After cooling, the resulting precipitates were collected by filtration and dried in air. The obtained crystals were dissolved in water, and the aqueous solution was adjusted to pH 7 by the addition of 10% NaOH solution. The resulting precipitates were collected by filtration and dried in vacuo to give **22** as a pale yellow powder (290 mg, 84%). Mp: 273−276 °C. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, J = 8.8 Hz, 2H), 8.29 (d, J = 2.4 Hz, 2H), 8.37 (dd, J = 8.8 Hz, 2.4 Hz, 2H), 11.28 (brs, 2H). IR (KBr): 2992, 1480, 1292 cm^{-1}. MS (EI) m/z: 188 (M^+). HRMS (EI) for $C_{10}H_8N_2O_2$ (M^+): calcd, 188.0586; found, 188.0587.

5,5′-Bis[(trifluoromethanesulfonyl)oxy]-2,2′-bipyridyl (23e). Trifluoromethanesulfonic anhydride (0.6 mL, 3.7 mmol) was added to a suspension of **22** (280 mg, 1.5 mmol) and 2,4,6-colidine (2.0 mL, 15 mmol) in CH_2Cl_2 (7 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. After adding more trifluoromethanesulfonic anhydride (0.6 mL, 3.7 mmol), the mixture was stirred at room temperature for 3 h and then diluted with ether. The resulting solution was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2) of the residue gave **23e** as colorless crystals (567 mg, 84%). Mp: 158−162 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (dd, J = 8.9 Hz, 2.4 Hz, 2H), 8.56 (d, J = 8.8 Hz, 2H), 8.65 (d, J = 2.4 Hz, 2H). IR (KBr): 1468, 1422, 1408, 1376, 1254, 1216, 1162, 1139 cm^{-1}. MS (EI) m/z: 452 (M^+). Anal. ($C_{12}H_6F_6N_2O_6S_2$) C, H, N.

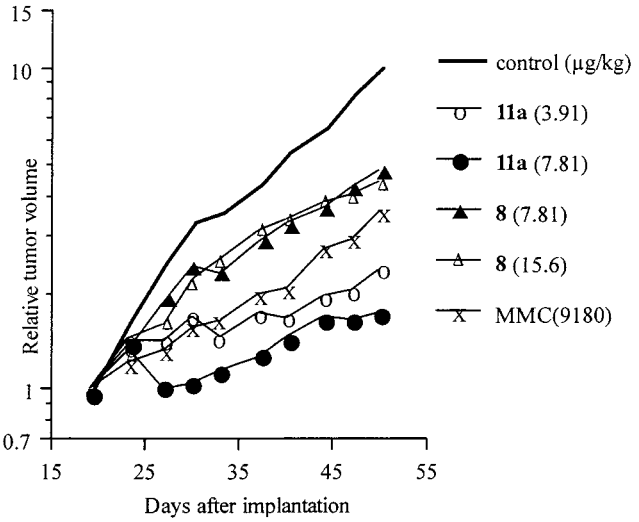


Figure 1. In vivo antitumor activity against human colon CX-1 tumor xenografts.

Diethyl 3,3′-(2,2′-Bipyridyl-5,5′-diyl)bisacrylate (16e). A mixture of **23e** (83.2 mg, 0.18 mmol), ethyl acrylate (0.4 mL, 3.6 mmol), triethylamine (0.1 mL, 0.72 mmol), 1,3-(diphenylphosphino)propane (7.4 mg, 18 μmol), and palladium(II) acetate (4.0 mg, 18 μmol) in DMF (14 mL) was stirred at 100 °C for 10 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2. The dichloromethane solution was washed with water, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2:AcOEt = 10:1) of the residue gave **16e** as yellow crystals (54.3 mg, 86%). Mp: 173.5−175 °C. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, J = 7.3 Hz, 6H), 4.30 (q, J = 7.3 Hz, 4H), 6.58 (d, J = 16.1 Hz, 2H), 7.73 (d, J = 16.1 Hz, 2H), 7.99 (dd, J = 8.3 Hz, 2.0 Hz, 2H), 8.48 (d, J = 8.3 Hz, 2H), 8.80 (d, J = 2.0 Hz, 2H). IR (KBr): 1705, 1637, 1472, 1369, 1308, 1266, 1208, 1175 cm^{-1}. MS (EI) m/z: 352 (M^+). Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

3,3′-(2,2′-Bipyridyl-5,5′-diyl)bisacrylic Acid (14e). A suspension of **16e** (100 mg, 0.28 mmol) and KOH (157 mg, 2.8 mmol) in EtOH (3 mL) was heated at reflux for 2 h and then concentrated in vacuo. The resulting residue was dissolved in water, and the pH of the aqueous solution was adjusted to 7 by the addition of 1 N HCl solution. The resulting precipitates were collected by filtration, washed with water and ethanol, and then dried in vacuo to give **14e** as colorless crystals (73.8 mg, 89%). Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.78 (d, J = 15.6 Hz, 2H), 7.71 (d, J = 15.6 Hz, 2H), 8.35 (dd, J = 8.8 Hz, 2.4 Hz, 2H), 8.45 (d, J = 8.8 Hz, 2H), 9.00 (d, J = 2.4 Hz, 2H). IR (KBr): 3435, 1692, 1593, 1547, 1468 cm^{-1}. MS (FAB$^+$) m/z: 297 (M^+ + 1). HRMS (FAB$^+$) for $C_{16}H_{13}N_2O_4$ (M^+ + 1): calcd, 297.0875; found, 297.0875. Anal. ($C_{16}H_{12}N_2O_4 \cdot 1/4H_2O$) C, H, N.

1,4-Bis[(trifluoromethanesulfonyl)oxy]naphthalene (23m). A suspension of **24** (500 mg, 3.2 mmol) and 10% Pd−C (50 mg) in THF (10 mL) was stirred at room temperature for 2 h under H_2 atmosphere (1 atm). After being ventilated with Ar gas, 2,4,6-collidine (3.3 mL, 25 mmol) and trifluoromethanesulfonic anhydride (1.4 mL, 8.3 mmol) were added to the resulting mixture at 0 °C, and the whole was stirred at room temperature for 18 h. After insoluble materials were filtered off, the filtrate was concentrated in vacuo, and the residue was dissolved in ether. The ethereal solution was washed with water, saturated $CuSO_4$ solution, and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (Hex:AcOEt = 15:1) of the residue gave **23m**

as a pale yellow solid (1.11 g, 83%). Mp: 35.5−37 °C. ^{1}H NMR ($CDCl_3$): δ 7.51 (s, 2H), 7.80 (dd, J = 6.3 Hz, 3.4 Hz, 2H), 8.15 (dd, J = 6.3 Hz, 3.4 Hz, 2H). IR (KBr): 1607, 1424, 1387, 1221, 1142 cm^{-1}. MS (EI) m/z: 424 (M^+). HRMS (EI) for $C_{12}H_6F_6O_6S_2$ (M^+): calcd, 423.9510; found, 423.9512. Anal. ($C_{12}H_6F_6O_6S_2$) C, H, N.

