5-Amino-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indoles: Relationships between Structure and Cytotoxicity for Analogues Bearing Different DNA Minor Groove Binding Subunits

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A series of 5-amino-*seco*-CBI compounds, designed for use as effectors for prodrugs, were prepared to study structure−activity relationships for the cytotoxicity of side chain analogues. Compounds were prepared by coupling 1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole to appropriate carboxylic acids, followed by nitro group reduction, or by coupling suitable 5-amino-protected indolines to α,β-unsaturated acids, followed by deblocking. These AT-specific DNA alkylating agents were evaluated for cytotoxicity in a series of tumor cell lines (AA8, UV4, EMT6, SKOV3). For those analogues bearing an indolecarbonyl side chain, the 5′-methoxy derivative was the most cytotoxic (IC_{50} 1.3 nM in AA8 cells, 4 h exposure), comparable to that of the parent CBI-TMI (5′,6′,7′-trimethoxyindole) derivative (IC_{50} 0.46 nM in the above assay). A subset of solubilized derivatives bearing $O(CH_2)_2NMe_2$ substituents were about 10-fold less potent. For compounds containing an acryloyl linker in the side chain, the 4′-methoxycinnamoyl derivative proved the most cytotoxic (IC_{50} 0.09 nM in the above assay). A number of these 5-amino-*seco*-CBI-TMI analogues (including the solubilized compounds) are of interest both as cytotoxins and as components of amine-based prodrugs designed for tumor-specific activation.

The cyclopropanoindolinone class of DNA alkylating agents are of current interest as cytotoxic anticancer drugs.[1−4] Both the natural products such as duocarmycin SA (**1**)[2] and the simpler synthetic analogues such as CI-TMI (**2**)[5] and CBI-TMI (**3**)[5] are extremely cytotoxic against a variety of cell lines, with some of the latter class having IC_{50}s in the low picomolar range. They possess a novel mechanism of action that involves highly sequence-specific alkylation at adenine N-3 sites in AT-rich regions.[5−7] The open-chain phenol *seco* forms of these agents [e.g., *seco*-CI-TMI (**4**) and *seco*-CBI-TMI (**5**)] have similar potencies[8,9] to the parent cyclopropanoindolinones, and undergo rapid ring closure to them. A number of these compounds have been evaluated clinically, including the CPI analogue adozelesin (**6**)[10] and the carbamate-type prodrugs carzelesin (**7**)[11] and KW-2189 (**8**).[12] Both **7** and **8** are prodrugs of the corresponding phenolic *seco* compounds and undergo rapid and nonspecific hydrolysis to the phenols by plasma esterases (Chart 1).[11,12]

Such extremely potent compounds are also of interest as potential effector components in tumor-specific prodrugs, for applications such as ADEPT and GDEPT.[13] However, as shown above[11,12] and elsewhere, ester and other[14] types of prodrugs of phenols are prone to rapid, nonspecific hydrolysis. We have thus been interested in amino analogues of the phenolic *seco* forms of cyclopropanoindolinones and have recently reported syntheses of both 6-amino-*seco*-CI-TMI (**9**)[15,16] and analogues,[16,17] and 5-amino-*seco*-CBI-TMI (**10a**).[18,19] While the racemic amino-*seco*-CI-TMI (**9**) was considerably less potent than the corresponding racemate of phenol **4** (IC_{50}s 320 and 6 nM respectively, AA8 cells, 4 h exposure),[15] the amino-*seco*-CBI-TMI [(+)-**10a**] showed high cytotoxic potency, being very similar to that of the corresponding phenol **5** (IC_{50}s both 0.21 nM in the above assay).[19] Previous work[5] with analogues of the structurally related antibiotic (+)-CC-1065 showed that modification of the side chain attached to the alkylating subunit can influence sequence selectivity of DNA binding and toxicity, as well as improving antitumor effectiveness. It has been suggested[5] that that the delayed fatal toxicity in mice observed with (+)-CC-1065 is due in part to the strong noncovalent binding provided by the side chain, which renders DNA alkylation irreversible, and may be overcome by side chains that allow stable but reversible adduct formation.

We now report the synthesis of a series of amino-*seco*-CBI analogues (**10a**−**10r**), designed to explore structure−activity relationships for cytotoxicity with varying DNA binding side chains.

Chemistry

We have previously reported the syntheses of the racemate[18] and enantiomers[19] of **10a**. The 5-amino-3-(chloromethyl)benzindolines (**10c**−**10k** and **10n**) of Table 1 were prepared similarly, from the key NBOC intermediate **11** (Scheme 1). NBOC deprotection of **11** in HCl-saturated dioxane gave the unstable amine **12**, which was coupled with the required carboxylic acid side chains using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl), to give the nitro compounds **13**. Examples **13c**−**13j** were then reduced with $PtO_2 \cdot xH_2O/H_2$ to give amines **10c**−**10j**. The mesylate analogue **10b** was prepared from the known[19] intermediate **14** via the nitro compound **13b** (Scheme

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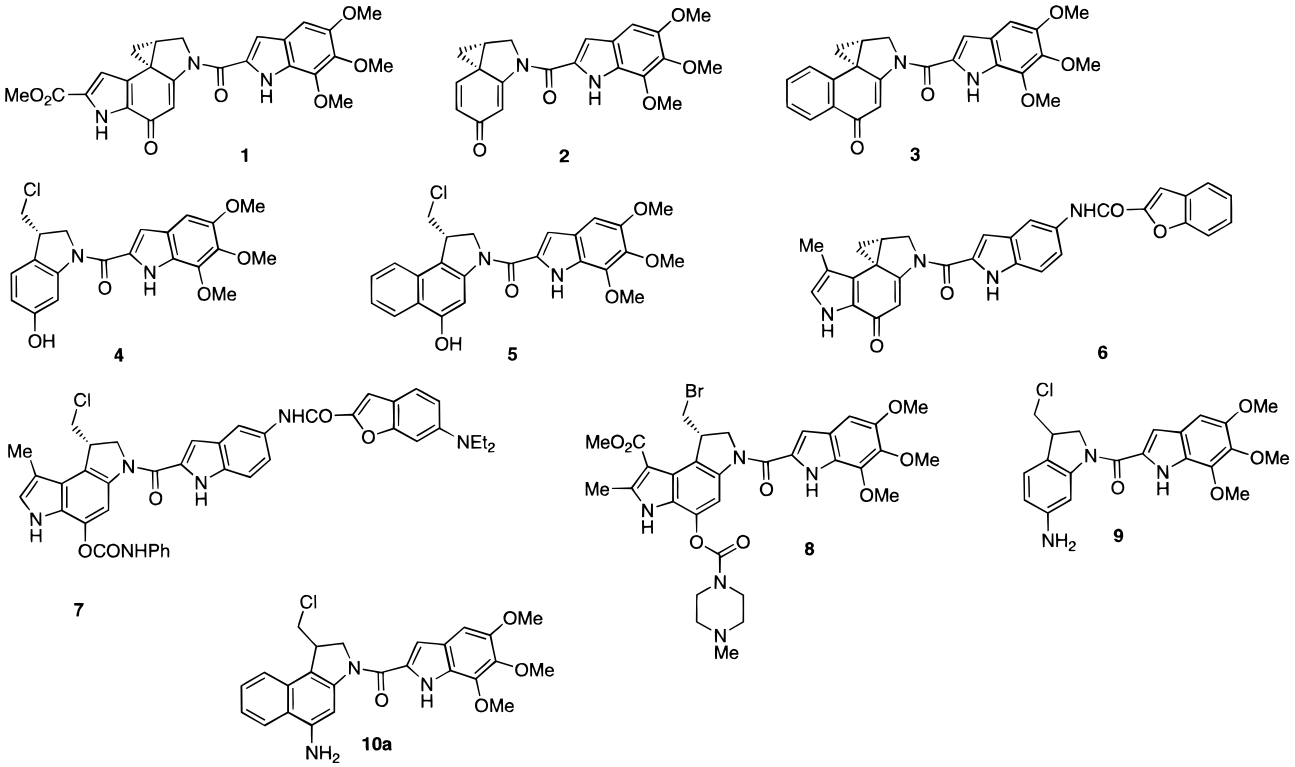
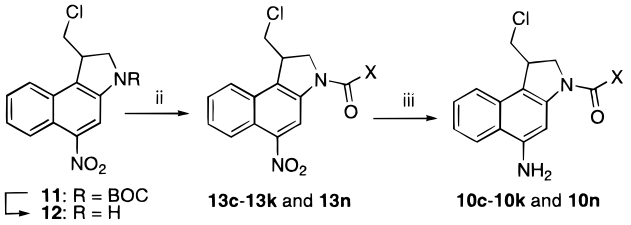
Chart 1

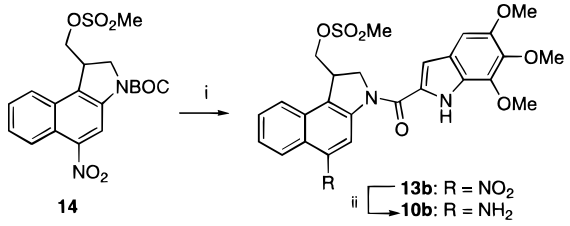


Scheme 1[a]



[a] Reagents and conditions: (i) HCl-satd. dioxane/20 °C/2 h; (ii) X-CO_2H/EDCI·HCl/DMA/20 °C/4 h; (iii) PtO_2/H_2/THF, or Raney nickel/H_2/EtOAc or Fe/H^+.

Scheme 2[a]



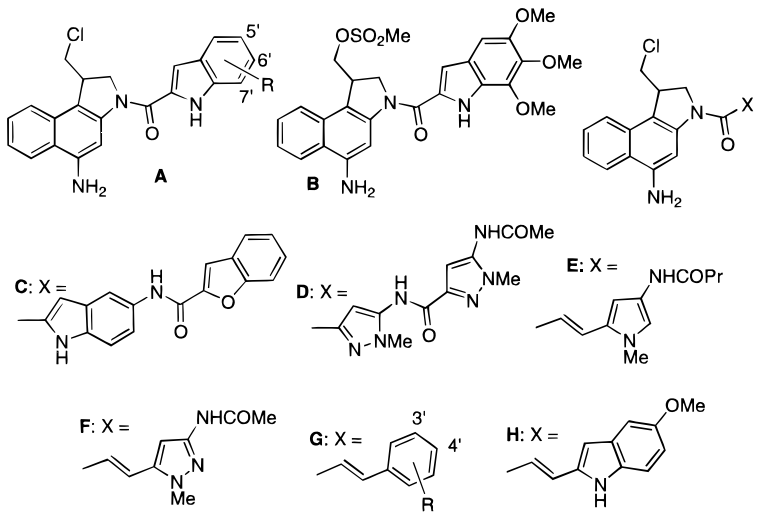
[a] Reagents and conditions: (i) HCl/dioxane/20 °C/2 h, then 5,6,7-triOMeindole-2-carboxylic acid/EDCI·HCl/DMA/20 °C/2.5 h; (ii) PtO_2/H_2/THF.

2). In general it was found that catalytic reduction of nitro compounds **13** containing an acryloyl linker gave extremely low yields of the required amines **10**, due to concomitant saturation of the double bond.

The pyrroleacryloyl analogue **10k** was prepared by Raney nickel reduction of the nitro compound **13k**, but in only 10% yield, while Fe/H^+ reduction of **13n** gave the cinnamoyl analogue **10n** in 54% yield (Scheme 1). Some of the required amines **10** were therefore prepared by other routes. In one alternative method (Scheme 3), the 5-nitro-NBOC derivative **11** was catalytically reduced to give amine **15**, and this was converted to the NFMOC compound **16**. Selective NBOC deprotection gave the unstable amine **17**, which was then coupled with the required acids to give intermediates **18**−**20**. These were deblocked in anhydrous base (piperidine/DMF) to give the target compounds **10l**, **10m**, and **10r**. In a variant of this (Scheme 4), amine **15** was protected as the NALLOC derivative **23**, and then NBOC was deprotected to give amine **24**. EDCI-induced coupling of this with the zwitterionic acid **22** gave **25**, and subsequent palladium-based removal of the ALLOC group with $Pd(PPh_3)_4$ gave the desired **10q**. Alternatively (Scheme 5), **12** was protected as the $NCOCF_3$ derivative **26**. This was reduced (PtO_2/H_2/benzene) to **27**, and then the 5-amino group was BOC-protected to give **28**. Hydrolysis of the $NCOCF_3$ function with Cs_2CO_3, followed by immediate coupling of the resulting unstable amine with cinnamic acids gave the intermediates **29** and **30**, which were NBOC-deprotected to give **10o** and **10p**.

