Synthesis of 1-Substituted 3-(Chloromethyl)-6-aminoindoline (6-Amino-*seco*-CI) DNA Minor Groove Alkylating Agents and Structure−Activity Relationships for Their Cytotoxicity

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A series of racemic 6-amino-*seco*-cyclopropylindole (*seco*-CI) compounds was prepared by coupling 1-(*tert*-butyloxycarbonyl)-3-(chloromethyl)-6-nitroindoline with appropriate acids, followed by nitro group reduction, and evaluated for cytotoxicity in AA8, UV4, EMT6, and SKOV3 cell lines. These compounds are of interest due to their close structural relationship to known AT-specific alkylating agents and cytotoxins and also for the possible construction of stable amine-based prodrugs designed for tumor-specific release. Variations included indole or furan side chains with different substituents, sulfonamide or carboxamide linkers, extension of the minor groove binding side chain to two subunits, and the use of a pyrroylacryloyl unit previously reported to give extremely potent analogues. The parent compound, with a trimethoxyindole side chain, was a moderately potent cytotoxin ($IC_{50} = 0.34\ \mu M$ in AA8 cells, 4 h exposure). A single 5-methoxy group on the indole minor groove binding unit was sufficient to maintain potency, and a series of dimethylaminoethoxy-substituted analogues retained the cytotoxicity of the parent compound, while providing increased aqueous solubility.

The cyclopropylindole class of antitumor antibiotics, exemplified by CC-1065 (**1**)[1] (Chart 1) and duocarmycin SA (**2**)[2] are extremely potent cytotoxins that have engendered great interest both as potential anticancer drugs[1−4] and as targets for synthesis.[5,6] These compounds alkylate DNA in a sequence-selective manner at adenine N-3 sites in the minor groove,[5−7] a selectivity that has been attributed in part to a binding-induced change in reactivity.[8] Simpler synthetic analogues such as **3** retain the high cytotoxicity of the natural products,[9] and open-chain *seco* precursors of these (e.g., **4**) are as cytotoxic as the corresponding ring-closed forms (to which they are presumably converted rapidly in cells).[6] While CC-1065 itself shows delayed toxicity in animals,[10] many simpler analogues such as adozelesin (**5**) do not. Adozelesin is in clinical trial as an anticancer drug,[11] as are the *seco* compounds KW-2189 (**6**) and carzelesin (**7**). Both **6** and **7** are prodrugs of the corresponding *seco* phenols, and are rapidly and nonspecifically hydrolyzed by plasma esterases.[12,13]

Many other synthetic analogues of this class have been prepared, bearing different types of cyclopropylindole alkylating subunits and modified DNA minor groove binding side chains.[5,6,14,15] These studies have identified structure **8** (and the corresponding *seco* form **9**) as representing the "minimum potent pharmacophore"[16] of this class (illustrated here with a trimethoxyindole minor groove binding side chain). Less work has focused on the nature of the 6-substituent in the alkylating subunit of **9**, and research has generally been limited to modification of the phenol by the formation of ethers, esters, and carbamates. The limited series of compounds described has, however, suggested a positive relationship between the electron-donating capability of this substituent and high cytotoxicity.[17,18]

We have recently reported the synthesis[19] and preliminary biological evaluation of (racemic) 6-amino-*seco*-cyclopropylindole (*seco*-CI) compounds such as **10a**, both as potential cytotoxins[20] (bearing an electron-donating amino group) and as effectors to be derived from stable amine-based prodrugs designed for tumor-specific release (e.g., by endogenous reductases, radiation, or gene therapy).[21] Compound **10a** appears to function similarly to the corresponding phenol analogue **9**, by alkylation of DNA at the N-3 position of adenine, with similar sequence specificity.[22] However, it is considerably less cytotoxic than **9** (IC_{50}s, AA8 cells, 4 h exposure; 320 and 6 nM, respectively).[20]

In this paper we report structure−activity relationships for amino-*seco*-CI analogues **10a**−**10j**, with varying minor groove binding side chains, seeking to improve both cytotoxicity and solubility for this class of compounds as cytotoxins and as components of tumor-specific prodrugs.

Chemistry

The amino-*seco*-CI compounds (**10a**−**10j**) of Table 1 were prepared by reduction of the corresponding nitro compounds (**12**) with hydrogen over platinum oxide or with iron dust (Scheme 1). Nitro compounds **12** were in turn prepared by deprotection of the BOC-protected *seco*-CI **11**,[19] followed by either coupling with acids in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) to prepare the amides **12a**−**12f**, **12i**, **12j**) or reaction with sulfonyl chlorides and *N*-methylimidazole to give the sulfonamides **12g** and **12h**.

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Chart 1

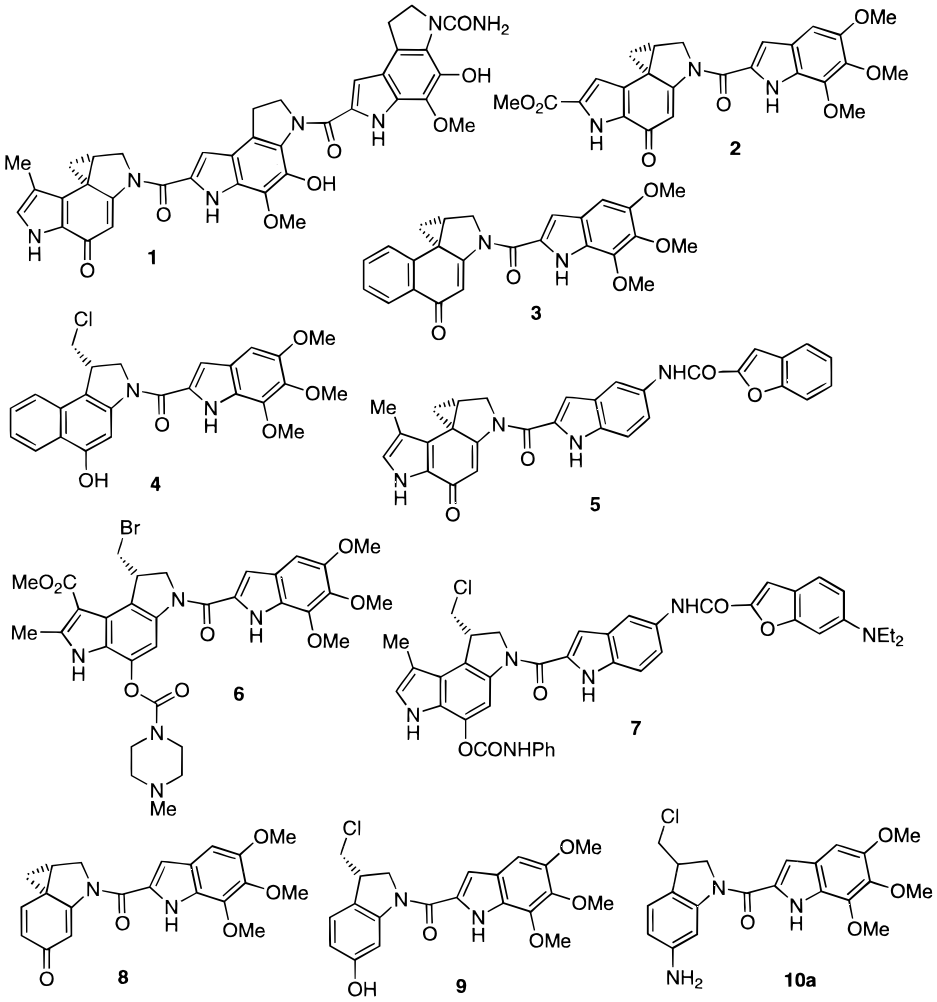
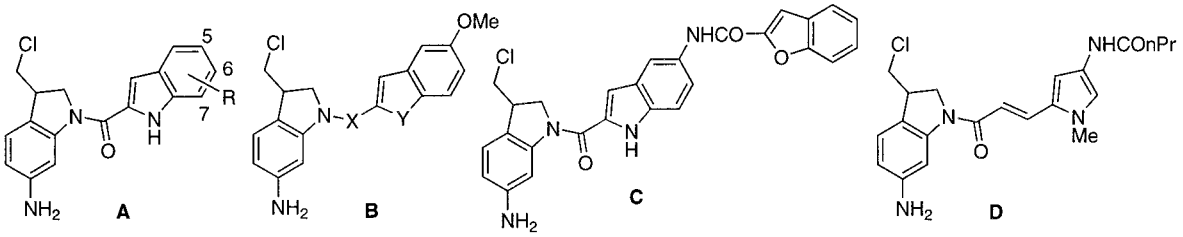


Table 1. Structures, Solubility, and Cytotoxicity of 1-Substituted 3-(Chloromethyl)-6-aminoindoline (6-Amino-*seco*-CI) Alkylating Agents

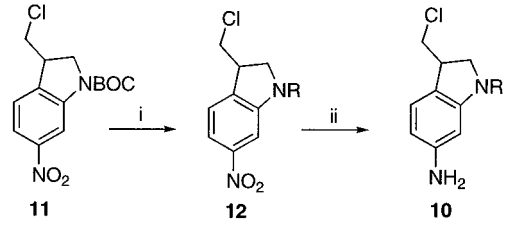


no.	form.	X	Y	R	sol.[a] (μM)	IC$_{50}$[b] (μM) AA8	UV4	EMT6	SKOV3
10a	A			5,6,7-triOMe	32	0.35 ± 0.02	0.055 ± 0.005	0.27 ± 0.04	0.63 ± 0.04
10b	A			5-OMe	23	0.31 ± 0.07	0.047 ± 0.001	0.23 ± 0.01	0.67 ± 0.04
10c	A			5-O(CH$_2$)$_2$NMe$_2$	700	0.16 ± 0.01	0.044 ± 0.001	0.12 ± 0.01	0.26 ± 0.04
10d	A			5-OMe, 6-O(CH$_2$)$_2$NMe$_2$	>1200	0.22 ± 0.04	0.039 ± 0.007	0.11 ± 0.02	0.15 ± 0.02
10e	A			5-OMe, 7-O(CH$_2$)$_2$NMe$_2$	47	0.14 ± 0.01	0.029 ± 0.002	0.09 ± 0.01	0.16 ± 0.01
10f	B	CO	O			0.88 ± 0.05	0.12 ± 0.01	0.64 ± 0.20	1.1 ± 0.01
10g	B	SO$_2$	NH			8.2 ± 2.2	4.3[c]	4.9 ± 1.1	2.7 ± 0.27
10h	B	SO$_2$	O			6.6[c]	2.8[c]	2.6 ± 0.40	4.4 ± 0.4
10i	C					0.16 ± 0.04	0.087 ± 0.003	0.19 ± 0.02	0.60 ± 0.02
10j	D					2.1 ± 0.4	0.31 ± 0.08	0.91 ± 0.03	1.9 ± 0.3

[a] Solubility in 0.1 M phosphate buffer (pH 7.0) at room temperature. [b] IC$_{50}$; concentration of drug to reduce cell numbers to 50% of controls following a 4 h drug exposure. Average of 2−5 determinations ± SEM. [c] One determination only.

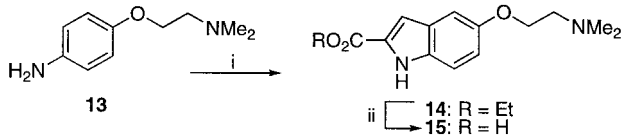
The acid used to prepare **12b** was commercially available, and those for **12f**,[23] **12h**,[24] and **12i**[25] were prepared by reported methods. Acid **15**, containing a 5-O(CH$_2$)$_2$NMe$_2$ side chain designed to provide a more water-soluble analogue, was prepared by Fischer indole synthesis from known[26] aniline **13**, followed by hydrolysis of the ester (Scheme 2). The related 6-O(CH$_2$)$_2$NMe$_2$ substituted acid **22** was prepared by a Hemetsberger

Scheme 1[a]



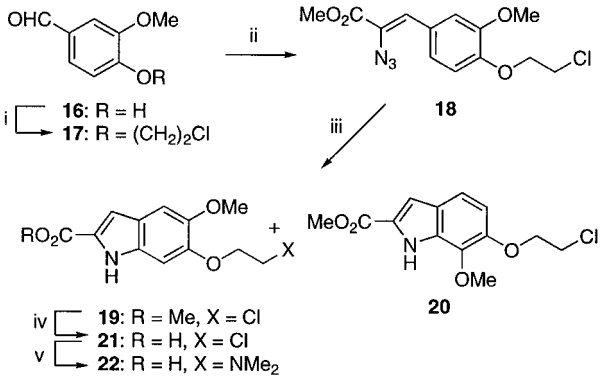
[a] Reagents and conditions: (i) HCl/dioxane/1 h, then R′CO_2H/EDCI/DMA/2−24 h, or R′SO_2Cl/*N*-methylimidazole/CH_2Cl_2; (ii) PtO_2/H_2/THF or Fe/AcOH/H_2O/reflux.