Diethyl 3,3′-(1,4-Naphthalene)bisacrylate (16m). The compound **16m** (19.5 mg, 85%) was prepared from **23m** (30.0 mg, 71 μmol) in the same manner as described for **16e**. Mp: 84−87 °C. ^{1}H NMR ($CDCl_3$): δ 1.38 (t, J = 7.3 Hz, 6H), 4.33 (q, J = 7.3 Hz, 4H), 6.55 (d, J = 15.6 Hz, 2H), 7.63 (dd, J = 6.3 Hz, 3.4 Hz, 2H), 7.76 (s, 2H), 8.24 (dd, J = 6.3 Hz, 3.4 Hz, 2H), 8.52 (d, J = 15.6 Hz, 2H). IR (KBr): 1705, 1638, 1628, 1616, 1393, 1371, 1312, 1259 cm^{-1}. MS (EI) m/z: 324 (M^+). Anal. ($C_{20}H_{20}O_4$) C, H, N.

3,3′-(1,4-Naphthalene)bisacrylic Acid (14m). The compound **14m** (90.2 mg, 96%) was prepared from **16m** (115 mg, 0.35 mmol) in a manner similar to that described for the preparation of **14d**. Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.66 (d, J = 15.7 Hz, 2H), 7.70 (dd, J = 6.9 Hz, 2.9 Hz, 2H), 7.98 (s, 2H), 8.28 (dd, J = 6.9 Hz, 2.9 Hz, 2H), 8.40 (d, J = 15.7 Hz, 2H), 12.66 (s, 2H). MS (EI) m/z: 268 (M^+). HRMS (EI) for $C_{16}H_{12}O_4$ (M^+): calcd, 268.0736; found, 268.0743. Anal. ($C_{16}H_{12}O_4$) C, H, N.

1,4-Bis[(trifluoromethanesulfonyl)oxy]-5,8-dimethoxynaphthalene (23n). A suspension of **25** (200 mg, 0.92 mmol) and 10% Pd−C (20 mg) in THF (3 mL) was stirred at room temperature for 1 h under H_2 atmosphere (1 atm). After insoluble materials were filtered off, the filtrate was concentrated in vacuo. To a solution of the residue in CH_2Cl_2 (3 mL) were added 4-(dimethylamino)pyridine (DMAP; 450 mg, 3.7 mmol) and trifluoromethanesulfonic anhydride (0.4 mL, 2.3 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The mixture was washed with water, 1 N HCl solution, and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (Hex:CH_2Cl_2 = 1:1) of the residue gave **23n** as a colorless solid (299 mg, 67%). Mp: 145.5−146.5 °C. ^{1}H NMR ($CDCl_3$): δ 3.97 (s, 6H), 7.00 (s, 2H), 7.29 (s, 2H). IR (KBr): 1609, 1431, 1421, 1379, 1272, 1248, 1217, 1202 cm^{-1}. MS (EI) m/z: 484 (M^+). Anal. ($C_{14}H_{10}F_6O_8S_2$) C, H, N.

Diethyl 3,3′-(5,8-Dimethoxy-1,4-naphthalene)bisacrylate (16n). The compound **16n** (219 mg, 92%) was prepared from **23n** (300 mg, 0.62 mmol) in the same manner as described for **16e**. Mp: 119−122 °C. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, J = 7.3 Hz, 6H), 3.90 (s, 6H), 4.29 (q, J = 7.3 Hz, 4H), 6.09 (d, J = 15.6 Hz, 2H), 6.86 (s, 2H), 7.42 (s, 2H), 8.81 (d, J = 15.6 Hz, 2H). IR (KBr): 1724, 1710, 1633, 1457, 1394 cm^{-1}. MS (EI) m/z: 384 (M^+). Anal. ($C_{22}H_{24}O_6$) C, H, N.

3,3′-(5,8-Dimethoxy-1,4-naphthalene)bisacrylic Acid (14n). The compound **14n** (79.5 mg, 93%) was prepared from **16n** (100 mg, 0.26 mmol) similarly to the preparation of **14d**. Mp: 290−299.5 °C dec. ^{1}H NMR (DMSO-d_6): δ 3.84 (s, 6H), 6.07 (d, J = 15.7 Hz, 2H), 7.07 (s, 2H), 7.54 (s, 2H), 8.63 (d, J = 15.7 Hz, 2H), 12.33 (s, 2H). IR (KBr): 2959, 2681, 2587, 1688, 1624, 1420, 1314, 1289, 1238 cm^{-1}. MS (FAB$^-$) m/z: 327 ($M^+ - 1$). HRMS (FAB$^-$) for $C_{18}H_{15}O_6$ ($M^+ - 1$): calcd, 327.0869; found, 327.0934. Anal. ($C_{18}H_{16}O_6 \cdot 1/2H_2O$) C, H, N.

Diethyl 3,3′-(9,10-Anthracenediyl)bisacrylate (16o). The compound **16o** (314 mg, 94%) was prepared from **27** (300 mg, 0.89 mmol) in the same manner as described for **16e**. ^{1}H NMR ($CDCl_3$): δ 1.42 (t, J = 7.3 Hz, 6H), 4.39 (q, J = 7.3 Hz, 4H), 6.40 (d, J = 16.1 Hz, 2H), 7.53 (dd, J = 6.8 Hz, 3.4 Hz, 4H), 8.25 (dd, J = 6.8 Hz, 3.4 Hz, 4H), 8.61 (d, J = 16.1 Hz, 2H). IR (KBr): 1713, 1281, 1046 cm^{-1}. MS (EI) m/z: 374 (M^+). HRMS (EI) for $C_{24}H_{22}O_4$ (M^+): calcd, 374.1518; found, 374.1521.

3,3′-(9,10-Anthracenediyl)bisacrylic Acid (14o). The compound **14o** (161 mg, 96%) was prepared from **16o** (200 mg, 0.53 mmol) in a manner similar to that described for the preparation of **14d**. Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.32 (d, J = 15.7 Hz, 2H), 7.64 (dd, J = 6.8 Hz, 2.9 Hz, 4H), 8.22 (dd, J = 6.8 Hz, 2.9 Hz, 4H), 8.48 (d, J = 15.7 Hz, 4H), 12.87 (s, 2H). IR (KBr): 1694, 1630, 1424, 1308, 1260, 1200 cm^{-1}. MS (EI) m/z: 318 (M^+). HRMS (EI) for $C_{20}H_{14}O_4$ (M^+): calcd, 318.0892; found, 318.0915. Anal. ($C_{20}H_{14}O_4 \cdot 1/5H_2O$) C, H, N.