The acids for **10b**, **10c**, **10e**−**10i**, **10k**, and **10m**−**10p** were commercially available or were prepared by reported methods (see Experimental Section). The acid **22** required for **10q** was prepared, as outlined in Scheme 4, by etherification of methyl (*E*)-4-hydroxycinnamate to give **21**, followed by ester group hydrolysis. The indole acid **46** for **10d** was prepared from the known[20] amine **44** via intermediate **45** (Scheme 6). The dipyrazole acid **34** for **10j** was prepared as shown in Scheme 7. NCBZ deprotection of the known[21] ester **31** gave amine **32**, which was acetylated to provide **33**, then subjected to ester hydrolysis. The pyrazoleacrylic acid **40** for **10l** was synthesized from the known[22] aminopyrazole **35** (Scheme 8). N-Acetylation gave **36**, which was hydrolyzed to acid **37**. Imidazolide formation followed by $NaBH_4$ reduction gave alcohol **38**, which was oxidized (MnO_2) to aldehyde **39**. Condensation of this with malonic acid then gave

Table 1. Cytotoxicity of 5-Amino-*seco*-CBI Analogues



				IC_{50}[a] (nM)			
no.	form.	R	ref/mp (°C)	AA8	UV4	EMT6	SKOV3
(±)-**10a**	A	5′,6′,7′-triOMe	ref 19	0.46 ± 0.05	0.29 ± 0.02	0.27 ± 0.03	1.04 ± 0.11
(−)-**10a**	A	5′,6′,7′-triOMe	ref 19	14 ± 3	2.7 ± 0.2	7.0 ± 0.6	7.9 ± 1.6
(+)-**10a**	A	5′,6′,7′-triOMe	ref 19	0.21 ± 0.03	0.14 ± 0.01	0.13 ± 0.01	0.54 ± 0.04
10b	B		>260	0.48 ± 0.18	0.46 ± 0.20	0.40 ± 0.16	1.20 ± 0.12
10c	A	5′-NH_2	>300	2.5 ± 1.2	1.1 ± 0.6	0.83 ± 0.27	3.0 ± 0.3
10d	A	5′-NHCOMe	>300	12.5 ± 0.2	7.6 ± 0.7	5.2 ± 2.3	17.3 ± 0.2
10e	A	5′-OMe	250−255	1.3 ± 0.1	0.84 ± 0.01	0.98 ± 0.06	1.86 ± 0.21
10f	A	5′-O$(CH_2)_2NMe_2$	>250	4.1 ± 0.8	1.7 ± 0.3	1.3 ± 0.2	7.0 ± 0.9
10g	A	5′-OMe, 6′-O$(CH_2)_2NMe_2$	130−133	3.6 ± 0.9	2.1 ± 0.2	2.0 ± 0.2	5.3 ± 0.4
10h	A	5′-OMe, 7′-O$(CH_2)_2NMe_2$	109−111	3.7 ± 1.4	1.9 ± 0.4	1.9 ± 1.0	4.2 ± 1.2
10i	C		>300	2.0 ± 0.3	1.5 ± 0.1	1.3 ± 0.1	3.5 ± 0.7
10j	D		>250	374 ± 20	253 ± 65	212 ± 120	49 ± 9
10k	E		245−250	31 ± 8	16 ± 5	5.9 ± 1.7	22
10l	F		>300	10.7 ± 1.5	5.4 ± 0.5	4.9 ± 1.4	13.0 ± 2.4
10m	G	3′-NHCOMe	>250	2.7 ± 1.6	1.5 ± 0.4	0.86 ± 0.31	1.5 ± 0.4
10n	G	3′-OMe	>200	0.37 ± 0.01	0.42 ± 0.13	0.63 ± 0.07	0.68 ± 0.05
10o	G	4′-NHCOMe	>250	2.6 ± 0.5	1.4 ± 0.2	1.2 ± 0.3	2.7 ± 0.3
10p	G	4′-OMe	114−116	0.090 ± 0.008	0.058 ± 0.002	0.089 ± 0.007	0.24 ± 0.03
10q	G	4′-O$(CH_2)_2NMe_2$	147−150	1.5 ± 0.3	0.56 ± 0.13	0.63 ± 0.07	1.9
10r	H		>250	0.28 ± 0.03	0.22 ± 0.02	0.23 ± 0.01	0.48 ± 0.01

[a] IC_{50}; concentration of drug to reduce cell numbers to 50% of controls, 4−5 days after a 4 h drug exposure. Average of 2−5 determinations ± SEM.

40. Finally, the indoleacrylic acid **43** for **10r** was prepared (Scheme 9) by Wittig olefination of the known[23] indole aldehyde **41** to give the acrylate ester **42**, followed by hydrolysis of this with Cs_2CO_3.

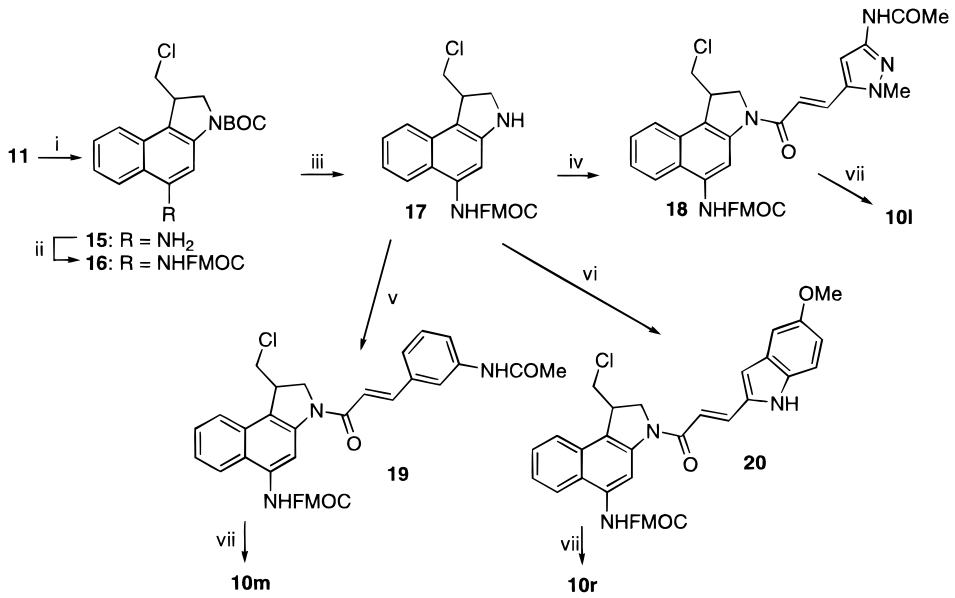
Results and Discussion

The amino-*seco*-CBI compounds were evaluated for growth inhibitory potency (measured as IC_{50} values for a 4 h drug exposure) in a series of tumor cell lines (Table 1). These included two Chinese hamster ovary lines: the wild-type AA8 and the repair-defective ERCC-1 mutant UV4, which is hypersensitive to agents that form bulky DNA adducts[24] and particularly so to DNA cross-linkers.[25] A murine mammary carcinoma line EMT6, and a human ovarian line SKOV3 were also used. Overall, as seen previously[17] with 6-amino-*seco*-CI derivatives, there were no large differences in the sensitivity of the wild-type cell lines AA8, EMT6, and SKOV3, but most of the compounds were slightly (mean 2.0-fold) more cytotoxic in the UV4 line than in AA8, in line with a mode of action involving DNA monoalkylation.[25] These differentials for UV4 relative to AA8 are lower than for the 6-amino-*seco*-CI compound **9** (AA8/UV4 ratio 6.8 ± 0.6), suggesting that the CBI adducts are less efficiently repaired than CI adducts by ERCC1-dependent nucleotide excision repair, which might contribute to the higher cytotoxic potency of the CBI compounds.

The amino-*seco*-CBI compounds are much more potent (up to 1000-fold) than the corresponding amino-*seco*-CI analogues.[17] It was shown previously[19] that the (+)- and (−)-enantiomers of **10a** had widely differing potencies (IC_{50}s of 0.21 and 14 nM, respectively, in AA8), similar to those (IC_{50}s of 0.21 and 67.1) for the (+)- and (−)-enantiomers of the corresponding phenolic *seco* compounds (**5** and its enantiomer).[26] For both **10a** and **5**, the cytotoxicity of the racemate was approximately half that of the more potent enantiomer, indicating that the less toxic enantiomer does not significantly interfere with cytotoxicity. Initial structure−activity relationships for side chain variations were therefore explored with the more readily available racemates.

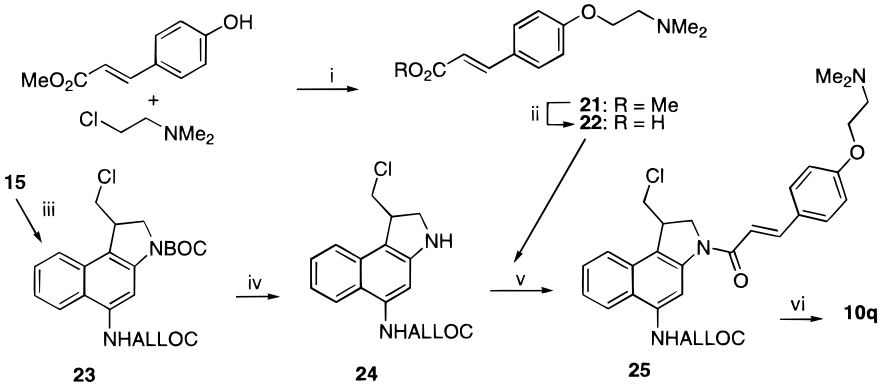
The first set of DNA binding side chains studied (compounds **10a**−**10i**) possessed substituted indolecarbonyl side chains and were variants of the 5′,6′,7′-trimethoxyindole (TMI) subunit present in the natural

Scheme 3[a]



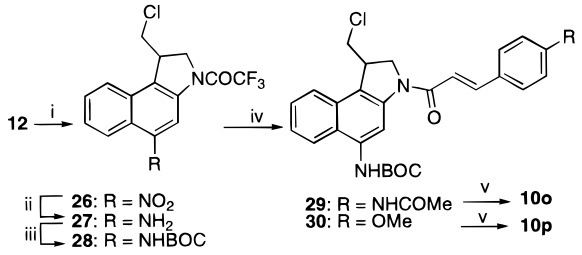
[a] Reagents and conditions: (i) PtO_2/H_2/THF; (ii) 9-fluorenylmethyl chloroformate/CH_2Cl_2/N-Meimidazole/20 °C/4.5 h; (iii) HCl/dioxane/5 °C/4 h; (iv−vi) **40**, (*E*)-3-(acetylamino)cinnamic acid or **43**/EDCI·HCl/DMA/20 °C/4 h; (vii) piperidine/DMF/20 °C/20 min.

Scheme 4[a]



[a] Reagents and conditions: (i) NaH/DMF/PhMe; (ii) NaOH/aq MeOH/reflux; (iii) allyl chloroformate/pyridine/−5 to 20 °C/2 h; (iv) HCl/dioxane/5 °C/3 h; (v) **22**/EDCI·HCl/DMA; (vi) $Pd(PPh_3)_4/PPh_3$/morpholine.

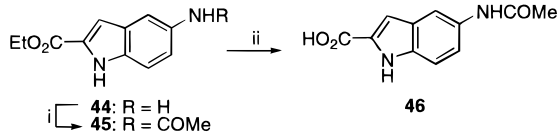
Scheme 5[a]



[a] Reagents and conditions: (i) $(CF_3CO)_2O$/pyridine/0−20 °C; (ii) PtO_2/H_2/benzene; (iii) $(BOC)_2O$/dioxane/65 °C/12 h; (iv) Cs_2CO_3/N-Mepyrrolidinone/water/20 °C/45 min, then (*E*)-4-(acetylamino)-cinnamic acid/EDCI·HCl/DMA/DMA·HCl, or (*E*)-4-methoxycinnamoyl chloride/pyridine/DMAP; (v) HCl/dioxane/20 °C/10 min.

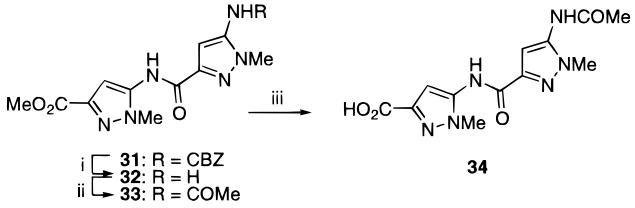
products. Previous work in both the duocarmycin[27] and amino-*seco*-CI[17] series showed that a single 5′-OMe group on the indole side chain was sufficient to retain potency. This was also seen in the present CBI series, with the 5′-OMe analogue **10e** showing IC_{50}s in the cell line panel only about 3-fold higher than the parent compound (±)-**10a**. The 5′-NH_2 analogue **10c** was also slightly less potent than ±-**10a**, while the 5′-NHCOMe analogue **10d** was significantly less effective. Derivatives **10f**−**10h**, bearing cationic side chains at the 5′-, 6′-, and 7′-positions, respectively, were about 5−10-fold less cytotoxic than (±)-**10a** in the cell panel. The analogue **10i**, bearing the adozelesin side chain, was

Scheme 6[a]



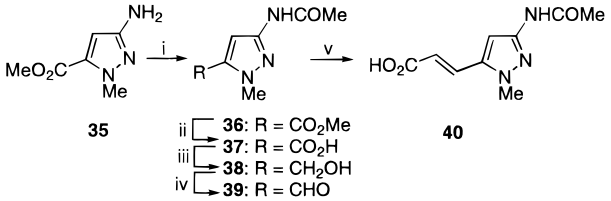
[a] Reagents and conditions: (i) Ac_2O/pyridine/20 °C; (ii) Cs_2CO_3/EtOH/H_2O/reflux.

Scheme 7[a]



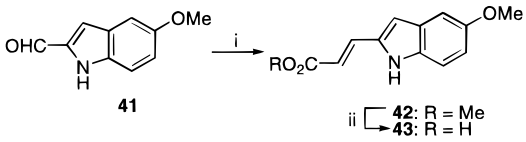
[a] Reagents and conditions: (i) Pd-C/H_2/MeOH; (ii) MeCOCl/THF/reflux/30 min; (iii) Cs_2CO_3/water/reflux/2 h.

Scheme 8[a]



[a] Reagents and conditions: (i) MeCOCl/THF/reflux; (ii) Cs_2CO_3/water/reflux; (iii) CDI/THF, then $NaBH_4$/water; (iv) MnO_2/EtOAc/reflux; (v) malonic acid/pyridine/piperidine/100 °C.

Scheme 9[a]



[a] Reagents and conditions: (i) $Ph_3P{=}CHCO_2Me$/PhH/reflux; (ii) Cs_2CO_3/aq MeOH/reflux.

considerably less potent than (±)-**10a**. This is somewhat surprising, since studies with various cyclopropylindoline alkylating subunits, including CBI,[5] show this larger DNA-binding subunit usually moderately increases potency.

The dipyrazole derivative **10j** possesses a relatively hydrophilic side chain that was used originally[21] in the design of a more stable analogue of the dipyrrolic AT-selective minor groove binder netropsin. The side chain of **10j** was designed to avoid an NMe group adjacent to the linking carbonyl function, as this was expected from the results of a previous study[20] to lower DNA binding. However, **10j** unexpectedly proved much less cytotoxic (by about 800-fold) than (±)-**10a** and was the least potent analogue of the series.

The second set of compounds studied (**10k**−**10r**) possessed an acryloyl linker in their DNA binding side chain. The pyrroleacryloyl and pyrazoleacryloyl analogues **10k** and **101** were considerably less potent than the parent (±)-**10a** (IC_{50}s in AA8 cells of 31, 9, and 0.46 nM, respectively). The reduced potency of **10k** is in contrast to a previous finding,[28] in which the pyrroleacrylolyl side chain was claimed to confer extraordinary potency on CPI analogues.