Scheme 2[a]



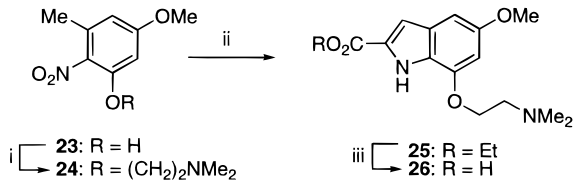
[a] Reagents and conditions: (i) $NaNO_2$/HCl, then ethyl 2-methylacetoacetate/NaOAc, then HCl/EtOH/reflux; (ii) Cs_2CO_3/MeOH/H_2O/reflux/2 h.

Scheme 3[a]



[a] Reagents and conditions: (i) $(CH_2Cl)_2/K_2CO_3$/DMF/70 °C/16 h; (ii) $N_3CH_2CO_2$Me/NaOMe/MeOH; (iii) Xylene/reflux; (iv) Cs_2CO_3/EtOH/H_2O/reflux/6 h; (v)Me_2NH/H_2O/100 °C/1.25 h.

Scheme 4[a]

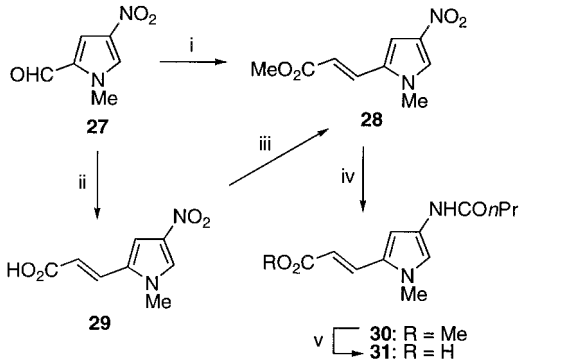


[a] Reagents and conditions: (i) $Cl(CH_2)_2NMe_2$·HCl/K_2CO_3/butanone/reflux; (ii) KOEt/$(CO_2Et)_2$/5 days, then Pd/C/H_2 in AcOH/EtOH; (iii) NaOH/EtOH/H_2O/reflux/1.5 h.

synthesis[27] (Scheme 3). Pyrolysis of azidocinnamate **18**, available in two steps from vanillin **16**, via diether **17**, gave a 3.8:1 mixture of isomers **19** and **20** which could be separated chromatographically. After hydrolysis of the ester group of **19** to give **21**, the chloro group was displaced with dimethylamine to provide **22**. The 7-O$(CH_2)_2NMe_2$ substituted acid **26** was prepared (Scheme 4) by alkylation of the nitrophenol **23** to give **24** and by annulation of this by a Reissert synthesis.[28] The resulting ester **25** was hydrolyzed to give the desired acid.

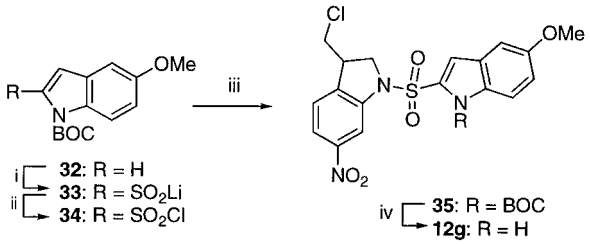
The pyrroleacrylic acid **31** was prepared in three steps from nitroaldehyde **27**.[29] Wittig olefination gave **28** (this was also prepared from **27** by Doebner reaction with

Scheme 5[a]



[a] Reagents and conditions: (i) Ph_3P=$CHCO_2$Me/benzene/reflux/24 h; (ii) $CH_2(CO_2H)_2$/pyridine/cat. piperidine/20 h, then 100 °C/4 h, then 30% aq H_2SO_4; (iii) $Me_2SO_4/NaHCO_3$/MeOH/H_2O; (iv) Fe/(*n*-PrCO)$_2$O/MeOH/H_2O/reflux/45 min; (v) NaOH/MeOH/H_2O/reflux/50 min.

Scheme 6[a]



[a] Reagents and conditions: (i) BuLi/THF/−78 °C, then SO_2; (ii) *N*-chlorosuccinimide/CH_2Cl_2/0 °C; (iii) **11**/HCl/dioxane, then **34**/*N*-methylimidazole/CH_2Cl_2; (iv) TFA.

malonic acid to give **29** and methylation), followed by reduction with iron dust and in situ acylation to give **30**, which was hydrolyzed to the desired acid **31** (Scheme 5).

The indolesulfonyl chloride **34** was prepared (Scheme 6) by lithiation of *N*-BOC-5-methoxyindole (**32**) and treatment with sulfur dioxide to give the lithium sulfinate **33**. This was chlorinated with *N*-chlorosuccinimide to give **34**, which was reacted without isolation with deprotected **11** to give the *N*-BOC derivative **35**. Deprotection of the indole nitrogen with trifluoroacetic acid gave the nitroindoline **12g**.

Results and Discussion

The cytotoxicities of the amino-*seco*-CI analogues **10a**−**10j** were determined (as IC_{50} values, for a 4 h drug exposure, using a growth inhibition assay[30,31]) in a panel of tumor cell lines, including the Chinese hamster ovary lines AA8 and UV4, the murine mammary carcinoma line EMT6, and the human ovarian line SKOV3 (Table 1). The UV4 cell line is a repair-defective ERCC-1 mutant and is hypersensitive to agents whose cytotoxicity is due to bulky DNA adducts[32] and particularly so to cross-links.[33] Overall, there were no large differences in the sensitivity of the wild-type cell lines AA8, EMT6, and SKOV3, but the compounds were 2- to 8-fold more cytotoxic in the UV4 line. This moderate hypersensitivity is at the low end of the range expected for monoalkylation.[33]

As reported previously,[20] the parent racemic compound **10a**, bearing a 5,6,7-trimethoxyindole (TMI) side chain, is a moderately potent cytotoxin (IC_{50}, AA8 cells,

0.35 μM). Because the two enantiomers of **10a** show only a 3-fold difference in cytotoxicity,[22] racemic mixtures of all compounds were used to explore structure−activity relationships for side chain variations in the present work.

Boger has reported that only the 5-methoxy group of the three on the TMI unit of duocarmycin SA (**2**) is required for high potency.[34] This appears to be true in the amino-*seco*-CI-TMI series also, with the 5-OMe analogue **10b** showing an essentially identical cytotoxic profile to **10a**. This fact was exploited in the design of more water-soluble analogues, of interest since both **10a** and **10b** show poor aqueous solubility (32 and 23 μM, respectively, in 0.1 M phosphate buffer, pH 7.0; see Table 1). Three new substituted indole-2-carboxylic acids (**15**, **22**, and **26**) were therefore designed as alternative minor groove binding subunits. Each of these retains a 5-alkoxy substituent for enhanced potency but also bears a solubilizing dimethylaminoethyl group in either the 5-, 6-, or 7-position. The data in Table 1 shows this design to be successful, as the amino-*seco*-CI products **10c**, **10d**, and **10e** are generally more cytotoxic than **10a** and **10b** across the cell line panel, while showing increased aqueous solubility (although the 7-isomer **10e** showed a surprisingly small increase).

The effects on cytotoxic potency of a number of other changes in the molecule were explored with compounds **10f**−**10h**, in which the 5-OMe group was also retained. A previous report[35] suggested that benzofuran analogues (in the CC-1065 series) can be more potent than the corresponding indoles. However, replacing the indole side chain of **10b** with a benzofuran in **10f** lowered potency slightly (about 2-fold). A further study[36a] on analogues of **3** in which the TMI group was replaced with simple substituents showed that cytotoxicity correlated with the electron-withdrawing ability of this substituent. Thus, of the four analogues investigated, potency decreased in the order SO_2Et > COEt > CO_2-Me > CONHMe. As these simple substituents have no intrinsic interaction with the minor groove, this correlation presumably reflects the influence of the substituent on the ease of carbonyl protonation (and subsequent cyclopropyl ring cleavage)[36a] or, as recently proposed,[36b] the extent of analogous amide stabilization.

We have investigated the influence on amino-*seco*-CI cytotoxicity of a sulfonamide versus carboxamide link to a minor groove binding subunit. Table 1 shows that in this system the sulfonamide link significantly reduces potency, both in the case of a 5-methoxyindole (**10g** compared to **10b**) and a 5-methoxybenzofuran (**10h** compared to **10f**).

Several studies with various cyclopropylindoline alkylating units[6] (and with CI agents in particular[17,18]) have shown that the potency conferred by a single suitably substituted minor groove binding unit such as TMI may be slightly increased (by a factor of between 1 and 3) by using two linked subunits. The reason for this is presumed to be increased noncovalent binding. Consistent with this, the analogue **10i**, bearing the adozelesin side chain, was found to be marginally more potent than either **10a** or **10b**.

Finally, Fregeau et al., building on earlier work,[37] reported[14] that a 1-methyl-2-pyrroleacryloyl CPI analogue had extraordinary potency, with an IC_{50} value of 0.76 fg/L (ca. 0.002 fM) against KB nasopharyngeal tumor cells. Details of the preparation of the required pyrroleacrylic acid side chain **31** for this analogue were not provided, so the route shown in Scheme 5 was developed, and the corresponding amino-*seco*-CI analogue **10j** was prepared. However, this showed slightly lower potency than the parent TMI compound **10a**, suggesting that while this side chain is acceptable, it confers no potency advantage in the amino-*seco*-CI series.

Conclusions

This study significantly expands the range of 6-amino-*seco*-CI cytotoxins known. For the series of (racemic) analogues of **10a** studied, some structure−activity relationships were similar to those observed previously for the phenol **9** and its analogues (the retention of potency by a single 5-OMe group on the indole minor groove binding unit, and the slight enhancement in potency with a two-unit side chain). However, a pyrroleacryloyl side chain did not give the large increase in potency reported in another series. Replacing the usual carboxamide link group between the alkylator and minor groove binding subunits by a sulfonamide greatly lowered cytotoxic potency (cf. **10a** and **10g**, **10h**). The most important observation was that analogues possessing both a 5-alkoxy group and a solubilizing dimethylaminoethyl group, either as part of the 5-alkoxy substituent (**10c**), or at other indole positions (**10d** and **10e**), retained or enhanced the cytotoxicity of the parent compound together with increased aqueous solubility. This strategy has potential application to other classes of these cyclopropylindole DNA alkylating agents.

Experimental Section

Chemistry. Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, New Zealand, and are within 0.4% of the theoretical values. Melting points were recorded on an electrothermal melting point apparatus. NMR spectra were obtained on a Bruker DRX-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C), and are referenced to Me_4-Si. Carbon signals were assigned by a DEPT pulse sequence. Column chromatography was carried out on Merck 300−400 mesh silica gel (flash) or Merck 24−40 μm silica gel (dry flash). Petroleum ether refers to the fraction boiling at 40−60 °C, hexanes refers to the fraction boiling at 60−65 °C. *N*,*N*-dimethylacetamide (DMA) and DMF were dried over molecular sieves. THF and Et_2O were dried over sodium/benzophenone. Mass spectra were determined on a VG-75SE mass spectrometer.