1,4-Bis[(trifluoromethanesulfonyl)oxy]anthracene (23p). The compound **23p** (526 mg, 23%) was prepared from **29** (1.00 g, 4.8 mmol), using 10% Pd−C (50 mg), 2,4,6-colidine (5.0 mL, 38 mmol), and trifluoromethanesulfonic anhydride (2.0 mL, 12 mmol), in the same manner as described for **23m**. Mp: 152.5−153.5 °C. ^{1}H NMR ($CDCl_3$): δ 7.47 (s, 2H), 7.67 (dd, J = 6.3 Hz, 3.4 Hz, 2H), 8.14 (dd, J = 6.3 Hz, 3.4 Hz, 2H), 8.71 (s, 2H). IR (KBr): 1423, 1213, 1139 cm^{-1}. MS (EI) m/z: 474 (M^+). Anal. ($C_{16}H_8F_6O_6S_2$) C, H, N.

Diethyl 3,3′-(1,4-Anthracenediyl)bisacrylate (16p). The compound **16p** (71.0 mg, 90%) was prepared from **23p** (100 mg, 0.21 mmol) in the same manner as described for **16e**. Mp: 98.5−99.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, J = 6.8 Hz, 6H), 4.37 (q, J = 6.8 Hz, 4H), 6.63 (d, J = 16.1 Hz, 2H), 7.56 (dd, J = 6.3 Hz, 3.4 Hz, 2H), 7.75 (s, 2H), 8.08 (dd, J = 6.3 Hz, 3.4 Hz, 2H), 8.67 (d, J = 16.1 Hz, 2H), 8.78 (s, 2H). IR (KBr): 1706, 1629, 1255, 1178 cm^{-1}. MS (EI) m/z: 374 (M^+). Anal. ($C_{24}H_{22}O_4$) C, H, N.

3,3′-(1,4-Anthracenediyl)bisacrylic Acid (14p). The compound **14p** (152 mg, 90%) was prepared from **16p** (200 mg, 0.53 mmol) similarly to the preparation of **14d**. Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.74 (d, J = 15.7 Hz, 2H), 7.60 (dd, J = 5.9 Hz, 2.9 Hz, 2H), 7.99 (s, 2H), 8.28 (dd, J = 5.9 Hz, 2.9 Hz, 2H), 8.58 (d, J = 15.7 Hz, 2H), 8.96 (s, 2H), 12.71 (br, 2H). IR (KBr): 1684, 1621, 1419, 1286, 1259, 1210 cm^{-1}. MS (EI) m/z: 318 (M^+). HRMS (EI) for $C_{20}H_{14}O_4$ (M^+): calcd, 318.0892; found, 318.0894. Anal. ($C_{20}H_{14}O_4 \cdot 1/4H_2O$) C, H, N.

Diethyl 3,3′-(1,4-Anthraquinoyl)bisacrylate (16q). The compound **16q** (49.0 mg, 60%) was prepared from **23q** (100 mg, 0.20 mmol) in the same manner as described for **16e**. Mp: 222.5−224.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.39 (t, J = 7.3 Hz, 6H), 4.34 (q, J = 7.3 Hz, 4H), 6.28 (d, J = 15.6 Hz, 2H), 7.77 (s, 2H), 7.81 (dd, J = 5.9 Hz, 3.4 Hz, 2H), 8.24 (dd, J = 5.9 Hz, 3.4 Hz, 2H), 8.58 (d, J = 15.6 Hz, 2H). IR (KBr): 1700, 1661, 1631, 1592, 1331, 1281 cm^{-1}. MS (EI) m/z: 404 (M^+). Anal. ($C_{24}H_{20}O_6$) C, H, N.

3,3′-(1,4-Anthraquinoyl)bisacrylic Acid (14q). The compound **14q** (215 mg, 100%) was prepared from **16q** (250 mg, 0.62 mmol) in a manner similar to that described for the preparation of **14d**. Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.40 (d, J = 15.7 Hz, 2H), 7.93 (dd, J = 5.9 Hz, 2.9 Hz, 2H), 8.01 (s, 2H), 8.13 (dd, J = 5.9 Hz, 2.9 Hz, 2H), 8.41 (d, J = 15.7 Hz, 2H), 12.61 (br, 2H). IR (KBr): 1694, 1667, 1629, 1589, 1419, 1326, 1278 cm^{-1}. MS (EI) m/z: 258 ($M^+ - 2CO_2H$). Anal. ($C_{20}H_{12}O_6$) C, H, N.

3,3′-(1,3-Phenylene)bisacrylic Acid (14b). A suspension of 1,3-benzenedicarboxaldehyde (500 mg, 3.7 mmol), malonic acid (1.72 g, 16.5 mmol), and pyridine−piperidine (70:1 v/v, 7 mL) was heated at reflux for 24 h. After cooling, the mixture was adjusted to pH 1 by the addition of 1 N HCl solution. The resulting precipitates were collected by filtration, washed with water, and then dried in vacuo to give **14b** as colorless crystals (741 mg, 91%). Mp: 287−290 °C. ^{1}H NMR (DMSO-d_6): δ 6.67 (d, J = 16.6 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.61 (d, J =16.6 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 8.08 (s, 1H), 12.46 (s, 2H). IR (KBr): 3005, 1680, 1631, 1440, 1302 cm^{-1}. MS (EI) m/z: 218 (M^+). Anal. ($C_{12}H_{10}O_4 \cdot 1/10H_2O$) C, H, N.

3,3′-[3,3″-(1,1′:4′,1″-Terphenyl)]bisacrylic Acid (14f). The compound **14f** (1.06 g, 95%) was prepared from [3,3″-(1,1′:4′,1″-terphenyl)]dicarboxaldehyde **(32f)** (80 mg, 0.28 mmol) in the same manner as described for **14b**. Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.70 (d, J = 16.1 Hz, 2H), 7.52 (t, J = 7.8 Hz, 2H), 7.69−7.81 (m, 6H), 7.88 (s, 4H), 8.01 (s, 2H), 12.43 (br, 2H). MS (FAB$^-$) m/z: 369 ($M^+ - 1$). HRMS (FAB$^-$) for $C_{24}H_{18}O_4$ ($M^+ - 1$): calcd, 369.1127; found, 369.1214. Anal. ($C_{24}H_{18}O_4$) C, H, N.

3,3′-[4,4″-(1,1′:4′,1″-Terphenyl)]bisacrylic Acid (14g). The compound **14g** (96.4 mg, 93%) was prepared from [4,4″-(1,1′:4′,1″-terphenyl)]dicarboxaldehyde **(32g)** (80 mg, 0.28 mmol) in the same manner as described for **14b**. Mp: >300 °C. ^{1}H NMR (DMSO-d_6): δ 6.60 (d, J = 15.7 Hz, 2H), 7.77 (d, J = 15.7 Hz, 2H), 7.81 (s, 8H), 7.85 (s, 4H), 12.43 (br, 2H). IR

(KBr): 1676, 1624, 1601, 1429, 1312, 1280, 1214 cm^{-1}. Anal. ($C_{24}H_{18}O_4$) C, H, N.