Previous work[29] on duocarmycin derivatives bearing cinnamoyl side chains showed that such agents were also potent cytotoxins. In particular, among the 4′-alkoxy derivatives, a 4′-OMe was the most cytotoxic, with larger alkoxy groups causing a decrease in potency. In the present study, cinnamoyl analogues also proved to be effective cytotoxins. While the 3′- and 4′-NHCOMe analogues **10m** and **10o** were somewhat less potent than the parent TMI compound (±)-**10a**, the 3′-OMe compound **10n** had comparable activity, and the 4′-OMe analogue **10p** was the most potent of the compounds studied (IC_{50} 0.09 nM in AA8). The corresponding 4′-$O(CH_2)_2NMe_2$ analogue **10q** proved the most potent of the cationic solubilized compounds although again showed a lower cytotoxicity than the corresponding OMe derivative. Finally, the 5′-methoxyindoleacryloyl derivative **10r** provided a direct comparison with the 5′-methoxyindolecarbonyl compound **10e** and proved significantly more cytotoxic (IC_{50}s in AA8 cells of 0.3 and 1.3 nM, respectively).

Toxicity of the above compounds is currently being investigated in C3H mice. Intraperitoneal doses of (±)-**10a** at above 5 μmol/kg resulted in death within 2−3 weeks, but at lower doses a delayed toxicity was observed. Affected animals showed distended abdomens, with extensive peritoneal masses at necropsy. Histologically, the peritoneal lesions showed inflammation and fibrosis surrounding normal bowel, with signs of fatty necrosis, presumably as a result of local toxicity at the site of injection. At 3.16 μmol/kg, 3/10 mice died between day 21 and day 30, and 6/7 of the remaining mice showed large peritoneal masses by day 60. At 2.37 μmol/kg, all mice survived to day 60, at which time 3/6 showed peritoneal masses. The less cytotoxic enantiomer (−)-**10a** showed similar toxicity: at 2.37 μmol/kg 2/6 mice died before day 60, and two of the four survivors showed peritoneal lesions. However, while the more cytotoxic enantiomer (+)-**10a** also gave 2/6 deaths before day 60 at this dose, all the surviving animals were normal at necropsy. These preliminary data indicate that (+)-**10a**, despite its greater cytotoxicity potency in culture, is not the more toxic enantiomer in mice and suggest the possibility of dissociating cytotoxicity against tumor cells from chronic host toxicity within this series.

Conclusions

These results show that the 5-amino-*seco*-CBI alkylating subunit remains a very potent cytotoxin (equivalent to the corresponding phenol moiety) when substituted with a range of DNA binding side chains of varying size and lipophilicity. TMI and 5′-methoxyindole were the best of the carbonyl-linked side chains, providing the parent TMI compound (±)-**10a** and **10e**, respectively, with the solubilized derivatives (**10f**−**10h**) being about 10-fold less potent. The best acryloyl-containing analogues were those with cinnamoyl side chains. The 4′-OMe derivative **10p** was the most cytotoxic of all the compounds studied (about 5-fold more potent than (±)-**10a**). A number of these latter agents, including the solubilized analogues, are being explored as potent effectors for prodrugs.[12]

Experimental Section

Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrothermal 2300 melting point apparatus. NMR spectra were obtained on a Bruker DRX-400 spectrometer and are referenced to Me_4Si. Thin-layer chromatography was carried out on aluminum-backed silica gel (Merck 60 F_{254}) or alumina plates. Flash column chromatography was carried out on Merck silica gel (230−400 mesh) or alumina. Petroleum ether refers to the fraction boiling at 40−60 °C. Mass spectra were determined using a VG 7070 spectrometer at nominal 5000 resolution. Compounds for biological testing were judged to be >96% pure by reverse-phase HPLC analysis with diode array detection.

5-Amino-1-[(methanesulfonyloxy)methyl]-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (10b). A solution of 3-(*tert*-butyloxycarbonyl)-1-[(methanesulfonyloxy)methyl]-5-nitro-1,2-dihydro-3*H*-benz[*e*]-indole[19] (**14**) (265 mg, 0.63 mmol) was stirred in HCl-saturated dioxane (12 mL) at 20 °C for 2 h and then evaporated to dryness under reduced pressure below 30 °C. 5,6,7-Trimethoxyindole-2-carboxylic acid (165 mg, 0.66 mmol), EDCI·HCl (301 mg, 1.57 mmol), and DMA (2.5 mL) were then added, and the mixture was stirred at 20 °C for 2.5 h. Addition of dilute $KHCO_3$ precipitated a solid which was collected, washed

well with water, and chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc (4:1) and crystallization of the product from EtOAc/petroleum ether gave 1-[(methanesulfonyloxy)-methyl]-5-nitro-3-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (**13b**) (264 mg, 76%): mp 213.5−214.5 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.61 (d, J = 1.6 Hz, 1 H, NH), 9.11 (s, 1 H, H-4), 8.36 (d, J = 8.7 Hz, 1 H, H-6), 8.21 (d, J = 7.6 Hz, 1 H, H-9), 7.82−7.71 (m, 2 H, H-7,8), 7.17 (d, J = 2.0 Hz, 1 H, H-3′), 6.98 (s, 1 H, H-4′), 4.88 (t, J = 9.8 Hz, 1 H, H-2), 4.66−4.46 (m, 4 H, H-1,2, CH_2O), 3.94 (s, 3 H, $ArOCH_3$), 3.83 (s, 3 H, $ArOCH_3$), 3.81 (s, 3 H, $ArOCH_3$), 3.06 (s, 3 H, SO_2CH_3). Anal. ($C_{26}H_{25}N_3O_9S$) C, H, N.

A solution of **13b** (162 mg, 0.29 mmol) in THF (25 mL) was hydrogenated over PtO_2 at 55 psi for 2 h. After removal of the catalyst, the solution was concentrated to a small volume under reduced pressure below 25 °C and diluted with ^{i}Pr$_2$O to give a crude product. This was purified by precipitation from a EtOAc solution with petroleum ether at 20 °C to give **10b** (116 mg, 76%): mp >260 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.41 (d, J = 1.6 Hz, 1 H, NH), 8.08 (d, J = 8.5 Hz, 1 H, H-6), 7.76 (d, J = 8.3 Hz, 1 H, H-9), 7.67 (s, 1 H, H-4), 7.49 (t, J = 7.6 Hz, 1 H, H-8), 7.30 (t, J = 7.6 Hz, 1 H, H-7), 7.04 (d, J = 2.0 Hz, 1 H, H-3′), 6.96 (s, 1 H, H-4′), 6.15 (v br s, 2 H, NH_2), 4.66 (dd, J = 10.9, 8.5 Hz, 1 H, H-2), 4.47 (dd, J = 9.9, 3.4 Hz, 1 H, H-2), 4.41 (d, J = 10.9 Hz, 1 H, C*H*HO), 4.17 (t, J = 9.2 Hz, 1 H, CH*H*O), 4.13−4.04 (m, 1 H, H-1), 3.94 (s, 3 H, $ArOCH_3$), 3.82 (s, 3 H, $ArOCH_3$), 3.80 (s, 3 H, $ArOCH_3$), 3.07 (s, 3 H, SO_2CH_3). Anal. ($C_{26}H_{27}N_3O_7S$) C, H, N.

5-Amino-3-[(5-aminoindol-2-yl)carbonyl]-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (10c). 3-(*tert*-Butyloxycarbonyl)-1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole[18,19] (**11**) (280 mg, 0.77 mmol) was stirred in HCl-saturated dioxane (10 mL) at 20 °C for 2 h and then evaporated to dryness under reduced pressure below 30 °C to give crude 1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**12**) as the hydrochloride salt. 5-Nitroindole-2-carboxylic acid[30] (167 mg, 0.81 mmol), EDCI·HCl (370 mg, 1.93 mmol), and DMA (3 mL) were then added, and the mixture was stirred at 20 °C for 4 h. Addition of dilute $KHCO_3$ precipitated a yellow solid which was collected, washed well with water, and recrystallized from THF to give 1-(chloromethyl)-5-nitro-3-[(5-nitroindol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (**13c**) (282 mg, 81%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.56 (s, 1 H, NH), 9.14 (s, 1 H, H-4), 8.74 (d, J = 2.2 Hz, 1 H, H-4′), 8.35 (dd, J = 7.0, 2.7 Hz, 1 H, H-6), 8.24 (dd, J = 6.8, 2.7 Hz, 1 H, H-9), 8.12 (dd, J = 9.1, 2.3 Hz, 1 H, H-6′), 7.80−7.72 (m, 2 H, H-7,8), 7.64 (d, J = 9.1 Hz, 1 H, H-7′), 7.58 (s, 1 H, H-3′), 4.96 (t, J = 10.1 Hz, 1 H, H-2), 4.71 (dd, J = 10.8, 2.3 Hz, 1 H, H-2), 4.68−4.61 (m, 1 H, H-1), 4.18−4.09 (m, 2 H, CH_2Cl). Anal. ($C_{22}H_{15}ClN_4O_5$) C, H, N, Cl.

A solution of **13c** (170 mg, 0.38 mmol) in THF (120 mL) was hydrogenated over PtO_2 at 50 psi for 2 h. After removal of the catalyst, the solution was concentrated to a small volume under reduced pressure below 25 °C and diluted with ^{i}Pr$_2$O to give **10c** (136 mg, 92%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.23 (d, J = 1.4 Hz, 1 H, NH), 8.07 (d, J = 8.4 Hz, 1 H, H-6), 7.75 (d, J = 8.2 Hz, 1 H, H-9), 7.70 (s, 1 H, H-4), 7.45 (t, J = 7.5 Hz, 1 H, H-8), 7.27 (t, J = 7.7 Hz, 1 H, H-7), 7.21 (d, J = 8.6 Hz, 1 H, H-7′), 6.88 (d, J = 1.8 Hz, 1 H, H-3′), 6.76 (d, J = 1.8 Hz, 1 H, H-4′), 6.68 (dd, J = 8.6, 2.1 Hz, 1 H, H-6′), 5.96 (s, 2 H, 5-NH_2), 4.70 (dd, J = 10.9, 8.9 Hz, 1 H, H-2), 4.64 (br s, 2 H, 5′-NH_2), 4.49 (dd, J = 11.0, 1.6 Hz, 1 H, H-2), 4.15−4.07 (m, 1 H, H-1), 3.97 (dd, J = 11.0, 3.0 Hz, 1 H, C*H*HCl), 3.74 (dd, J = 11.0, 8.0 Hz, 1 H, CH*H*Cl). Anal. ($C_{22}H_{19}ClN_4O$) C, N: H, found 5.5, calculated 4.9%.

3-[[5-(Acetylamino)indol-2-yl]carbonyl]-5-amino-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (10d). Ethyl 5-aminoindole-2-carboxylate[20] (**44**) was treated with Ac_2O/pyridine at 20 °C to give ethyl 5-(acetylamino)indole-2-carboxylate (**45**) (89%): mp (EtOAc/^{i}Pr$_2$O) 216.5−217 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.78 (s, 1 H, indole NH), 9,82 (s, 1 H, NHCO), 8.01 (d, J = 1.6 Hz, 1 H, H-4), 7.37 (d, J = 8.8 Hz, 1 H, H-7), 7.32 (dd, J = 8.9, 1.9 Hz, 1 H, H-6), 7.09 (d, J = 1.5 Hz, 1 H, H-3), 4.33 (q, J = 7.1 Hz, 2 H, CH_2CH$_3$), 2.04 (s, 3 H, COCH_3), 1.43 (t, J = 7.0 Hz, 3 H, CH$_2$CH_3). Anal. ($C_{13}H_{14}N_2O_3$) C, H, N.

Ester **45** was hydrolyzed in a hot 2 N solution of Cs_2CO_3 in aqueous EtOH to give 5-(acetylaminoindole-2-carboxylic acid (**46**) (91%): mp (EtOAc/MeOH 279−280 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 12.81 (br s, 1 H, CO_2H), 11.65 (s, 1 H, indole NH), 9.81 (s, 1 H, NHCO), 7.99 (d, J = 1.5 Hz, 1 H, H-4), 7.35 (d, J = 8.9 Hz, 1 H, H-7), 7.30 (dd, J = 8.9, 1.9 Hz, 1 H, H-6), 7.03 (d, J = 1.6 Hz, 1 H, H-3), 2.04 (s, 3 H, COCH_3). Anal. ($C_{11}H_{10}N_2O_3$) C, H, N.

Similar deprotection of **11** (300 mg, 0.83 mmol) and treatment with **46** (181 mg, 0.83 mmol) and EDCI·HCl (397 mg, 2.07 mmol) in DMA (3 mL) gave 3-[[5-(acetylamino)indol-2-yl]carbonyl]-1-chloromethyl-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13d**) (301 mg, 79%): mp (THF/H_2O) 252−253 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.77 (d, J = 1.2 Hz, 1 H, indole NH), 9.86 (s, 1 H, NHCO), 9.16 (s, 1 H, H-4), 8.35 (dd, J = 7.1, 2.6 Hz, 1 H, H-6), 8.24 (dd, J = 6.8, 2.5 Hz, 1 H, H-9), 8.10 (d, J = 1.3 Hz, H-4′), 7.79−7.70 (m, 2 H, H-7,8), 7.43 (d, J = 8.8 Hz, 1 H, H-7′), 7.35 (dd, J = 8.8, 1.8 Hz, 1 H, H-6′), 7.27 (d, J = 1.8 Hz, 1 H, H-3′), 4.94 (t, J = 10.2 Hz, 1 H, H-2), 4.71 (dd, J = 11.0, 2.3 Hz, 1 H, H-2), 4.66−4.58 (m, 1 H, H-1), 4.13 (d, J = 4.3 Hz, 2 H, CH_2Cl), 2.06 (s, 3 H, COCH_3). Anal. ($C_{24}H_{19}ClN_4O_4$) C, H, N, Cl.

A solution of **13d** (170 mg, 0.37 mmol) in THF (60 mL) was hydrogenated over PtO_2 at 50 psi for 2 h. After removal of the catalyst, the solution was concentrated to a small volume under reduced pressure below 25 °C and diluted with EtOAc/^{i}Pr$_2$O to give **10d** (141 mg, 89%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.61 (d, J = 1.4 Hz, 1 H, indole NH), 9.84 (s, 1 H, NHCO), 8.08 (d, J = 8.5 Hz, 1 H, H-6), 8.05 (d, J = 1.4 Hz, 1 H, H-4′), 7.76 (d, J = 8.2 Hz, 1 H, H-9), 7.71 (s, 1 H, H-4), 7.46 (t, J = 7.5 Hz, 1 H, H-8), 7.42 (d, J = 8.9 Hz, 1 H, H-7′), 7.33 (dd, J = 8.8, 1.9 Hz, 1 H, H-6′), 7.29 (t, J = 7.5 Hz, 1 H, H-7), 7.14 (d, J = 1.7 Hz, 1 H, H-3′), 5.98 (s, 2 H, NH_2), 4.74 (dd, J = 10.8, 9.0 Hz, 1 H, H-2), 4.51 (dd, J = 11.0, 1.6 Hz, 1 H, H-2), 4.17−4.08 (m, 1 H, H-1), 3.97 (dd, J = 11.0, 3.0 Hz, 1 H, C*H*HCl), 3.77 (dd, J = 10.9, 7.8 Hz, 1 H, CH*H*Cl), 2.06 (s, 3 H, CH_3). Anal. ($C_{24}H_{21}ClN_4O_2$) C, H, N, Cl.

