Supporting Information

Hypoxia Activated Prodrugs: Substituent Effects on the Properties of Nitro *seco*-1,2,9,9a-Tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (nitroCBI) Prodrugs of DNA Minor Groove Alkylating Agents

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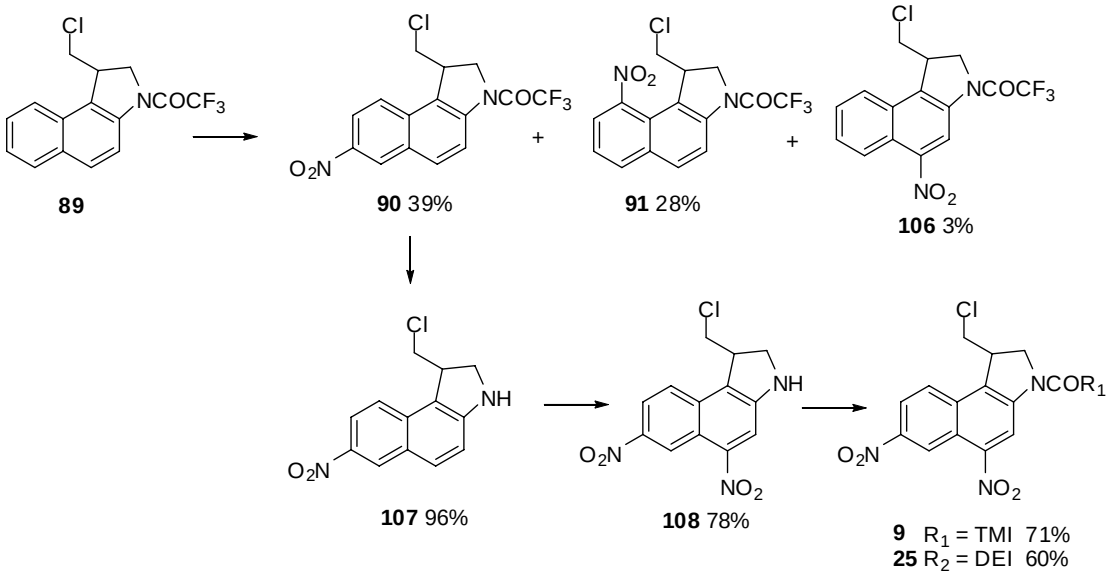
Synthesis of all 7-, 8-, and 9-substituted nitroCBIs of Tables 1 and 2 and aminoCBIs of Table 3 (compounds 9-18, 25-38, 41-52).

Synthesis of 9 and 25.



1-(Chloromethyl)-3-(trifluoroacetyl)-7-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (90). A stirred solution of **89** (5.24 g, 16.7 mmol) in dry CH_2Cl_2 (70 mL) was treated dropwise at 10 °C with $fHNO_3$ (2.0 mL, 48 mmol) and then warmed to room temperature for 5 min. The mixture was diluted with CH_2Cl_2 (100 mL) and the resulting solution was washed with water, dried, filtered through a column of silica gel, then concentrated to 25 mL and diluted with EtOAc (25 mL). Following refrigeration the precipitate was collected and washed with EtOAc to give **90** (2.31 g, 39%) as a pale yellow solid: mp (CH_2Cl_2/iPr_2O) 213-214 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.06 (s, 1 H), 8.48 (d, *J* = 9.0 Hz, 1 H), 8.36 (d, *J* = 9.1 Hz, 1 H), 8.33-8.25 (m, 2 H) 4.67-4.51 (m, 2 H), 4.46 (br d, *J* = 10.6 Hz, 1 H), 4.17 (dd, *J* = 11.3, 3.0 Hz, 1 H), 4.07 (dd, *J* = 11.3, 5.5 Hz, 1 H). Anal. ($C_{15}H_{10}ClF_3N_2O_3$) C, H, N.

The mother liquor from the above crystallization was evaporated under reduced pressure, and the residue was chromatographed on silica gel. Elution with CH_2Cl_2/petroleum ether (1:1) gave 1-(chloromethyl)-3-(trifluoroacetyl)-9-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (**91**) (1.67 g, 28%) as a pale yellow solid: mp (EtOAc/petroleum ether) 139-140 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.58 (d, *J* = 9.1 Hz, 1 H), 8.39 (d, *J* = 8.1 Hz, 1 H), 8.30 (d, *J* = 9.1 Hz, 1 H), 8.20 (dd, *J* = 7.6, 0.9 Hz, 1 H), 7.69 (t, *J* = 7.9 Hz, 1 H), 4.60 (dd, *J* = 11.1, 8.7 Hz, 1 H), 4.33 (d, *J* = 11.3 Hz, 1 H), 4.03-3.90 (m, 1 H), 3.73 (dd, *J* = 11.4, 3.3 Hz, 1 H), 3.51 (dd, *J* = 11.4, 6.8 Hz, 1 H). Anal. ($C_{15}H_{10}ClF_3N_2O_3$) C, H, N.

Further elution gave 1-(chloromethyl)-3-(trifluoroacetyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (**106**)[1] (165 mg, 3%).

1-(Chloromethyl)-7-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (107). A solution of **90** (1.00 g, 2.79 mmol) in dioxane (30 mL) was treated with a solution of Cs_2CO_3 (3.26 g, 10 mmol) in water (3 mL) and MeOH (17 mL), and the mixture was stirred vigorously at room temperature for 15 min. The resulting solution was treated with AcOH (1.2 mL), then concentrated to a small volume under reduced pressure and partitioned between water and CH_2Cl_2. The organic phase was washed with water (×2),

dried, and filtered through a column of silica gel. Evaporation and trituration with petroleum ether/iPr_2O gave **107** (702 mg, 96%) as an orange-red solid: mp (CH_2Cl_2/petroleum ether) 121-122 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.76 (d, *J* = 2.2 Hz, 1 H), 8.05 (dd, *J* = 9.3, 2.3 Hz, 1 H), 7.97 (d, *J* = 8.7 Hz, 1 H), 7.76 (d, *J* = 9.3 Hz, 1 H), 7.09 (d, *J* = 8.7 Hz, 1 H), 6.79 (s, 1 H), 4.17-4.04 (m, 1 H), 3.95-3.78 (m, 2 H), 3.76-3.63 (m, 2 H). Anal. ($C_{13}H_{11}ClN_2O_2$) C, H, N.

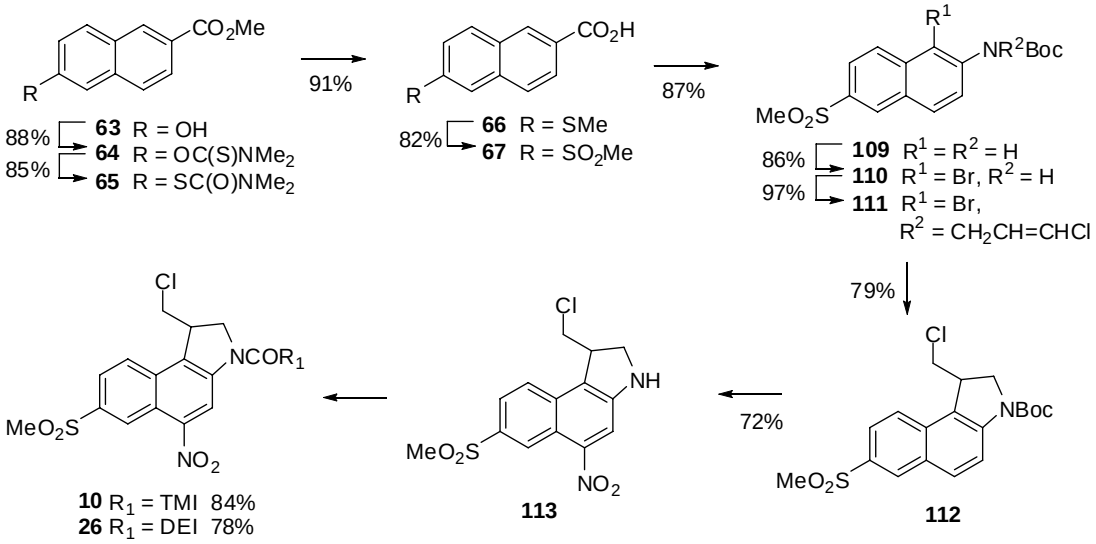
1-(Chloromethyl)-5,7-dinitro-1,2-dihydro-3*H*-benzo[*e*]indole (108). A stirred solution of **107** (901 mg, 3.43 mmol) in cH_2SO_4 (10 mL) was cooled to –5 °C and treated with powdered KNO_3 (520 mg, 5.14 mmol). The mixture was stirred at 0 °C for a further 15 min, then poured into ice-water and the solid was collected. This was dissolved in warm EtOAc, and the solution was diluted with an equal volume of CH_2Cl_2 and filtered through a short column of silica gel. The eluate was concentrated to a small volume and MeOH was added to precipitate **108** (824 mg, 78%) as a red solid: mp (EtOAc/iPr_2O) 239-240 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.06 (d, *J* = 2.3 Hz, 1 H), 8.17 (dd, *J* = 9.3, 2.2 Hz, 1 H), 8.00 (d, *J* = 9.3 Hz, 1 H), 7.83 (s, 1 H), 7.14 (s, 1 H), 4.33-4.24 (m, 1 H), 3.98-3.88 (m, 2 H), 3.84 (dd, *J* = 11.1, 7.9 Hz, 1 H), 3.77 (dd, *J* = 10.7, 3.2 Hz, 1 H). Anal. ($C_{13}H_{10}ClN_3O_4$) C, H, N, Cl.

1-(Chloromethyl)-5,7-dinitro-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (9). A suspension of 5,6,7-trimethoxyindole-2-carboxylic acid (122 mg, 0.49 mmol) in dry CH_2Cl_2 (10 mL) was treated with oxalyl chloride (0.13 mL, 1.49 mmol) followed by DMF (10 μL). The mixture was stirred at room temperature for 15 min, then evaporated under reduced pressure and azeotroped dry with benzene. The resulting acid chloride was cooled to –5 °C and treated with an ice-cold solution of amine **108** (100 mg, 0.33 mmol) in dry pyridine (2 mL) containing DMAP (5 mg). The stirred mixture was warmed to room temperature for 30 min, then poured into dilute aqueous $KHCO_3$. The precipitate was collected, purified by chromatography on silica gel eluting with CH_2Cl_2/EtOAc (19:1), then crystallised from CH_2Cl_2/EtOAc to give **9** (124 mg, 71%) as an orange solid: mp 251-252 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.66 (d, *J* = 1.6 Hz, 1 H), 9.33 (d, *J* = 2.2 Hz, 1 H), 9.31 (s, 1 H), 8.45 (d, *J* = 9.3 Hz, 1 H), 8.39 (dd, *J* = 9.3, 2.2 Hz, 1 H), 7.20 (d, *J* = 2.2 Hz, 1 H), 6.97 (s, 1 H), 4.95 (dd, *J* = 11.1, 10.3 Hz, 1 H), 4.72-4.58 (m, 2 H), 4.18-4.06 (m, 2 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H). HRMS (FAB) calcd. for $C_{25}H_{21}{}^{35}ClN_4O_8$ (M^+) m/z 540.1048, found 540.1043. Anal. ($C_{25}H_{21}ClN_4O_8$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5,7-dinitro-1,2-dihydro-3*H*-benzo[*e*]indole (25). A mixture of amine **108** (100 mg, 0.33 mmol), 5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (111 mg, 0.39 mmol), EDCI (249 mg, 1.30 mmol) and anhydrous TsOH (4.0 mg, 0.02 mmol) in dry DMA (8 mL) was stirred at room temperature under N_2 for 6 h, then poured into dilute aqueous NH_3. The basic mixture was stirred for 1 h, then the precipitate was collected and dissolved in EtOAc (300 mL) at room temperature. The solution was washed with water, dried, and then concentrated to 10 mL under reduced pressure below 30 °C to give crude **25**. Treatment of a suspension of the free base in MeOH with HCl(g)/EtOAc, followed by crystallization from MeOH/Me_2CO/EtOAc gave **25**·HCl (114 mg, 60%) as a yellow solid: mp 263-264 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.88 (s, 1 H), 10.15 (br s, 1 H), 9.36 (s, 1 H), 9.34 (d, *J* = 2.2 Hz, 1 H), 8.48 (d, *J* = 9.3 Hz, 1 H), 8.41 (dd, *J* = 9.3, 2.2 Hz, 1 H), 7.46 (d, *J* = 8.9 Hz, 1 H), 7.26 (s, 2

H), 7.03 (dd, *J* = 8.9, 2.3 Hz, 1 H), 5.00 (t, *J* = 10.5 Hz, 1 H), 4.78-4.65 (m, 2 H), 4.36 (t, *J* = 4.9 Hz, 2 H), 4.22-4.09 (m, 2 H), 3.52 (t, *J* = 4.5 Hz, 2 H), 2.80 (s, 6 H). Anal. ($C_{26}H_{24}ClN_5O_6$·HCl) C, H, N.