Dimethyl 2,3-Dimethoxyterephthalate (31h). A suspension of **30** (5.00 g, 22 mmol) and cesium carbonate (17.3 g, 53 mmol) in DMF (50 mL) was stirred at room temperature for 0.5 h. Methyl iodide (3.3 mL, 53 mmol) was added to the resulting mixture, and the whole was stirred at room temperature for 2 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2. The dichloromethane solution was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo to give **31h** as a pale brown oil (5.55 g, 99%). ^1H NMR ($CDCl_3$): δ 3.93 (s, 6H), 3.95 (s, 6H), 7.50 (s, 2H). IR (Neat): 1734, 1290 cm^{-1}. MS (EI) *m/z*: 254 (M^+). HRMS (EI) for $C_{12}H_{14}O_6$ (M^+): calcd, 254.0790; found, 254.0776.

2,3-Dimethoxyterephthalaldehyde (32h). A solution of *N*-methylpiperazine (5.20 g, 52 mmol) in toluene (16 mL) was added to a solution of sodium bis(methoxyethoxy)aluminum hydride (13.6 g, 47 mmol, 70% toluene solution) at 0 °C for 0.5 h. The obtained toluene solution was added to a solution of **31h** (3.00 g, 12 mmol) in toluene (120 mL) at −20 °C over 50 min, and the mixture was stirred at the same temperature for 10 min. After the reaction was quenched by adding water (20 mL), the insoluble materials formed were filtered off. The filtrate was washed with 1 N HCl solution, water, and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2) of the residue gave **32h** as colorless crystals (1.84 g, 80%). Mp: 99.5−100.5 °C. ^1H NMR ($CDCl_3$): δ 4.06 (s, 6H), 7.64 (s, 2H), 10.45 (s, 2H). IR (KBr): 1688, 1570, 1464, 1420, 1395, 1385, 1250 cm^{-1}. MS (EI) *m/z*: 194 (M^+). Anal. ($C_{10}H_{10}O_4$) C, H, N.

3,3′-(2,3-Dimethoxy-1,4-phenylene)bisacrylic Acid (14h). The compound **14h** (1.34 g, 93%) was prepared from **32h** (1.00 g, 5.2 mmol) in the same manner as described for **14b**. Mp: >300 °C. ^1H NMR (DMSO-d_6): δ 3.84 (s, 6H), 6.62 (d, J = 16.6 Hz, 2H), 7.57 (s, 2H), 7.76 (d, J = 16.6 Hz, 2H), 12.53 (s, 2H). IR (KBr): 1686, 1629, 1460, 1413, 1308, 1282, 1263, 1223 cm^{-1}. MS (EI) *m/z*: 278 (M^+). HRMS (EI) for $C_{14}H_{14}O_6$ (M^+): calcd, 278.0790; found, 278.0781. Anal. ($C_{14}H_{14}O_6$) C, H, N.

Dimethyl 2,3-(Methylenedioxy)terephthalate (31i). A suspension of **30** (5.00 g, 22 mmol) and cesium carbonate (17.3 g, 53 mmol) in DMF (50 mL) was stirred at room temperature for 0.5 h. Bromochloromethane (3.5 mL, 53 mmol) was added to the DMF solution, and the mixture was stirred at 50 °C for 10 h and then diluted with CH_2Cl_2. The dichloromethane solution was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo to give **31i** as a colorless solid (5.14 g, 98%). Mp: 208−210 °C. ^1H NMR ($CDCl_3$): δ 3.94 (s, 6H), 6.25 (s, 2H), 7.43 (s, 2H). IR (KBr): 1723, 1439, 1298 cm^{-1}. MS (EI) *m/z*: 238 (M^+). HRMS (EI) for $C_{11}H_{10}O_6$ (M^+): calcd, 238.0477; found, 238.0494.

2,3-(Methylenedioxy)terephthaladehyde (32i). The compound **32i** (1.52 g, 68%) was prepared from **31i** (3.00 g, 13 mmol) in a manner similar to that described for the preparation of **32h**. Mp: 151.5−152 °C. ^1H NMR ($CDCl_3$): δ 6.34 (s, 2H), 7.39 (s, 2H), 10.21 (s, 2H). IR (KBr): 1696, 1472, 1454, 1400, 1364, 1254, 1219 cm^{-1}. MS (EI) *m/z*: 178 (M^+). Anal. ($C_9H_6O_4$) C, H, N.

3,3′-(2,3-Methylenedioxy-1,4-phenylene)bisacrylic Acid (14i). The compound **14i** (1.39 g, 95%) was prepared from **31i** (1.00 g, 5.6 mmol) in a manner similar to that described for the preparation of **14b**. Mp: >300 °C. ^1H NMR (DMSO-d_6): δ 6.29 (s, 2H), 6.61 (d, J = 16.6 Hz, 2H), 7.18 (s, 2H), 7.51 (d, J = 16.6 Hz, 2H), 12.53 (s, 2H). IR (KBr): 1689, 1617, 1437, 1320, 1267, 1233 cm^{-1}. MS (EI) *m/z*: 262 (M^+). HRMS (EI) for $C_{13}H_{10}O_6$ (M^+): calcd, 262.0477; found, 262.0462. Anal. ($C_{13}H_{10}O_6$) C, H, N.

Dimethyl 2,3-(Ethylenedioxy)terephthalate (31j). A suspension of **30** (5.00 g, 22 mmol) and cesium carbonate (17.3 g, 53 mmol) in DMF (50 mL) was stirred at room temperature for 0.5 h. 1,2-Dibromoethane (2.5 mL, 29 mmol) was added to the DMF solution, and the mixture was stirred at 80 °C for 2 h and then diluted with CH_2Cl_2. The dichloromethane solution was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo to give **31j** as a colorless solid (5.54 g, 98%). Mp: 107.5−110 °C. ^1H NMR ($CDCl_3$): δ 3.90 (s, 6H), 4.41 (s, 4H), 7.35 (s, 2H). IR (KBr): 1730, 1442, 1278, 1238 cm^{-1}. MS (EI) *m/z*: 252 (M^+). HRMS (EI) for $C_{12}H_{12}O_6$ (M^+): calcd, 252.0634; found, 252.0641.

2,3-(Ethylenedioxy)terephthaladehyde (32j). The compound **32j** (1.01 g, 66%) was prepared from **31j** (2.00 g, 7.9 mmol) in a manner similar to that described for the preparation of **32h**. Mp: 139−140.5 °C. ^1H NMR ($CDCl_3$): δ 4.48 (s, 4H), 7.44 (s, 2H), 10.43 (s, 2H). IR (KBr): 1688, 1578, 1466, 1451, 1404, 1379, 1280, 1256, 1240 cm^{-1}. MS (EI) *m/z*: 192 (M^+). Anal. ($C_{10}H_8O_4$) C, H, N.