5-Amino-1-(chloromethyl)-3-[(5-methoxyindol-2-yl)carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (10e). Similar deprotection of **11** (260 mg, 0.72 mmol) and reaction with 5-methoxyindole-2-carboxylic acid (145 mg, 0.76 mmol) and EDCI·HCl (344 mg, 1.80 mmol) in DMA (3 mL) gave 1-(chloromethyl)-3-[(5-methoxyindol-2-yl)carbonyl]-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13e**) (237 mg, 76%): mp (2 × EtOAc/^{i}Pr$_2$O): 241−243 °C; ^{1}NMR [$(CD_3)_2SO$] δ 11.73 (d, J = 1.3 Hz, 1 H, NH), 9.16 (s, 1 H, H-4), 8.35 (dd, J = 7.2, 2.5 Hz, 1 H, H-6), 8.23 (dd, J = 6.9, 2.4 Hz, 1 H, H-9), 7.79−7.70 (m, 2 H, H-7,8), 7.42 (d, J = 8.9 Hz, 1 H, H-7′), 7.20 (d, J = 1.9 Hz, 1 H, H-3′), 7.17 (d, J = 2.4 Hz, 1 H, H-4′), 6.94 (dd, J = 9.0, 2.4 Hz, 1 H, H-6′), 4.93 (dd, J = 10.6, 9.2 Hz, 1 H, H-2), 4.70 (dd, J = 10.9, 2.4 Hz, 1 H, H-2), 4.65−4.57 (m, 1 H, H-1), 4.18−4.07 (m, 2 H, CH_2Cl), 3.79 (s, 3 H, CH_3). Anal. ($C_{23}H_{18}ClN_3O_4$) C, H, N, Cl.

Reduction of **13e** in THF as for **13d** gave **10e** (95%): mp (THF/H_2O) 250−255 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (d, J = 1.6 Hz, 1 H, NH), 8.08 (d, J = 8.4 Hz, 1 H, H-6), 7.76 (d, J = 8.2 Hz, 1 H, H-9), 7.70 (s, 1 H, H-4), 7.46 (t, J = 7.6 Hz, 1 H, H-8), 7.40 (d, J = 8.8 Hz, 1 H, H-7′), 7.28 (t, J = 7.6 Hz, 1 H, H-7), 7.16 (d, J = 2.4 Hz, 1 H, H-4′), 7.08 (d, J = 1.8 Hz, 1 H, H-3′), 6.91 (dd, J = 8.8, 2.5 Hz, 1 H, H-6′), 5.98 (s, 2 H, NH_2), 4.73 (dd, J = 10.8, 8.9 Hz, 1 H, H-2), 4.51 (dd, J = 10.9, 1.7 Hz, 1 H, H-2), 4.17−4.08 (m, 1 H, H-1), 3.98 (dd, J = 11.0, 3.1 Hz, 1 H, C*H*HCl), 3.78 (s, 3 H, CH_3), 3.75 (dd, J = 11.0, 8.1 Hz, 1 H, CH*H*Cl). Anal. ($C_{23}H_{20}ClN_3O_2$) C, H, N, Cl.

5-Amino-1-(chloromethyl)-3-[[5-[2-(dimethylamino)-ethoxy]indol-2-yl]carbonyl]-1,2-dihydro-3*H*-benz[*e*]-indole (10f). Similar deprotection of **11** (260 mg, 0.72 mmol) and reaction with 5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride[17] (210 mg, 0.74 mmol) and EDCI·HCl (345 mg, 1.80 mmol) in DMA (3 mL), followed by addition of the reaction mixture to saturated $KHCO_3$, gave a crude product. This was purified by precipitation from a CH_2Cl_2

solution with $^{i}Pr_2O$ (2×) to give 1-(chloromethyl)-3-[[5-[2-(dimethylamino)ethoxy]indol-2-yl]carbonyl]-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13f**) (237 mg, 67%): mp 224−227 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.72 (d, J = 1.5 Hz, 1 H, NH), 9.16 (s, 1 H, H-4), 8.35 (dd, 7.2, 2.5 Hz, 1 H, H-6), 8.23 (dd, J = 6.9, 2.5 Hz, 1 H, H-9), 7.79−7.71 (m, 1 H, H-7,8), 7.41 (d, J = 8.9 Hz, 1 H, H-7′), 7.21−7.16 (m, 2 H, H-3′,4′), 6.94 (dd, J = 9.0, 2.4 Hz, 1 H, H-6′), 4.93 (dd, J = 10.6, 9.8 Hz, 1 H, H-2), 4.70 (dd, J = 10.9, 2.4 Hz, 1 H, H-2), 4.65−4.58 (m, 1 H, H-1), 4.18−4.09 (m, 2 H, CH_2Cl), 4.07 (t, J = 5.9 Hz, 2 H, OCH_2), 2.66 (t, J = 5.8 Hz, 2 H, OCH_2CH_2), 2.24 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{26}H_{25}ClN_4O_4$) C, H, N, Cl.

Reduction of **13f** in THF as for **13d** gave **10f** (98%): mp (THF/$^{i}Pr_2O$) >250 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (d, J = 1.4 Hz, 1 H, NH), 8.08 (d, J = 8.5 Hz, 1 H, H-6), 7.76 (d, J = 8.2 Hz, 1 H, H-9), 7.70 (s, 1 H, H-4), 7.46 (t, J = 7.4 Hz, 1 H, H-8), 7.39 (d, J = 8.9 Hz, 1 H, H-7′), 7.28 (t, J = 7.7 Hz, 1 H, H-7), 7.17 (d, J = 2.2 Hz, 1 H, H-4′), 7.07 (d, J = 1.8 Hz, 1 H, H-3′), 6.91 (dd, J = 8.9, 2.4 Hz, 1 H, H-6′), 5.98 (s, 2 H, NH_2), 4.73 (dd, J = 10.6, 9.1 Hz, 1 H, H-2), 4.51 (dd, J = 10.9, 1.4 Hz, 1 H, H-2), 4.16−4.08 (m, 1 H, H-1), 4.06 (t, J = 5.9 Hz, 2 H, OCH_2), 3.98 (dd, J = 10.9, 3.0 Hz, 1 H, C*H*HCl), 3.75 (dd, J = 10.9, 8.1 Hz, 1 H, CH*H*CL), 2.65 (t, J = 5.9 Hz, 2 H, OCH_2CH_2), 2.24 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{26}H_{27}ClN_4O_2$) C, H, N, Cl.

5-Amino-1-(chloromethyl)-3-[[6-[2-(dimethylamino)-ethoxy]-5-methoxyindol-2-yl]carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (10g). Similar deprotection of **11** (261 mg, 0.72 mmol) and reaction with 6-[2-(dimethylamino)ethoxy]-5-methoxy-1*H*-indole-2-carboxylic acid hydrochloride[17] (230 mg, 0.73 mmol) and EDCI·HCl (345 mg, 1.80 mmol), in DMA (3 mL) at 20 °C for 3 h gave a solidified mixture. This was shaken with dilute $KHCO_3$, and the resulting gelatinous solid was collected and chromatographed on alumina-90. Elution with EtOAc/MeOH (10:1) provided a crude product which was recrystallized from EtOAc/$^{i}Pr_2O$, followed by CH_2Cl_2/petroleum ether, to give 1-(chloromethyl)-3-[[6-[2-(dimethylamino)ethoxy]-5-methoxyindol-2-yl]carbonyl]-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13g**) (180 mg, 48%): mp 224−234 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.54 (d, J = 1.6 Hz, 1 H, NH), 9.17 (s, 1 H, H-4), 8.34 (dd, J = 7.5, 2.2 Hz, 1 H, H-6), 8.22 (dd, J = 7.1, 1.8 Hz, 1 H, H-9), 7.79−7.69 (m, 2 H, H-7,8), 7.17 (d, J = 1.6 Hz, 1 H, H-3′), 7.16 (s, 1 H, H-4′ or 7′), 6.99 (s, 1 H, H-4′ or 7′), 4.91 (t, J = 10.2 Hz, 1 H, H-2), 4.68 (dd, J = 10.9, 2.4 Hz, 1 H, H-2), 4.65−4.57 (m, 1 H, H-1), 4.17−4.09 (m, 2 H, CH_2Cl), 4.06 (t, J = 6.0 Hz, 2 H, OCH_2), 3.79 (s, 3 H, OCH_3), 2.69 (t, J = 5.9 Hz, 2 H, OCH_2CH_2), 2.26 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{27}H_{27}ClN_4O_5$) C, H, N, Cl.

A solution of **13g** (130 mg, 0.25 mmol) in THF (20 mL) was hydrogenated over PtO_2 (30 mg) at 55 psi for 2 h. The catalyst was removed, and the solution was concentrated under reduced pressure below 30 °C. The residue was dissolved in a small volume of CH_2Cl_2, the solution was diluted with petroleum ether to precipitate impurities which were removed by filtration, and then further addition of petroleum ether precipitated **10g** (87 mg, 71%): mp 130−133 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.38 (d, J = 1.6 Hz, 1 H, NH), 8.07 (d, J = 8.5 Hz, 1 H, H-6), 7.75 (d, J = 8.3 Hz, 1 H, H-9), 7.72 (s, 1 H, H-4), 7.45 (t, J = 7.4 Hz, 1 H, H-8), 7.27 (t, J = 7.7 Hz, 1 H, H-7), 7.15 (s, 1 H, H-3′), 7.05 (s, 1 H, H-4′ or 7′), 6.99 (s, 1 H, H-4′ or 7′), 5.96, 5.94 (2 × s, 2 H, NH_2), 4.71 (dd, J = 10.6, 9.1 Hz, 1 H, H-2), 4.50 (dd, J = 10.9 Hz, 1.6 Hz, 1 H, H-2), 4.16−4.08 (m, 1 H, H-1), 4.05 (t, J = 6.0 Hz, 2 H, OCH_2), 3.98 (dd, J = 11.0, 3.0 Hz, 1 H, C*H*HCl), 3.79 (s, 1 H, OCH_3), 3.74 (dd, J = 10.9, 8.2 Hz, 1 H, CH*H*Cl), 2.68 (t, J = 5.9 Hz, 2 H, OCH_2CH_2), 2.25 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{27}H_{29}ClN_4O_3\cdot 0.5H_2O$) C, H, N. Treatment of the free base with EtOAc/petroleum ether/HCl gave the dihydrochloride salt.

5-Amino-1-(chloromethyl)-3-[[7-[2-(dimethylamino)-ethoxy]-5-methoxyindol-2-yl]carbonyl]-1,2-dihydro-3*H*-benz[*e*]indole (10h). Deprotection of **11** (160 mg, 0.44 mmol) as above, and reaction of the product with EDCI·HCl (211 mg, 1.10 mmol) and 7-[2-(dimethylamino)ethoxy]-5-methoxyindole-2-carboxylic acid hydrochloride[17] (145 mg, 0.46 mmol) in DMA (2 mL) at 20 °C for 3 h, followed by addition of dilute $KHCO_3$, precipitated a solid. This was recrystallized from CH_2Cl_2/$^{i}Pr_2O$ followed by CH_2Cl_2/EtOAc to give 1-chloromethyl)-3-[[7-[2-(dimethylamino)ethoxy]-5-methoxyindol-2-yl]carbonyl]-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13h**) (193 mg, 84%): mp 230−240 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.64 (s, 1 H, NH), 9.11 (s, 1 H, H-4), 8.36 (dd, J = 7.1, 2.7 Hz, 1 H, H-6), 8.23 (dd, J = 6.7, 2.6 Hz, 1 H, H-9), 7.79−7.71 (m, 2 H, H-7,8), 7.14 (s, 1 H, H-3′), 6.75 (d, J = 2.0 Hz, 1 H, H-4′ or 6′), 6.50 (d, J = 2.0 Hz, 1 H, H-4′ or 6′), 4.89 (dd, J = 10.6, 9.6 Hz, 1 H, H-2), 4.65−4.55 (m, 2 H, H-1,2), 4.19 (t, J = 5.7 Hz, 2 H, OCH_2), 4.16−4.05 (m, 2 H, CH_2Cl), 3.78 (s, 3 H, OCH_3), 2.74 (t, J = 5.7 Hz, 2 H, OCH_2CH_2), 2.28 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{27}H_{27}ClN_4O_5$) C, H, N, Cl.

A solution of **13h** (120 mg, 0.23 mmol) in THF (45 mL) was hydrogenated over PtO_2 (30 mg) at 55 psi for 1.5 h. After removal of the catalyst, the solution was concentrated to a small volume under reduced pressure below 30 °C and then diluted with petroleum ether to give **10h** (104 mg, 92%): mp 109−111 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.41 (s, 1 H, NH), 8.07 (d, J = 8.8 Hz, 1 H, H-6), 7.75 (d, J = 8.2 Hz, 1 H, H-9), 7.64 (s, 1 H, H-4), 7.45 (t, J = 7.5 Hz, 1 H, H-8), 7.28 (t, J = 7.6 Hz, 1 H, H-7), 7.00 (d, J = 1.2 Hz, 1 H, H-3'), 6.73 (d, J = 1.9 Hz, 1 H, H-4′ or 6′), 6.48 (d, J = 2.0 Hz, 1 H, H-4′ or 6′), 5.98, 5.96 (2 × s, 2 H, NH_2), 4.66 (dd, J = 10.7, 9.0 Hz, 1 H, H-2), 4.41 (dd, J = 11.0, 1.4 Hz, 1 H, H-2), 4.19 (t, J = 5.7 Hz, 2 H, OCH_2), 4.12−4.04 (m, 1 H, H-1), 3.96 (dd, J = 10.9, 3.0 Hz, C*H*HCl), 3.77 (s, 3 H, OCH_3), 3.72 (dd, J = 11.0, 8.2 Hz, 1 H, CH*H*Cl), 2.73 (t, J = 5.7 Hz, 2 H, OCH_2CH_2), 2.28 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{27}H_{29}ClN_4O_3\cdot 1.5H_2O$) C, H, N, Cl. Treatment of the free base with EtOAc/petroleum ether/HCl gave the dihydrochloride salt.