Synthesis of 10 and 26.



Methyl 6-{[(dimethylamino)carbothioyl]oxy}-2-naphthoate (64). A mixture of methyl 6-hydroxy-2-naphthoate[2] (**63**) (5.95 g, 29.4 mmol), DABCO (1,4-diazabicyclo[2,2,2]octane) (6.61 g, 58.9 mmol) and dimethylthiocarbamoyl chloride (5.46 g, 44.2 mmol) in dry DMF (40 mL) was stirred at room temperature for 8 h. The precipitated solid was collected, washed with water and dissolved in CH_2Cl_2. The solution was filtered through a column of silica gel and the product was triturated with i-Pr_2O and recrystallized from CH_2Cl_2/hexane to give **64** (7.47 g, 88%) as a white solid: mp 144-147 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.66 (s, 1 H), 8.16 (d, *J* = 9.0 Hz, 1 H), 8.03 (d, *J* = 8.7 Hz, 1 H), 8.00 (dd, *J* = 8.6, 1.5 Hz, 1 H), 7.70 (d, *J* = 2.3 Hz, 1 H), 7.38 (dd, *J* = 8.9, 2.3 Hz, 1 H), 3.93 (s, 3 H), 3.40 (s, 3 H), 3.38 (s, 3 H). Anal. ($C_{15}H_{15}NO_3S$) C, H, N.

Methyl 6-{[(dimethylamino)carbonyl]sulfanyl}-2-naphthoate (65). Thiocarbamate **64** (8.10g, 28 mmol) was heated under N_2 at 225 °C for 3 h. The cooled mixture was purified by chromatography on silica gel, eluting with CH_2Cl_2/EtOAc, followed by trituration with i-Pr_2O to give **65** (6.91 g, 85%) as a white solid: mp (CH_2Cl_2/petroleum ether) 130-132 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.67 (s, 1 H), 8.17 (d, *J* = 0.8 Hz, 1 H), 8.16 (d, *J* = 8.8 Hz, 1 H), 8.07 (d, *J* = 8.7 Hz, 1 H), 8.03 (dd, *J* = 8.5, 1.6 Hz, 1 H), 7.60 (dd, *J* = 8.5, 1.8 Hz, 1 H), 3.93 (s, 3 H), 3.09 (br s, 3 H), 2.97 (br s, 3 H). Anal. ($C_{15}H_{15}NO_3S$) C, H, N.

6-(Methylsulfanyl)-2-naphthoic acid (66). A suspension of **65** (6.36 g, 22 mmol) in a mixture of aq KOH (5N, 340 mL, 1.7 mol) and MeOH (205 mL) was stirred at reflux for 3 h, then cooled to 5 °C and treated dropwise with Me_2SO_4 (26 mL, 275 mmol). After stirring at room temperature for a further 4 h the mixture was concentrated to half volume, acidified with dilute aq HCl, and the precipitated product was crystallized from EtOAc/hexane to give **66** (4.39 g, 91%) as a white solid: mp (MeOH) 231-233 °C; ^{1}H NMR [$(CD_3)_2SO$] δ (CO_2H not observed) 8.53 (s, 1 H), 8.01 (d, *J* = 8.9 Hz, 1 H), 7.96 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.90 (d, *J* = 8.7 Hz, 1 H), 7.77 (d, *J* = 1.7 Hz, 1 H), 7.47 (dd, *J* = 8.7, 1.9 Hz, 1 H), 2.61 (s, 3 H). Anal. ($C_{12}H_{10}O_2S$) C, H.

6-(Methylsulfonyl)-2-naphthoic acid (67). A mixture of **66** (4.24 g, 19.4 mmol) and $NaBO_3{\cdot}4H_2O$ (20.0 g, 130 mmol) in AcOH (150 mL) was stirred at 55 °C for 2 h. Additional

$NaBO_3 \cdot 4H_2O$ (5.4 g, 35 mmol) was added and the mixture was stirred at 55 °C for a further 2 h, then diluted with water (1 L). The precipitated solid was collected, washed with water, and recrystallized from MeOH then DMF/H_2O to give **67** (3.98 g, 82%) as a white solid: mp 301-304 °C; ^{1}H NMR [$(CD_3)_2SO$] δ (CO_2H not observed) 8.74 (s, 1 H), 8.66 (s, 1 H), 8.39 (d, *J* = 8.8 Hz, 1 H), 8.30 (d, *J* = 8.8 Hz, 1 H), 8.13 (dd, *J* = 8.6, 1.7 Hz, 1 H), 8.03 (dd, *J* = 8.7, 1.9 Hz, 1 H), 3.32 (s, 3 H). Anal. ($C_{12}H_{10}O_4S$) C, H.

***tert*-Butyl 6-(methylsulfonyl)-2-naphthylcarbamate (109).** A suspension of acid **67** (4.08 g, 16.30 mmol) in dry t-BuOH (70 mL) containing powdered molecular sieves (2 g) was treated with Et_3N (2.73 mL, 19.59 mmol) and stirred under N_2 at room temperature for 30 min. DPPA (3.87 mL, 17.96 mmol) was added and the mixture was stirred at reflux for 6 h, then concentrated to a small volume under reduced pressure and poured into dilute aqueous $NaHCO_3$. The resulting solid was purified by chromatography on silica gel, eluting with CH_2Cl_2, to give **109** (4.57 g, 87%) as a white solid: mp (EtOAc/hexane) 203-204 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.81 (s, 1 H), 8.44 (d, *J* = 1.2 Hz, 1 H), 8.26 (s, 1 H), 8.08 (d, *J* = 9.0 Hz, 1 H), 8.01 (d, *J* = 8.7 Hz, 1 H), 7.84 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.66 (dd, *J* = 8.9, 2.0 Hz, 1 H), 3.25 (s, 3 H), 1.52 (s, 9 H). Anal. ($C_{16}H_{19}NO_4S$) C, H, N.

***tert*-Butyl 1-bromo-6-(methylsulfonyl)-2-naphthylcarbamate (110).** A mixture of **109** (4.47 g, 13.91 mmol) and NBS (2.72 g, 15.28 mmol) in MeCN (80 mL) was stirred at reflux for 3 h, then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and the solution was washed with 10% aq Na_2SO_3 and water, dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with CH_2Cl_2, to give **110** (4.79 g, 86%) as a white solid: mp (MeOH) 190 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.95 (s, 1 H), 8.61 (d, *J* = 1.8 Hz, 1 H), 8.36 (d, *J* = 9.0 Hz, 1 H), 8.22 (d, *J* = 8.8 Hz, 1 H), 8.08 (dd, *J* = 9.0, 1.9 Hz, 1 H), 7.96 (d, *J* = 8.9 Hz, 1 H), 3.25 (after D_2O exchange, s, 3 H), 1.50 (s, 9 H). Anal. ($C_{16}H_{18}BrNO_4S$) C, H, N.

***tert*-Butyl 1-bromo-6-(methylsulfonyl)-2-naphthyl(3-chloro-2-propen-1-yl)carbamate (111).** A stirred suspension of **110** (4.70 g, 11.74 mmol) in dry DMF (40 mL) was treated portionwise at 0°C with NaH (564 mg, 60% in oil, 14.10 mmol). The mixture was warmed to room temperature for 1 h then cooled to 0 °C and treated with 1,3-dichloropropene (3.4 mL, 37 mmol, mixed isomers). The mixture was stirred at room temperature for a further 6 h, then diluted with 10% aqueous NaCl and extracted with EtOAc (×2). The combined organic layers were washed with water (×2), dried, and concentrated to dryness under reduced pressure at 100 °C. The residue was chromatographed on silica gel, eluting with CH_2Cl_2/EtOAc (9:1) to give **111** (5.41 g, 97%) as a foam; ^{1}H NMR [$(CD_3)_2SO$] (mixture of rotamers and E and Z forms) δ 8.73-8.69 (m, 1 H), 8.46 (d, *J* = 9.0 Hz, 1 H), 8.30, 8.29 (2 d, *J* = 8.6 Hz, 1 H), 8.14 (dd, *J* = 9.0, 1.8 Hz, 1 H), 7.71, 7.68 (2 d, *J* = 8.6 Hz, 1 H), 6.43-6.28 (m, 1 H), 6.19-6.01 (m, 1 H), 4.59-4.48, 4.44-4.23, 4.19-4.05 (3 m, 2 H), 3.27 (after D_2O exchange, s, 3 H), 1.50, 1.26 (2 s, 9 H). HRMS (FAB) calcd. for $C_{19}H_{22}{}^{79}Br^{35}ClNO_4S$ (MH^+) m/z 474.0141, found 474.0142.

***tert*-Butyl 1-(chloromethyl)-7-(methylsulfonyl)-1,2-dihydro-3*H*-benzo[*e*]indole 3-carboxylate (112).** A mixture of **111** (5.38 g, 11.33 mmol), Bu_3SnH (3.05 mL, 11.34 mmol) and AIBN (0.25 g, 1.5 mmol) in dry benzene (80 mL) under N_2 was stirred at reflux for 2 h, then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and the solution was diluted with excess

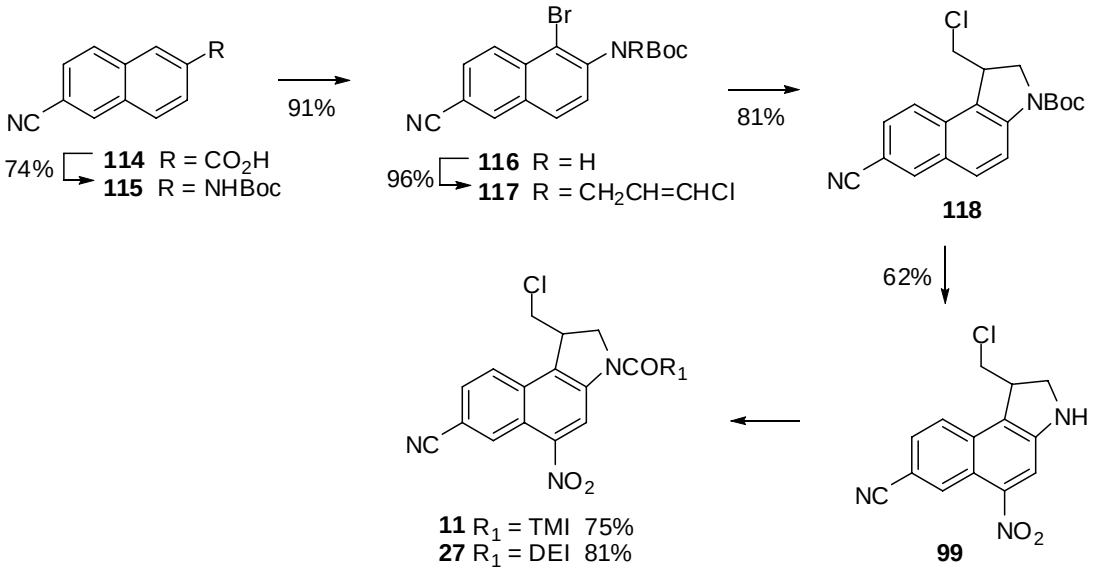
hexane and refrigerated. The precipitated semisolid was purified by chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (19:1), to give **112** (3.53 g, 79%) as a white solid: mp (iPr_2O) 125-126 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.54 (d, *J* = 1.8 Hz, 1 H), 8.25-8.05 (m, 3 H), 7.91 (dd, *J* = 8.9, 1.9 Hz, 1 H), 4.36-4.27 (m, 1 H), 4.23 (t, *J* = 10.5 Hz, 1 H), 4.10 (dd, *J* = 11.4, 2.9 Hz, 1 H), 4.05 (dd, *J* = 11.1, 3.2 Hz, 1 H), 3.94 (dd, *J* = 11.1, 6.7 Hz, 1 H), 3.21 (after D_2O exchange, s, 3 H), 1.56 (s, 9 H). Anal. ($C_{19}H_{22}ClNO_4S$) C, H, N.