3,3′-(2,3-Ethylenedioxy-1,4-phenylene)bisacrylic Acid (14j). The compound **14j** (1.39 g, 95%) was prepared from **32j** (1.01 g, 5.3 mmol) in the same manner as that described for **14b**. Mp: >300 °C. ^1H NMR (DMSO-d_6): δ 4.40 (s, 4H), 6.57 (d, J = 15.6 Hz, 2H), 7.29 (s, 2H), 7.74 (d, J = 15.6 Hz, 2H), 12.43 (s, 2H). IR (KBr): 1687, 1618, 1442, 1419, 1322, 1286, 1229 cm^{-1}. MS (EI) *m/z*: 276 (M^+). HRMS (EI) for $C_{14}H_{12}O_6$ (M^+): calcd, 276.0634; found, 276.0634. Anal. ($C_{14}H_{12}O_6$) C, H, N.

2,2′-(2,3-Dimethoxy-1,4-phenylene)bis(4,4-dimethyl-2-oxazoline) (34). (a) Preparation of *N*,*N*′-bis(2-hydroxy-1,1-dimethylethyl)-2,3-dimethoxyterephthalamide: To a solution of 2-amino-2-methyl-1-propanol (6.06 g, 68 mmol) in CH_2Cl_2 (8 mL) was added a solution of **33** (4.47 g, 17 mmol) in CH_2Cl_2 (8 mL) at 5−10 °C, and the mixture was stirred at room temperature for 2 h. After insoluble materials were filtered off, the filtrate was kept standing at room temperature. The precipitates formed were collected by filtration and dried in vacuo to give *N*,*N*′-bis(2-hydroxy-1,1-dimethylethyl)-2,3-dimethoxyterephthalamide as colorless crystals (6.27 g, 100%). Mp: 151−153 °C. ^1H NMR ($CDCl_3$): δ 1.43 (s, 12H), 3.71 (s, 4H), 3.96 (s, 6H), 4.55 (brs, 2H), 7.89 (s, 2H), 8.06 (brs, 2H). IR (KBr): 1651, 1631, 1546, 1453, 1402, 1311, 1274, 1246 cm^{-1}. MS (EI) *m/z*: 368 (M^+). Anal. ($C_{18}H_{28}N_2O_6$) C, H, N.

(b) Preparation of 2,2′-(2,3-dimethoxy-1,4-phenylene)-bis(4,4-dimethyl-2-oxazoline) (34): A mixture of *N*,*N*′-bis-(2-hydroxy-1,1-dimethylethyl)-2,3-dimethoxyterephthalamide (6.00 g, 16 mmol) and thionyl chloride (7 mL) was stirred at room temperature for 3 h. After an additional thionyl chloride (7 mL) was added, the mixture was stirred at room temperature for 1 h. After the addition of ether (50 mL), the supernatant was removed by decantation. The lower residue was dissolved in water (50 mL), and the aqueous solution was adjusted to pH 8 by the addition of 10% NaOH solution. The aqueous solution was extracted with ether, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (CH_2Cl_2:EtOH = 20:1) of the residue gave **34** as colorless crystals (2.52 g, 47%). Mp: 84.5−85.5 °C. ^1H NMR ($CDCl_3$): δ 1.40 (s, 12H), 3.90 (s, 6H), 4.11 (s, 4H), 7.50 (s, 2H). IR (KBr): 1643, 1489, 1460, 1401, 1349, 1307, 1237, 1189 cm^{-1}. MS (EI) *m/z*: 332 (M^+). Anal. ($C_{18}H_{24}N_2O_4$) C, H, N.

2,2′-(2,3-Diethyl-1,4-phenylene)bis(4,4-dimethyl-2-oxazoline) (35). Ethylmagnesium bromide (16.4 mL, 1.0 M solution in THF) was added to a solution of **34** (2.00 g, 6.0 mmol) in THF (20 mL) at 0 °C over 0.5 h, and the mixture was stirred at room temperature for 2 h. After the reaction was quenched by the addition of saturated NH_4Cl solution and water, the mixture was extracted with ether. The combined ethereal extracts washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo gave **35** as pale yellow crystals (1.98 g, 100%). Mp: 49−50 °C. ^1H NMR ($CDCl_3$): δ 1.16 (t, J = 7.8 Hz, 6H), 1.39 (s, 12H), 2.98 (q, J = 7.8 Hz, 4H), 4.08 (s, 4H), 7.44 (s, 2H). IR (KBr): 2967, 2932, 1653, 1460, 1346, 1287, 1188, 1132, 1049 cm^{-1}. MS (EI) *m/z*: 328 (M^+). Anal. ($C_{20}H_{28}N_2O_2$) C, H, N.

2,3-Diethylterephthalaldehyde (32l). (a) Preparation of 2,2′-(2,3-diethyl-1,4-phenylene)bis(4,4-dimethyl-2-oxazolinium iodide): A mixture of **35** (1.86 g, 5.7 mmol) and methyl iodide (7 mL) in nitromethane (5 mL) was stirred at 80 °C for 4 h. After dilution with ether, the resulting precipitates were collected by filtration and dried in vacuo to give 2,2′-(2,3-diethyl-1,4-phenylene)bis(4,4-dimethyl-2-oxazo-

linium iodide) as colorless crystals (2.62 g, 76%). Mp: 281−285 °C (EtOH). ^{1}H NMR (DMSO-d_6): δ 1.15 (t, J = 7.8 Hz, 6H), 1.66 (s, 12H), 2.70 (q, J = 7.8 Hz, 4H), 3.24 (s, 6H), 5.09 (s, 4H), 8.00 (s, 2H). IR (KBr): 3441, 2969, 2936, 2882, 1730, 1657, 1495, 1427, 1416 cm^{-1}. MS (EI) *m/z*: 358 (M^+-2I). Anal. ($C_{22}H_{34}I_2N_2O_2$) C, H, N.

(b) Preparation of 2,3-diethylterephthalaldehyde (32l): To a suspension of 2,2′-(2,3-diethyl-1,4-phenylene)bis-(4,4-dimethyl-2-oxazolinium iodide) (2.45 g, 5.1 mmol) in EtOH (50 mL) was added sodium borohydride (0.77 g, 20 mmol) at 0 °C for 1 h, and the mixture was stirred at 5 °C for 3 h. After the reaction was quenched by the addition of 2 N HCl solution, the mixture was extracted with ether. The ethereal organic extracts were washed with brine. After treatment with activated carbon, the organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo to give **32l** as a pale yellow oil (102 mg, 13%). Mp: 32−34.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.3 Hz, 6H), 3.14 (q, J = 7.3 Hz, 4H), 7.84 (s, 2H), 10.41 (s, 2H). IR (KBr): 3443, 2973, 2932, 1690, 1458, 1393, 1229 cm^{-1}. MS (EI) *m/z*: 190 (M^+). HRMS (EI) for $C_{12}H_{14}O_2$ (M^+): calcd, 190.0994; found, 190.0990. Anal. ($C_{12}H_{14}O_2 \cdot 1/4H_2O$) C, H, N.