5-[2-(Dimethylamino)ethoxy]-1*H*-indole-2-carboxylic Acid Hydrochloride (15) (Scheme 2). A stirred solution of 4-[2-(dimethylamino)ethoxy]aniline[26] (**13**) (3.61 g, 20 mmol) in water (34 mL) and concentrated HCl (10 mL) was diazotized at 0 °C with a solution of $NaNO_2$ (1.52 g, 22 mmol) in water (4 mL). The cold solution was added in one portion to a vigorously stirred ice-cold mixture of ethyl 2-methylacetoacetate (3.03 g, 21 mmol), anhydrous NaOAc (17 g), EtOH (25 mL), and freshly added ice (20 g). After being stirred at 20 °C for 1 h, the mixture was cooled to 0 °C, basified by the slow addition of solid Na_2CO_3, and extracted immediately with CH_2Cl_2 (×2). The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated. The residue was extracted with hot hexanes in the presence of decolorizing charcoal, and the clarified solution was evaporated. The resulting oil (4.55 g) was dissolved in absolute EtOH (6 mL), treated with saturated ethanolic HCl (10 mL), and heated at reflux for 25 min. The solution was then concentrated, and the residue was

partitioned between dilute Na_2CO_3 and CH_2Cl_2. The organic layer was washed with water and saturated NaCl solution, dried, and evaporated. The residue was triturated with $^iPr_2O$/petroleum ether, and the resulting solid was recrystallized from $^iPr_2O$/petroleum ether to give ethyl 5-[2-(dimethylamino)-ethoxy]-1*H*-indole-2-carboxylate (**14**) (1.32 g, 24% overall yield): mp 110 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.72 (s, 1 H, NH), 7.34 (d, J = 9.0 Hz, 1 H, H-7), 7.12 (d, J = 2.4 Hz, 1 H, H-4), 7.03 (d, J = 1.6 Hz, 1 H, H-3), 6.91 (dd, J = 9.0, 2.4 Hz, 1 H, H-6), 4.32 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.03 (t, J = 5.9 Hz, 2 H, OCH_2CH_3), 2.63 (t, J = 5.9 Hz, 2 H, OCH_2CH_2), 2.22 (s, 6 H, $N(CH_3)_2$), 1.33 (t, J = 7.1 Hz, 3 H, CH_2CH_3). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

A mixture of ester **14** (0.75 g, 2.7 mmol), Cs_2CO_3 (3.0 g, 9.2 mmol), MeOH (6 mL), and water (3 mL) was heated at reflux for 2 h and then evaporated to dryness. The residue was dissolved in water (5 mL), and the filtered solution was adjusted to pH 6.5 with HCl and cooled to 0 °C for 24 h. The resulting crystalline solid was collected, washed with ice-cold water and Me_2CO, and treated with dry HCl/dioxane/EtOAc. The resulting solid was recrystallized from MeOH/EtOAc/trace HCl to give **15** (0.69 g, 89%): mp 239−240 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 12.88 (br s, 1 H, CO_2H), 11.69 (s, 1 H, indole NH^+), 10.56 (br s, 1 H, NH^+), 7.37 (d, J = 9.1 Hz, 1 H, H-7), 7.20 (d, J = 2.4 Hz, 1 H, H-4), 7.01 (d, J = 1.7 Hz, 1 H, H-3), 6.98 (dd, J = 9.0, 2.4 Hz, 1 H, H-6), 4.34 (t, J = 5.1 Hz, 2 H, OCH_2), 3.50 (t, J = 5.1 Hz, 2 H, OCH_2CH_2), 2.85 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{13}H_{16}N_2O_3$.HCl) C, H, N, Cl.

6-[2-(Dimethylamino)ethoxy]-5-methoxy-1*H*-indole-2-carboxylic Acid Hydrochloride (22) (Scheme 3). A mixture of vanillin (**16**) (10.00 g, 65.7 mmol), K_2CO_3 (45.4 g, 0.329 mol), 1,2-dichloroethane (104 mL, 1.31 mol), and DMF (300 mL) was stirred at 65−70 °C for 16 h. The dichloroethane was evaporated, and the remaining slurry was poured onto ice. The oil that separated was extracted with Et_2O (×4) and EtOAc (×3). The combined extracts were washed with water (×3) and saturated NaCl solution, dried (Na_2SO_4/$MgSO_4$), and evaporated to give a clear oil that solidified upon trituration with hexanes. Crystallization from Et_2O gave 4-(2-chloroethoxy)-3-methoxybenzaldehyde (**17**) (12.04 g, 85%): mp 60−61 °C; ^{1}H NMR ($CDCl_3$) δ 9.87 (s, 1 H, CHO), 7.46 (dd, J = 8.0, 2.0 Hz, 1 H, H-6), 7.43 (d, J = 2.0 Hz, 1 H, H-2), 6.99 (d, J = 8.0 Hz, 1 H, H-5), 4.36 (t, J = 6.1 Hz, 2 H, OCH_2), 3.94 (s, 3 H, OCH_3), 3.89 (t, J = 6.1 Hz, 2 H, CH_2Cl); ^{13}C NMR δ 190.8 (CHO), 153.0 (C-4), 150.0 (C-3), 130.8 (C-1), 126.3 (C-6), 112.3 (C-2), 109.8 (C-5), 68.9 (OCH_2), 56.0 (OCH_3), 41.2 (CH_2Cl). Anal. ($C_{10}H_{11}ClO_3$) C, H, Cl.

A solution of **17** (4.50 g, 20.97 mmol) and methyl azidoacetate[38] (8.20 g, 71.3 mmol) in MeOH (18 mL) was added to a cooled (ice/salt) solution of sodium methoxide (from 7.45 g of sodium, 62.9 mmol) in MeOH (36 mL) over 1 h. The white slurry was allowed to stand at 5 °C for 1.5 h and then at −15 °C for 18 h and diluted with ice-cold water (200 mL). The precipitate was collected, washed with water, and taken up in CH_2Cl_2. This solution was washed with water, dried ($MgSO_4$), and evaporated to give methyl α-azido-4-(2-chloroethoxy)-3-methoxycinnamate (**18**) (5.08 g, 78%): mp 115−116 °C (dec), that was used without further purification; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, J = 2.0 Hz, 1 H, H-2), 7.33 (dd, J = 8.6, 2.0 Hz, 1 H, H-6), 6.89 (d, J = 8.6 Hz, 1 H, H-5), 6.87 (s, 1 H, H-β), 4.31 (t, J = 6.2 Hz, 2 H, OCH_2), 3.91, 3.90 (2 × s, 3 H each, OCH_3), 3.85 (t, J = 6.2 Hz, 2 H, CH_2Cl); ^{13}C NMR δ 164.1 (CO_2), 149.2, 148.7 (C-3, 4), 127.3 (C-1), 125.6, 124.7 (C-6, β), 123.7 (C-α), 113.9, 113.3 (C-2, 5), 69.0 (OCH_2), 56.1 (OCH_3), 52.8 (CO_2CH_3), 41.4 (CH_2Cl).

A warmed (40 °C) solution of **18** (5.08 g, 16.3 mmol) in xylenes (140 mL) was added to boiling xylenes (60 mL) over 1 h. After a further 15 min at reflux, most of the xylene was removed by distillation. The precipitate that formed in the cooled residue was isolated by filtration, washed with $CHCl_3$ and hexanes, and crystallized from MeOH to give methyl 6-(2-chloroethoxy)-5-methoxy-1*H*-indole-2-carboxylate (**19**) (2.42 g, 52%): mp 110 °C (subl), 164−164 °C (melt); ^{1}H NMR [$(CD_3)_2SO$] δ 11.65 (br s, 1 H, NH), 7.13 (s, 1 H, H-4), 7.03 (d, J = 1.6 Hz, 1 H, H-3), 6.91 (s, 1 H, H-7), 4.24 (t, J = 5.2 Hz, 2 H, OCH_2), 3.98 (t, J = 5.2 Hz, 2 H, CH_2Cl), 3.84, 3.78 (2 × s, 3 H each, OCH_3); ^{13}C NMR δ 161.5 (CO_2), 147.8, 145.8, 132.4, 125.5, 120.3 (C-2, 3a, 5, 6, 7a), 107.8 (C-3), 103.0 (C-4), 96.3 (C-7), 68.9 (OCH_2), 55.7 (OCH_3), 51.4 (CO_2CH_3), 42.9 (CH_2Cl). Anal. ($C_{13}H_{14}ClNO_4$) C, H, N, Cl. Purification of the evaporated mother liquors by flash chromatography (CH_2Cl_2) followed by crystallization from 1,2-dichloroethane and then MeOH gave further **19** (0.42 g, 9%).

Purification of the preliminary fractions by dry flash chromatography (5−60% EtOAc/hexanes) and by crystallization from $^iPr_2O$ gave isomeric methyl 6-(2-chloroethoxy)-7-methoxy-1*H*-indole-2-carboxylate (**20**) (1.20 g, 16%): mp 103−104 °C; ^{1}H NMR ($CDCl_3$) δ 9.16 (br s, 1 H, indole NH), 7.31 (dd, J = 8.7, 0.6 Hz, 1 H, H-4), 7.16 (d, J = 2.3 Hz, 1 H, H-3), 6.85 (d, J = 8.7 Hz, 1 H, H-5), 4.33 (t, J = 5.7 Hz, 2 H, OCH_2), 4.03, 3.92 (2 × s, 3 H each, OCH_3), 3.83 (t, J = 5.7 Hz, 2 H, CH_2Cl); ^{13}C NMR δ 162.2 (CO_2), 147.4, 135.3, 132.1, 127.3, 124.6 (C-2, 3a, 6, 7, 7a), 117.7 (C-4), 112.2 (C-5), 109.3 (C-3), 70.6 (OCH_2), 61.2 (OCH_3), 52.0 (CO_2CH_3), 42.4 (CH_2Cl). Anal. ($C_{13}H_{14}ClNO_4$) C, H, N, Cl.

A mixture of ester **19** (1.00 g, 3.52 mmol), Cs_2CO_3(1.723 g, 5.29 mmol), 95% EtOH (20 mL), and water (10 mL) was stirred at reflux for 6 h. Water (15 mL) was added, and the EtOH was evaporated. The solution was filtered through Celite and acidified with 2 M HCl. The precipitate that formed was collected by filtration, washed with water, and dried to give 6-(2-chloroethoxy)-5-methoxy-1*H*-indole-2-carboxylic acid (**21**) (0.95 g, 100%): mp (MeOH) 187−189 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.63 (br s, 1 H, CO_2H), 11.47 (s, 1 H, NH), 7.12 (s, 1 H, H-4), 6.97 (d, J = 1.6 Hz, 1 H, H-3), 6.91 (s, 1 H, H-7), 4.23 (t, J = 5.2 Hz, 2 H, OCH_2), 3.97 (t, J = 5.2 Hz, 2 H, CH_2Cl), 3.78 (s, 3 H, OCH_3); ^{13}C NMR 162.5 (CO_2), 147.5, 145.6, 132.1, 126.9, 120.4 (C-2, 3a, 5, 6, 7a), 107.4 (C-3), 103.1 (C-4), 96.5 (C-7), 68.9 (OCH_2), 55.7 (OCH_3), 43.0 (CH_2Cl). Anal. ($C_{12}H_{12}ClNO_4$·0.25MeOH) C, H, N, Cl.