1-(Chloromethyl)-7-(methylsulfonyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (113). Powdered **112** (1.50 g, 3.79 mmol) was added to stirred cH_2SO_4 (16 mL) at 0 °C, and the mixture was warmed to room temperature for 30 min. The resulting solution was cooled to -5°C and treated dropwise with a solution of KNO_3 (421 mg, 4.16 mmol) in cH_2SO_4 (3 mL). The mixture was stirred at 0 °C for a further 10 min then poured into ice/water and neutralized with aqueous NH_3. The resulting solid was purified by chromatography on silica gel, eluting with CH_2Cl_2, to give **113** (926 mg, 72%) as a red solid: mp (EtOAc) 199-200 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.68 (d, *J* = 1.6 Hz, 1 H), 8.06 (dd, *J* = 8.9, 0.4 Hz, 1 H), 7.90 (dd, *J* = 8.9, 1.8 Hz, 1 H), 7.79 (s, 1 H), 6.83 (s, 1 H), 4.31-4.23 (m, 1 H), 3.95-3.86 (m, 2 H), 3.82 (dd, *J* = 11.1, 8.1 Hz, 1 H), 3.76 (dd, *J* = 10.1, 3.1 Hz, 1 H), 3.25 (s, 3 H). Anal. ($C_{14}H_{13}ClN_2O_4S$) C, H, N, Cl.

1-(Chloromethyl)-7-(methylsulfonyl)-5-nitro-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (10). A mixture of amine **113** (250 mg, 0.73 mmol), 5,6,7-trimethoxyindole-2-carboxylic acid (221 mg, 0.88 mmol), EDCI (563 mg, 2.94 mmol) and anhydrous TsOH (100 mg, 0.58 mmol) in dry DMA (8 mL) was stirred at room temperature for 4 h, then poured into dilute aqueous $KHCO_3$. The precipitate was collected and crystallized from DMF/H_2O to give **10** (353 mg, 84%) as a yellow solid: mp 296-297 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.62 (s, 1 H), 9.27 (s, 1 H), 8.98 (d, *J* = 1.7 Hz, 1 H), 8.48 (d, *J* = 8.9 Hz, 1 H), 8.15 (dd, *J* = 8.9, 1.8 Hz, 1 H), 7.21 (d, *J* = 2.2 Hz, 1 H), 6.99 (s, 1 H), 4.95 (t, *J* = 10.7 Hz, 1 H), 4.70-4.61 (m, 2 H), 4.20-4.06 (m, 2 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.28 (s, 3 H). Anal. ($C_{26}H_{24}ClN_3O_8S\cdot½H_2O$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-7-(methylsulfonyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (26). A mixture of amine **113** (350 mg, 1.03 mmol), 5-[2-(dimethylamino)ethoxy]indol-2-carboxylic acid hydrochloride (351 mg, 1.23 mmol), EDCI (788 mg, 4.11 mmol) and anhydrous TsOH (140 mg, 0.81 mmol) in dry DMF (20 mL) was stirred under N_2 at room temperature for 6 h, then poured into dilute aq NH_3. The precipitated solid was collected, dissolved in CH_2Cl_2, and the dried solution was diluted with EtOAc and concentrated under reduced pressure below 25°C to a small volume to give crude **26**. Treatment of a suspension of the free base in MeOH with HCl(g)/EtOAc/hexane followed by crystallization from MeOH/EtOAc gave **26**·HCl (484 mg, 78%) as a yellow solid: mp 250-252 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.83 (d, *J* = 1.7 Hz, 1 H), 10.19 (br s, 1 H), 9.32 (s, 1 H), 8.98 (d, *J* = 1.7 Hz, 1 H), 8.50 (d, *J* = 8.9 Hz, 1 H), 8.17 (dd, *J* = 8.9, 1.8 Hz, 1 H), 7.47 (d, *J* = 8.9 Hz, 1 H), 7.27 (d, *J* = 2.3 Hz, 1 H), 7.25 (d, *J* = 1.7 Hz, 1 H), 7.04 (dd, *J* = 8.9, 2.4 Hz, 1 H), 5.00 (t, *J* = 10.1 Hz, 1 H), 4.77-4.65 (m, 2 H), 4.37 (t, *J* = 5.0 Hz, 2 H), 4.20-4.09 (m, 2 H), 3.51 (br s, 2 H), 3.36 (s, 3 H), 2.86 (s, 6 H). Anal. ($C_{27}H_{27}ClN_4O_6S\cdot HCl$) C, H, N.

Synthesis of 11 and 27.



***tert*-Butyl 6-cyano-2-naphthylcarbamate (115).** A suspension of 6-cyano-2-naphthoic acid[3] (**114**) (4.62 g, 23.4 mmol) in dry t-BuOH (120 mL) containing powdered molecular sieves (2 g) was treated with Et_3N (3.91 mL, 28.1 mmol) and the mixture was stirred at room temperature under N_2 for 30 min. DPPA (5.55 mL, 25.8 mmol) was added, and the mixture was stirred at reflux for 6 h, then concentrated to half volume and poured into dilute aq $NaHCO_3$. The resulting solid was purified by chromatography on silica gel, eluting with CH_2Cl_2, to give **115** (4.68 g, 74%): mp (MeOH/H_2O) 135-136 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.85 (s, 1 H), 8.42 (d, *J* = 0.9 Hz, 1 H), 8.23 (d, *J* = 1.0 Hz, 1 H), 7.95 (d, *J* = 8.7 Hz, 2 H), 7.68 (dd, *J* = 8.5, 1.6 Hz, 1 H), 7.64 (dd, *J* = 9.0, 2.0 Hz, 1 H), 1.52 (s, 9 H). Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

***tert*-Butyl 1-bromo-6-cyano-2-naphthylcarbamate (116).** A solution of **115** (4.48 g, 18 mmol) and NBS (3.85 g, 21.6 mmol) in MeCN (80 mL) was stirred at reflux for 1 h, then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with 10% aqueous Na_2SO_3, water, dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with CH_2Cl_2, to give **116** (5.69 g, 91%): mp (iPr_2O/hexane) 164-166 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.01 (s, 1 H), 8.63 (d, *J* = 1.5 Hz, 1 H), 8.27 (d, *J* = 9.0 Hz, 1 H), 8.07 (d, *J* = 9.0 Hz, 1 H), 7.94 (d, *J* = 8.9 Hz, 1 H), 7.93 (dd, *J* = 8.9, 1.8 Hz, 1 H), 1.50 (s, 9 H). Anal. ($C_{16}H_{15}BrN_2O_2$) C, H, N, Br.

***tert*-Butyl 1-bromo-6-cyano-2-naphthyl(3-chloro-2-propenyl)carbamate (117).** A stirred solution of **116** (5.78 g, 16.6 mmol) in dry DMF (50 mL) was treated at 0 °C with NaH (0.80 g, 20.0 mmol, 60% in oil). The resulting suspension was warmed to room temperature for 30 min, then cooled to 0 °C again and treated with 1,3-dichloropropene (4.8 mL, 52 mmol, mixed isomers). After stirring at room temperature for a further 6 h, the mixture was diluted with water and extracted with EtOAc (×3). The combined organic extracts were washed with water (×3), dried, and concentrated to dryness under high vacuum at 80 °C. The residue was chromatographed on silica gel, eluting with CH_2Cl_2, to give **117** (6.77 g, 96%) as a foam; ^{1}H NMR [$(CD_3)_2SO$] (mixture of rotamers and E and Z forms) δ 8.69 (s, 1 H),

8.35 (d, *J* = 8.8 Hz, 1 H), 8.13, 8.12 (2 d, *J* = 8.6 Hz, 1 H), 7.96 (d, *J* = 8.9 Hz, 1 H), 7.69, 7.63 (2d, *J* = 8.7 Hz, 1 H), 6.42-6.29 (m, 1 H), 6.17-5.99 (m, 1 H), 4.55-4.45, 4.40-4.19, 4.15-3.98 (3 m, 2 H), 1.48, 1.24 (2 s, 9 H). HRMS (FAB) calcd. for $C_{19}H_{19}{}^{79}Br^{35}ClN_2O_2$ (MH^+) m/z 421.0318, found 421.0306.

***tert*-Butyl 1-(chloromethyl)-7-cyano-1,2-dihydro-3*H*-benzo[*e*]indole-3-carboxylate (118).** A solution of **117** (6.78 g, 16.1 mmol) in dry benzene (80 mL) was treated with Bu_3SnH (4.33 mL, 16.1 mmol), followed by AIBN (0.3 g, 1.8 mmol). The mixture was stirred at reflux under N_2 for 2 h, then concentrated under reduced pressure, and the residue was chromatographed on silica gel. Elution with CH_2Cl_2 gave an oil that was triturated with iPr_2O, to provide **118** contaminated with *tert*-butyl 7-cyano-1-methyl-1,2-dihydro-3*H*-benzo[*e*]indole-3-carboxylate. Two recrystallizations from CH_2Cl_2/iPr_2O gave pure **118** (4.49 g, 81%): mp 171-172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.55 (d, *J* = 1.4 Hz, 1 H), 8.18 (v br, 1 H), 8.07 (d, *J* = 8.7 Hz, 1 H), 8.01 (d, *J* = 8.9 Hz, 1 H), 7.75 (dd, *J* = 8.7, 1.7 Hz, 1 H), 4.34-4.25 (m, 1 H), 4.21 (t, *J* = 10.5 Hz, 1 H), 4.09 (dd, *J* = 11.3, 2.8 Hz, 1 H), 4.03 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.93 (dd, *J* = 11.1, 6.7 Hz, 1 H), 1.55 (s, 9 H). Anal. ($C_{19}H_{19}ClN_2O_2 \cdot ¼H_2O$) C, H, N.

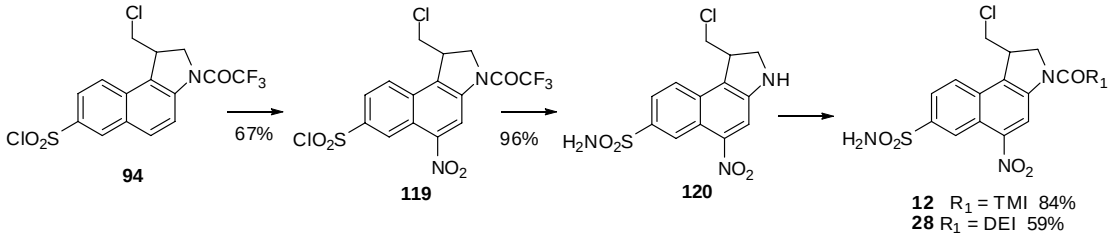
1-(Chloromethyl)-7-cyano-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (99). Powdered **118** (1.00 g, 2.9 mmol) was added portionwise to stirred cH_2SO_4 (10 mL) at 0 °C, and the mixture was warmed to room temperature for 10 min. The resulting solution was cooled to -5 °C and treated dropwise with a solution of KNO_3 (324 mg, 3.2 mmol) in cH_2SO_4 (2 mL). After stirring for a further 5 min at 0 °C, the mixture was poured into ice/water and neutralized with dilute aq NH_3. The resulting solid was purified by chromatography on silica gel, eluting with CH_2Cl_2, followed by recrystallization from CH_2Cl_2, then EtOAc, to give **99** (522 mg, 62%) as a red solid: mp 237-238 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.55 (d, *J* = 1.4 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.77 (s, 1 H), 7.74 (dd, *J* = 8.8, 1.5 Hz, 1 H), 6.87 (s, 1 H), 4.29-4.21 (m, 1 H), 3.94-3.85 (m, 2 H), 3.80 (dd, *J* = 11.1, 8.1 Hz, 1 H), 3.75 (dd, *J* = 10.6, 3.1 Hz, 1 H). Anal. ($C_{14}H_{10}ClN_3O_2$) C, H, N, Cl.