3,3′-(2,3-Diethyl-1,4-phenylene)bisacrylic Acid (14l). The compound **14l** (62.6 mg, 74%) was prepared from **31l** (59.8 mg, 0.31 mmol) in the same manner as that described for **14b**. Mp: 264−268 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.11 (t, J = 7.8 Hz, 6H), 2.77 (q, J = 7.8 Hz, 4H), 6.44 (d, J = 15.7 Hz, 2H), 7.57 (s, 2H), 7.88 (d, J = 15.7 Hz, 2H), 12.50 (br, 2H). IR (KBr): 3432, 2971, 1688, 1628, 1416, 1287 cm^{-1}. MS (EI) *m/z*: 274 (M^+). HRMS (EI) for $C_{16}H_{18}O_4$ (M^+): calcd, 274.1205; found, 274.1160. Anal. ($C_{16}H_{18}O_4$) C, H, N.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(1,4-Phenylene)diacryloyl]bis-[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11a). A solution of **12** (13.5 mg, 30 μmol) in 3 M HCl−AcOEt (0.6 mL) was stirred at room temperature for 1 h. Concentration of the mixture in vacuo gave the crude hydrochloride **13** as a pale yellow powder, which was directly added to a solution of **14a** (3.3 mg, 15 μmol) and EDCI (17.3 mg, 90 μmol) in DMF (0.3 mL). The mixture was stirred at room temperature overnight. After dilution with water, the mixture was extracted with $CHCl_3$−MeOH (5:1), dried over anhydrous Na_2SO_4, filtered, then concentrated in vacuo. Flash chromatography ($CHCl_3$:MeOH:acetone = 5:1:1) of the residue gave **11a** as pale yellow crystals (3.3 mg, 25%). $[\alpha]_D^{24} = -21°$ (c = 0.20, THF). ^{1}H NMR (DMSO-d_6): δ 3.48 (t, J = 8.3 Hz, 2H), 3.83 (d, J = 8.3 Hz, 2H), 3.88 (s, 6H), 4.28 (br, 2H), 4.40−4.49 (m, 4H), 7.30 (d, J = 15.1 Hz, 2H), 7.70 (d, J = 15.6 Hz, 2H), 7.87 (s, 4H), 8.11 (brs, 2H), 10.52 (br, 2H), 13.02 (br, 2H). MS (FAB^+) *m/z*: 879 ($M^+ + 1$). HRMS (FAB^+) for $C_{40}H_{31}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 879.1423; found, 879.1442.

The other seco MCTFCPI bisalkylators **11b**−**q** were prepared in a manner similar to that described for the preparation of **11a**.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(1,3-Phenylene)diacryloyl]bis-[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11b). The compound **11b** (3.5 mg, 27%) was prepared from **12** (13.5 mg, 30 μmol) and **14b** (3.3 mg, 15 μmol). $[\alpha]_D^{27} = -28°$ (c = 0.05, THF). ^{1}H NMR (DMSO-d_6): δ 3.51 (dd, J = 10 Hz, 9 Hz, 2H), 3.75−3.93 (m, 2H), 3.88 (s, 6H), 4.24−4.33 (m, 2H), 4.38−4.53 (m, 4H), 7.33 (d, J = 16 Hz, 2H), 7.52 (t, J = 8 Hz, 1H), 7.73 (d, J = 16 Hz, 2H), 7.88 (d, J = 8 Hz, 2H), 8.12 (s, 2H), 8.25 (s, 1H), 10.56 (s, 2H), 13.06 (s, 2H). MS (FAB^+) *m/z*: 879 ($M^+ + 1$). HRMS (FAB^+) for $C_{40}H_{31}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 879.1423; found, 879.1410.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(1,2-Phenylene)diacryloyl]bis-[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11c). The compound **11c** (3.9 mg, 29%) was prepared from **12** (13.5 mg, 30 μmol) and **14c** (3.3 mg, 15 μmol). $[\alpha]_D^{28} = -107°$ (c = 0.05, THF). ^{1}H NMR (DMSO-d_6): δ 3.51 (t, J = 9 Hz, 2H), 3.75−3.92 (m, 2H), 3.87 (s, 6H), 4.22−4.32 (m, 2H), 4.38−4.50 (m, 4H), 7.16 (d, J = 15 Hz, 2H), 7.52 (dd, J = 6 Hz, 4 Hz, 2H), 7.97 (m, 2H), 8.05 (d, J = 15 Hz, 2H), 8.11 (s, 2H), 10.57 (s, 2H), 13.06 (s, 2H). MS (FAB^+) *m/z*: 879 ($M^+ + 1$). HRMS (FAB^+) for $C_{40}H_{31}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 879.1423; found, 879.1401.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(1,1′-Diphenyl-4,4′-diyl)diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate](11d). The compound **11d** (1.7 mg, 12%) was prepared from **12** (13.5 mg, 30 μmol) and **14d** (4.4 mg, 15 μmol). $[\alpha]_D^{32} = -36°$ (c = 0.05, THF). ^{1}H NMR (DMSO-d_6): δ 3.50 (dd, J = 11 Hz, 9 Hz, 2H), 3.78−3.90 (m, 2H), 3.88 (s, 6H), 4.23−4.32 (m, 2H), 4.38−4.52 (m, 4H), 7.29 (d, J = 15 Hz, 2H), 7.71 (d, J = 15 Hz, 2H), 7.84 (d, J = 8 Hz, 4H), 7.93 (d, J = 8 Hz, 4H), 8.11 (s, 2H), 10.56 (s, 2H), 13.07 (s, 2H). MS (FAB^+) *m/z*: 955 ($M^+ + 1$). HRMS (FAB^+) for $C_{46}H_{35}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 955.1736; found, 955.1703.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(2,2′-Bipyridyl-5,5′-diyl)diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11e). The compound **11e** (2.4 mg, 16%) was prepared from **12** (13.5 mg, 30 μmol) and **14e** (4.4 mg, 15 μmol). $[\alpha]_D^{32} = -35°$ (c = 0.05, THF). ^{1}H NMR (DMSO-d_6): δ 3.51 (dd, J = 10 Hz, 9 Hz, 2H), 3.77−3.92 (m, 2H), 3.88 (s, 6H), 4.25−4.33 (m, 2H), 4.39−4.55 (m, 4H), 7.47 (d, J = 15 Hz, 2H), 7.78 (d, J = 15 Hz, 2H), 8.13 (s, 2H), 8.51 (s, 4H), 9.08 (s, 2H), 10.60 (s, 2H), 13.09 (s, 2H). MS (FAB^+) *m/z*: 957 ($M^+ + 1$). HRMS (FAB^+) for $C_{44}H_{33}Cl_2F_6N_6O_8$ ($M^+ + 1$): calcd, 957.1641; found, 957.1594.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(3,3″-(1,1′:4′,1″-Terphenyl))diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11f). The compound **11f** (3.1 mg, 10%) was prepared from **12** (27.0 mg, 60 μmol) and **14f** (11.2 mg, 30 μmol). $[\alpha]_D^{28} = -19°$ (c = 0.05, THF). ^{1}H NMR (DMSO-d_6): δ 3.51 (dd, J = 10 Hz, 9 Hz, 2H), 3.78−3.94 (m, 2H), 3.88 (m, 6H), 4.24−4.34 (m, 2H), 4.39−4.54 (m, 4H), 7.37 (d, J = 15 Hz, 2H), 7.58 (t, J = 8 Hz, 2H), 7.78 (d, J = 15 Hz, 2H), 7.81 (d, J = 8 Hz, 2H), 7.83 (d, J = 8 Hz, 2H), 7.92 (s, 4H), 8.13 (s, 2H), 8.18 (s, 2H), 10.56 (s, 2H), 13.07 (s, 2H). MS (FAB^+) *m/z*: 1031 ($M^+ + 1$). HRMS (FAB^+) for $C_{52}H_{39}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 1031.2049; found, 1031.2085.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(4,4″-(1,1′:4′,1″-Terphenyl))diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11g). The compound **11g** (4.9 mg, 31%) was prepared from **12** (13.5 mg, 30 μmol) and **14g** (5.6 mg, 15 μmol). $[\alpha]_D^{28} = -17°$ (c = 0.05, THF). ^{1}H NMR (DMSO-d_6): δ 3.50 (t, J = 10 Hz, 2H), 3.79−3.93 (m, 2H), 3.88 (s, 6H), 4.23−4.33 (m, 2H), 4.38−4.53 (m, 4H), 7.29 (d, J = 16 Hz, 2H). 7.72 (d, J = 16 Hz, 2H), 7.83 (d, J = 8 Hz, 4H), 7.88 (s, 4H), 7.93 (d, J = 8 Hz, 4H), 8.13 (s, 2H), 10.56 (s, 2H), 13.06 (s, 2H). MS (FAB^+) *m/z*: 1031 ($M^+ + 1$). HRMS (FAB^+) for $C_{52}H_{39}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 1031.2049; found, 1031.1991.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(2,3-Dimethoxy-1,4-phenylene)-diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11h). The compound **11h** (1.1 mg, 8%) was prepared from **12** (13.5 mg, 30 μmol) and **14h** (4.2 mg, 15 μmol). $[\alpha]_D^{32} = -26°$ (c = 0.05, THF). ^{1}H NMR (DMSO-d_6): δ 3.51 (dd, J = 10 Hz, 9 Hz, 2H), 3.79−3.94 (m, 2H), 3.88 (s, 6H), 3.90 (s, 6H), 4.24−4.33 (m, 2H), 4.39−4.49 (m, 4H), 7.31 (d, J = 16 Hz, 2H), 7.78 (s, 2H), 7.88 (d, J = 16 Hz, 2H), 8.11 (s, 2H), 10.57 (s, 2H), 13.08 (s, 2H). MS (FAB^+) *m/z*: 939 ($M^+ + 1$). HRMS (FAB^+) for $C_{42}H_{35}Cl_2F_6N_4O_{10}$ ($M^+ + 1$): calcd, 939.1634; found, 939.1617.