5-Amino-3-[[5-[(benzofuran-2-yl)carboxamido]-indol-2-yl]carbonyl]-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (10i). Deprotection of **11** (300 mg, 0.83 mmol) as above, and reaction of the product with 5-[(benzofuran-2-yl)carboxamido]indole-2-carboxylic acid[31] (278 mg, 0.87 mmol) and EDCI·HCl (397 mg, 2.07 mmol) in DMA (10 mL) at 20 °C for 4 h, followed by addition of dilute $KHCO_3$, precipitated a solid. This was collected, washed with water, and recrystallized from THF/$^{i}Pr_2O$ followed by EtOAc to give 3-[[5-[(benzofuran-2-yl)carboxamido]indol-2-yl]carbonyl]-1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13i**) (341 mg, 73%): mp 277 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 11.88 (d, J = 1.5 Hz, 1 H, indole NH), 10.50 (s, 1 H, NHCO), 9.18 (s, 1 H, H-4), 8.36 (dd, J = 7.0, 2.8 Hz, 1 H, H-6), 8.27 (d, J = 1.5 Hz, 1 H, H-4′), 8.25 (dd, J = 6.7, 2.6 Hz, 1 H, H-9), 7.84 (d, J = 7.7 Hz, 1 H, H-4″), 7.80−7.71 (m, 3 H, H-7,8,7″), 7.78 (d, J = 0.6 Hz, 1 H, H-3″), 7.65 (dd, J = 8.9, 1.9 Hz, 1 H, H-6′), 7.55−7.48 (m, 1 H, H-6″), 7.52 (d, J = 8.8 Hz, 1 H, H-7′), 7.38 (t, J = 7.5 Hz, 1 H, H-5″), 7.34 (d, J = 1.6 Hz, 1 H, H-3′), 4.97 (dd, J = 10.6, 9.9 Hz, 1 H, H-2), 4.74 (dd, J = 11.0, 2.3 Hz, 1 H, H-2), 4.68−4.60 (m, 1 H, H-1), 4.15 (d, J = 4.3 Hz, 2 H, CH_2Cl). Anal. ($C_{31}H_{21}ClN_4O_5$) C, H, N, Cl.

A solution of **13i** (200 mg, 0.35 mmol) in THF (35 mL) was hydrogenated over PtO_2 at 50 psi for 2 h. THF was added to dissolve the precipitated product, and after removal of the catalyst the solution was concentrated to a small volume below 25 °C under reduced pressure and diluted with $^{i}Pr_2O$ to give **10i** (187 mg, 99%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.72 (d, J = 1.3 Hz, 1 H, indole NH), 10.48 (s, 1 H, NHCO), 8.22 (d, J = 1.4 Hz, 1 H, H-4′), 8.09 (d, J = 8.5 Hz, 1 H, H-6), 7.84 (d, J = 7.8 Hz, 1 H, H-4″), 7.80−7.69 (m, 3 H, H-4,9,7″), 7.77 (s, 1 H, H-3″), 7.62 (dd, J = 8.9, 1.9 Hz, 1 H, H-6′), 7.54−7.43 (m, 2 H, H-8,6″), 7.50 (d, J = 8.6 Hz, 1 H, H-7′), 7.38(t, J = 7.5 Hz, 1 H, H-5″), 7.29 (t, J = 7.7, 1 H, H-7), 7.21 (d, J = 0.9 Hz, 1 H, H-3′), 6.00, 5.98 (2 × s, 2 H, NH_2), 4.77 (dd, J = 10.9, 9.0 Hz, 1 H, H-2), 4.54 (dd, J = 10.8, 1.3 Hz, 1 H, H-2), 4.19−4.10 (m, 1 H, H-1), 3.99 (dd, J = 10.9, 2.9 Hz, 1 H, C*H*HCl), 3.79 (dd, J = 10.9, 7.8 Hz, 1 H, CH*H*Cl). Anal. ($C_{31}H_{23}ClN_4O_3\cdot 0.5H_2O$) C, H, N.

3-[[5-[[5-(Acetylamino)-1-methylpyrazol-3-yl]carboxamido]-1-methylpyrazol-3-yl]carbonyl]-5-amino-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (10j). A solution of methyl 5-[[5-(benzyloxycarbonylamino)-1-meth-

ylpyrazol-3-yl]carboxamido]-1-methylpyrazole-3-carboxylate[21] (**31**) in MeOH was hydrogenated over Pd−C at 55 psi for 2 h. Recrystallization of the product from a small volume of EtOAc gave methyl 5-[(5-amino-1-methylpyrazol-3-yl)carboxamido]-1-methylpyrazole-3-carboxylate **(32)** (93%): mp 167−168 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.01 (s, 1 H, NH), 6.62 (s, 1 H, H-4), 5.77 (s, 1 H, H-4′), 5.49 (s, 2 H, NH_2), 3.78 (s, 3 H, CH_3), 3.74 (s, 3 H, CH_3), 3.64 (s, 3 H, CH_3). Anal. ($C_{11}H_{14}N_6O_3$) C, H, N.

A suspension of the powdered amine **32** (0.39 g, 1.40 mmol) in THF (20 mL) containing MeCOCl (2 mL) was heated at reflux with stirring for 30 min. The mixture was cooled and then diluted with ^{i}Pr$_2$O, and the resulting solid was recrystallized from MeOH/EtOAc to give methyl 5-[(5-acetylamino-1-methylpyrazol-3-yl)carboxamido]-1-methylpyrazole-3-carboxylate (**33**) (0.35 g, 78%): mp 215−216 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.28 (s, 1 H, NH), 10.19 (s, 1 H, NH), 6.73 (s, 1 H, H-4 or H-4′), 6.65 (s, 1 H, H-4 or H-4′), 3.80 (s, 3 H, CH_3), 3.79 (s, 3 H, CH_3), 3.76 (s, 3 H, CH_3), 2.11 (s, 3 H, $COCH_3$). Anal. ($C_{13}H_{16}N_6O_4$) C, H, N.

A mixture of the ester **33** (0.38 g, 1.19 mmol) and Cs_2CO_3 (3.26 g) in water (10 mL) was heated at reflux for 2 h, then concentrated, cooled to 0 °C, and acidified with concentrated HCl. After prolonged cooling, the crude product was collected and recrystallized from MeOH/EtOAc to give 5-[(5-acetylamino-1-methylpyrazol-3-yl)carboxamido]-1-methylpyrazole-3-carboxylic acid (**34**) (0.19 g, 52%): mp 263−264 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 12.62 (s, 1 H, CO_2H), 10.24 (s, 1 H, NH), 10.18 (s, 1 H, NH), 6.72 (s, 1 H, H-4 or H-4′), 6.59 (s, 1 H, H-4 or H-4′), 3.80 (s, 3 H, N−CH_3), 3.74 (s, 3 H, N−CH_3), 2.11 (s, 3 H, $COCH_3$). Anal. ($C_{12}H_{14}N_6O_4$) C, H, N.

Deprotection of **11** (153 mg, 0.42 mmol) as above, followed by reaction with the acid **34** (135 mg, 0.44 mmol) and EDCI·HCl (201 mg, 1.05 mmol) in DMA (2 mL) gave a solid which was collected, washed with water, and dried. This was dissolved in THF (10 mL), and the solution was diluted with EtOAc (5 mL) and then filtered through a column of silica gel, eluting with further THF/EtOAc (2:1). The solution was concentrated under reduced pressure to a small volume and diluted with ^{i}Pr$_2$O to precipitate the crude product which was twice recrystallized from THF/EtOAc/^{i}Pr$_2$O to give 3-[[5-[(5-acetylamino-1-methylpyrazol-3-yl)carboxamido]-1-methylpyrazol-3-yl]carbonyl]-1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13j**) (125 mg, 54%): mp 158−160 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.35 (s, 1 H, NH), 10.20 (s, 1 H, NH), 9.19 (s, 1 H, H-4), 8.35 (dd, J = 7.1, 2.7 Hz, 1 H, H-6), 8.21 (dd, J = 6.8, 2.6 Hz, 1 H, H-9), 7.79−7.70 (m, 2 H, H-7,8), 6.78 (s, 1 H, H-4 or H-4′), 6.75 (s, 1 H, H-4 or H-4′), 4.92 (dd, J = 11.9, 1.6 Hz, 1 H, H-2), 4.79 (dd, J = 12.0, 9.4 Hz, 1 H, H-2), 4.59−4.50 (m, 1 H, H-1), 4.16−4.05 (m, 2 H, CH_2Cl), 3.84 (s, 3 H, N−CH_3), 3.82 (s, 3 H, N−CH_3), 2.12 (s, 3 H, $COCH_3$). Anal. ($C_{25}H_{23}ClN_8O_5$) C, H, N.

A solution of **13j** (77 mg, 0.14 mmol) in THF (50 mL) was hydrogenated over PtO_2 at 55 psi for 2.5 h. After removal of the catalyst, the solution was concentrated to a small volume under reduced pressure below 25 °C and diluted with ^{i}Pr$_2$O to give **10j** (63 mg, 87%) as an unstable solid: mp >250 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.30 (s, 1 H, NH), 10.19 (2, 1 H, NH), 8.06 (d, J = 8.5 Hz, 1 H, H-6), 7.75 (br s, 1 H, H-4), 7.73 (d, J = 8.3 Hz, 1 H, H-9), 7.44 (t, J = 7.5 Hz, 1 H, H-8), 7.27 (t, J = 7.6 Hz, 1 H, H-7), 6.75 (s, 1 H, H-4 or H-4′), 6.69 (s, 1 H, H-4 or H-4′), 5.95, 5.93 (2 × s, 2 H, NH_2), 4.69 (d, J = 11.5 Hz, 1 H, H-2), 4.56 (dd, J = 11.9, 8.8 Hz, 1 H, H-2), 4.10−4.03 (m, 1 H, H-1), 3.94 (dd, J = 10.9, 3.0 Hz, 1 H, C*H*HCl), 3.82 (s, 3 H, N−CH_3), 3.80 (s, 3 H, N−CH_3), 3.69 (dd, J = 10.9, 8.3 Hz, 1 H, CH*H*Cl), 2.12 (s, 3 H, $COCH_3$). Anal. ($C_{25}H_{25}ClN_8O_3$) C, H, N, Cl.

5-Amino-3-[(*E*)-3-[4-(butyrylamino)-1-methylpyrrol-2-yl]-acryloyl]-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]-indole (10k). Deprotection of **11** (300 mg, 0.83 mmol) as above and reaction with (*E*)-3-[4-(butyrylamino)-1-methylpyrrol-2-yl]acrylic acid[17] (197 mg, 0.83 mmol) and EDCI·HCl (397 mg, 2.07 mmol) in DMA gave a product that was chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc (1:1), followed by crystallization of the product from CH_2Cl_2/^{i}Pr$_2$O, gave 3-[(*E*)-3-[4-(butyrylamino)-1-methylpyrrol-2-yl]acryloyl]-1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13k**) (246 mg, 62%): mp 216 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.79 (s, 1 H, NH), 9.22 (s, 1 H, H-4), 8.32 (d, J = 8.7 Hz, 1 H, H-6), 8.17 (d, J = 8.1 Hz, 1 H, H-9), 7.76−7.65 (m, 2 H, H-7,8), 7.64 (d, J = 14.9 Hz, 1 H, COCH=C*H*), 7.25 (d, J = 1.6 Hz, 1 H, H-5′), 6.81 (d, J = 1.6 Hz, 1 H, H-3′), 6.71 (d, J = 15.0 Hz, 1 H, COC*H*=CH), 4.65−4.50 (m, 3 H, 2 × H-2, H-1), 4.08 (d, J = 3.6 Hz, 2 H, CH_2Cl), 3.71 (s, 3 H, NCH_3), 2.22 (t, J = 7.3 Hz, 2 H, $COCH_2$), 1.65−1.54 (m, 2 H, CH_2CH_3), 0.90 (t, J = 7.4 Hz, 3 H, CH_2CH_3). Anal. ($C_{25}H_{25}ClN_4O_4$) C, H, N.

A solution of **13k** (100 mg, 0.21 mmol) in EtOAc was hydrogenated over EtOAc-washed Raney nickel (ca. 100 mg) at 40 psi for 3 h. The filtered solution was evaporated to dryness below 30 °C, and the residue was chromatographed on silica gel. Later EtOAc eluates gave a yellow oil which was crystallized from EtOAc/^{i}Pr$_2$O/petroleum ether to give **10k** (9 mg, 10%): mp 245−250 (dec); ^{1} H NMR [$(CD_3)_2SO$] δ 9.76 (s, 1 H, NH), 8.04 (d, J = 8.4 Hz, 1 H, H-6), 7.79 (v br s 1 H, H-4), 7.71 (d, J = 8.1 Hz, 1 H, H-9), 7.55 (d, J = 15.0 Hz, 1 H, COCH=C*H*), 7.43 (t, J = 7.3 Hz, 1 H, H-8), 7.28−7.20 (m, 2 H, H-7,5′), 6.75−6.65 (m, 2 H, COC*H*=CH, H-3′), 5.94 (br s, 2 H, NH_2), 4.47−4.34 (m, 1 H, H-2), 4.33 (dd, J = 10.9, 2.1 Hz, 1 H, H-2), 4.13−4.04 (m, 1 H, H-1), 3.95 (dd, J = 10.9, 3.0 Hz, 1 H, C*H*HCl), 3.73 (dd, J = 11.0, 8.3 Hz, 1 H, CH*H*Cl), 3.69 (s, 3 H, NCH_3), 2.21 (t, J = 7.3 Hz, 2 H, $COCH_2$), 1.64−1.53 (m, 2 H, CH_2CH_3), 0.90 (t, J = 7.4 Hz, 3 H, CH_2CH_3). Anal. ($C_{25}H_{27}ClN_4O_2$) C, H, N.