1-(Chloromethyl)-5-nitro-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole-7-carbonitrile (11). A suspension of 5,6,7-trimethoxyindole-2-carboxylic acid (79 mg, 0.31 mmol) in dry CH_2Cl_2 (6 mL) was treated with oxalyl chloride (80 μL, 0.92 mmol) followed by DMF (10 μL). The mixture was stirred at room temperature for 30 min, then evaporated to dryness under reduced pressure and re-evaporated after addition of benzene. The resulting acid chloride was cooled to –5 °C and treated with an ice-cold solution of **99** (60 mg, 0.21 mmol) in dry pyridine (1.5 mL) containing DMAP (5 mg). The mixture was stirred at room temperature for 15 min, then poured into dilute aq $KHCO_3$. The resulting solid was purified by chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (9:1), to give **11** (81 mg, 75%) as a yellow solid: mp (CH_2Cl_2/EtOAc) 257-258 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.62 (s, 1 H), 9.23 (s, 1 H), 8.86 (d, *J* = 1.4 Hz, 1 H), 8.39 (d, *J* = 8.8 Hz, 1 H), 8.02 (dd, *J* = 8.8, 1.4 Hz, 1 H), 7.19 (d, *J* = 2.1 Hz, 1 H), 6.98 (s, 1 H), 4.93 (t, *J* = 10.6 Hz, 1 H), 4.69-4.59 (m, 2 H), 4.16-4.05 (m, 2 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H). Anal. ($C_{26}H_{21}ClN_4O_6$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-carbonitrile (27). A mixture of **99** (60 mg, 0.21 mmol), 5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (71 mg, 0.25 mmol), EDCI (160 mg, 0.83 mmol) and anhydrous TsOH (25 mg, 0.15 mmol) in dry DMA (3 mL) was stirred under N_2 at

room temperature for 6 h, then poured into dilute aq NH_3. The precipitated solid was collected, washed with water, and dissolved in CH_2Cl_2. The dried solution was concentrated under reduced pressure below 25 ^oC to a small volume and diluted with i-Pr_2O to give crude **27**. Treatment of a solution of the free base in CH_2Cl_2 with HCl(g)/EtOAc/hexane, gave **27**·HCl (94 mg, 81%) as a yellow solid: mp (MeOH/EtOAc) >300 ^oC; ^1H NMR [$(CD_3)_2SO$] δ 11.86 (s, 1 H), 10.04 (v br s, 1 H), 9.31 (s, 1 H), 8.90 (d, *J* = 1.2 Hz, 1 H), 8.44 (d, *J* = 8.8 Hz, 1 H), 8.06 (dd, *J* = 8.8, 1.5 Hz, 1 H), 7.50 (d, *J* = 8.9 Hz, 1 H), 7.31 (d, *J* = 2.3 Hz, 1 H), 7.28 (d, *J* = 1.7 Hz, 1 H), 7.08 (dd, *J* = 8.9, 2.4 Hz, 1 H), 5.00 (t, *J* = 10.2 Hz, 1 H), 4.79-4.65 (m, 2 H), 4.39 (t, *J* = 5.1 Hz, 2 H), 4.21-4.10 (m, 2 H), 3.56 (t, *J* = 5.0 Hz, 2 H), 2.90 (s, 6 H). Anal. ($C_{27}H_{24}ClN_5O_4$·HCl) C, H, N.

Synthesis of 12 and 28.



1-(Chloromethyl)-5-nitro-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole-7-sulfonyl chloride (119). A solution of **94** (250 mg, 0.63 mmol) in cH_2SO_4 (10 mL) was nitrated with KNO_3 (65 mg, 0.65 mmol) in H_2SO_4 (5 mL) according to the general method, to give **119** (192 mg, 67%) as a red solid: mp (EtOAc/petroleum ether) 184-189 °C; ^{1}H NMR [($CDCl_3$)] δ 9.34 (s, 1 H), 9.28 (d, *J* = 1.8 Hz, 1 H), 8.22 (dd, *J* = 9.0, 1.9 Hz, 1 H), 8.11 (d, *J* = 9.0 Hz, 1 H), 4.77-4.71 (m, 1 H), 4.58 (dd, *J* = 11.5, 8.8 Hz, 1 H), 4.42-4.33 (m, 1 H), 3.95 (dd, *J* = 11.7, 3.5 Hz, 1 H), 3.73 (dd, *J* = 11.7, 7.7 Hz, 1 H); ^{13}C NMR δ 153.4 (q, J_{C-F} 38 Hz), 153.0, 148.2, 147.0, 138.7, 133.2, 129.1, 126.7, 124.5, 122.0, 119.3, 115.9 (q, J_{C-F} 288 Hz), 52.6, 47.3, 41.2. Anal. ($C_{15}H_9Cl_2F_3N_2O_5S$) C, H, N, Cl.

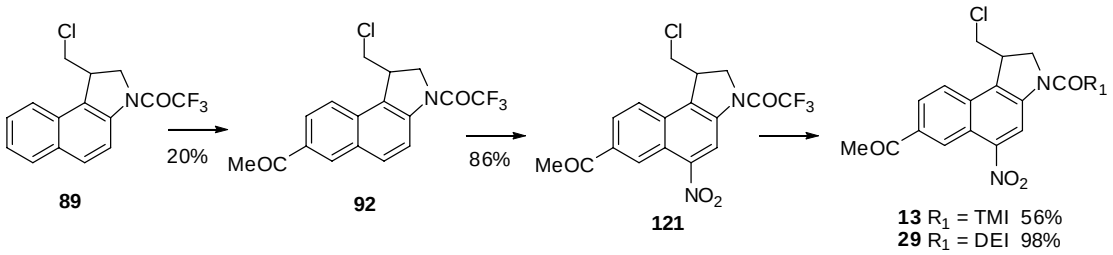
1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-sulfonamide (120). Conc. aq NH_3 (0.5 mL, 7.3 mmol) was added to a solution of **119** (299 mg, 0.65 mmol) in THF (10 mL) at 0 ºC, and the ice bath was removed. The mixture was stirred for 7 min and then Cs_2CO_3 (0.55 g, 1.7 mmol) and MeOH (4 mL) were added. After stirring for a further 15 min the mixture was diluted with brine and extracted with CH_2Cl_2 (×3). The combined extracts were dried and evaporated to give **120** (214 mg, 96%) as an orange solid. A sample was triturated with EtOAc: mp 183-187 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 8.59 (d, *J* = 1.7 Hz, 1 H), 8.03 (d, *J* = 8.9 Hz, 1 H), 7.85 (dd, *J* = 8.9, 1.7 Hz, 1 H), 7.75 (s, 1 H), 7.42 (s, 2 H), 6.68 (s, 1 H), 4.28-4.21 (m, 1 H), 3.95-3.85 (m, 2 H), 3.81 (dd, *J* = 11.2, 8.3 Hz, 1 H), 3.73 (dd, *J* = 10.4, 3.0 Hz, 1 H). Anal. ($C_{13}H_{12}ClN_3O_4S$) C, H, N.

1-(Chloromethyl)-5-nitro-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole-7-sulfonamide (12). A mixture of **120** (161 mg, 0.47 mmol), 5,6,7-trimethoxyindole-2-carboxylic acid (154 mg, 0.61 mmol), EDCI (361 mg, 1.88 mmol), and TsOH (16 mg, 0.09 mmol) in DMA (3 mL) was stirred at room temperature for 22 h and then cooled to 0 ºC. Ice-cold aq $NaHCO_3$ was added. The precipitated solid was filtered off and washed with aq $NaHCO_3$, water, and then dried in a vacuum desiccator. The crude product was triturated with EtOAc to give **12** (228 mg, 84%) as a yellow-brown solid: mp 280-285 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.60 (d, *J* = 1.7 Hz, 1 H), 9.23 (s, 1 H), 8.87 (d, *J* = 1.7 Hz, 1 H), 8.43 (d, *J* = 8.9 Hz, 1 H), 8.06 (dd, *J* = 8.9, 1.7 Hz, 1 H), 7.62 (s, 2 H), 7.19 (d, *J* = 2.2 Hz, 1 H), 6.98 (s, 1 H), 4.93 (dd, *J* = 11.1, 10.0 Hz, 1 H), 4.68-4.59 (m, 2 H), 4.17-4.09 (m, 2 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H). Anal. ($C_{25}H_{23}ClN_4O_8S$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-sulfonamide (28). The amine **120** was reacted with 5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid as described in the general method. The product crystallized from CH_2Cl_2/MeOH to give **28**. This proved to be unstable as the free base and was immediately dissolved in CH_2Cl_2/MeOH (1:1, 20 mL) and treated with methanolic HCl (5 mL), followed by precipitation with petroleum ether. The solid was collect by filtration and air-dried to give

28·HCl (110 mg, 59%): mp >350 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.82 (s, 1 H), 10.05 (br, 1 H), 9.28 (s, 1 H), 8.85 (d, *J* = 1.7 Hz, 1 H), 8.44 (d, *J* = 8.9 Hz, 1 H), 8.06 (dd, *J* = 8.9, 1.7 Hz, 1 H), 7.63 (s, 2 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 7.24 (d, *J* = 1.7 Hz, 1 H), 7.04 (dd, *J* = 8.9, 2.4 Hz, 1 H), 5.02-4.94 (m, 1 H), 4.74-4.62 (m, 2 H), 4.38-4.33 (m, 2 H), 4.18-4.12 (m, 2 H), 3.57-3.51 (m, 2 H), 2.88 (s, 6 H); ^{13}C NMR δ 160.6, 152.1, 147.0, 142.6, 142.5, 132.3, 132.2, 130.4, 130.0, 127.3, 125.6, 124.4, 121.3, 120.5, 116.2, 116.0, 113.4, 106.0, 104.0, 62.7, 55.5, 54.8, 47.6, 42.8, 41.4. Anal. ($C_{26}H_{26}ClN_5O_6S$·HCl·½H_2O) C, H, N.

Synthesis of 13 and 29.



7-Acetyl-1-(chloromethyl)-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole (92). Acylation of **89** (0.88 g, 2.8 mmol) with $AlCl_3$ and AcCl in $PhNO_2$ at 0 °C, stirring at room temperature for 16 h, and workup as above, gave a crude product. Chromatography on silica gel, eluting with EtOAc/petroleum ether (from 0:1 to 1:3) gave **92** (196 mg, 33% based on consumption of starting material): mp (EtOAc/petroleum ether) 168-170 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 8.9 Hz, 1 H), 8.51 (s, 1 H), 8.14 (dd, J = 8.8, 1.7 Hz, 1 H), 8.02 (d, J = 9.0 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 1 H), 4.68-4.62 (m, 1 H), 4.49-4.41 (m, 1 H), 4.28-4.19 (m, 1 H), 3.99-3.93 (m, 1 H), 3.61-3.55 (m, 1 H), 2.74 (s, 3 H); ^{13}C NMR δ 197.6, 182.8, 154.9 (q, J_{C-F} 38.4 Hz), 142.1, 134.1, 132.2, 131.3, 131.1, 125.7, 125.5, 131.1, 118.1, 116.0 (q, J_{C-F} 288 Hz), 52.7, 45.4, 42.6, 26.6. Anal. ($C_{17}H_{13}ClF_3NO_2$) C, H, N.

Further elution gave recovered **89** (360 mg, 40%).

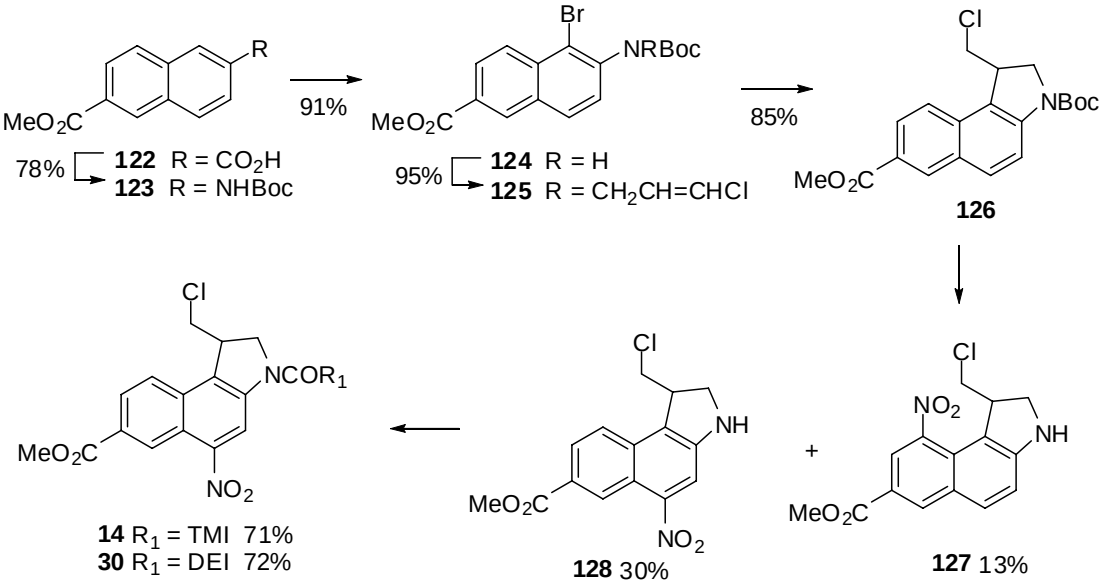
7-Acetyl-1-(chloromethyl)-5-nitro-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole (121). A solution of **92** (200 mg, 0.56 mmol) in cH_2SO_4 (10 mL) was cooled to 5 °C and treated with KNO_3 (60 mg, 0.6 mmol) in one portion. The mixture was stirred vigorously for 30 min at 5 °C. The reaction was quenched with cold water and the mixture was extracted with EtOAc (3×50 ml). The extracts were dried and concentrated under reduced pressure. Chromatography of the residue on silica gel, eluting with EtOAc/petroleum ether (from 1:4 to 1:1) gave **121** (177 mg, 86%) as an orange solid: mp (EtOAc/petroleum ether) 158-160 °C; ^{1}H NMR ($CDCl_3$) δ 9.18 (s, 1 H), 9.06 (d, J = 1.4 Hz, 1 H), 8.28 (dd, J = 8.8, 1.6 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 1 H), 4.74-4.68 (m, 1 H), 4.58-4.51 (m, 1 H), 4.40-4.31 (m, 1 H), 4.00-3.92 (m, 1 H), 3.74-3.66 (m, 1 H), 2.75 (s, 3 H); ^{13}C NMR δ 196.9, 149.1 (q, J_{C-F} 38.8 Hz), 140.7, 136.5, 131.5, 130.9, 130.8, 127.0, 126.5, 123.6, 123.1, 115.7 (q, J_{C-F} 288 Hz), 115.5, 52.8, 45.3, 42.7, 26.5. Anal. ($C_{17}H_{12}ClF_3N_2O_4$) C, H, N.