(*S*,*S*)-Dimethyl 6,6′-[3,3′-(2,3-(Methylenedioxy)-1,4-phenylene)diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11i). The compound **11i** (2.4 mg, 17%) was prepared from **12** (13.5 mg, 30 μmol) and **14i** (3.9 mg, 15 μmol). $[\alpha]_D^{30} = -12°$ (c = 0.05, THF). ^{1}H NMR (DMSO-d_6): δ 3.52 (dd, J = 11 Hz, 9 Hz, 2H), 3.78−3.85 (m, 2H), 3.88 (s, 6H), 4.24−4.32 (m, 2H), 4.32−4.45 (m, 4H), 6.38 (s, 2H), 7.28 (d, J = 16 Hz, 2H), 7.37 (s, 2H), 7.65 (d, J = 16 Hz, 2H), 8.10 (s, 2H), 10.58 (s, 2H), 13.17 (s, 2H). MS (FAB^+) *m/z*: 923 ($M^+ +$

1). HRMS (FAB$^+$) for $C_{41}H_{31}Cl_2F_6N_4O_{10}$ ($M^+ + 1$): calcd, 923.1321; found, 923.1298.

(*S,S*)-Dimethyl 6,6′-[3,3′-(2,3-(Ethylenedioxy)-1,4-phenylene)diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11j). The compound **11j** (4.1 mg, 15%) was prepared from **12** (26.9 mg, 60 μmol) and **14j** (8.3 mg, 30 μmol). $[\alpha]_D^{30} = -12°$ ($c = 0.05$, THF). ^{1}H NMR (DMSO-d_6): δ 3.51 (t, $J = 10$ Hz, 2H), 3.79−3.85 (m, 2H), 3.88 (s, 6H), 4.23−4.32 (m, 2H), 4.38−4.44 (m, 4H), 4.46 (s, 4H), 7.25 (d, $J = 16$ Hz, 2H), 7.52 (s, 2H), 7.89 (d, $J = 16$ Hz, 2H), 8.10 (s, 2H), 10.56 (s, 2H), 13.07 (s, 2H). MS (FAB$^+$) *m/z*: 937 ($M^+ + 1$). HRMS (FAB$^+$) for $C_{42}H_{33}Cl_2F_6N_4O_{10}$ ($M^+ + 1$): calcd, 937.1478; found, 937.1411.

(*S,S*)-Dimethyl 6,6′-[3,3′-(2,5-Dimethoxy-1,4-phenylene)-diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11k). The compound **11k** (2.1 mg, 15%) was prepared from **12** (13.5 mg, 30 μmol) and **14k** (4.2 mg, 15 μmol). $[\alpha]_D^{32} = -56°$ ($c = 0.05$, THF). ^{1}H NMR (DMSO-d_6): δ 3.52 (dd, $J =$ 11 Hz, 8 Hz, 2H), 3.78−3.90 (m, 2H), 3.88 (s, 6H), 3.98 (s, 6H), 4.23−4.33 (m, 2H), 4.38−4.48 (m, 4H), 7.30 (d, $J = 16$ Hz, 2H), 7.53 (s, 2H), 7.96 (d, $J = 16$ Hz, 2H), 8.10 (s, 2H), 10.56 (s, 2H), 13.07 (s, 2H). MS (FAB$^+$) *m/z*: 939 ($M^+ + 1$). HRMS (FAB$^+$) for $C_{42}H_{35}Cl_2F_6N_4O_{10}$ ($M^+ + 1$): calcd, 939.1634; found, 939.1699.