A mixture of **21** (1.20 g, 4.45 mmol), 25% aqueous Me_2NH (16 mL, 89 mmol), Na_2CO_3 (1.18 g, 11.1 mmol), and water (80 mL) was heated at 100 °C for 1.25 h, then evaporated. The residue was taken up in 0.4 M aqueous Na_2CO_3 (30 mL), extracted with Et_2O (×2), acidified to pH 1 with 2 M HCl, and evaporated. The residue was extracted with hot CH_3CN (×8), and the extracts were concentrated. The precipitate that formed was removed by filtration and washed with CH_3CN and Et_2O to give **22** (1.06 g, 76%): mp 204−205 °C (dec), hygroscopic; ^{1}H NMR [$(CD_3)_2SO$] δ 12.7 (br s, 1 H, CO_2H), 11.57 (d, J = 1.9 Hz, 1 H, indole NH), 10.7 (br s, 1 H, NH^+), 7.16 (s, 1 H, H-4), 6.98 (d, J = 1.9 Hz, 1 H, H-3), 6.96 (s, 1 H, H-7), 4.38 (t, J = 4.9 Hz, 2 H, OCH_2), 3.80 (s, 3 H, OCH_3), 3.53 (t, J = 4.9 Hz, 2 H, NCH_2), 2.88 (s, 6 H, $N(CH_3)_2$); ^{13}C NMR δ 162.5 (CO_2), 147.0, 145.6, 132.0, 127.1, 120.7 (C-2, 3a, 5, 6, 7a), 107.4 (C-3), 102.9 (C-4), 97.1 (C-7), 64.0 (OCH_2), 55.7 (OCH_3), 55.3 (NCH_2), 42.9 ($N(CH_3)_2$). HRMS (EI) $C_{14}H_{18}N_2O_4$ requires M^+ 278.1267; found 278.1269.

7-[2-(Dimethylamino)ethoxy]-5-methoxy-1*H*-indole-2-carboxylic Acid Hydrochloride (26) (Scheme 4). A mixture of 5-methoxy-3-methyl-2-nitrophenol[39] (**23**) (5.00 g, 27.3 mmol), dimethylaminoethyl chloride hydrochloride (4.33 g, 30 mmol), K_2CO_3 (15.1 g, 109 mmol), NaI (0.41 g, 2.7 mmol), and butanone (50 mL) was heated at reflux for 1 h and then cooled to room temperature. A mixture of dimethylaminoethyl chloride hydrochloride (4.33 g, 30 mmol), K_2CO_3 (7.6 g, 54.6 mmol), and butanone (15 mL) that had been shaken for 5 min was added, and the mixture was heated at reflux for 1.5 h. The mixture was concentrated, and the remaining slurry was diluted with water and extracted with EtOAc (×4). The combined extracts were washed with 1 M aqueous Na_2CO_3 (×10) and extracted with 2 M aqueous HCl (×5). The combined extracts were washed with EtOAc, made basic with Na_2CO_3, and extracted with EtOAc (×4). These extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to give 2-(5-methoxy-3-methyl-2-nitrophenyloxy)-*N*,*N*-dimethylethanamine (**24**) (4.38 g, 63%): oil; ^{1}H NMR ($CDCl_3$) δ 6.38 (d, J = 2.4 Hz, 1 H, H-6′), 6.32 (d, J = 2.4 Hz, 1 H, H-4′), 4.12

(t, J = 5.8 Hz, 2 H, OCH_2), 3.81 (s, 3 H, OCH_3), 2.73 (t, J = 5.8 Hz, 2 H, NCH_2), 2.31 (s, 6 H, $N(CH_3)_2$), 2.28 (s, 3 H, 3′-CH_3); ^{13}C NMR δ 161.0 (C-5′), 151.8 (C-1′), 136.1 (C-2′), 132.7 (C-3′), 106.7 (C-4′), 97.9 (C-6′), 68.1 (OCH_2), 57.4 (NCH_2), 55.5 (OCH_3), 45.8 ($N(CH_3)_2$), 17.7 (3′-CH_3). HRMS (EI) $C_{12}H_{18}N_2O_4$ requires M^+ 254.1267; found 254.1276. Starting material (1.178 g, 24%) was recovered from the basic washes by acidification and extraction.

A suspension of potassium (0.308 g, 7.87 mmol) in xylenes (6 mL) was heated to 100 °C and stirred rapidly as it was allowed to cool. The xylenes were removed, and the potassium was washed with Et_2O (×3) and covered with Et_2O (10 mL). The mixture was treated with absolute EtOH (1.30 mL, 2.2 mmol) and stirred at reflux until the potassium had dissolved (3 h). The cooled mixture was treated with diethyl oxalate (1.07 mL, 7.87 mmol) and then with a solution of **24** (2.00 g, 7.87 mmol) in dry Et_2O (5 mL). After 115 h, the dark red precipitate was removed by filtration and washed with Et_2O. The red solid (1.189 g) was dissolved in absolute EtOH (45 mL), acidified with HOAc (0.78 mL), and hydrogenated over Pd/C (10%, 0.44 g) at 1 atm H_2 for 8 h. The mixture was filtered through Celite, concentrated, diluted with 0.2 M aqueous Na_2CO_3 (100 mL), and extracted with EtOAc (×4). The combined extracts were washed with water (×2) and saturated NaCl solution, dried (Na_2SO_4), evaporated, and purified by flash chromatography (2% Et_3N/EtOAc) to give ethyl 7-[2-(dimethylamino)ethoxy]-5-methoxy-1*H*-indole-2-carboxylate (**25**): oil (0.44 g, 18%); ^{1}H NMR ($CDCl_3$) δ 10.93 (br s, 1 H, NH), 7.09 (d, J = 2.1 Hz, 1 H, H-3), 6.67 (d, J = 2.0 Hz, 1 H, H-4), 6.43 (d, J = 2.0 Hz, 1 H, H-6), 4.38 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 4.16 (t, J = Hz, 2 H, OCH_2CH_2N), 8.38 (s, 3 H, OCH_3), 2.79 (t, J = Hz, 2 H, NCH_2), 2.37 (s, 6 H, $N(CH_3)_2$), 1.40 (t, J = Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 161.9 (CO_2), 155.0, 146.0, 128.1, 127.7, 124.9 (C-2, 3a, 5, 7, 7a), 108.1 (C-3), 99.1 (C-4), 94.6 (C-6), 65.9 (OCH_2CH_2N), 60.6 (OCH_2CH_3), 58.3 (NCH_2), 55.6 (OCH_3), 45.1 ($N(CH_3)_2$), 14.4 (OCH_2CH_3). HRMS (EI) $C_{16}H_{22}N_2O_4$ requires M^+ 306.1580; found 306.1577. Starting material (0.77 g, 39%) was recovered from the ethereal washes by extraction into acid, basification, and extraction with Et_2O.

A mixture of **25** (0.410 g, 1.34 mmol), 95% EtOH (21 mL), and 1.0 M aqueous NaOH (2.7 mL, 2.7 mmol) was stirred at reflux for 1.5 h. The EtOH was evaporated, 2 M aqueous HCl (5 mL) was added, and the solution was evaporated. The residue was extracted with hot CH_3CN (×3), and the extracts were concentrated and diluted with Et_2O. The precipitate that formed was collected by filtration and washed with Et_2O to give **26** (0.372 g, 88%): mp 175−178 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.85 (br s, 1 H, CO_2H), 11.52 (s, 1 H, indole NH), 10.48 (br s, 1 H, NH^+), 7.00 (d, J = 2.1 Hz, 1 H, H-3), 6.72 (d, J = 2.1 Hz, 1 H, H-4), 6.49 (d, J = 2.1 Hz, 1 H, H-6), 4.41 (t, J = 4.8 Hz, 2 H, OCH_2), 3.76 (s, 3 H, OCH_3), 3.58 (t, J = 4.8 Hz, 2 H, NCH_2), 2.88 (s, 6 H, $N(CH_3)_2$); ^{13}C NMR δ 162.5 (CO_2H), 154.4 (C-5), 144.9 (C-7), 128.5, 127.6, 123.5 (C-2, 3a, 7a), 107.7 (C-3), 97.6 (C-4), 94.4 (C-6), 61.3 (OCH_2), 55.3 (OCH_3), 54.8 (NCH_2), 42.0 ($N(CH_3)_2$). HRMS (EI) $C_{14}H_{18}N_2O_4$ requires M^+ 278.1267; found 278.1263.

(*E*)-4-Butyramido-1-methyl-2-pyrroleacrylic Acid (31) (Scheme 5). A mixture of 1-methyl-4-nitro-2-pyrrolecarboxaldehyde[29] (**27**) (0.24 g, 1.56 mmol), methyl triphenylphosphorylideneacetate (0.57 g, 1.71 mmol), and benzene (25 mL) was heated under reflux for 24 h. The still-warm solution was purified directly by dry flash chromatography (0−5% Et_2O/CH_2Cl_2) to give methyl (*E*)-1-methyl-4-nitro-2-pyrroleacrylate (**28**) (0.33 g, 100%): mp 146−147 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 1.8 Hz, 1 H, H-5), 7.47 (d, J = 15.8 Hz, 1 H, H-β), 7.07 (d, J = 1.8 Hz, 1 H, H-3), 6.27 (d, J = 15.8 Hz, 1 H, H-α), 3.77, 3.75 (2 × s, 3 H each, CO_2CH_3, NCH_3); ^{13}C NMR δ 166.9 (CO_2), 136.6, 129.7 (C-2, 4), 130.3, 125.4 (C-3, 5), 117.8, 106.0 (CH=CH), 51.8 (CO_2CH_3), 35.3 (NCH_3). Anal. ($C_9H_{10}N_2O_4$) C, H, N.

Alternatively, a mixture of **27** (0.20 g, 1.30 mmol), malonic acid (0.68 g, 6.5 mmol), piperidine (2 drops), and pyridine (2 mL) was stirred at room temperature at for 20 h and at 100 °C for 4 h, and then 30% aqueous H_2SO_4 (10 mL) was added. The precipitate that formed was removed by filtration and washed with water to give (*E*)-1-methyl-4-nitro-2-pyrroleacrylic acid (**29**) (0.23 g, 92%): mp 180 °C (subl), 242−244 °C (melt); ^{1}H NMR [$(CD_3)_2SO$] δ 12.35 (br s, 1 H, CO_2H), 8.13 (d, J = 1.9 Hz, 1 H, H-5), 7.44 (d, J = 15.9 Hz, 1 H, H-β), 7.41 (d, J = 1.9 Hz, 1 H, H-3), 6.46 (d, J = 15.9 Hz, 1 H, H-α), 3.79 (s, 3 H, NCH_3); ^{13}C NMR δ 167.4 (CO_2H), 135.3, 129.9 (C-2, 4), 130.6, 127.0, 118.6, 105.8 (C-3, 5, α, β), 34.8 (NCH_3). Anal. ($C_8H_8N_2O_4$) C, H, N.

A mixture of **29** (0.10 g, 0.51 mmol), $NaHCO_3$ (0.10 g, 0.61 mmol), MeOH (6 mL), and water (2 mL) at reflux was treated with dimethyl sulfate (0.12 mL, 1.27 mmol), heated at reflux for 1 h, diluted with water, and extracted with EtOAc (×3). The combined extracts were washed with water (×2) and saturated NaCl solution, dried ($MgSO_4$), evaporated, and purified by dry flash chromatography (0−5% Et_2O/CH_2Cl_2) to give **28** (63 mg, 59%), identical to the material prepared above.