7-Acetyl-1-(chloromethyl)-5-nitro-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (13). Deprotection of **121** (80 mg, 0.2 mmol) and reaction with 5,6,7-trimethoxyindole-2-carboxylic acid chloride as described in the general method, and purification of the crude product by chromatography, gave **13** (60 mg, 56%): mp (CH_2Cl_2/petroleum ether) 257-260 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.58 (s, 1 H), 9.17 (s, 1 H), 8.96 (d, J = 1.4 Hz, 1 H), 8.29 (d, J = 8.8 Hz, 1 H), 8.15 (dd, J = 8.8, 1.6 Hz, 1 H), 7.18 (d, J = 2.2 Hz, 1 H), 6.97 (s, 1 H), 4.95-4.87 (m, 1 H), 4.67-4.58 (m, 2 H), 4.17-4.05 (m, 2 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 2.75 (s, 3 H); ^{13}C NMR δ 197.2, 160.6, 149.3, 147.5, 142.6, 140.3, 139.0, 134.9, 131.8, 131.3, 129.6, 126.0, 125.8, 125.1, 124.5, 123.1, 120.9, 115.5, 107.2, 98.0, 61.0, 60.8, 55.9, 54.9, 47.5, 41.2, 26.6. Anal. ($C_{27}H_{24}ClN_3O_7$) C, H, N.

7-Acetyl-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (29). Similar deprotection of **121** (177 mg, 0.44 mmol) and reaction with

5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride gave **29** (230 mg, 98%): mp (CH_2Cl_2/MeOH) >350 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.71 (s, 1 H), 9.23 (s, 1 H), 8.97 (d, *J* = 1.3 Hz, 1 H), 8.33 (d, *J* = 8.8 Hz, 1 H), 8.16 (dd, *J* = 8.8, 1.5 Hz, 1 H), 7.40 (d, *J* = 8.9 Hz, 1 H), 7.20 (d, *J* = 1.7 Hz, 1 H), 7.18 (d, *J* = 2.3 Hz, 1 H), 6.94 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.92-4.80 (m, 1 H), 4.74-4.60 (m, 2 H), 4.18-4.03 (m, 4 H), 2.73 (s, 3 H), 2.66 (t, *J* = 7.8 Hz, 2 H), 2.24 (s, 6 H). Anal. ($C_{28}H_{27}ClN_4O_5 \cdot H_2O$) C, H, N, Cl.

Synthesis of 14 and 30.



Methyl 6-[(*tert*-butoxycarbonyl)amino]-2-naphthoate (123). A suspension of 6-(methoxycarbonyl)-2-naphthoic acid[3] (**122**) (1.21 g, 5.26 mmol) in dry t-BuOH (20 mL) containing powdered molecular sieves (1 g) was treated with Et_3N (0.88 mL, 6.31 mmol) and stirred under N_2 at room temperature for 30 min. DPPA (1.25 mL, 5.80 mmol) was added and the mixture was stirred at reflux for 7 h, then cooled and poured into dilute aq $NaHCO_3$. The resulting solid was purified by chromatography on silica gel, eluting with CH_2Cl_2, followed by trituration with iPr_2O and recrystallization from EtOAc to give **123** (1.24 g, 78%) as a white solid: mp 178-180 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.76 (s, 1 H), 8.51 (s, 1 H), 8.19 (s, 1 H), 8.02 (d, *J* = 9.0 Hz, 1 H), 7.90 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.86 (d, *J* = 8.7 Hz, 1 H), 7.59 (dd, *J* = 8.9, 2.1 Hz, 1 H), 3.89 (s, 3 H), 1.52 (s, 9 H). Anal. ($C_{17}H_{19}NO_4$) C, H, N.

Methyl 2-[(*tert*-butoxycarbonyl)amino]-1-bromo-6-naphthoate (124). A mixture of **123** (977 mg, 3.24 mmol) and NBS (664 mg, 3.73 mmol) in CH_3CN (25 mL) was stirred at reflux for 45 min, then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and the solution was washed with 10% aq Na_2SO_3 and water (×2), dried, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with CH_2Cl_2, to give **124** (1.12 g, 91%) as a white solid: mp (petroleum ether) 130-131 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.93 (s, 1 H), 8.65 (d, *J* = 1.6 Hz, 1 H), 8.64 (d, *J* = 8.9 Hz, 1 H), 8.16 (d, *J* = 8.9 Hz, 1 H), 8.11 (dd, *J* = 8.9, 1.7 Hz, 1 H), 7.86 (d, *J* = 8.9 Hz, 1 H), 3.93 (s, 3 H), 1.50 (s, 9 H). Anal. ($C_{17}H_{18}BrNO_4$) C, H, N, Br.

Methyl 2-[(*tert*-butoxycarbonyl)(3-chloro-2-propen-1-yl)amino]-1-bromo-6-naphthoate (125). A stirred solution of **124** (1.05 g, 2.76 mmol) in dry DMF (8 mL) was treated at 0 °C with NaH (132 mg, 60% in oil, 3.30 mmol). The resulting suspension was warmed to room temperature for 30 min, then cooled to 0 °C and treated with 1,3-dichloropropene (0.80 mL, 8.7 mmol, mixed isomers). The mixture was stirred at room temperature for a further 4 h then poured into dilute aqueous AcOH and extracted with EtOAc (×2). The combined organic layers were washed with dilute aq $NaHCO_3$ and water (×2), dried, and concentrated to dryness under reduced pressure at 100 °C. The residue was

chromatographed on silica gel, eluting with CH_2Cl_2/EtOAc (19:1) to give **125** (1.19 g, 95%) as a gum; ^{1}H NMR [$(CD_3)_2SO$] (mixture of rotamers and E and Z forms) δ 8.73 (s, 1 H), 8.34 (d, *J* = 8.9 Hz, 1 H), 8.16 (d, *J* = 8.9 Hz, 1 H), 7.63, 7.58 (2 d, *J* = 8.7 Hz, 1 H), 8.25, 8.24 (2 d, *J* = 8.6 Hz, 1 H), 6.45-6.31 (m, 1 H), 6.20-6.00 (m, 1 H), 4.58-4.48, 4.43-4.21, 4.16-4.00 (3 m, 2 H), 3.95 (s, 3 H), 1.50, 1.27 (2 s, 9 H). HRMS (FAB) calcd. for $C_{20}H_{22}{}^{79}Br^{35}ClNO_4$ (MH^+) m/z 454.0421, found 454.0410.

Methyl 3-(*tert*-butoxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxylate (126). A mixture of **125** (1.16 g, 2.55 mmol), Bu_3SnH (0.69 mL, 2.56 mmol) and AIBN (50 mg, 0.30 mmol) in dry benzene (15 mL) under N_2 was stirred at reflux for 2 h, then concentrated under reduced pressure. The residue was triturated with i-Pr_2O and the resulting solid was purified by chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (19:1), to give **126** (817 mg, 85%) as a white solid: mp (EtOAc) 187-189 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.60 (d, *J* = 1.2 Hz, 1 H), 8.1 (v br, 1 H), 8.09 (d, *J* = 8.6 Hz, 1 H), 8.00 (d, *J* = 8.8 Hz, 1 H), 7.97 (dd, *J* = 8.8, 1.6 Hz, 1 H), 4.31-4.23 (m, 1 H), 4.20 (t, *J* = 10.4 Hz, 1 H), 4.09 (dd, *J* = 11.2, 2.5 Hz, 1 H), 4.04 (dd, *J* = 11.1, 3.1 Hz, 1 H), 3.96-3.88 (m, 4 H), 1.55 (s, 9 H). Anal. ($C_{20}H_{22}ClNO_4$) C, H, N.

Methyl 1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxylate (128). Powdered **126** (900 mg, 2.39 mmol) was added to stirred cH_2SO_4 (6 mL) at 0 °C and the mixture was warmed to room temperature for 15 min. The resulting solution was cooled to -5 °C and treated dropwise with a solution of KNO_3 (266 mg, 2.63 mmol) in cH_2SO_4 (1.5 mL). The mixture was stirred at -5 °C for a further 5 min, then poured into ice/water and neutralized with dilute aqueous NH_3. The resulting solid was chromatographed on silica gel, eluting with CH_2Cl_2 to give crude methyl 1-(chloromethyl)-9-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxylate (**127**) (102 mg, 13%) as an orange-brown solid; ^{1}H NMR [$(CD_3)_2SO$] δ 8.66 (d, *J* = 1.7 Hz, 1 H), 8.30 (d, *J* = 1.7 Hz, 1 H), 8.08 (d, *J* = 8.8 Hz, 1 H), 7.25 (s, 1 H), 7.18 (d, *J* = 8.8 Hz, 1 H), 3.92-3.83 (m, 4 H), 3.74-3.67 (m, 1 H), 3.63 (dd, *J* = 10.6, 2.3 Hz, 1 H), 3.39-3.28 (m, 2 H).

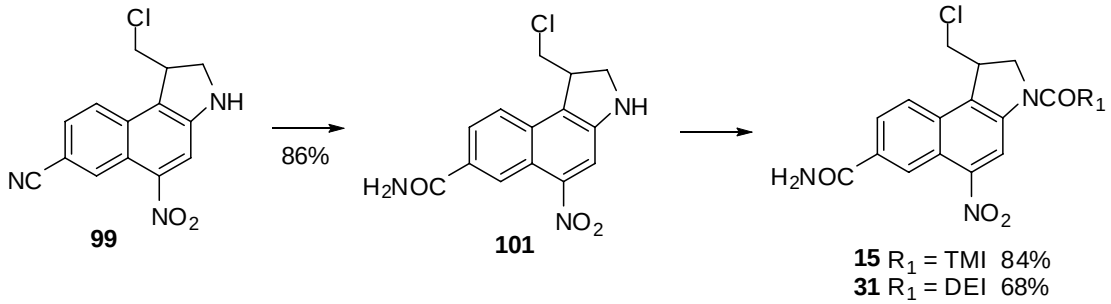
Further elution with CH_2Cl_2 gave **128** (228 mg, 30%) as a red solid: mp (CH_2Cl_2/i-Pr_2O) 191-192 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.77 (s, 1 H), 7.96 (dd, *J* = 8.9, 1.5 Hz, 1 H), 7.93 (dd, *J* = 8.9, 0.7 Hz, 1 H), 7.73 (s, 1 H), 6.74 (s, 1 H), 4.27-4.19 (m, 1 H), 3.94-3.85 (m, 5 H), 3.79 (dd, *J* = 11.0, 8.4 Hz, 1 H), 3.74 (dd, *J* = 10.5, 3.1 Hz, 1 H). Anal. ($C_{15}H_{13}ClN_2O_4$) C, H, N, Cl.

Methyl 1-(chloromethyl)-3-(5,6,7-trimethoxyindol-2-carbonyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxylate (14). A suspension of 5,6,7-trimethoxyindole-2-carboxylic acid (47 mg, 0.19 mmol) in dry CH_2Cl_2 (2 mL) was treated with oxalyl chloride (50 µl, 0.57 mmol) followed by DMF (10 µl). The mixture was stirred at room temperature for 30 min, then evaporated to dryness under reduced pressure and re-evaporated after addition of benzene. The resulting acid chloride was cooled to -5 °C and treated with an ice-cold solution of amine **128** (40 mg, 0.12 mmol) in dry pyridine (1 mL) containing DMAP (4 mg). The mixture was stirred at room temperature for 15 min, then poured into dilute aqueous $KHCO_3$. The precipitated solid was purified by chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (9:1), to give **14** (49 mg, 71%) as an orange solid: mp (CH_2Cl_2/iPr_2O) 256-257 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.60 (d, *J* = 1.8 Hz, 1 H), 9.19 (s, 1 H), 9.03 (d, *J* = 1.5 Hz, 1 H), 8.34 (d, *J* = 8.8 Hz, 1 H), 8.16 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.19 (d, *J* = 2.2 Hz, 1 H), 6.98 (s, 1 H), 4.92 (dd, *J*

= 10.6, 9.6 Hz, 1 H), 4.69-4.57 (m, 2 H), 4.18-4.05 (m, 2 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H). Anal. ($C_{27}H_{24}ClN_3O_8$) C, H, N.