(*S,S*)-Dimethyl 6,6′-[3,3′-(2,3-Diethyl-1,4-phenylene)-diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11l). The compound **11l** (5.5 mg, 19%) was prepared from **12** (26.9 mg, 60 μmol) and **14l** (8.2 mg, 30 μmol). $[\alpha]_D^{31} = -16°$ ($c = 0.05$, THF). ^{1}H NMR (DMSO-d_6): δ 1.18 (t, $J = 8$ Hz, 6H), 2.85 (q, $J = 8$ Hz, 4H), 3.51 (t, $J = 10$ Hz, 2H), 3.72−3.85 (m, 2H), 3.88 (s, 6H), 4.22−4.32 (m, 2H), 4.38−4.48 (m, 4H), 7.12 (d, $J = 16$ Hz, 2H), 7.78 (s, 2H), 7.99 (d, $J = 16$ Hz, 2H), 8.11 (s, 2H), 10.54 (s, 2H), 13.06 (s, 2H). MS (FAB$^+$) *m/z*: 935 ($M^+ + 1$). HRMS (FAB$^+$) for $C_{44}H_{39}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 935.2049; found, 935.2008.

(*S,S*)-Dimethyl 6,6′-[3,3′-(1,4-Naphthalene)diacryloyl]-bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11m). The compound **11m** (3.0 mg, 21%) was prepared from **12** (13.5 mg, 30 μmol) and **14m** (4.0 mg, 15 μmol). $[\alpha]_D^{32} = -41°$ ($c = 0.05$, THF). ^{1}H NMR (DMSO-d_6): δ 3.53 (t, $J = 10$ Hz, 2H), 3.78−3.92 (m, 2H), 3.88 (s, 6H), 4.25−4.34 (m, 2H), 4.45−4.54 (m, 4H), 7.36 (d, $J = 15$ Hz, 2H), 7.74 (dd, $J = 6$ Hz, 3 Hz, 2H), 8.16 (s, 2H), 8.20 (s, 2H), 8.36 (dd, $J = 6$ Hz, 3 Hz, 2H), 8.51 (d, $J = 15$ Hz, 2H), 10.60 (s, 2H), 13.09 (s, 2H). MS (FAB$^+$) *m/z*: 929 ($M^+ + 1$). HRMS (FAB$^+$) for $C_{44}H_{33}Cl_2F_6N_4O_8$ ($M^+ +$ 1): calcd, 929.1580; found, 929.1530.

(*S,S*)-Dimethyl 6,6′-[3,3′-(5,8-Dimethoxy-1,4-naphthalene)diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11n). The compound **11n** (2.2 mg, 15%) was prepared from **12** (13.5 mg, 30 μmol) and **14n** (4.9 mg, 15 μmol). $[\alpha]_D^{30} = -56°$ ($c = 0.05$, THF). ^{1}H NMR (DMSO-d_6): δ 3.52 (dd, $J = 9$ Hz, 11 Hz, 2H), 3.80−3.87 (m, 2H), 3.88 (s, 6H), 3.89 (s, 6H), 4.23−4.31 (m, 2H), 4.40−4.47 (m, 4H), 6.77 (d, $J = 15$ Hz, 2H), 7.10 (s, 2H), 7.75 (s, 2H), 8.16 (s, 2H), 8.77 (d, $J = 15$ Hz, 2H), 10.54 (s, 2H), 13.06 (s, 2H). MS (FAB$^+$) *m/z*: 989 ($M^+ + 1$). HRMS (FAB$^+$) for $C_{46}H_{37}Cl_2F_6N_4O_{10}$ (M^+ + 1): calcd, 989.1791; found, 989.1769.

(*S,S*)-Dimethyl 6,6′-[3,3′-(9,10-Anthracene)diacryloyl]-bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11o). The compound **11o** (3.7 mg, 25%) was prepared from **12** (13.5 mg, 30 μmol) and **14o** (4.8 mg, 15 μmol). $[\alpha]_D^{29} = -144°$ ($c = 0.05$, THF). ^{1}H NMR (DMSO-d_6): δ 3.56 (t, $J = 10$ Hz, 2H), 3.79−3.85 (m, 2H), 3.87 (s, 6H), 4.22−4.29 (m, 2H), 4.33−4.47 (m, 4H), 7.05 (d, $J = 16$ Hz, 2H), 7.66 (dd, $J = 4$ Hz, 7 Hz, 4H), 8.22 (s, 2H), 8.37 (dd, $J = 7$ Hz, 4 Hz, 4H), 8.55 (d, $J = 16$ Hz, 2H), 10.64 (s, 2H), 13.11 (s, 2H). MS (FAB$^+$) *m/z*: 979 ($M^+ +$ 1). HRMS (FAB$^+$) for $C_{48}H_{35}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 979.1736; found, 979.1787.

(*S,S*)-Dimethyl 6,6′-[3,3′-(1,4-Anthracene)diacryloyl]-bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11p). The compound **11p** (2.3 mg, 15%) was prepared from **12** (13.5 mg, 30 μmol) and **14p** (4.8 mg, 15 μmol). $[\alpha]_D^{32} = -36°$ ($c = 0.05$, THF). ^{1}H NMR (DMSO-d_6): δ 3.54 (t, $J = 10$ Hz, 2H), 3.78−3.93 (m, 2H), 3.89 (s, 6H), 4.27−4.36 (m, 2H), 4.46−4.57 (m, 4H), 7.43 (d, $J = 15$ Hz, 2H), 7.62 (dd, $J = 6$ Hz, 3 Hz, 2H), 8.19 (s, 4H), 8.30 (dd, $J = 6$ Hz, 3 Hz, 2H), 8.67 (d, $J = 15$ Hz, 2H), 9.04 (s, 2H), 10.60 (s, 2H), 13.07 (s, 2H). MS (FAB$^+$) *m/z*: 979 ($M^+ + 1$). HRMS (FAB$^+$) for $C_{48}H_{35}Cl_2F_6N_4O_8$ ($M^+ + 1$): calcd, 979.1736; found, 979.1699.

(*S,S*)-Dimethyl 6,6′-[3,3′-(1,4-(9,10-Anthraquinoyl))diacryloyl]bis[4-chloromethyl-8-hydroxy-2-trifluoromethyl-1,4,5,6-tetrahydropyrrolo[3,2-*e*]indole-3-carboxylate] (11q). The compound **11q** (1.6 mg, 4%) was prepared from **12** (40.4 mg, 90 μmol) and **14q** (15.7 mg, 45 μmol). $[\alpha]_D^{32} = -48°$ ($c = 0.05$, THF). ^{1}H NMR (DMSO-d_6): δ 3.53 (dd, $J = 10$ Hz, 9 Hz, 2H), 3.79−3.91 (m, 2H), 3.88 (s, 6H), 4.24−4.34 (m, 2H), 4.41−4.51 (m, 4H), 7.11 (d, $J = 16$ Hz, 2H), 7.95 (dd, $J = 6$ Hz, 3 Hz, 2H), 8.10−8.19 (m, 4H), 8.21 (s, 2H), 8.53 (d, $J = 16$ Hz, 2H), 10.61 (s, 2H), 13.10 (s, 2H). MS (FAB$^+$) *m/z*: 1009 ($M^+ + 1$). HRMS (FAB$^+$) for $C_{48}H_{33}Cl_2F_6N_4O_{10}$ ($M^+ + 1$): calcd, 1009.1478; found, 1009.1534.

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