3-[(*E*)-3-[3-(Acetylamino)-1-methylpyrazol-5-yl]-acryloyl]-5-amino-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (10l). A solution of methyl 3-amino-1-methylpyrazole-5-carboxylate[22] (**35**) (2.50 g, 16.1 mmol) in THF (90 mL) was treated at 20 °C with acetyl chloride (2.29 mL, 32.2 mmol) and heated at reflux for 15 min. The mixture was concentrated under reduced pressure, and the residue was dissolved in warm EtOAc (250 mL). The solution was filtered through a short column of silica gel, concentrated to a small volume, and diluted with ^{i}Pr$_2$O to precipitate methyl 3-(acetylamino)-1-methylpyrazole-5-carboxylate (**36**) (3.09 g, 97%): mp (EtOAc) 202−203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.60 (s, 1 H, NH), 7.01 (s, 1 H, H-4), 3.99 (s, 3 H, NCH_3 or CO_2CH_3), 3.83 (s, 3 H, NCH_3 or CO_2CH_3), 2.01 (s, 3 H, CH_3CO). Anal. ($C_8H_{11}N_3O_3$) C, H, N.

A mixture of **36** (3.04 g, 15.4 mmol) and Cs_2CO_3 (8.0 g) in water (24 mL) was heated at reflux for 45 min, then concentrated to 10 mL, and acidified in the cold with 0.5 N HCl. The precipitated solid was recrystallized from MeOH to give 3-(acetylamino)-1-methylpyrazole-5-carboxylic acid (**37**) (2.44 g, 86%): mp 286 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 13.2 (br s, 1 H, CO_2H), 10.54 (s, 1 H, NH), 6.96 (s, 1 H, H-4), 3.98 (s, 3 H, NCH_3), 2.00 (s, 3 H, CH_3CO). Anal. ($C_7H_9N_3O_3$) C, H, N.

A suspension of **37** (751 mg, 4.10 mmol) in THF (20 mL) was treated with 1,1′-carbonyldiimidazole (864 mg, 5.33 mmol). The mixture was stirred at 45 °C for 15 min and at 20 °C for 15 min, and it was then was added to a stirred freshly prepared solution of $NaBH_4$ (620 mg, 16.4 mmol) in water (10 mL) at 5 °C. This mixture was stirred at 20 °C for 30 min, then treated slowly with AcOH (2.5 mL), and evaporated to complete dryness under reduced pressure. The residue was extracted with boiling EtOAc (2 × 125 mL), and the combined extracts were concentrated to a small volume and cooled at 0 °C for 24 h. The resulting solid was collected and recrystallized from EtOAc/^{i}Pr$_2$O to give 3-(acetylamino)-5-(hydroxymethyl)-1-methylpyrazole (**38**) (468 mg, 67%): mp 148 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.24 (s, 1 H, NH), 6.38 (s, 1 H, H-4), 5.23 (br s, 1 H, OH), 4.42 (d, J = 4.2 Hz, 2 H, CH_2), 3.66 (s, 3 H, NCH_3), 1.96 (s, 3 H, CH_3CO). Anal. ($C_7H_{11}N_3O_2$) C, H, N.

A mixture of **38** (450 mg, 2.66 mmol) and activated MnO_2 (1.36 g, 85%, 13.3 mmol) in EtOAc (30 mL) was heated under reflux for 2 h. The mixture was filtered, passed through a short column of silica gel, and concentrated under reduced pressure to give 3-(acetylamino)-1-methylpyrazole-2-carboxaldehyde (**39**) (382 mg, 86%): mp (^{i}Pr$_2$O) 148 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.65

(s, 1 H, NH), 9.85 (s, 1 H, CHO), 7.17 (s, 1 H, H-4), 4.00 (s, 3 H, NCH_3), 2.02 (s, 3 H, CH_3CO). Anal. ($C_7H_9N_3O_2$) C, H, N.

A mixture of **39** (425 mg, 2.54 mmol) and malonic acid (396 mg, 3.81 mmol) in pyridine (5 mL) containing piperidine (1 drop) was heated at 100 °C for 2 h and then heated at reflux for 5 min. The mixture was concentrated under reduced pressure, the residue was shaken with 0.5 N HCl, and the resulting solid was recrystallized from DMF/H_2O to give (*E*)-3-[3-(acetylamino)-1-methylpyrazol-5-yl]acrylic acid (**40**) (454 mg, 85%): mp 286−287 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.56 (br s, 1 H, CO_2H), 10.43 (s, 1 H, NH), 7.49 (d, J = 15.9 Hz, 1 H, C*H*=CHCO_2H), 6.91 (s, 1 H, H-4), 6.36 (d, J = 15.8 Hz, 1 H, CH=C*H*CO_2H), 3.82 (s, 3 H, NCH_3), 1.99 (S, 3 H, CH_3CO). Anal. ($C_9H_{11}N_3O_3$·0.25H_2O) C, H, N.

A solution of **11** (200 mg, 0.55 mmol) in THF (15 mL) was hydrogenated over PtO_2 at 55 psi for 1.5 h. The catalyst was removed, the solvent was evaporated, and the resulting solid was triturated with petroleum ether to give 5-amino-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (**15**) (166 mg, 90%) as an unstable solid: mp >200 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.01 (d, J = 8.4 Hz, 1 H, H-6), 7.64 (d, J = 8.3 Hz, 1 H, H-9), 7.45−7.25 (underlying br, 1 H, H-4), 7.40 (t, J = 7.4 Hz, 1 H, H-8), 7.20 (t, J = 7.4 Hz, 1 H, H-7), 5.91 (s, 2 H, NH_2), 4.11−3.87 (m, 4 H, H-1,2, C*H*HCl), 3.66 (dd, J = 10.5, 8.3 Hz, 1 H, CH*H*Cl), 1.53 (s, 9 H, C(CH_3)$_3$). Anal. ($C_{18}H_{21}ClN_2O_2$) C, H, N, Cl.

A solution of 9-fluorenylmethyl chloroformate (97%, 270 mg, 1.01 mmol) in dry CH_2Cl_2 (20 mL) was treated with 1-methylimidazole (90 mg, 1.10 mmol), followed by **15** (280 mg, 0.84 mmol). The mixture was stirred at 20 °C for 1.5 h and then treated with additional 1-methylimidazole (18 mg, 0.22 mmol) and 9-fluorenylmethyl chloroformate (54 mg, 0.20 mmol). The mixture was stirred for a further 3 h and was then concentrated under reduced pressure, and the residue was chromatographed on silica gel. Elution with CH_2Cl_2/petroleum ether (9:1) gave a gum that was recrystallized from ^{i}Pr$_2$O/petroleum ether to give give 3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-5-(9-fluorenylmethyloxycarbonylamino)-1,2-dihydro-3*H*-benz[*e*]indole (**16**) (417 mg, 89%): mp 103−106 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.73 (s, 1 H, $NHCO_2$), 8.21 (br s, 1 H, H-4), 7.98 (d, J = 8.5 Hz, 1 H, ArH), 7.95−7.85 (m, 3 H, ArH), 7.76 (br s, 2 H, ArH), 7.54 (t, J = 7.5 Hz, 1 H, ArH), 7.48−7.27 (m, 5 H, ArH), 4.46 (d, J = 7.0 Hz, 2 H, aliphatic H), 4.32 (t, J = 6.8 Hz, 1 H, aliphatic H), 4.26−4.11 (m, 2 H, aliphatic H), 4.11−3.97 (m, 2 H, C*H*HCl, aliphatic H), 3.88 (dd, J = 10.7, 6.9 Hz, 1 H, CH*H*Cl), 1.52 (s, 9 H, C(CH_3)$_3$). Anal. ($C_{33}H_{31}ClN_2O_4$) C, H, N, Cl.

A solution of **16** (234 mg, 0.42 mmol) in HCl-saturated dioxane (12 mL) was stirred at 5 °C for 4 h and then evaporated to dryness under reduced pressure below 30 °C to give crude **17**. Acid **40** (92 mg, 0.44 mmol), EDCI·HCl (202 mg, 1.05 mmol), and DMA (2.5 mL) were then added, and the mixture was stirred at 20 °C for 4 h. Basification by the slow addition of dilute $KHCO_3$ gave a precipitate that was collected, washed with water, dried, dissolved in EtOAc, and filtered through a short column of silica gel. The eluate was concentrated to a small volume under reduced pressure below 30 °C and then diluted with ^{i}Pr$_2$O to complete the separation of crude 3-[(*E*)-3-[3-(acetylamino)-1-methylpyrazol-5-yl]acryloyl]-1-(chloromethyl)-5-(9-fluorenylmethyloxycarbonylamino)-1,2-dihydro-3*H*-benz[*e*]indole (**18**) (87 mg, 32%): mp 256 °C (dec) as an unstable solid that was used without further characterization.

A solution of **18** (77 mg, 0.12 mmol) in DMF (1.0 mL) was treated with piperidine (0.1 mL), stirred at 20 °C for 20 min, and then diluted with ^{i}Pr$_2$O. The resulting crude product was collected, washed with ^{i}Pr$_2$O, and purified by dissolving in warm DMA and precipitating by addition of EtOAc/^{i}Pr$_2$O, giveing **10l** (44 mg, 87%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.45 (s, 1 H, NH), 8.06 (d, J = 8.5 Hz, 1 H, H-6), 7.81 (s, 1 H, H-4), 7.72 (d, J = 8.3 Hz, 1 H, H-9), 7.55 (d, J = 15.2 Hz, 1 H, C*H*=CHCO), 7.44 (t, J = 7.5 Hz, 1 H, H-8), 7.26 (t, J = 7.7 Hz, 1 H, H-7), 7.11 (d, J = 15.1 Hz, 1 H, CH=C*H*CO), 7.10 (s, 1 H, pyrazole H-4), 5.95 & 5.94 (2 × s, 2 H, NH_2), 4.50−4.37 (m, 2 H, H-2), 4.17−4.08 (m, 1 H, H-1), 3.95 (dd, J = 11.0, 2.8 Hz, 1 H, C*H*HCl), 3.86 (s, 3 H, NCH_3), 3.76 (dd, J = 10.9, 7.9 Hz, 1 H, CH*H*Cl), 2.02 (s, 3 H, CH_3CO). Anal. ($C_{22}H_{22}ClN_5O_2$·0.25H_2O) C, H, N, Cl.

3-[(*E*)-3-(Acetylamino)cinnamoyl]-5-amino-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (10m). Deprotection of **16** (94 mg, 0.17 mmol) as above, followed by reaction with EDCI·HCl (81 mg, 0.42 mmol) and (*E*)-3-(acetylamino)cinnamic acid (37 mg, 0.18 mmol) in DMA (2 mL), gave a solid that was dissolved in EtOAc. Addition of petroleum ether precipitated impurities that were removed by filtration. The solution was then concentrated to small volume and diluted with ^{i}Pr$_2$O to give crude 3-[(*E*)-3-(acetylamino)cinnamoyl]-1-(chloromethyl)-5-(9-fluorenylmethyloxycarbonylamino-1,2-dihydro-3*H*-benz[*e*]indole (**19**) (47 mg, 43%): mp 208−209 °C, which was used without further purification; ^{1}H NMR [$(CD_3)_2SO$] δ 10.06 (s, 1 H, NHCO), 9.75 (s, 1 H, $NHCO_2$), 8.65 (s, 1 H, H-4), 8.01−7.87 (m, 4 H, ArH), 7.85 (s, 1 H, H-2′), 7.77 (br s, 2 H, ArH), 7.69−7.30 (m, 9 H, ArH), 7.62 (d, J = 15.5 Hz, 1 H, PhC*H*=CH), 7.14 (d, J = 15.4 Hz, 1 H, PhCH=C*H*), 4.65−4.27 (m, 6 H, aliphatic H), 4.06 (dd, J = 11.1, 3.0 Hz, 1 H, C*H*HCl), 3.96 (dd, J = 11.0, 7.2 Hz, 1 H, CH*H*Cl), 2.07 (s, 3 H, CH_3).

A solution of **19** (31 mg, 0.048 mmol) in dry DMF (0.4 mL) was treated at 20 °C with piperidine (0.04 mL). After 20 min the mixture was poured into water and the precipitated solid was collected, dried, and dissolved in EtOAc. The solution was filtered through a short column of silica gel, and the eluates were concentrated to small volume and diluted with ^{i}Pr$_2$O. The resulting solid was recrystallized from EtOAc/^{i}Pr$_2$O/petroleum ether to give **10m** (17 mg, 84%): mp >250 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.06 (s, 1 H, NH), 8.06 (d, J = 8.5 Hz, 1 H, H-6), 7.86 (s, 1 H, H-2'), 7.83 (br s, 1 H, H-4), 7.72 (d, J = 8.3 Hz, 1 H, H-9), 7.65 (d, J = 8.0 Hz, 1 H, H-4′), 7.59 (d, J = 15.3 Hz, 1 H, PhC*H*=CH), 7.50 (d, J = 7.6 Hz, 1 H, H-6′), 7.44 (t, J = 7.6 Hz, 1 H, H-8), 7.38 (t, J = 7.9 Hz, 1 H, H-5′), 7.26 (t, J = 7.7 Hz, 1 H, H-7), 7.11 (d, J = 15.4 Hz, 1 H, PhCH=C*H*), 5.97 (s, 2 H, NH_2), 4.54−4.42 (m, 1 H, H-2), 4.39 (d, J = 9.5 Hz, 1 H, H-2), 4.18−4.07 (m, 1 H, H-1), 3.96 (dd, J = 10.9, 2.9 Hz, 1 H, C*H*HCl), 3.75 (dd, J = 10.9, 8.3 Hz, 1 H, CH*H*Cl), 2.07 (s, 3 H, CH_3). Anal. ($C_{24}H_{22}ClN_3O_2$) C, H, N, Cl.

5-Amino-1-(chloroethyl)-3-[(*E*)-3-(5-methoxyindol-2-yl)acryloyl]-1,2-dihydro-3*H*-benz[*e*]indole (10r). A mixture of 5-methoxyindole-2-carboxaldehyde[23] (**41**) (601 mg, 3.43 mmol) and methyl (triphenylphosphoranylidene)acetate (1.43 g, 4.28 mmol) in dry benzene (30 mL) was heated at reflux for 1 h and then concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/EtOAc (9:1), to give methyl (*E*)-3-(5-methoxyindol-2-yl)acrylate (**42**) (613 mg, 77%): mp (EtOAc/^{i}Pr$_2$O) 180−181 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.45 (s, 1 H, NH), 7.61 (d, J = 16.0 Hz, 1 H, C*H*=CHCO), 7.27 (d, J = 8.8 Hz, 1 H, H-7), 7.04 (d, J = 2.4 Hz, 1 H, H-4), 6.85 (dd, J = 8.8, 2.5 Hz, 1 H, H-6), 6.83 (s, 1 H, H-3), 6.50 (d, J = 15.9 Hz, 1 H, CH=C*H*CO), 3.75 (s, 3 H, CH_3), 3.72 (s, 3 H, CH_3). Anal. ($C_{13}H_{13}NO_3$) C, H, N.