Methyl 1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxylate (30). A mixture of **128** (80 mg, 0.25 mmol), 5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (85 mg, 0.30 mmol), EDCI (191 mg, 1.00 mmol) and anhydrous TsOH (25 mg, 0.15 mmol) in dry DMA (4 mL) was stirred under N_2 at room temperature for 7 h, then poured into dilute aqueous NH_3. The resulting solid was recrystallized twice from CH_2Cl_2/EtOAc/i-Pr_2O to give **30**. Treatment of a solution of **30** in CH_2Cl_2 with HCl(g)/EtOAc/hexane gave **30**·HCl (106 mg, 72%) as a yellow solid: mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.82 (d, *J* = 1.8 Hz, 1 H), 10.14 (br s, 1 H), 9.24 (s, 1 H), 9.03 (d, *J* = 1.4 Hz, 1 H), 8.35 (d, *J* = 8.7 Hz, 1 H), 8.17 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.47 (d, *J* = 8.9 Hz, 1 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 7.24 (d, *J* = 1.6 Hz, 1 H), 7.04 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.97 (dd, *J* = 10.7, 9.7 Hz, 1 H), 4.71 (dd, *J* = 10.9, 2.4 Hz, 1 H), 4.68-4.61 (m, 1 H), 4.37 (t, *J* = 5.1 Hz, 2 H), 4.18-4.08 (m, 2 H), 3.96 (s, 3 H), 3.53 (t, *J* = 5.0 Hz, 2 H), 2.87 (s, 6 H). Anal. ($C_{28}H_{27}ClN_4O_6$·HCl·0.5H_2O) C, H, N.

Synthesis of 15 and 31.



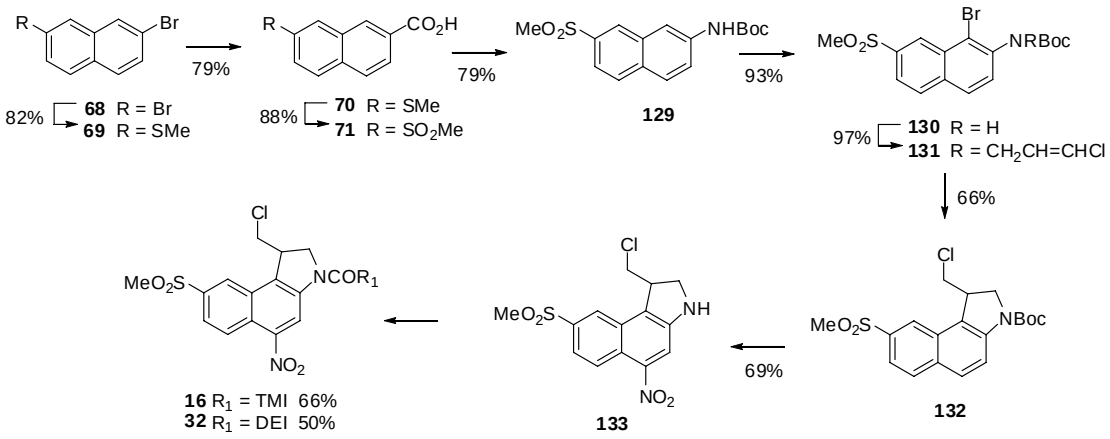
1-(Chloromethyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxamide (101). A solution of **99** (100 mg, 0.35 mmol) in a mixture of cH_2SO_4 (1.8 mL) and water (0.2 mL) was heated at 65 °C for 1 h, then cooled and neutralized with saturated aq $KHCO_3$. The precipitate was collected, washed with water, and dissolved in warm EtOAc. The solution was filtered through a column of silica gel and then concentrated and diluted with iPr_2O to give **101** (92 mg, 86%) as a red solid: mp (EtOAc/iPr_2O) >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.61 (d, *J* = 1.3 Hz, 1 H), 8.09, 7.39 (2 br s, 2 H), 7.95 (dd, *J* = 8.8, 1.7 Hz, 1 H), 7.89 (d, *J* = 8.7 Hz, 1 H), 7.66 (s, 1 H), 6.54 (s, 1 H), 4.26-4.18 (m, 1 H), 3.91 (dd, *J* = 11.0, 3.8 Hz, 1 H), 3.86 (td, *J* = 9.9, 2.3 Hz, 1 H), 3.78 (dd, *J* = 11.0, 8.5 Hz, 1 H), 3.72 (dd, *J* = 10.3, 2.6 Hz, 1 H). Anal. ($C_{14}H_{12}ClN_3O_3$) C, H, N.

1-(Chloromethyl)-5-nitro-3-[5,6,7-trimethoxyindol-2-carbonyl]-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxamide (15). A suspension of 5,6,7-trimethoxyindole-2-carboxylic acid (63 mg, 0.25 mmol) in dry CH_2Cl_2 (2 mL) was treated with oxalyl chloride (65 μL, 0.75 mmol), followed by DMF (10 μL), and the mixture was stirred at room temperature for 30 min. The mixture was evaporated under reduced pressure and then azeotroped with benzene. The resulting acid chloride was cooled to -5 °C and treated with an ice-cold solution of **101** (50 mg, 0.16 mmol) in dry pyridine (1 mL) containing DMAP (4 mg). After stirring at room temperature for 30 min the mixture was poured into dilute aq $KHCO_3$, and the precipitate was collected, washed with water, and dissolved in EtOAc/THF (4:1). This solution was filtered through a column of silica gel and then concentrated to give **15** (74 mg, 84%) as a yellow solid: mp (THF/EtOAc) 287-289 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.58 (d, *J* = 1.6 Hz, 1 H), 9.12 (s, 1 H), 8.85 (d, *J* = 1.4 Hz, 1 H), 8.28 (d, *J* = 8.7 Hz, 1 H), 8.27, 7.60 (2 s, 2 H), 8.15 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.18 (d, *J* = 2.2 Hz, 1 H), 6.99 (s, 1 H), 4.92 (dd, *J* = 10.7, 9.5 Hz, 1 H), 4.68-4.56 (m, 2 H), 4.18-4.06 (m, 2 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H). Anal. ($C_{26}H_{23}ClN_4O_7$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxamide (31). A mixture of **101** (86 mg, 0.28 mmol), 5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (96 mg, 0.34 mmol), EDCI (216 mg, 1.13 mmol) and anhydrous TsOH (30 mg, 0.17 mmol) in dry DMA (4 mL) was stirred at room temperature under N_2 for 2 h, then poured into dilute aq NH_3. The precipitate was collected, washed with water, stirred as a suspension in MeCN (30 mL) for 1 h, and then re-collected to provide crude **31**. Treatment of a suspension of the free base in MeOH with HCl(g)/EtOAc/hexane, followed by crystallization from MeOH, gave **31**·HCl (109 mg, 68%) as a yellow solid: mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.80 (d, *J* = 1.7 Hz, 1 H), 10.09 (br s, 1 H), 9.16 (s, 1 H), 8.85 (d, *J* = 1.5 Hz, 1 H), 8.30

(d, *J* = 8.7 Hz, 1 H), 8.29, 7.61 (2 br s, 2 H), 8.16 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.47 (d, *J* = 8.9 Hz, 1 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 7.23 (d, *J* = 1.7 Hz, 1 H), 7.04 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.96 (dd, *J* = 10.7, 9.7 Hz, 1 H), 4.70 (dd, *J* = 10.9, 2.5 Hz, 1 H), 4.68-4.59 (m, 1 H), 4.36 (t, *J* = 5.1 Hz, 2 H), 4.20-4.07 (m, 2 H), 3.50 (t, *J* = 4.9 Hz, 2 H), 2.87 (s, 6 H). Anal. ($C_{26}H_{26}ClN_5O_5 \cdot HCl \cdot H_2O$) C, H, N.

Synthesis of 16 and 32.



2-Bromo-7-(methylsulfanyl)naphthalene (69). A stirred solution of 2,7-dibromonaphthalene (**68**) (5.72 g, 20.0 mmol) in THF (80 mL) was treated dropwise at -78 °C with n-BuLi (2.5 M in hexanes, 8.40 mL, 21.0 mmol) under N_2. The mixture was stirred at -78 °C for 20 min, then treated slowly with dimethyl disulfide (2.16 mL, 24 mmol) and allowed to warm to room temperature. The solvent was removed under reduced pressure to give a residue that was shaken with water, and the resulting solid was crystallized from petroleum ether to give **69** (4.14 g, 82%): mp 80-81 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.11 (d, *J* = 1.9 Hz, 1 H), 7.86 (d, *J* = 9.1 Hz, 1 H), 7.83 (d, *J* = 9.1 Hz, 1 H), 7.71 (d, *J* = 1.8 Hz, 1 H), 7.54 (dd, *J* = 8.72, 2.0 Hz, 1 H), 7.44 (dd, *J* = 8.6, 2.0 Hz, 1 H), 2.58 (s, 3 H). Anal. ($C_{11}H_9BrS$) C, H, S.

7-(Methylsulfanyl)-2-naphthoic acid (70). A stirred solution of **69** (850 mg, 3.36 mmol) in THF (10 mL) was treated at -78 °C with n-BuLi (2.5 M in hexanes, 1.48 mL, 3.70 mmol) under N_2. The mixture was stirred at -78 °C for 15 min, then treated with excess CO_2(g) and allowed to warm to room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between water and EtOAc. The aqueous layer was acidified, and the resulting solid was crystallized from MeOH to give **70** (577 mg, 79%): mp 217 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.0 (v br, 1 H), 8.53 (d, *J* = 0.7 Hz, 1 H), 7.98-7.87 (m, 4 H), 7.53 (dd, *J* = 8.7, 1.9 Hz, 1 H), 2.60 (s, 3 H). Anal. ($C_{12}H_{10}O_2S$) C, H.

7-(Methylsulfonyl)-2-naphthoic acid (71). A mixture of **70** (2.00 g, 9.16 mmol) and $NaBO_3 \cdot 4H_2O$ (8.00 g, 52 mmol) in AcOH (50 mL) was stirred at 55 °C for 2 h, then cooled and diluted with water. The resulting solid was recrystallized twice from EtOAc to give **71** (2.02 g, 88%) as a white solid: mp 273-274 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.3 (br s, 1 H), 8.85 (d, *J* = 0.5 Hz, 1 H), 8.79 (d, *J* = 1.8 Hz, 1 H), 8.27 (d, *J* = 8.7 Hz, 1 H), 8.18 (2 s, 2 H), 8.08 (dd, *J* = 8.7, 1.9 Hz, 1 H), 3.25 (after D_2O exchange, s, 3 H). Anal. ($C_{12}H_{10}O_4S$) C, H.

***tert*-Butyl 7-(methylsulfonyl)-2-naphthylcarbamate (129).** A suspension of acid **71** (2.08 g, 8.31 mmol) in dry t-BuOH (30 mL) containing powdered molecular sieves (1 g) was treated with Et_3N (1.39 mL, 9.97 mmol) and stirred under N_2 at room temperature for 30 min. DPPA (1.97 mL, 9.14 mmol) was added and the mixture was stirred at reflux for 7 h, then concentrated to half volume under reduced pressure and poured into dilute aq $KHCO_3$. The resulting solid was purified by

chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (19:1), followed by recrystallization from CH_2Cl_2/iPr_2O to give **129** (2.11 g, 79%) as a white solid: mp 179-180 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.76 (s, 1 H), 8.39 (d, *J* = 1.5 Hz, 1 H), 8.28 (d, *J* = 1.5 Hz, 1 H), 8.06 (d, *J* = 8.6 Hz, 1 H), 7.98 (d, *J* = 9.0 Hz, 1 H), 7.77 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.74 (dd, *J* = 9.2, 2.0 Hz, 1 H), 3.27 (s, 3 H), 1.52 (s, 9 H). Anal. ($C_{16}H_{19}NO_4S$) C, H, N.