A solution of **28** (50 mg, 0.24 mmol) in aqueous MeOH (1: 12.5, 5.4 mL) at reflux was treated with iron powder (70 mg, 1.25 mmol) and butyric anhydride (0.40 mL, 2.45 mmol). After 30 min further butyric anhydride (0.10 mL, 0.61 mmol) was added, and 45 min after the addition of the iron the mixture was allowed to cool. The solids were removed by filtration and washed with MeOH and water. The combined filtrates were diluted with water and extracted with EtOAc (×3). The combined extracts were washed sequentially with water, saturated aqueous $NaHCO_3$, water, and saturated NaCl solution and then dried ($MgSO_4$), evaporated, and purified by dry flash chromatography (0−50% EtOAc/CH_2Cl_2) to give methyl (*E*)-4-butyramido-1-methyl-2-pyrroleacrylate (**30**) (45 mg, 75%): mp 109−110 °C; ^{1}H NMR ($CDCl_3$) δ 7.41 (br s, 1 H, NH), 7.51 (d, J = 15.6 Hz, 1 H, H-β), 7.31 (d, J = 1.8 Hz, 1 H, H-5), 6.39 (d, J = 1.8 Hz, 1 H, H-3), 6.03 (d, J = 15.6 Hz, 1 H, H-α), 3.72, 3.62 (2 × s, 3 H each, CO_2CH_3, NCH_3), 2.27 (t, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 1.71 (sx, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 0.96 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$); ^{13}C NMR δ 170.3, 168.1 (NHCO, CO_2), 131.9, 118.5, 112.5, 102.0 (C-3, 5, α, β), 126.7, 123.5 (C-2, 4), 51.5 (CO_2CH_3), 38.8 (NCH_3), 34.2 ($CH_2CH_2CH_3$), 19.1 ($CH_2CH_2CH_3$), 13.7 ($CH_2CH_2CH_3$). Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

A solution of **30** (0.167 g, 0.667 mmol) and 0.2 M aqueous NaOH (5.7 mL, 1.13 mmol) in MeOH (10 mL) was heated under reflux for 50 min. The mixture was cooled in ice, acidified with 2 M aqueous HCl, and poured onto ice. The precipitate that formed was collected by filtration and washed with water to give acid **31** (0.133 g, 85%): mp 74−76 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 12.02 (br s, 1 H, CO_2H), 9.76 (br s, 1 H, CONH), 7.44 (d, J = 15.6 Hz, 1 H, H-β), 7.27 (d, J = 1.6 Hz, 1 H, H-5), 6.53 (d, J = 1.6 Hz, 1 H, H-3), 6.02 (d, J = 15.6 Hz, 1 H, H-α), 3.66 (s, 3 H, NCH_3), 2.19 (t, J = 7.3 Hz, 2 H, $CH_2CH_2CH_3$), 1.57 (sx, J = 7.3 Hz, 2 H, $CH_2CH_2CH_3$), 0.88 (t, J = 7.3 Hz, 3 H, $CH_2CH_2CH_3$); ^{13}C NMR δ 169.2, 168.0 (NHCO, CO_2), 131.9, 117.8, 113.6, 101.9 (C-3, 5, α, β), 125.8, 124.2 (C-2, 4), 37.5 ($CH_2CH_2CH_3$), 33.6 (NCH_3), 18.7 ($CH_2CH_2CH_3$), 13.6 ($CH_2CH_2CH_3$). Anal. ($C_{12}H_{16}N_2O_3$) C, H, N.

6-Amino-3-(chloromethyl)-1-[(5-methoxyindol-2-yl)carbonyl]indoline (10b): General Example of Scheme 1. A suspension of 1-(*tert*-butyloxycarbonyl)-3-chloromethyl-6-nitroindoline[19] (**11**) (470 mg, 1.60 mmol) in dioxane (30 mL) was saturated with HCl, allowed to stand for 1 h, and evaporated. A solution of 5-methoxy-1*H*-indole-2-carboxylic acid (0.31 g, 1.60 mmol) was added, followed by EDCI·HCl (2.5−3.0 equiv), and the mixture was stirred for 28 h and poured onto ice. The product was recovered by filtration and crystallized from acetone/water to give 3-(chloromethyl)-1-[(5-methoxyindol-2-yl)carbonyl]-6-nitroindoline (**12b**) (0.37 g, 60%): mp > 235 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.70 (br s, 1 H, NH), 8.96 (d, J = 2.2 Hz, 1 H, H-7), 8.02 (dd, J = 8.3, 2.2 Hz, 1 H, H-5), 7.72 (d, J = 8.3 Hz, 1 H, H-4), 7.40 (d, J = 8.9 Hz, 1 H, H-7′), 7.15 (d, J = 2.5 Hz, 1 H, H-4′), 7.13 (d, J = 2.2 Hz, 1 H, H-3′), 6.93 (dd, J = 8.9, 2.5 Hz, 1 H, H-6′), 4.83 (dd, J = 10.7, 9.7 Hz, 1 H, H-2), 4.48 (dd, J = 10.7, 5.0 Hz, 1 H, H-2), 4.03−4.16 (m, 3 H, H-3, CH_2Cl), 3.78 (s, 3 H, 5′-OCH_3); ^{13}C NMR δ 160.5 (NCO), 153.8 (C-5′), 147.6 (C-6), 144.8 (C-3a), 139.8 (C-7a), 131.8,

129.9, 127.4 (C-2′, 3a′, 7a′), 125.4 (C-4), 119.2 (C-5), 115.9, 113.2 (C-4′, 6′), 111.1 (C-7), 106.0 (C-7′), 102.0 (C-3′), 55.2 (5′-OCH_3), 54.0 (C-2), 47.0 (CH_2Cl), 42.0 (C-3). Anal. ($C_{19}H_{16}ClN_3O_4$) C, H, N.

A solution of **12b** (0.12 g, 0.31 mmol) in THF (60 mL) was hydrogenated over platinum oxide (28 mg) at 50 psi H_2 for 45 min, filtered through Celite, evaporated, and purified by dry flash chromatography (0−60% EtOAc/hexanes) to give **10b** (92 mg, 83%): mp (EtOAc/Et_2O/hexanes) 205−206 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.52 (br s, 1 H, NH), 7.50 (d, J = 2.0 Hz, 1 H, H-7), 7.37 (d, J = 9.0 Hz, 1 H, H-7′), 7.14 (d, J = 2.3 Hz, 1 H, H-4′), 7.06 (d, J = 8.1 Hz, 1 H, H-4), 7.00 (d, J = 1.8 Hz, 1 H, H-3′), 6.89 (dd, J = 9.0, 2.3 Hz, 1 H, H-6′), 6.31 (dd, J = 8.1, 2.0 Hz, 1 H, H-5), 5.19 (br s, 2 H, NH_2), 4.61 (dd, J = 10.7, 8.8 Hz, 1 H, H-2), 4.27 (dd, J = 10.7, 4.3 Hz, 1 H, H-2), 3.87−3.95 (m, 1 H, C*H*HCl), 3.77 (s, 3 H, 5′-OCH_3), 3.65−3.72 (m, 2 H, CH*H*Cl, H-3); ^{13}C NMR δ 159.8 (NCO), 153.7 (C-5′), 149.0 (C-6), 144.3 (C-7a), 131.3, 131.1, 127.4 (C-2′, 3a′, 7a′), 124.6 (C-4), 118.8 (C-3a), 115.2, 113.0 (C-4′, 6′), 109.6, 104.9 (C-5, 7′), 103.1, 102.0 (C-7, 3′), 55.2 (5′-OCH_3), 54.4 (C-2), 48.0 (CH_2Cl), 41.9 (C-3). Anal. ($C_{19}H_{18}ClN_3O_2$) C, H, N.

6-Amino-3-(chloromethyl)-1-[[5-[2-(dimethylamino)-ethoxy]-1*H*-indol-2-yl]carbonyl]indoline Hydrochloride (10c). Deprotected **11** (from 53 mg, 0.18 mmol) and the hydrochloride of acid **15** (50 mg, 0.18 mmol) were reacted as above for 3 h. The precipitate was recovered by filtration and converted to the hydrochloride salt to give 3-(chloromethyl)-1-[[5-[2-(dimethylamino)ethoxy]-1*H*-indol-2-yl]carbonyl]-6-nitroindoline hydrochloride **(12c)** (56 mg, 67%): mp (Me_2CO/water then MeOH/Et_2O) 228−232 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.79 (d, J = 1.8 Hz, 1 H, indole NH), 10.7 (br s, 1 H, NH^+), 8.96 (d, J = 2.2 Hz, 1 H, H-7), 8.03 (dd, J = 8.3, 2.2 Hz, 1 H, H-5), 7.74 (d, J = 8.3 Hz, 1 H, H-4), 7.45 (d, J = 8.9 Hz, 1 H, H-7′), 7.26 (d, J = 2.4 Hz, 1 H, H-4′), 7.16 (d, J = 1.8 Hz, 1 H, H-3′), 7.02 (dd, J = 8.9, 2.4 Hz, 1 H, H-6′), 4.84 (dd, J = 10.7, 9.7 Hz, 1 H, H-2), 4.46 (dd, J = 10.7, 5.0 Hz, 1 H, H-2), 4.37 (t, J = 5.0 Hz, 2 H, OCH_2), 4.04−4.18 (m, 3 H, CH_2Cl, H-3), 3.50 (t, J = 5.0 Hz, 2 H, NCH_2), 2.83 (s, 6 H, $N(CH_3)_2$); ^{13}C NMR δ 160.5 (NCO), 152.1, 147.6, 144.7, 139.8, 132.1, 130.2, 127.3 (C-3a, 6, 7a, 2′, 3a′, 5′, 7a′), 125.5, 119.3, 116.1, 113.3, 111.1, 106.0, 103.9 (C-4, 5, 7, 3′, 4′, 6′, 7′), 62.9 (OCH_2), 55.3 (NCH_2), 54.0 (C-2), 47.7 (CH_2Cl), 42.7 ($N(CH_3)_2$), 42.0 (C-3). Anal. ($C_{22}H_{23}ClN_4O_4$·HCl) C, H, N, Cl.

The free base of **12c** (20 mg, 0.045 mmol) was hydrogenated at 50 psi H_2 in THF (10 mL) over PtO_2 (10 mg) for 2 h. The mixture was filtered through Celite and evaporated to give **10c** (8 mg, 43%): mp 173−175 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.50 (br s, 1 H, NH), 7.49 (d, J = 2.0 Hz, 1 H, H-7), 7.37 (d, J = 8.8 Hz, 1 H, H-7′), 7.15 (d, J = 1.7 Hz, 1 H, H-4′), 7.04 (d, J = 8.0 Hz, 1 H, H-4), 6.98 (d, J = 1.0 Hz, 1 H, H-3′), 6.88 (dd, J = 8.8, 1.7 Hz, 1 H, H-6′), 6.31 (dd, J = 8.0, 2.0 Hz, 1 H, H-5), 5.17 (br s, 2 H, NH_2), 4.61 (dd, J = 11.0, 8.6 Hz, 1 H, H-2), 4.26 (dd, J = 11.0, 3.5 Hz, 1 H, H-2), 4.05 (t, J = 5.8 Hz, 2 H, OCH_2), 3.65−3.93 (m, 3 H, CH_2Cl, H-3), 2.64 (t, J = 5.8 Hz, 2 H, NCH_2), 2.23 (s, 6 H, $N(CH_3)_2$). HRMS (EI) $C_{22}H_{25}ClN_4O_3$ requires M^+ 412.1666, 414.1637; found 412.1653, 414.1634.

6-Amino-3-(chloromethyl)-1-[[6-[2-(dimethylamino)ethoxy]-5-methoxy-1*H*-indol-2-yl]carbonyl]indoline Hydrochloride (10d). Deprotected **11** (from 85 mg, 0.29 mmol) and the hydrochloride of acid **22** (90 mg, 0.29 mmol) were reacted as above for 3 h. The precipitate was recovered by filtration and converted to the hydrochloride salt to give 3-(chloromethyl)-1-[6-[2-(dimethylamino)ethoxy]-5-methoxy-1*H*-indol-2-yl]carbonyl-6-nitroindoline hydrochloride (**12d**) (82 mg, 57%): mp (MeOH/^{i}PrOH) 218−222 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.65 (d, J = 1.8 Hz, 1 H, indole NH), 10.80 (br s, 1 H, NH^+), 8.96 (d, J = 2.2 Hz, 1 H, H-7), 8.00 (dd, J = 8.3, 2.2 Hz, 1 H, H-5), 7.72 (d, J = 8.3 Hz, 1 H, H-4), 7.21 (s, 1 H, H-4′), 7.13 (d, J = 1.8 Hz, 1 H, H-3′), 7.04 (s, 1 H, H-7′), 4.81 (dd, J = 10.6, 9.8 Hz, 1 H, H-2), 4.46 (dd, J = 10.6, 5.0 Hz, 1 H, H-2), 4.41 (t, J = 5.6 Hz, 2 H, OCH_2), 4.02−4.19 (m, 3 H, CH_2Cl, H-3), 3.82 (s, 3 H, OCH_3), 3.55 (t, J = 4.6, 2 H, NCH_2), 2.89 (s, 6 H, $N(CH_3)_2$); ^{13}C NMR δ 160.3 (NCO), 147.6, 147.3, 145.7, 144.9, 139.7, 131.4, 128.5, 121.1 (C-3a, 6, 7a, 2′, 3a′, 5′, 6′, 7a′) 125.4 (C-4), 119.0 (C-5), 111.0 (C-7), 106.6 (C-3′), 103.0 (C-4′), 96.8 (C-7′), 64.0 (OCH_2), 55.8 (OCH_3), 55.3 (NCH_2), 53.9 (C-2), 47.1 (CH_2Cl), 43.0 ($N(CH_3)_2$), 42.0 (C-3). Anal. ($C_{23}H_{25}ClN_4O_5$·HCl) C, H, N, Cl.