A stirred mixture of **42** (0.55 g, 2.38 mmol), $CsCO_3$ (3.26 g, 10.0 mmol), MeOH (8 mL), and water (2 mL) was heated at reflux until homogeneous and then for a further 30 min. The mixture was diluted with water (60 mL), concentrated under reduced pressure, and acidified with aqueous HCl. The resulting precipitate was recrystallized from MeOH/H_2O and then EtOAc/^{i}Pr$_2$O to give (*E*)-3-(5-methoxyindol-2-yl)acrylic acid (**43**) (0.47 g, 91%), mp 213−215 °C (dec); ^{1}H NMR [$(CD_3)_2SO$] δ 12.28 (br s, 1 H, CO_2H), 11.41 (s, 1 H, NH). 7.53 (d, J = 16.0 Hz, 1 H, C*H*=CHCO), 7.26 (d, J = 8.8 Hz, 1 H, H-7), 7.04 (d, J = 2.4 Hz, 1 H, H-4), 6.83 (dd, J = 8.8, 2.4 Hz, 1 H, H-6), 6.77 (s, 1 H, H-3), 6.41 (d, J = 16.0 Hz, 1 H, CH=C*H*CO), 3.75 (s, 3 H, CH_3). Anal. ($C_{12}H_{11}NO_3$) C, H, N.

Deprotection of **16** (361 mg, 0.65 mmol) as above was followed by reaction with acid **43** (148 mg, 0.68 mmol) and EDCI·HCl (312 mg, 1.63 mmol) in DMA (2.5 mL) at 20 °C for 4 h. The mixture was diluted with $KHCO_3$ solution, and the precipitated solid was collected, washed with $KHCO_3$ solution and water, and dried to give crude, unstable 1-(chloromethyl)-5-(9-fluorenylmethyloxycarbonylamino)-3-[(*E*)-3-(5-methoxyindol-2-yl)acryloyl]-1,2-dihydro-3*H*-benz[*e*]indole (**20**) (360 mg). A solution of this in DMF (2 mL) was treated at 20 °C with piperidine (0.2 mL), left at 20 °C for 30 min, and then diluted

with $^{i}Pr_2O$/petroleum ether (1:1) (350 mL). After prolonged cooling at 5 °C, the precipitated solid was collected and chromatographed on silica gel, eluting with CH_2Cl_2/EtOAc (3:2), to give a crude product which was recrystallized from CH_2Cl_2/EtOAc/$^{i}Pr_2O$ to give **10r** (114 mg, 41% overall): mp >250 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.53 (s, 1 H, NH), 8.06 (d, J = 8.4 Hz, 1 H, H-6), 7.85 (br s, 1 H, H-4), 7.72 (d, J = 8.3 Hz, H-9), 7.62 (d, J = 15.2 Hz, 1 H, PhC*H*=CH), 7.45 (t, J = 7.6 Hz, 1 H, H-8), 7.31 (d, J = 8.8 Hz, 1 H, H-7′), 7.26 (t, J = 7.6 Hz, 1 H, H-7), 7.16 (d, J = 15.3 Hz, 1 H, PhCH=C*H*), 7.06 (d, J = 2.2 Hz, 1 H, H-4′), 6.85 (dd, J = 8.8, 2.4 Hz, 1 H, H-6′), 6.82 (s, 1 H, H-3′), 5.97 & 5.95 (2 × s, 2 H, NH_2), 4.50−4.38 (m, 2 H, H-2), 4.19−4.10 (m, 1 H, H-1), 3.98 (dd, J = 10.9, 2.8 Hz, 1 H, C*H*HCl), 3.77 (s, 3 H, CH_3), 3.73 (dd, J = 10.9, 9.2 Hz, 1 H, CH*H*Cl). Anal. ($C_{25}H_{22}ClN_3O_2$) C, H, N, Cl.

5-Amino-1-(chloromethyl)-3-[(*E*)-3-methoxycinnamoyl]-1,2-dihydro-3*H*-benz[*e*]indole (10n). Deprotection of **11** (250 mg, 0.69 mmol) as above and reaction of the product with EDCI·HCl (331 mg, 1.73 mmol) and (*E*)-3-methoxycinnamic acid (129 mg, 0.72 mmol) in DMA (3 mL) at 20 °C for 3 h, followed by addition of dilute $KHCO_3$, gave a solid. This was recrystallized from CH_2Cl_2/$^{i}Pr_2O$ followed by EtOAc to give 1-(chloromethyl)-3-[(*E*)-3-methoxycinnamoyl]-5-nitro-1,2-dihydro-3*H*-benz[*e*]indole (**13n**) (215 mg, 74%): mp 200 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.22 (s, 1 H, H-4), 8.33 (dd, J = 7.9, 1.8 Hz, 1 H, H-6), 8.19 (dd, J = 7.5, 1.7 Hz, 1 H, H-9), 7.78−7.68 (m, 2 H, H-7,8), 7.72 (d, J = 15.4 Hz, 1 H, PhC*H*=CH), 7.45−7.34 (m, 2 H, H-5′,6′), 7.39 (s, 1 H, H-2′), 7.26 (d, J = 15.4 Hz, 1 H, PhCH=C*H*), 7.02 (dt, J = 7.2, 2.2 Hz, 1 H, H-4′), 4.71−4.56 (m, 3 H, H-1,2), 4.11−4.05 (m, 2 H, CH_2Cl), 3.84 (s, 3 H, CH_3). Anal. ($C_{23}H_{19}ClN_2O_4$) C, H, N, Cl.

MeOH (5 mL), H_2O (2 mL), AcOH (0.2 mL), and Fe powder (0.5 g) were added sequentially to a hot solution of **13n** (110 mg, 0.26 mmol) in THF (10 mL). The mixture was heated at reflux for 1 h, then basified with CaO (1 g), filtered, concentrated to a small volume under reduced pressure below 30 °C, and diluted with water. The resulting precipitate was chromatographed on silica gel, eluting with CH_2Cl_2/EtOAc (9:1), to give a solid which was recrystallized from CH_2Cl_2/petroleum ether to give **10n** (55 mg, 54%): mp >200 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.06 (d, J = 8.5 Hz, 1 H, H-6), 7.83 (br s, 1 H, H-4), 7.72 (d, J = 8.3 Hz, 1 H, H-9), 7.63 (d, J = 15.4 Hz, 1 H, PhC*H*=CH), 7.44 (t, J = 7.4 Hz, 1 H, H-8), 7.40−7.34 (m, 3 H, PhH), 7.26 (t, partially obscured, J = 7.9 Hz, 1 H, H-7), 7.22 (d, J = 15.4 Hz, 1 H, PhCH=C*H*), 7.04−6.97 (m, 1 H, PhH), 5.95 (br s, 2 H, NH_2), 4.53−4.38 (m, 2 H, H-2), 4.19−4.08 (m, 1 H, H-1), 3.95 (dd, J = 11.0, 2.9 Hz, 1 H, C*H*HCl), 3.83 (s, 3 H, OCH_3), 3.76 (dd, J = 10.9, 8.1 Hz, 1 H, CH*H*Cl). Anal. ($C_{23}H_{21}ClN_2O_2$) C, H, N, Cl.

3-[(*E*)-4-(Acetylamino)cinnamoyl]-5-amino-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (10o). Deprotection of **11** (302 mg, 0.83 mmol) as above and evaporation of the reaction to dryness under reduced pressure gave **12** that was dissolved in pyridine (5 mL). The stirred solution was treated dropwise at 0 °C with trifluoroacetic anhydride (0.14 mL, 0.99 mmol). The mixture was stirred for a further 10 min at 20 °C and then poured into water, and the precipitated solid was dissolved in CH_2Cl_2 and filtered through a column of silica gel. The solvent was removed under reduced pressure, and the residue was crystallized from EtOAc/petroleum ether to give 1-(chloromethyl)-5-nitro-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benz[*e*]indole (**26**) (241 mg, 81%): mp 182 °C; ^{1}H NMR ($CDCl_3$) δ 9.10 (s, 1 H, H-4), 8.49−8.43 (m, 1 H, H-6), 7.93−7.87 (m, 1 H, H-9), 7.76−7.68 (m, 2 H, H-7,8), 4.70 (dt, J = 11.4, 1.4 Hz, 1 H, H-2), 4.51 (dd, J = 11.5, 8.6 Hz, 1 H, H-2), 4.35−4.28 (m, 1 H, H-1), 3.97 (dd, J = 11.7, 3.4 Hz, 1 H, C*H*HCl), 3.64 (dd, J = 11.7, 8.8 Hz, 1 H, CH*H*Cl). Anal. ($C_{15}H_{10}ClF_3N_2O_3$) C, H, N, Cl.

A solution of **26** (175 mg, 0.49 mmol) in benzene (30 mL) was hydrogenated over PtO_2 (45 mg) at 50 psi for 1 h. Removal of the catalyst and solvent provided a solid which was recrystallized from $^{i}Pr_2O$/petroleum ether to give 5-amino-1-(chloromethyl)-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benz[*e*]indole (**27**) (143 mg, 89%): mp 177 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (d, J = 8.4 Hz, 1 H, H-6), 7.80 (d, J = 8.3 Hz, 1 H, H-9), 7.60 (s, 1 H, H-4), 7.50 (t, J = 7.7 Hz, 1 H, H-8), 7.35 (t, J = 7.7 Hz, 1 H, H-7), 6.14 (s, 2 H, NH_2), 4.45 (dd, J = 11.0, 8.7 Hz, 1 H, H-2), 4.33 (d, J = 11.2 Hz, 1 H, H-2), 4.24−4.16 (m, 1 H, H-1), 4.03 (dd, J = 11.0, 3.0 Hz, 1 H, C*H*HCl), 3.84 (dd, J = 11.0, 7.1 Hz, 1 H, CH*H*Cl). Anal. ($C_{15}H_{12}ClF_3N_2O$) C, H, N, Cl. When catalytic reductions of the nitro compound were conducted in a more polar solvent than benzene (e.g., THF), more than one product was obtained.

A mixture of **27** (200 mg, 0.61 mmol) and di-*tert*-butyl dicarbonate (266 mg, 1.22 mmol) in dioxane (20 mL) was stirred at 65 °C under N_2 with the exclusion of light for 4 h. Additional di-*tert*-butyl dicarbonate (200 mg, 0.92 mmol) was added, and the mixture was stirred for a further 8 h at 70 °C and then concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with petroleum ether/CH_2Cl_2 (1:3), to provide a solid which was recrystallized from $^{i}Pr_2O$/petroleum ether to give 5-(*tert*-butyloxycarbonylamino)-1-(chloromethyl)-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benz[*e*]indole (**28**) (192 mg, 74%): mp 185 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.41 (s, 1 H, NH), 8.48 (s, 1 H, H-4), 8.10 (d, J = 8.4 Hz, 1 H, H-6), 8.01 (d, J = 8.2 Hz, 1 H, H-9), 7.61 (t, J = 7.1 Hz, 1 H, H-8), 7.52 (t, J = 7.7 Hz, 1 H, H-7), 4.56 (dd, J = 11.1, 9.7 Hz, 1 H, H-2), 4.47−4.37 (m, 2 H, H-1,2), 4.12 (dd, J = 11.1, 2.8 Hz, 1 H, C*H*HCl), 4.01 (dd, J = 11.2, 5.8 Hz, 1 H, CH*H*Cl), 1.50 (s, 9 H, $C(CH_3)_3$). Anal. ($C_{20}H_{20}ClF_3N_2O_3$) C, H, N, Cl.

A stirred solution of **28** (180 mg, 0.42 mmol) in *N*-methylpyrrolidone (4.5 mL) was treated dropwise at 20 °C with a solution of Cs_2CO_3 (1.2 g) in water (2.7 mL). The mixture was stirred for a further 45 min at 20 °C, then diluted with water (35 mL), and extracted with benzene (2 × 25 mL). The combined organic extracts were washed with water (2×), dried (Na_2SO_4), and concentrated under reduced pressure below 30 °C. The residue was treated sequentially with EDCI·HCl (201 mg, 1.05 mmol), (*E*)-4-(acetylamino)cinnamic acid (86 mg, 0.42 mmol), DMA (2 mL), and DMA·HCl (52 mg, 0.42 mmol). The mixture was stirred at 20 °C for 30 min and then diluted with $KHCO_3$ solution. The precipitated solid was collected, washed with water, dried, and dissolved in warm EtOAc. This solution was filtered through a short column of silica gel, then concentrated to a small volume, and diluted with $^{i}Pr_2O$/petroleum ether to give 3-[(*E*)-4-(acetylamino)cinnamoyl]-5-(*tert*-butyloxycarbonylamino)-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (**29**) (97 mg, 44%): mp >300 °C, that was used without further purification; ^{1}H NMR [$(CD_3)_2SO$] δ 10.15 (br s, 1 H, NHCO), 9.28 (br s, 1 H, $NHCO_2$), 8.64 (br s, 1 H, H-4), 8.02 (d, J = 8.1 Hz, 1 H, H-6), 7.92 (d, J = 8.3 Hz, 1 H, H-9), 7.76 (d, J = 8.6 Hz, 2 H, H-3′,5′), 7.67 (d, J = 9.1 Hz, 2 H, H-2′,6′), 7.64 (d, J = 15.6 Hz, 1 H, PhC*H*=CH), 7.55 (t, J = 7.3 Hz, 1 H, H-8), 7.43 (t, J = 7.5 Hz, 1 H, H-7), 7.13 (br d, J = 15.3 Hz, 1 H, PhCH=C*H*), 4.60−4.45 (m, 2 H, H-2), 4.35 (br s, 1 H, H-1), 4.02 (dd, J = 11.1, 3.0 Hz, 1 H, C*H*HCl), 3.92 (dd, J = 11.0, 7.2 Hz, 1 H, CH*H*Cl), 2.08 (s, 3 H, CH_3CO), 1.51 (s, 9 H, $C(CH_3)_3$).