***tert*-Butyl 1-bromo-7-(methylsulfonyl)-2-naphthylcarbamate (130).** A mixture of **129** (2.05 g, 6.38 mmol) and NBS (1.31 g, 7.36 mmol) in MeCN (40 mL) was stirred at reflux for 2 h, then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with 10% aq Na_2SO_3 and water, dried and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (19:1), followed by recrystallization from MeOH to give **130** (2.37 g, 93%) as a white solid: mp 166-167 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.99 (s, 1 H), 8.70 (d, *J* = 1.7 Hz, 1 H), 8.25 (d, *J* = 8.5 Hz, 1 H), 8.10 (d, *J* = 8.8 Hz, 1 H), 8.00 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.97 (d, *J* = 8.9 Hz, 1 H), 3.32 (s, 3 H), 1.50 (s, 9 H). Anal. ($C_{16}H_{18}BrNO_4S$) C, H, N.

***tert*-Butyl 1-bromo-7-(methylsulfonyl)-2-naphthyl(3-chloro-2-propen-1-yl)carbamate (131).** A stirred solution of **130** (2.29 g, 5.72 mmol) in dry DMF (20 mL) was treated portionwise at 0°C with NaH (275 mg, 60% in oil, 6.88 mmol). The mixture was warmed to room temperature for 30 min, then cooled to 0°C and treated with 1,3-dichloropropene (1.66 mL, 18 mmol, mixed isomers). The mixture was stirred at room temperature for a further 6 h, then diluted with 10% aq NaCl and extracted with EtOAc (×2). The combined organic layers were washed with water (×2), dried, and concentrated to dryness under reduced pressure at 100°C. The residue was chromatographed on silica gel, eluting with CH_2Cl_2 /EtOAc (19:1) to give crude **131** (2.63 g, 97%) as a foam: ^{1}H NMR [$(CD_3)_2SO$] (mixture of rotamers and E and Z forms) δ 8.78 (s, 1 H), 8.32 (dd, *J* = 8.6, 2.2 Hz, 1 H), 8.18, 8.17 (2d, *J* = 8.7 Hz, 1 H), 8.13-8.06 (m, 1 H), 7.75, 7.70 (2 d, *J* = 8.7 Hz, 1 H), 6.44-6.29 (m, 1 H), 6.20-6.01 (m, 1 H), 4.58-4.48, 4.43-4.22, 4.16-4.05 (3 m, 2 H), 3.35 (s, 3 H), 1.50, 1.27 (2 s, 9 H). HRMS (FAB) calcd. for $C_{19}H_{22}{}^{79}Br^{35}ClNO_4S$ (MH^+) m/z 474.0141, found 474.0143.

***tert*-Butyl 1-(chloromethyl)-8-(methylsulfonyl)-1,2-dihydro-3*H*-benzo[*e*]indole-3-carboxylate (132).** A solution of **131** (1.60 g, 3.37 mmol) in dry benzene (30 mL) was treated with Bu_3SnH (0.91 mL, 3.38 mmol) followed by AIBN (0.1 g, 0.6 mmol). The mixture was stirred under N_2 at reflux for 2 h, then concentrated under reduced pressure. The residue was dissolved in EtOAc, and the solution was diluted with hexane and refrigerated. The resulting semisolid was chromatographed on silica gel, eluting with CH_2Cl_2/EtOAc (19:1), and the product was triturated with i-Pr_2O/hexane to give **132** (0.88 g, 66%) as an amorphous solid: ^{1}H NMR [$(CD_3)_2SO$] δ 8.41 (d, *J* = 1.6 Hz, 1 H), 8.2 (v br, 1 H), 8.17 (d, *J* = 8.6 Hz, 1 H), 8.03 (d, *J* = 8.9 Hz, 1 H), 7.80 (dd, *J* = 8.6, 1.8 Hz, 1 H), 4.42-4.33 (m, 1 H), 4.21 (t, *J* = 10.4 Hz, 1 H), 4.12 (dd, *J* = 11.6, 2.9 Hz, 1 H), 4.07 (dd, *J* = 11.2, 3.4 Hz, 1 H). 3.89 (dd, *J* = 11.2, 7.1 Hz, 1 H), 3.33 (s, 3 H), 1.55 (s, 9 H). Anal. ($C_{19}H_{22}ClNO_4S\cdot$½i-Pr_2O) C, H, N.

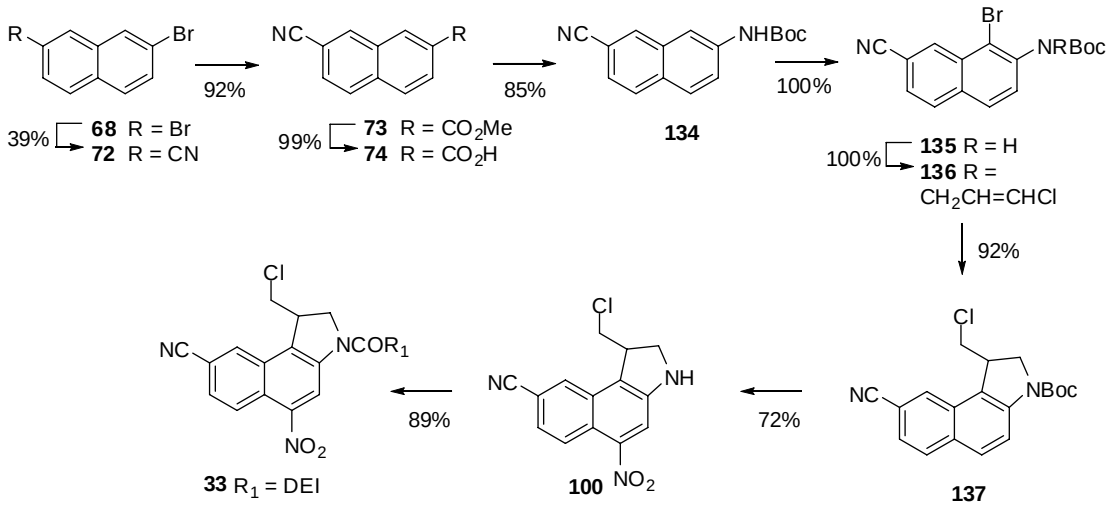
1-(Chloromethyl)-8-(methylsulfonyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (133). Powdered **132** (350 mg, 0.88 mmol) was added to stirred cH_2SO_4 (4 mL) at 0 °C and the mixture was warmed to room temperature for 20 min. The resulting solution of amine was cooled to -5°C and treated dropwise with a solution of KNO_3 (98 mg, 0.97 mmol) in cH_2SO_4 (1 mL). The mixture was

stirred at 0°C for a further 5 min, then poured into ice/water and neutralized with dilute aq NH_3. The resulting solid was filtered off, dissolved in CH_2Cl_2, and the solution was filtered through a column of silica gel and evaporated to dryness. Recrystallization from CH_2Cl_2/i-Pr_2O followed by EtOAc gave **133** (207 mg, 69%) as a red solid: mp 193-194 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.34 (d, *J* = 1.5 Hz, 1 H), 8.31 (d, *J* = 9.1 Hz, 1 H), 7.82 (s, 1 H), 7.76 (dd, *J* = 9.1, 1.9 Hz, 1 H), 6.62 (br s, 1 H), 4.37-4.28 (m, 1 H), 3.93 (dd, *J* = 11.1, 4.1 Hz, 1 H), 3.87 (td, *J* = 9.8, 2.3 Hz, 1 H), 3.80-3.70 (m, 2 H), 3.33 (s, 3 H). Anal. ($C_{14}H_{13}ClN_2O_4S$) C, H, N. The structure of **133** was confirmed by x-ray crystallography.

1-(Chloromethyl)-8-(methylsulfonyl)-5-nitro-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (16). A suspension of 5,6,7-trimethoxyindole-2-carboxylic acid (77 mg, 0.31 mmol) in dry CH_2Cl_2 (3 mL) was treated with oxalyl chloride (80 μL, 0.92 mmol) followed by DMF (10 μl). The mixture was stirred at room temperature for 30 min, then evaporated to dryness under reduced pressure and re-evaporated after addition of benzene. The resulting acid chloride was cooled to -5°C and treated with an ice-cold solution of **133** (70 mg, 0.21 mmol) in dry pyridine (2 mL) containing DMAP (5 mg). The mixture was warmed to room temperature for 15 min then poured into dilute aq $KHCO_3$ and the precipitated solid was collected and dissolved in CH_2Cl_2/EtOAc (8:1). The solution was filtered through a column of silica gel and the product was recrystallized from CH_2Cl_2/EtOAc to give **16** (78 mg, 66%) as an orange solid: mp 265 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.61 (d, *J* = 1.8 Hz, 1 H), 9.26 (s, 1 H), 8.69 (d, *J* = 1.5 Hz, 1 H), 8.59 (d, *J* = 9.2 Hz, 1 H), 8.13 (dd, *J* = 9.2, 1.8 Hz, 1 H), 7.21 (d, *J* = 2.2 Hz, 1 H), 6.98 (s, 1 H), 4.93 (dd, *J* = 10.7, 9.4 Hz, 1 H), 4.78-4.70 (m, 1 H), 4.66 (dd, *J* = 10.9, 2.1 Hz, 1 H), 4.16 (dd, *J* = 11.3, 3.5 Hz, 1 H), 4.07 (t, *J* = 5.7 Hz, 1 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.42 (s, 3 H). Anal. ($C_{26}H_{24}ClN_3O_8S$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-8-(methylsulfonyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (32). A mixture of **133** (80 mg, 0.23 mmol), 5-[2-(dimethylamino)ethoxy]-indol-2-carboxylic acid hydrochloride (80 mg, 0.28 mmol), EDCI (180 mg, 0.94 mmol) and anhydrous TsOH (30 mg, 0.17 mmol) in dry DMA (5 mL) under N_2 was stirred at room temperature for 3 h, then poured into dilute aq NH_3. The precipitated solid was collected, stirred as a suspension in MeOH (10 mL) for 15 min, cooled to 0°C and then recollected to give crude **32**. Treatment of **32** in MeOH/CH_2Cl_2 with HCl(g)/EtOAc/hexane, followed by crystallization from MeOH gave **32**·HCl (71 mg, 50%) as a yellow solid: mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.82 (s, 1 H), 10.0 (v br, 1 H), 9.31 (s, 1 H), 8.70 (d, *J* = 1.5 Hz, 1 H), 8.60 (d, *J* = 9.2 Hz, 1 H), 8.14 (dd, *J* = 9.2, 1.8 Hz, 1 H), 7.47 (d, *J* = 8.9 Hz, 1 H), 7.27 (d, *J* = 2.3 Hz, 1 H), 7.25 (d, *J* = 1.7 Hz, 1 H), 7.04 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.97 (t, *J* = 9.8 Hz, 1 H), 4.82-4.69 (m, 2 H), 4.35 (t, *J* = 5.0 Hz, 2 H), 4.18 (dd, *J* = 11.3, 3.2 Hz, 1 H), 4.08 (dd, *J* = 11.4, 5.7 Hz, 1 H), 3.52 (br s, 2 H), 3.42 (s, 3H), 2.87 (s, 6 H). Anal. ($C_{27}H_{27}ClN_4O_6S$·HCl) C, H, N.

Synthesis of 33.



7-Bromo-2-naphthonitrile (72). A solution of 2,7-dibromonaphthalene (**68**) (20.0 g, 0.07 mol) in 1-methyl-2-pyrrolidinone (60 mL) was purged with N_2 for 10 min. CuCN (7.52 g, 0.09 mol) and pyridine (0.5 mL) were added and the mixture was heated at 180 °C under N_2 for 1.5 h. After cooling to 80 °C, $FeCl_3$ (40 g), water (200 mL) and cHCl (50 mL) were added and the mixture was stirred for 1 h at 80 °C. The mixture was cooled, brine was added, and the mixture was extracted with CH_2Cl_2 (×3). The organic extracts were washed with aq HCl (2N, ×2), water, 10% aq NaOH, brine, and dried. Chromatography eluting with CH_2Cl_2/petroleum ether (1:1, then 4:1) gave **72** (6.40 g, 39%) as a cream powder. A sample was recrystallized (petroleum ether) to give colorless needles: mp 126-128 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1 H), 8.06 (d, *J* = 1.5 Hz, 1 H), 7.89 (d, *J* = 8.5 Hz, 1 H), 7.76 (d, *J* = 8.8 Hz, 1 H), 7.71 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.62 (dd, *J* = 8.4, 1.5 Hz, 1 H); ^{13}C NMR δ 133.2, 133.0, 132.4, 130.6, 130.3, 129.6, 129.2, 126.8, 121.9, 118.7, 110.6. Anal. ($C_{11}H_6BrN$) C, H, N, Br.