The free base of **12d** (46 mg, 0.086 mmol) was hydrogenated at 50 psi H_2 in THF (10 mL) over PtO_2 (18 mg) for 2 h. The mixture was filtered through Celite, evaporated, and purified by preparative reverse-phase HPLC on C-18 silica gel, eluting with a mixture of 0.05 M ammonium formate (pH 4.5)/80% MeCN (59:41). Appropriate fractions were pooled, the CH_3CN was evaporated, and the aqueous layer was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (×3). The extracts were dried (Na_2SO_4), evaporated, and treated with HCl to give **10d** as the hydrochloride salt (12 mg, 24%): mp 206−208 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.57 (br s, 1 H, NH), 10.57 (br s, 1 H, NH^+), 9.6 (very br s, 3 H, NH_3^+), 8.11 (br s, 1 H, H-3′), 7.45 (d, J = 8.0 Hz, 1 H, H-4), 7.22 (s, 1 H, H-4′), 7.09 (d, J = 1.9 Hz, 1 H, H-7), 7.05 (s, 1 H, H-7′), 6.96 (br d, J = 8.0 Hz, 1 H, H-5), 4.72 (t, J = 9.9 Hz, 1 H, H-2), 4.35−4.40 (m, 3 H, H-2, OCH_2), 3.88−4.06 (m, 3 H, CH_2Cl, H-3), 3.82 (s, 3 H, OCH_3), 3.56 (t, J = 4.6 Hz, 2 H, NCH_2), 2.90 (s, 6 H, $N(CH_3)_2$). HRMS (EI) $C_{23}H_{27}ClN_4O_3$ requires M^+ 442.1772, 444.1742; found 442.1782, 444.1758.

6-Amino-3-(chloromethyl)-1-[[7-[2-(dimethylamino)-ethoxy]-5-methoxy-1*H*-indol-2-yl]carbonyl]indoline Hydrochloride (10e). Deprotected **11** (from 188 mg, 0.64 mmol) and the hydrochloride of acid **26** (0.20 g, 0.64 mmol) were reacted as above for 3 h. The precipitate was recovered by filtration and converted to the hydrochloride salt to give 3-(chloromethyl)-1-[[7-[2-(dimethylamino)ethoxy]-5-methoxy-1*H*-indol-2-yl]carbonyl]-6-nitroindoline hydrochloride (**12e**) (0.24 g, 75%): mp (MeOH) 181−183 °C and 207−209 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.61 (d, J = 2.3 Hz, 1 H, indole NH), 10.39 (br s, 1 H, NH^+), 8.94 (d, J = 2.2 Hz, 1 H, H-7), 8.02 (dd, J = 8.3, 2.2 Hz, 1 H, H-5), 7.74 (d, J = 8.3 Hz, 1 H, H-4), 7.13 (d, J = 2.3 Hz, 1 H, H-3′), 7.21 (d, J = 1.9 Hz, 1 H, H-4′), 7.04 (d, J = 1.9 Hz, 1 H, H-6′), 4.83 (t, J = 10.2 Hz, 1 H, H-2), 4.39−4.48 (m, 3 H, H-2, OCH_2), 4.04−4.17 (m, 3 H, CH_2Cl, H-3), 3.78 (s, 3 H, OCH_3), 3.60 (t, J = 4.8 Hz, 2 H, NCH_2), 2.89 (s, 6 H, $N(CH_3)_2$); ^{13}C NMR δ 160.5 (NCO), 154.6, 147.6, 144.73, 144.65, 139.9, 129.9, 127.9, 122.7 (C-3a, 6, 7a, 2′, 3a′, 5′, 7′, 7a′), 125.5 (C-4), 119.3 (C-5), 111.0 (C-7), 106.5 (C-3′), 97.8 (C-4′), 94.5 (C-6′), 61.4 (OCH_2), 55.3 (OCH_3), 54.8 (NCH_2), 54.0 (C-2), 47.1 (CH_2Cl), 42.0 ($N(CH_3)_2$), 41.9 (C-3). Anal. ($C_{23}H_{25}ClN_4O_5$·HCl·1.5H_2O) C, H, N.

The free base of **12e** (93 mg, 0.18 mmol) was hydrogenated at 50 psi H_2 in THF (20 mL) over PtO_2 (46 mg) for 2 h. The mixture was filtered through Celite and evaporated to give **10e** (66 mg, 76%): mp 189−191.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.34 (br s, 1 H, NH), 7.43 (d, J = 2.0 Hz, 1 H, H-7), 7.04 (d, J = 8.0 Hz, 1 H, H-4), 6.93 (d, J = 1.8 Hz, 1 H, H-3′), 6.71 (d, J = 1.8 Hz, 1 H, H-4′), 6.46 (d, J = 1.8 Hz, 1 H, H-6′), 6.30 (dd, J = 8.0, 2.0 Hz, 1 H, H-5), 5.17 (br s, 2 H, NH_2), 4.53 (dd, J = 11.3, 9.1 Hz, 1 H, H-2), 4.15−4.24 (m, 1 H, H-2), 4.17 (t, J = 5.6 Hz, 2 H, OCH_2), 3.83−3.94 (m, 1 H, C*H*HCl), 3.76 (s, 3 H, OCH_3), 3.61−3.72 (m, 2 H, H-3, CH*H*Cl), 2.73 (t, J = 5.6 Hz, 2 H, NCH_2), 2.27 (s, 6 H, $N(CH_3)_2$). HRMS (EI) $C_{23}H_{27}ClN_4O_3$ requires M^+ 442.1772, 444.1742; found 442.1759, 444.1752.

6-Amino-3-(chloromethyl)-1-[(5-methoxybenzofuran-2-yl)carbonyl]indoline (10f). Deprotected **11** (from 0.415 g, 1.41 mmol) and methoxybenzofuran-2-carboxylic acid[23] (0.27 g, 1.41 mmol) were reacted as above for 3.5 h. The precipitate was recovered by filtration to give 3-(chloromethyl)-1-[(5-methoxybenzofuran-2-yl)carbonyl]-6-nitroindoline **(12f)** (0.42 g, 75%): mp (Me_2CO/water) 206−207 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.90 (br s, 1 H, H-7), 8.05 (dd, J = 8.3, 2.2 Hz, 1 H, H-5), 7.75 (d, J = 8.3 Hz, 1 H, H-4), 7.73 (s, 1 H, H-3′), 7.65 (d, J = 9.1 Hz, 1 H, H-7′), 7.31 (d, J = 2.6 Hz, 1 H, H-4′), 7.12 (dd, J = 9.1, 2.6 Hz, 1 H, H-6′), 4.68 (dd, J = 11.0, 9.8 Hz, 1 H, H-2), 4.52 (dd, J = 11.0, 5.0 Hz, 1 H, H-2), 4.05−4.17 (m, 3 H, H-3, CH_2Cl), 3.82 (s, 3 H, 5′-OCH_3); ^{13}C NMR δ 157.6 (NCO), 156.2 (C-5′), 149.4 (C-7a′), 148.4 (C-6), 147.6 (C-2′), 144.3 (C-7a), 140.0 (C-3a), 127.2 (C-3a′), 125.6 (C-4), 119.8 (C-5), 117.0 (C-

6′), 113.7 (C-3′), 112.7 (C-7′), 111.2 (C-7), 104.1 (C-4′), 55.6 (5′-OCH_3), 53.6 (C-2), 46.9 (CH_2Cl), 41.9 (C-3). Anal. ($C_{19}H_{15}ClN_2O_5$) C, H, N, Cl.

A solution of **12f** (0.10 g, 0.27 mmol) in THF (50 mL) was hydrogenated over platinum oxide (20 mg) at 50 psi H_2 for 30 min, filtered through Celite, and evaporated. The crude material was purified by dry flash chromatography (0−55% EtOAc/CH_2Cl_2) and precipitated from EtOAc/Et_2O with hexanes to give **10f** (0.06 g, 59%): mp 167−169 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.62 (d, J = 9.1 Hz, 1 H, H-7′), 7.57 (s, 1 H, H-3′), 7.45 (br s, 1 H, H-7), 7.28 (d, J = 2.6 Hz, 1 H, H-4′), 7.08 (dd, J = 9.1, 2.6 Hz, 1 H, H-6′), 7.06 (d, J = 8.1 Hz, 1 H, H-4), 6.33 (dd, J = 8.1, 2.1 Hz, 1 H, H-5), 5.20 (br s, 2 H, NH_2), 4.61 (dd, J = 11.1, 8.8 Hz, 1 H, H-2), 4.28 (dd, J = 11.1, 4.4 Hz, 1 H, H-2), 3.91 (dd, J = 10.1, 3.6 Hz, 1 H, C*H*HCl), 3.82 (s, 3 H, 5′-OCH_3), 3.74 (dd, J = 10.1, 7.9 Hz, 1 H, CH*H*Cl), 3.69 (dddd, J = 8.8, 7.9, 4.4, 3.6 Hz, 1 H, H-3); ^{13}C NMR δ 156.9 (NCO), 156.0 (C-5′), 149.4, 149.1, 149.0 (C-6, 2′, 7a′), 143.8 (C-7a), 127.4 (C-3a′), 124.7 (C-4), 118.9 (C-3a), 116.3 (C-6′), 112.5 (C-3′), 112.0 (C-7′), 110.0 (C-5), 104.0 (C-4′), 102.9 (C-7), 55.5 (5′-OCH_3), 53.9 (C-2), 47.9 (CH_2Cl), 41.7 (C-3). Anal. ($C_{19}H_{17}ClN_2O_3$) C, H, N, Cl.

6-Amino-1-[[5-[[(benzofuran-2-yl)carbonyl]amino]-1*H*-indol-2-yl]carbonyl]-3-(chloromethyl)indoline (10i). Deprotected **11** (from 0.39 g, 1.33 mmol) and 5-[[(benzofuran-2-yl)carbonyl]amino]-1*H*-indole-2-carboxylic acid[25] (0.425 g, 1.33 mmol) were reacted as above for 2.5 h. The precipitate was recovered by filtration to give 1-[[5-[[(benzofuran-2-yl)carbonyl]-amino]-1*H*-indol-2-yl]carbonyl]-3-(chloromethyl)-6-nitroindoline **(12i)** (0.45 g, 69%): mp (THF/water) > 230 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.86 (d, J = 1.1 Hz, 1 H, indole NH), 10.50 (s, 1 H, amide NH), 8.99 (d, J = 2.1 Hz, 1 H, H-7), 8.25 (d, J = 2.0 Hz, 1 H, H-4′), 8.05 (dd, J = 8.2, 2.1 Hz, 1 H, H-5), 7.84 (d, J = 7.7 Hz, 1 H, H-4″), 7.77 (s, 1 H, H-3″), 7.74 (d, J = 8.3 Hz, 1 H, H-7″), 7.73 (d, J = 8.2 Hz, H-4), 7.64 (dd, J = 9.0, 2.0 Hz, 1 H, H-6′), 7.52 (dd, J = 8.3, 7.1 Hz, 1 H, H-6″), 7.50 (d, J = 9.0 Hz, 1 H, H-7′), 7.37 (dd, J = 7.7, 7.1 Hz, 1 H, H-5″), 7.28 (s, 1 H, H-3′), 4.88 (dd, J = 10.8, 9.5 Hz, 1 H, H-2), 4.52 (dd, J = 10.8, 5.1 Hz, 1 H, H-2), 4.16 (ddt, J = 9.5, 5.1, 4.7 Hz, 1 H, H-3), 4.11 (d, J = 4.6 Hz, 2 H, CH_2Cl); ^{13}C NMR δ 160.5, 156.4, 154.3, 149.1, 147.6, 144.8, 139.9, 133.7, 131.2, 130.3, 127.1, 126.94 (2 × CO, C-3a, 6, 7a, 2′, 3a′, 5′, 7a′, 2″, 3a″, 7a″), 126.89, 125.5, 123.7, 122.8, 119.8, 119.3, 113.3, 112.3, 111.8, 111.1, 110.1, 106.5 (C-4, 5, 7, 3′, 4′, 6′, 7′, 3″, 4″, 5″, 6″, 7″), 53.9 (C-2), 47.0 (CH_2Cl), 41.9 (C-3). Anal. ($C_{27}H_{19}ClN_4O_5$) C, H, N, Cl.