A cold suspension of **29** (83 mg, 0.16 mmol) in dioxane (8 mL) was saturated with HCl gas and left at 20 °C for 10 min. The mixture was diluted with EtOAc/petroleum ether, and the product was collected and partitioned between dilute $KHCO_3$ and EtOAc. The organic layer was washed with water, dried (Na_2SO_4), and filtered through a short column of silica gel. The solution was concentrated to small volume under reduced pressure below 30 °C and then diluted with petroleum ether to give **10o** (54 mg, 81%): mp >250 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.14 (s, 1 H, NH), 8.05 (d, J = 8.5 Hz, 1 H, H-6), 7.83 (br s, 1 H, H-4), 7.74 (d, J = 8.8 Hz, 2 H, H-3′,5′), 7.72 (d, J = 9.1 Hz, 1 H, H-9), 7.66 (d, J = 8.5 Hz, 2 H, H-2′,6′), 7.60 (d, J = 15.3 Hz, 1 H, PhC*H*=CH), 7.44 (t, J = 7.5 Hz, 1 H, H-8), 7.26 (t, J = 7.6 Hz, 1 H, H-7), 7.10 (d, J = 15.3 Hz, 1 H, PhCH=C*H*), 5.97 (br s, 2 H, NH_2), 4.50−4.35 (m, 2 H, H-2), 4.12 (br s, 1 H, H-1), 3.95 (dd, J = 10.9, 2.6 Hz, 1 H, C*H*HCl), 3.74 (dd, J = 10.6, 8.5 Hz, 1 H, CH*H*Cl), 2.07 (s, 3 H, CH_3). Anal. ($C_{24}H_{22}ClN_3O_2$) C, H, N, Cl.

5-Amino-1-(chloromethyl)-3-[(*E*)-4-methoxycinnamoyl]-1,2-dihydro-3*H*-benz[*e*]indole (10p). A stirred solution of **28** (100 mg, 0.23 mmol) in *N*-methylpyrrolidone (2.5 mL) was hydrolyzed with Cs_2CO_3 as above, and the resulting crude product was dissolved in pyridine (2 mL), cooled to −5 °C, and

treated with (*E*)-4-methoxycinnamoyl chloride (46 mg, 0.23 mmol) followed by DMAP (5 mg). The mixture was stirred at 20 °C for 45 min and then diluted with $KHCO_3$ solution. The precipitated solid was collected, washed with water, dried, and chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc gave a crude product that was recrystallized from CH_2Cl_2/petroleum ether to give 5-(*tert*-butyloxycarbonylamino)-1-(chloromethyl)-3-[(*E*)-4-methoxycinnamoyl]-1,2-dihydro-3*H*-benz[*e*]indole (**30**) (55 mg, 48%): mp 185−185.5 °C, that was used without further purification; ^{1}H NMR [$(CD_3)_2SO$] δ 9.28 (br s, 1 H, NH), 8.64 (br s, 1 H, H-4), 8.01 (d, J = 8.1 Hz, 1 H, H-6), 7.92 (d, J = 8.3 Hz, 1 H, H-9), 7.78 (d, J = 8.6 Hz, 2 H, H-2′,6′), 7.66 (d, J = 15.3 Hz, 1 H, PhC*H*═CH), 7.54 (t, J = 7.6 Hz, 1 H, H-8), 7.42 (t, J = 7.7 Hz, 1 H, H-7), 7.10 (d, J = 15.2 Hz, 1 H, PhCH═C*H*), 7.01 (d, J = 8.7 Hz, 2 H, H-3',5'), 4.60−4.44 (m, 2 H, H-2), 4.41−4.28 (m, 1 H, H-1), 4.02 (dd, J = 11.1, 3.0 Hz, 1 H, C*H*HCl), 3.92 (dd, J = 11.1, 7.2 Hz, 1 H, CH*H*Cl), 3.82 (s, 3 H, OCH_3), 1.51 (s, 9 H, $C(CH_3)_3$).

A cold suspension of **30** (46 mg, 0.09 mmol) in dioxane (5 mL) was saturated with HCl gas and left at 20 °C for 10 min. The mixture was diluted with EtOAc/petroleum ether, and the product was collected and partitioned between dilute $KHCO_3$ and EtOAc. The organic layer was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure below 30 °C, and the residue was chromatographed on silica gel. Elution with CH_2Cl_2/EtOAc (2:1) gave a solid which was recrystallized from CH_2Cl_2/petroleum ether to give **10p** (26 mg, 71%): mp 114−116 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.05 (d, J = 8.4 Hz, 1 H, H-6), 7.82 (br s, 1 H, H-4), 7.76 (d, J = 8.7 Hz, 2 H, H-2′,6′), 7.71 (d, J = 8.3 Hz, 1 H, H-9), 7.62 (d, J = 15.3 Hz, 1 H, PhC*H*═CH), 7.44 (t, J = 7.5 Hz, 1 H, H-8), 7.01 (d, J = 8.7 Hz, 2 H, H-3′,5′), 5.96 (br s, 2 H, NH_2), 4.49−4.36 (m, 2 H, H-2), 4.17−4.06 (m, 1 H, H-1), 3.94 (dd, J = 11.0, 2.9 Hz, 1 H, C*H*HCl), 3.82 (s, 3 H, OCH_3), 3.74 (dd, J = 10.9, 8.3 Hz, 1 H, CH*H*Cl). Anal. ($C_{23}H_{21}ClN_2O_2$) C, H, N, Cl.

5-Amino-1-(chloromethyl)-3-[(*E*)-4-[2-(dimethylamino)-ethoxy]cinnamoyl]-1,2-dihydro-3*H*-benz[*e*]indole (10q). An ice-cold solution of 2-(dimethylamino)ethyl chloride hydrochloride (5.0 g, 34.7 mmol) in water (16 mL) was treated with an ice-cold solution of NaOH (1.67 mL, 41.75 mmol) in water (8 mL) and then saturated by addition of solid NaCl. The mixture was extracted with toluene (16 mL × 4), and the combined extracts were dried over KOH pellets. A stirred solution of methyl (*E*)-4-hydroxycinnamate (4.12 g, 23.1 mmol) in DMF (10 mL) was treated portionwise at 0 °C with NaH (925 mg, 23.1 mmol, 60% in oil) and then stirred at 20 °C for a further 1 h. The above toluene solution of 2-(dimethylamino)-ethyl chloride was added, and the mixture was stirred at reflux for 2 h, then treated with AcOH (1 mL), and concentrated under reduced pressure. The residue partitioned between dilute $KHCO_3$ and EtOAc (125 mL). The organic layer was washed with water and then extracted with 1 N HCl (2 × 50 mL). The combined acidic layers were washed with EtOAc, treated with excess solid $KHCO_3$, then extracted with EtOAc (50 mL × 2). The combined organic layers were dried and concentrated under reduced pressure to give methyl (*E*)-4-[2-(dimethylamino)ethoxy]cinnamate (**21**) (4.02 g, 70%): mp (petroleum ether) 47−48 °C; ^{1}H NMR [$(CD_3)SO$] δ 7.66 (d, J = 8.8 Hz, 2 H, H-2′,6′), 7.61 (d, J = 16.0 Hz, 1 H, PhC*H*═CH), 6.98 (d, J = 8.8 Hz, 2 H, H-3′,5′), 6.49 (d, J = 16.0 Hz, 1 H, PhCH═C*H*), 4.09 (t, J = 5.8 Hz, 2 H, OCH_2CH_2), 3.71 (s, 3 H, OCH_3), 2.62 (t, J = 5.8 Hz, 2 H, OCH_2CH_2), 2.21 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

The ester **21** (2.0 g, 8.0 mmol) was added to a solution of NaOH (0.5 g) in water (6 mL) and MeOH (6 mL), and the mixture was heated at reflux for 45 min. The solution was diluted with water, concentrated to 10 mL, and acidified with excess 12 N HCl. After cooling, the resulting solid was collected, washed with cold 2 N HCl and acetone, and recrystallized from water to give (*E*)-4-[2-(dimethylamino)-ethoxy]cinnamic acid hydrochloride (**22**) (1.57 g, 72%): mp (MeOH/EtOAc) 257−258 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.27 (br s, 1 H, CO_2H), 10.73 (br s, 1 H, NH^+), 7.68 (d, J = 8.8 Hz, 2 H, H-2′,6′), 7.56 (d, J = 16.0 Hz, 1 H, PhC*H*═CH), 7.05 (d, J = 8.8 Hz, 2 H, H-3′,5′), 6.42 (d, J = 16.1 Hz, 1 H, PhCH═C*H*), 4.42 (t, J = 5.1 Hz, 2 H, OCH_2CH_2), 3.51 (t, J = 5.1 Hz, 2 H, OCH_2CH_2), 2.83 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{13}H_{17}NO_3$.HCl) C, H, N, Cl.

A stirred solution of **15** (456 mg, 1.37 mmol) in pyridine (5 mL) was treated dropwise at −5 °C with allyl chloroformate (0.29 mL, 2.74 mmol). The mixture was stirred at 0 °C for 1 h, at 20 °C for a further 1 h, then concentrated under reduced pressure below 30 °C. The residue was shaken with water, the precipitated oil was collected and dissolved in CH_2Cl_2, and the solution was washed with water, dried, and concentrated under reduced pressure. The residue was extracted with hot petroleum ether, and treated with decolorizing charcoal, and the filtered solution was evaporated to give 5-(allyloxycarbonylamino)-3-(*tert*-butyloxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-benz[*e*]indole (**23**) (479 mg, 84%) as a foam: ^{1}H NMR [$(CD_3)_2SO$] δ 9.67 (s, 1 H, NH), 8.24 (br s, 1 H, H-4), 8.03 (d, J = 8.5 Hz, 1 H, H-6), 7.87 (d, J = 8.3 Hz, 1 H, H-9), 7.52 (t, J = 7.5 Hz, 1 H, H-8), 7.39 (td, J = 7.7, 0.9 Hz, 1 H, H-7), 6.07−5.95 (m, 1 H, C*H*═CH_2), 5.39 (d, J = 14.1 Hz, 1 H, CH═C*H*H), 5.25 (dd, J = 10.4, 1.2 Hz, 1 H, CH═CH*H*), 4.65 (d, J = 5.3 Hz, 2 H, OCH_2), 4.25−4.12 (m, 2 H, H-1,2), 4.07 (d, J = 9.3 Hz, 1 H, H-2), 4.01 (dd, J = 11.0, 2.4 Hz, 1 H, C*H*HCl), 3.87 (dd, J = 10.8, 6.7 Hz, 1 H, CH*H*Cl). Anal. ($C_{22}H_{25}ClN_2O_4$) C, H, N.

A solution of **23** (489 mg, 1.17 mmol) in HCl-saturated dioxane (8 mL) was stirred at 5 °C for 3 h and then evaporated to dryness under reduced pressure below 25 °C to give **24**. Acid **22** (335 mg, 1.23 mmol), EDCI·HCl (562 mg, 2.93 mmol), and DMA (5 mL) were then added, and the mixture was stirred at 20 °C in the dark for 12 h and then poured into dilute $KHCO_3$. The precipitated solid was collected, washed with water, and dissolved in CH_2Cl_2. The solution was washed with water, dried, and concentrated under reduced pressure below 25 °C to give crude 5-(allyloxycarbonylamino)-1-(chloromethyl)-3-[(*E*)-4-[2-(dimethylamino)ethoxy]cinnamoyl]-1,2-dihydro-3*H*-benz[*e*]indole (**25**). This intermediate (346 mg, 0.65 mmol) was immediately dissolved in THF (15 mL), and the solution was treated with morpholine (0.40 mL, 4.59 mmol), PPh_3 (8 mg, 5 mol %), and $Pd(PPh_3)_4$ (75 mg, 10 mol %). The mixture was stirred at 20 °C under N_2 for 1.5 h and then concentrated under reduced pressure below 25 °C. The residue was dissolved in EtOAc, and the solution was diluted with ^{i}Pr$_2$O/petroleum ether (1:1), precipitating a solid that was chromatographed on alumina-90. Elution with EtOAc/MeOH (19:1) provided a crude product that was crystallized twice from EtOAc/^{i}Pr$_2$O/petroleum ether to give **10q** (79 mg, 15% over two steps): mp 147−150 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.05 (d, J = 8.5 Hz, 1 H, H-6), 7.82 (br s, 1 H, H-4), 7.74 (d, J = 8.7 Hz, 2 H, H-2′,6′), 7.71 (d, J = 8.6 Hz, 1 H, H-9), 7.61 (d, J = 15.3 Hz, 1 H, PhC*H*═CH), 7.44 (H, J = 7.3 Hz, 1 H, H-8), 7.25 (t, J = 7.6 Hz, 1 H, H-7), 7.07 (d, J = 15.3 Hz, 1 H, PhCH═C*H*), 7.01 (d, J = 8.7 Hz, 2 H, H-3′,5′), 5.94, 5.92 (2 × s, 2 H, NH_2), 4.47−4.37 (m, 2 H, H-2), 4.16−4.06 (m, 3 H, H-1, OCH_2), 3.95 (dd, J = 11.0, 3.0 Hz, 1 H, C*H*HCl), 3.73 (dd, J = 10.9, 8.3 Hz, 1 H, CH*H*Cl), 2.64 (t, J = 5.8 Hz, 2 H, OCH_2CH_2), 2.22 (s, 6 H, $N(CH_3)_2$). Anal. ($C_{26}H_{28}ClN_3O_2$) C, H, N, Cl. Treatment of the free base with HCl/EtOAc/petroleum ether, followed by crystallization from MeOH/EtOAc, gave the hydrochloride salt.

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 <1%. Drug concentrations were checked routinely by spectrophotometry in 0.1 N HCl, or by HPLC. 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 medium per well. After 24 h, drugs were added 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 medium, and cell density was then determined by staining with sulforhodamine B.[32] The IC_{50} was calculated as the drug concentration providing 50%

inhibition of growth relative to controls on the same multiwell plate.

Mouse Toxicity. Compounds were formulated in DMSO/poly(ethylene glycol) (MW 400)/water (1:4:5, v/v/v) immediately before use. Male C_3H mice (ca. 25 g) were treated ip with single doses of compounds at 0.01 mL/g body weight, using $10^{1/8}$-fold dose increments, and were observed daily. Animals becoming moribund during the study, and those still alive after 60 days, were terminated and a necropsy was performed. Grossly identifiable lesions were fixed in neutral buffered formalin, paraffin embedded, and processed for histology with hematoxylin and eosin staining.

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