A solution of **12i** (150 mg, 0.29 mmol) in THF/water (49:1, 70 mL) was hydrogenated over platinum oxide (60 mg) at 50 psi H_2 for 2 h, filtered through Celite, and evaporated. The residue was triturated with EtOAc/acetone (1:1, 8 mL) and diluted with Et_2O (20 mL), and the precipitate was collected by filtration and washed with EtOAc to give **10i** (113 mg, 80%): mp > 230 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.68 (br s, 1 H, indole NH), 10.48 (s, 1 H, amide NH), 8.20 (d, J = 1.7 Hz, 1 H, H-4′), 7.83 (d, J = 7.7 Hz, 1 H, H-4″), 7.77 (s, 1 H, H-3″), 7.73 (dd, J = 8.3, 0.7 Hz, 1 H, H-7″), 7.61 (dd, J = 8.9, 2.1 Hz, 1 H, H-6′), 7.51 (ddd, J = 8.3, 7.8, 1.0 Hz, 1 H, H-6″), 7.50 (d, J = 2.0 Hz, 1 H, H-7), 7.47 (d, J = 8.9 Hz, 1 H, H-7′), 7.38 (ddd, J = 7.8, 7.7, 0.7 Hz, 1 H, H-5″), 7.13 (d, J = 1.1 Hz, 1 H, H-3′), 7.06 (d, J = 8.0 Hz, H-4), 6.31 (dd, J = 8.0, 2.0 Hz, 1 H, H-5), 5.19 (br s, 2 H, NH_2), 4.65 (dd, J = 10.7, 8.9 Hz, 1 H, H-2), 4.30 (dd, J = 10.7, 4.1 Hz, 1 H, H-2), 3.90 (dd, J = 10.0, 3.6 Hz, H, C*H*HCl), 4.16 (m, 2 H, CH*H*Cl, H-3); ^{13}C NMR δ 159.7, 156.4, 154.3, 149.1, 149.0, 144.3, 133.3, 131.6, 130.9, 127.2, 126.94, 118.9 (2 × CO, C-3a, 6, 7a, 2′, 3a′, 5′, 7a′, 2″, 3a″, 7a″), 126.88, 124.7, 123.7, 122.8, 119.2, 113.3, 112.1, 111.9, 110.0, 109.7, 105.4, 103.1 (C-4, 5, 7, 3′, 4′, 6′, 7′, 3″, 4″, 5″, 6″, 7″), 54.3 (C-2), 48.0 (CH_2Cl), 41.8 (C-3). Anal. ($C_{27}H_{21}ClN_4O_3$·0.25EtOAc) C, H, N, Cl.

6-Amino-1-[(*E*)-4-butyramido-1-methyl-2-pyrroleacryloyl]-3-(chloromethyl)indoline (10j). Deprotected **11** and acid **31s** were reacted as above for 20 h. The product was recovered by extraction with EtOAc and purified by dry flash chromatography (0−100% EtOAc/CH_2Cl_2) to give 1-[(*E*)-4-butyramido-1-methyl-2-pyrroleacryloyl]-3-(chloromethyl)-6-nitroindoline **(12j)** (62%): mp 205−207 °C; ^{1}H NMR ($CDCl_3$) δ 9.09 (br s, 1 H, H-7), 7.94 (dd, J = 8.2, 2.2 Hz, 1 H, H-5), 7.77 (d, J = 14.9 Hz, 1 H, H-β′), 7.36 (d, J = 8.2 Hz, 1 H, H-4), 7.24 (d, J = 1.6 Hz, 1 H, H-5′), 7.19 (br s, 1 H, NH), 6.66 (d, J = 1.6 Hz, 1 H, H-3′), 6.47 (d, J = 14.9 Hz, 1 H, H-α′), 4.46 (d, J = 10.7, 9.8 Hz, 1 H, H-2), 4.25 (d, J = 10.7, 5.0 Hz, 1 H, H-2), 3.95−3.61 (m, 3 H, CH_2Cl, H-3), 3.70 (s, 3 H, NCH_3), 2.32 (t, J = 7.4 Hz, 2 H, CH_2CH$_2$CH$_3$), 1.75 (sx, J = 7.4 Hz, 2 H, CH$_2$CH_2CH$_3$), 1.00 (t, J = 7.4 Hz, 3 H, CH$_2$CH$_2$CH_3); ^{13}C NMR δ 170.4, 165.2 (2 × NHCO), 148.9, 144.6, 137.7, 127.5, 123.7 (C-3a, 5, 7a, 2′, 6′), 132.2, 124.3, 119.0, 118.5, 112.4, 112.0, 102.4 (C-4, 5, 7, 3′, 5′, α, β), 52.8 (C-2), 46.2 (CH_2Cl), 42.5 (C-3), 38.9 (*C*H$_2$CH$_2$CH$_3$), 34.2 (NCH_3), 19.1 (CH$_2$*C*H$_2$CH$_3$), 13.8 (CH$_2$CH$_2$*C*H$_3$). Anal. ($C_{21}H_{23}ClN_4O_4$) C, H, N.

A mixture of **12j** (0.40 g, 0.93 mmol), AcOH (0.60 mL, 9.3 mmol), MeOH (90 mL), and water (16 mL) was treated at reflux with iron powder (0.52 g, 9.28 mmol). After 15 min the mixture was cooled in ice, diluted with saturated aqueous $NaHCO_3$ (20 mL), filtered through Celite, diluted with water, and extracted with EtOAc (×4). The combined extracts were washed with dilute aqueous $NaHCO_3$ (×2) and saturated NaCl solution, dried ($MgSO_4$), evaporated, and purified by dry flash chromatography (1−4.5% MeOH/CH_2Cl_2) to give **10j** (0.26 g, 69%): mp 142−144 °C; ^{1}H NMR ($CDCl_3$) 7.76 (br s, 1 H, H−7), 7.68 (d, J = 14.9 Hz, 1 H, H-β), 7.35 (br s, 1 H, NH), 7.24 (d, J = 1.7 Hz, 1 H, H-5′), 6.97 (d, J = 8.0 Hz, 1 H, H-4), 6.59 (br s, 1 H, H-3′), 6.49 (br d, J = 14.9 Hz, 1 H, H-α), 6.37 (dd, J = 8.0, 2.2 Hz, 1 H, H-5), 4.29 (dd, J = 8.0, 2.2 Hz, 1 H, H-2), 4.11 (dd, J = 10.8, 4.4 Hz, 1 H, H-2), 3.74 (dd, J = 10.7, 4.3 Hz, 1 H, C*H*HCl), 3.64 (s, 3 H, NCH_3), 3.71−3.59 (m, 1 H, H-3), 3.49 (dd, J = 10.7, 9.7 Hz, 1 H, CH*H*Cl), 2.29 (t, J = 7.4 Hz, 2 H, CH_2CH$_2$CH$_3$), 1.73 (sx, J = 7.4 Hz, 2 H, CH$_2$CH_2CH$_3$), 0.98 (t, J = 7.4 Hz, 3 H, CH$_2$CH$_2$CH_3); ^{13}C NMR δ 169.2, 163.7 (2 × NHCO), 148.6, 144.2, 126.7, 124.1, 119.0 (C-3a, 6, 7a, 2′, 4′), 129.9, 124.6, 117.3, 113.9, 109.1, 102.7, 101.9 (C-4, 5, 7, 3′, 5′, α, β), 52.4 (C-2), 48.2 (CH_2Cl), 41.1 (C-3), 37.5 (*C*H$_2$CH$_2$CH$_3$), 33.6 (NCH_3), 18.7 (CH$_2$*C*H$_2$CH$_3$), 13.6 (CH$_2$CH$_2$*C*H$_3$). Anal. ($C_{21}H_{25}ClN_4O_2$·0.5H_2O) C, H, N.

6-Amino-3-(chloromethyl)-1-[(5-methoxyindol-2-yl)sulfonyl]indoline (10g): Method of Scheme 6. *n*-Butyllithium (2.5 M in hexanes, 2.7 mL, 6.8 mmol) was added to a cooled (dry ice/acetone) solution of 5-methoxyindole (1.00 g, 6.8 mmol) in THF (10 mL) at such a rate that the internal temperature did not exceed −60 °C (15 min). The mixture was allowed to warm to −15 °C over 30 min; it was then re-cooled to −70 °C, and a solution of di-*tert*-butyl dicarbonate (2.6 g, 11.9 mmol) in THF (5 mL) was added at such a rate that the internal temperature did not exceed −60 °C (15 min). The mixture was allowed to warm to room temperature over 30 min and was stirred at that temperature for a further 30 min. Water was added, and after 30 min the mixture was extracted with Et_2O (×3). The combined extracts were washed with water (×2) and saturated NaCl solution, dried ($MgSO_4$), and evaporated. Crystallization of the residue from pentane gave *tert*-butyl 5-methoxyindole-1-carboxylate (**32**) (1.43 g, 85%): mp 76−77 °C (lit.[40] 74−76 °C).

n-Butyllithium (2.5 M in hexanes, 2.7 mL, 6.8 mmol) was added to a cooled (dry ice/acetone) solution of **32** (1.00 g, 4.0 mmol) in THF (10 mL) over 15 min and the resulting bright yellow solution stirred for a further 30 min. Sulfur dioxide was passed through a needle just above the solution until an aliquot was acidic to damp litmus. The mixture was allowed to warm to room temperature over 30 min, and then pentane (25 mL) was added. The mixture was concentrated to a volume of 2 mL whereupon Et_2O (2 mL) and pentane (25 mL) were added to give a precipitate of the lithium salt of 1-*tert*-butyl 5-methoxy-2-sulfinoindole-1-carboxylate (**33**) (1.08 g, 84%), which was used directly: ^{1}H NMR (D_2O) δ 7.72 (d, J = 9.1 Hz, 1 H, H-7), 7.06 (d, J = 2.6 Hz, 1 H, H-4), 6.94 (s, 1 H, H-3), 6.82 (dd, J = 9.1, 2.6 Hz, 1 H, H-6), 3.81 (s, 3 H, 5-OCH_3), 1.67 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR δ 157.6, 155.9, 153.0 (C-2, 5, CO), 134.4, 131.4 (C-3a, 7a), 118.7, 116.8, 110.0 (C-4, 6, 7), 107.0 (C-3), 89.0 (*C*(CH_3)$_3$), 58.3 (5-OCH_3), 30.2 (C(*C*H_3)$_3$).

A chilled (ice/water) solution of the sulfinate **33** (0.48 g, 1.50 mmol) in CH_2Cl_2 (5 mL) was treated with *N*-chlorosuccinimide (0.21 g, 1.55 mmol). The mixture was stirred for 20 min, the cooling bath was removed, and the mixture was stirred for a further 15 min. The mixture was filtered, and the resulting solution of crude sulfonyl chloride **34** was added to **11** (0.31 g, 1.00 mmol; deprotected as described above) and *N*-methylimidazole (0.40 mL, 5.0 mmol). This mixture was stirred for 22 h, diluted with 0.5 M aqueous HCl, and extracted with EtOAc (×3). The combined extracts were washed with water (×2) and saturated NaCl solution, dried ($MgSO_4$), evaporated, and purified by dry flash chromatography (5−60% EtOAc/hexanes) to give 3-(chloromethyl)-1-[(1-*tert*-butyloxycarbonyl-5-methoxyindol-2-yl)sulfonyl]-6-nitroindoline (**35**) (0.38 g, 73%): mp 78−82 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (d, J = 2.0 Hz, 1 H, H-7), 7.94 (d, J = 9.3 Hz, 1 H, H-7′), 7.88 (dd, J = 8.3, 2.0 Hz, 1 H, H-5), 7.40 (d, J = 8.3 Hz, 1 H, H-4), 7.26 (s, 1 H, H-3′), 7.09 (dd, J = 9.3, 2.6 Hz, H-6′), 7.01 (d, J = 2.6 Hz, 1 H, H-4′), 4.53 (dd, J = 10.8, 9.2 Hz, 1 H, H-2), 4.40 (dd, J = 10.8, 5.3 Hz, 1 H, H-2), 3.95−3.80 (m, 1 H, H-3), 3.83 (s, 3 H, 5′-OCH_3), 3.76 (d, J = 6.3 Hz, 2 H, CH_2Cl), 1.70 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR δ 156.4 (C-5′), 149.0 (C-6), 148.2 (CO), 143.5 (C-3a), 137.3 (C-7a), 133.5, 133.4, 126.5 (C-2′, 3a′, 7a′), 125.3 (C-4), 118.5 (3 × C), 116.8 (C-5, 4′, 6′, 7′), 108.8 (C-7), 103.5 (C-3′), 86.5 ($C(CH_3)_3$), 55.6 (5′-OCH_3), 55.0 (C-2), 45.5 (CH_2Cl), 42.3 (C-3), 21.0 ($C(CH_3)_3$). HRMS (EI) $C_{23}H_{24}ClN_3O_7S$ requires M^+ 421.0499, 423.0470; found 421.0494, 423.0478.

A solution of protected indole **35** (0.30 g, 0.59 mmol) in trifluoroacetic acid (1.5 mL) was stirred for 70 min, and then water (60 mL) was added. The resulting precipitate was removed by filtration, dissolved in EtOAc, washed with water (×2) and saturated NaCl solution, dried ($MgSO_4$), evaporated, and purified by dry flash chromatography (0−45% EtOAc/hexanes) to give 3-(chloromethyl)-1-[(5-methoxyindol-2-yl)-sulfonyl]-6-nitroindoline (**12g**) (0.22 g, 88%): mp (^{i}PrOH/hexanes) 163−164 °C; ^{1}H NMR ($CDCl_3$) δ 9.08 (br s, 1 H, NH), 8.47 (d, J = 2.1 Hz, 1 H, H-7), 7.91 (dd, J = 8.3, 2.1 Hz, 1 H, H-5), 7.32 (d, J = 8.5 Hz, 1 H, H-7′), 7.30 (d, J = 8.3 Hz, 1 H, H-4), 7.07 (d, J = 2.4 Hz, 1 H, H-4′), 7.02 (s, 1 H, H-3′), 7.00 (dd, J = 8.5, 2.4 Hz, 1 H, H-6′), 4.21 (dd, J = 11.0, 9.2 Hz, 1 H, H-2), 4.10 (dd, J = 11.0, 5.0 Hz, 1 H, H-2), 4.82 (s, 3 H, 5′-OCH_3), 3.67 (dddd, J = 9.0, 8.1, 5.1, 5.0 Hz, 1 H, H-3), 3.57 (dd, J = 11.2, 5.2 Hz, 1 H, C*H*HCl), 3.34 (dd, J = 11.2, 8.1 Hz, 1 H, CH*H*Cl); ^{13}C NMR δ 155.3 (C-5′), 149.1 (C-6), 142.9 (C-3a), 138.2 (C-7a), 132.2, 128.7, 127.1 (C-2′, 3a′, 7a′), 125.5 (C-4), 119.6 (C-5), 118.2, 113.3 (C-4′, 6′), 109.6 (C-7′), 108.7 (C-7), 102.3 (C-3′), 55.6 (5′-OCH_3), 54.1 (C-2), 45.4 (CH_2Cl), 42.3 (C-3). Anal. ($C_{18}H_{16}ClN_3O_5S$) C, H, N.

A solution of **12g** (0.11 g, 0.26 mmol) in THF (50 mL) was hydrogenated over platinum oxide (50 mg) at 50 psi H_2 for 2.5 h, filtered through Celite, evaporated, and purified by dry flash chromatography (20−60% EtOAc/hexanes) to give **10g** (75 mg, 73%): mp (Et_2O/pentane) 88−90 °C; ^{1}H NMR ($CDCl_3$) δ 8.58 (br s, 1 H, NH), 7.27 (d, J = 9.5 Hz, 1 H, H-7′), 7.08 (d, J = 2.1 Hz, H-7), 6.97−7.03 (m, 3 H, H-3′, 4′, 6′), 6.88 (d, J = 8.1 Hz, 1 H, H-4), 6.36 (dd, J = 8.1, 2.1 Hz, 1 H, H-5), 3.96−4.06 (m, 2 H, H-2), 3.84 (br s, 2 H, NH_2), 3.81 (s, 3 H, 5′-OCH_3), 3.34−3.46 (m, 2 H, C*H*HCl, H-3), 2.95 (dd, J = 10.2, 9.1 Hz, CH*H*Cl); ^{13}C NMR δ 155.0 (C-5′), 147.6 (C-6), 142.6 (C-7a), 132.0, 129.5, 126.9 (C-2′, 3a′, 7a′), 125.6 (C-4), 121.3 (C-3a), 117.4, 113.2 (C-4′, 6′), 111.2, 107.9 (C-5, 7′), 102.26, 102.23 (C-7, 3′), 55.6 (5′-OCH_3), 54.4 (C-2), 46.7 (CH_2Cl), 42.3 (C-3). Anal. ($C_{18}H_{18}ClN_3O_3S$) C, H, N, Cl.

6-Amino-3-(chloromethyl)-1-[(5-methoxybenzofuran-2-yl)sulfonyl]indoline (10h). A cooled (ice/water) suspension of lithium 5-methoxybenzofuran-2-sulfinate[24] (0.315 g, 1.45 mmol) in dry CH_2Cl_2 (3 mL) was treated with *N*-chlorosuccinimide (0.20 g, 1.45 mmol). The mixture was stirred for 15 min, the cooling bath was removed, and the mixture was stirred a further 15 min. The resulting solution of crude sulfonyl chloride was filtered through Celite, and the Celite was washed with dry CH_2Cl_2 (4 mL). Deprotected **11** (as the free base, 0.205 g, 0.96 mmol) and *N*-methylimidazole (0.15 mL, 1.88 mmol) were added to the filtrate. The mixture was stirred for 18 h, diluted with 0.5 M aqueous HCl, and extracted with EtOAc (×3). The combined organic phases were washed with 0.5 M aqueous HCl (×1), water (×2), and saturated NaCl solution, dried ($MgSO_4$), and concentrated to a volume of 4 mL. Addition of hexanes (12 mL) gave a precipitate that was crystallized from MeOH to give 3-(chloromethyl)-1-[(5-methoxybenzofuran-2-yl)sulfonyl]-6-nitroindoline **(12h)** (0.354 g, 87%): mp 141.5−142.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.17 (d, J = 2.1 Hz, 1 H, H-7), 8.00 (dd, J = 8.4, 2.1 Hz, 1 H, H-5), 7.84 (d, J = 0.7 Hz, 1 H, H-3′), 7.64 (d, J = 8.4 Hz, 1 H, H-4), 7.56 (d, J = 9.2 Hz, 1 H, H-7′), 7.26 (d, J = 2.6 Hz, 1 H, H-4′), 7.10 (dd, J = 9.2, 2.6 Hz, 1 H, H-6′), 4.38 (dd, J = 9.5, 9.5 Hz, 1 H, H-2), 4.07 (dd, J = 9.5, 5.9 Hz, 1 H, H-2), 4.04 (dddd, J = 9.5, 5.9, 5.3, 3.7 Hz, 1 H, H-3), 3.96 (dd, J = 11.1, 3.7 Hz, 1 H, C*H*HCl), 3.90 (dd, J = 11.1, 5.3 Hz, 1 H, CH*H*Cl), 3.77 (s, 3 H, 5′-OCH_3); ^{13}C NMR δ 156.4 (C-5′), 150.4 (C-7a′), 148.0 (C-6), 146.6 (C-2′), 142.0 (C-7a), 139.5 (C-3a), 126.4 (C-4), 126.0 (C-3a′), 119.7 (C-5), 118.2 (C-6′), 115.1 (C-3′), 113.0 (C-7′), 107.8 (C-7), 104.4 (C-4′), 55.6 (5′-OCH_3), 53.6 (C-2), 46.3 (CH_2Cl), 40.9 (C-3). Anal. ($C_{18}H_{15}N_2O_6S$) C, H, N, Cl.

A solution of **12h** (0.15 g, 0.355 mmol) in THF (30 mL) was hydrogenated over platinum oxide (60 mg) at 50 psi H_2 for 2 h, filtered through Celite, evaporated, and purified by dry flash chromatography (20−50% EtOAc/hexanes) to give **10g** (60 mg, 43%): mp (Et_2O/pentane) 60−62 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (dd, J = 9.9, 0.8 Hz, 1 H, H-7′), 7.46 (d, J = 0.8 Hz, H-3′), 7.05−7.02 (m, 2 H, H-4′,6′), 6.93 (d, J = 2.1 Hz, 1 H, H-7), 6.90 (d, J = 8.1 Hz, 1 H, H-4), 6.33 (dd, J = 8.1, 2.1 Hz, 1 H, H-5), 4.28−4.15 (m, 2 H, H-2), 3.83 (s, 3 H, 5′-OCH_3), 3.77 (br s, 2 H, NH_2), 3.57−3.47 (m, 2 H, C*H*HCl, H-3), 3.28−3.21 (m, 1 H, CH*H*Cl); ^{13}C NMR δ 156.8 (C-5′), 150.8 (C-7a′), 148.8 (C-6), 147.7 (C-2′), 142.1 (C-7a), 126.2 (C-3a′), 125.5 (C-4), 120.9 (C-3a), 117.7 (C-6′), 113.6 (C-3′), 113.0 (C-7′), 110.8 (C-5), 103.9 (C-4′), 101.7 (C-7), 55.9 (5′-OCH_3), 54.8 (C-2), 46.7 (CH_2Cl), 42.3 (C-3). Anal. ($C_{18}H_{17}ClN_2O_4S$) C, H, N.

Aqueous Solubilities. Solids were added to 0.1 M phosphate buffer, pH 7.0, and the suspensions were sonicated for 5 min at room temperature and then centrifuged for 5 min. The supernatants were analyzed by HPLC, and concentrations were determined from a standard curve constructed from HPLC of a series of known concentrations of the compounds in acetonitrile. Determinations were repeated three times and averaged.

Growth Inhibition Assay. Cell lines were maintained as monolayers in exponential phase growth using α-MEM containing fetal bovine serum (5% v/v) without antibiotics. Drug stock solutions were stored frozen in DMSO and diluted into culture medium (with adjustment of pH to 7.4 under 5% CO_2 if necessary) immediately before use to give final DMSO concentrations of <1%. Drug concentrations were checked routinely by spectrophotometry in 0.1 N HCl. Growth inhibitory potency under aerobic conditions was determined using log-phase cultures in 96-well plates. Cultures were initiated using 200 AA8 cells, 300 UV4 cells, 50 EMT6 cells, or 600 SKOV3 cells in 50 μL of medium per well. After 24 h, drugs were added in culture medium adjusted to final pH values of 7.4, and cultures were incubated at 37 °C in a 5% CO_2 incubator for 4 h. Cultures were then washed thoroughly with fresh medium and grown for a further 4 days (5 days for SKOV3) in 150 μL of medium, and cell density was then determined by staining with methylene blue.[30] The IC_{50} was calculated as the drug concentration providing 50% inhibition of growth relative to controls on the same multiwell plate.

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