Methyl 7-cyano-2-naphthoate (73). Nitrile **72** (6.0 g, 26 mmol), $Pd(OAc)_2$ (0.58 g, 2.59 mmol), 1,3-bis(diphenylphosphino)propane (1.07 g, 2.59 mmol), MeOH (30 mL), Et_3N (12 mL) and DMSO (30 mL) were placed in a Berghof reactor (HR-200) and purged with CO(g) for 5 min. The reactor was then pressurized with CO(g) (15 bar) and heated at 70 °C for 20 h. After cooling, EtOAc was added and the mixture was filtered through Celite/silica gel. The solvents were removed under reduced pressure and the residue partitioned between CH_2Cl_2 and brine. The organic layer was dried and evaporated, and the residue was recrystallized (MeOH) to give **73** (5.15 g, 92%), as a colorless solid: mp 136-136.5 °C (Lit mp[4] 137-139 °C); ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1 H), 8.34 (s, 1 H), 8.22 (d, *J* = 8.2 Hz, 1 H), 7.97 (d, *J* = 8.9 Hz, 1 H), 7.95 (d, *J* = 8.9 Hz, 1 H), 7.72 (d, *J* = 8.2 Hz, 1 H), 4.01 (s, 3 H).

7-Cyano-2-naphthoic acid (74). A solution of NaOH (1.36 g, 34 mmol) in water (35 mL) was added dropwise to a solution of **73** (4.95 g, 24 mmol) in EtOH (100 mL) and CH_2Cl_2 (30 mL) and the mixture was stirred for 15 h. Water was added to dissolve the white solid and the mixture was extracted with CH_2Cl_2 (×2) and EtOAc. The aqueous portion was acidified (pH 2) with aq HCl (2N) and the resulting precipitate was filtered off, washed with water, and dried in a vacuum desiccator to

give **74** (4.60 g, 99%), as a colorless powder: mp 279-283 °C (Lit mp[4] 286-288 °C); ^{1}H NMR [$(CD_3)_2SO$] δ 13.25 (br s, 1 H), 8.81 (s, 1 H), 8.75 (s, 1 H), 8.20 (d, *J* = 8.5 Hz, 1 H), 8.17 (d, *J* = 8.5 Hz, 2 H), 8.15 (d, *J* = 8.5 Hz, 2 H), 7.92 (dd, *J* = 8.5, 1.3 Hz, 1 H).

***tert*-Butyl 7-cyano-2-naphthylcarbamate (134).** A solution of **74** (6.60 g, 23 mmol), DPPA (7.71 g, 28 mmol) and Et_3N (5.19 g, 51 mmol) in *t*-BuOH (50 mL) was heated under reflux for 6 h. The mixture was partitioned between EtOAc and brine. The EtOAc layer was dried and filtered through silica gel. Chromatography eluting with CH_2Cl_2/petroleum ether/MeOH (25:24:1) followed by recrystallization (CH_2Cl_2/petroleum ether) gave **134** (5.30 g, 85%) as colorless needles. A sample was recrystallized (EtOAc/*n*-hexane): mp 126-128 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1 H), 8.07 (s, 1 H), 7.82 (d, *J* = 8.1 Hz, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.51-7.48 (m, 2 H), 6.71 (br s, 1 H), 1.56 (s, 9 H); ^{13}C NMR δ 152.5, 137.5, 133.4, 133.1, 131.0, 128.9, 128.8, 124.9, 122.0, 119.3, 114.4, 110.0, 81.3, 28.3. Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

***tert*-Butyl 1-bromo-7-cyano-2-naphthylcarbamate (135).** A mixture of **134** (1.90 g, 7.09 mmol), NBS (1.41 g, 7.20 mmol) and K_2CO_3 (1.11 g, 8.50 mmol) in MeCN (20 mL) was heated at 60 °C under N_2 for 30 min. The solvent was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with water (×2), brine, and dried. Filtration through silica gel gave **135** (2.45 g, 100%) as a colorless powder. A sample was recrystallized (petroleum ether) to give colorless needles: mp 139-141 °C; ^{1}H NMR ($CDCl_3$) δ 8.58 (d, *J* = 9.1 Hz, 1 H), 8.54 (d, *J* = 1.0 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 9.1 Hz, 1 H), 7.56 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.36 (br s, 1 H), 1.57 (s, 9 H); ^{13}C NMR δ 152.3, 136.7, 132.5, 132.0, 131.4, 129.4, 128.3, 125.6, 122.4, 119.0, 111.3, 109.4, 81.9, 28.3. Anal. ($C_{16}H_{15}BrN_2O_2$) C, H, N, Br.

***tert*-Butyl 1-bromo-7-cyano-2-naphthyl(3-chloro-2-propen-1-yl)carbamate (136).** A solution of **135** (2.50 g, 7.21 mmol) in DMF (20 mL) was added to a suspension of NaH (350 mg, 8.65 mmol, 60% in oil) in DMF (20 mL) at 0 °C. 1,3-Dichloropropene (1.60 g, 14 mmol) was added and the mixture was allowed to warm to room temperature over 2 h. The DMF was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with water (×2), brine (×2), and dried. Filtration through silica gel gave **136** (3.28 g, 100%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) (mixture of rotamers and E and Z forms) δ 8.73 (s, 1 H), 7.93-7.96 (m, 1 H), 7.83-7.87 (m, 1 H), 7.68-7.70 (m, 1 H), 7.39-7.46 (m, 1 H), 6.00-6.11 (m, 2 H), 4.49-4.62 (m, 1 H), 4.33-4.43 (m, 1 H), 1.33, 1.32 (2 s, 9 H). HRMS (FAB) calcd. for $C_{19}H_{18}{}^{79}Br^{35}ClN_2O_2$ (MH^+) m/z 421.0318, found 421.0330.

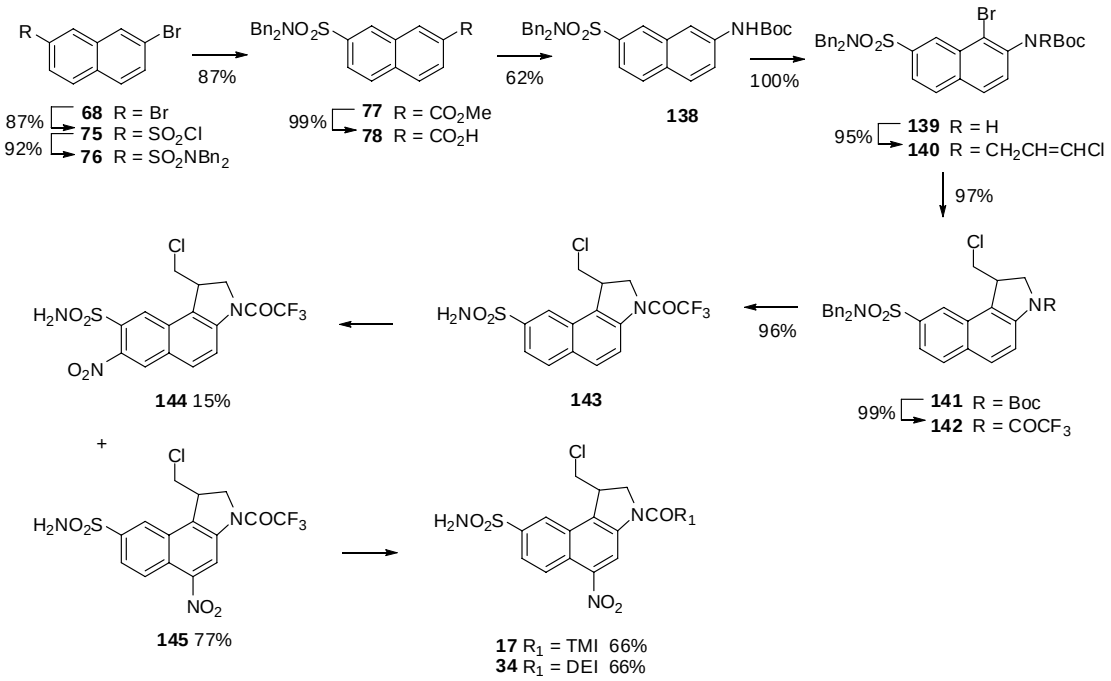
***tert*-Butyl 1-(chloromethyl)-8-cyano-1,2-dihydro-3*H*-benzo[*e*]indole-3-carboxylate (137).** A mixture of **136** (3.00 g, 7.13 mmol), Bu_3SnH (2.49 g, 8.55 mmol) and AIBN (120 mg, 0.71 mmol) in benzene (20 mL) was heated under reflux for 1.5 h. The benzene was removed under reduced pressure and the residue was triturated with pentane (×4) and recrystallized (MeOH) to give **137** (2.24 g, 92%) as colorless needles: mp 138-140 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (br s, 1 H), 8.09 (s, 1 H), 7.90 (d, *J* = 8.5 Hz, 1 H), 7.82 (d, *J* = 9.0 Hz, 1 H), 7.48 (dd, *J* = 8.5, 1.5 Hz, 1 H), 4.30 (br d, *J* = 11.2 Hz, 1 H), 4.18 (dd, *J* = 11.8, 8.7 Hz, 1 H), 4.50 (tt, *J* = 9.3, 3.0 Hz, 1 H), 3.87 (dd, *J* = 11.3, 3.3 Hz, 1 H), 3.53 (dd, *J* =

11.2, 9.6 Hz, 1 H), 1.61 (s, 9 H); ^{13}C NMR δ 152.3, 142.9, 131.2, 130.2, 130.0, 128.9, 128.2, 124.2, 123.3, 119.2, 118.8, 110.5, 81.8, 52.8, 46.2, 41.5, 28.4. Anal. ($C_{19}H_{19}ClN_2O_2$) C, H, N.

1-(Chloromethyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-carbonitrile (100). A solution of **137** (30 mg, 0.088 mmol) in HCl(g) saturated dioxane (3 mL) was stirred for 1 h. The solvent was evaporated to provide the crude amine hydrochloride (24 mg, 100%). This solid was cooled to 0 °C and treated with cH_2SO_4 (2 mL). A cooled (0 °C) solution of KNO_3 (9 mg, 0.088 mmol) in cH_2SO_4 (0.5 mL) was then added dropwise. After 15 min, the mixture was poured into ice water and conc. aq NH_3 was carefully added until the pH of the mixture was 3-4. Solid $KHCO_3$ was then carefully added until the pH of the mixture was 8. The mixture was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine and dried. The CH_2Cl_2 was removed under reduced pressure and the residue was triturated with MeOH to give **100** (18 mg, 72%) as red crystals: mp 231-234°C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.54 (dd, *J* = 1.5, 0.5 Hz, 1 H), 8.22 (dd, *J* = 9.0, 0.4 Hz, 1 H), 7.80 (s, 1 H), 7.59 (dd, *J* = 9.0, 1.6 Hz, 1 H), 6.63 (d, *J* = 1.3 Hz, 1 H), 4.32-4.23 (m, 1 H), 3.95 (dd, *J* = 11.0, 3.8 Hz, 1 H), 3.84 (td, *J* = 10.3, 2.3 Hz, 1 H), 3.79-3.70 (m, 2 H); ^{13}C NMR δ 151.8, 148.1, 130.6, 129.9, 126.8, 125.7, 125.0, 120.0, 119.6, 112.8, 111.4, 51.8, 47.5, 43.5. Anal. ($C_{14}H_{10}ClN_3O_2$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-carbonitrile (33). A solution of **100** (160 mg, 0.56 mmol) in HCl(g) saturated dioxane (15 mL) was stirred for 1 h, then the dioxane was removed under reduced pressure to give the crude amine hydrochloride (180 mg, 0.56 mmol, 100%). 5-[2-(Dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (190 mg, 0.67 mmol), EDCI (319 mg, 1.67 mmol), and DMA (5 mL) were added and the mixture was stirred under a N_2 atmosphere for 4 h. The mixture was then partitioned between CH_2Cl_2 and cold (0 °C) 5% aq $KHCO_3$. The aqueous layer was extracted with cold CH_2Cl_2 (×4) and the combined extracts were washed with water (×3), brine, and dried. The solvent was evaporated and the residue was dissolved in CH_2Cl_2/MeOH and solvents were concentrated under reduced pressure until precipitation began. The precipitate was filtered off and washed with MeOH to give **33** (256 mg, 89%) as an orange powder: mp >340 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.67 (d, *J* = 1.5 Hz, 1 H), 9.29 (s, 1 H), 8.91 (d, *J* = 1.0 Hz, 1H), 8.49 (d, *J* = 9.1 Hz, 1 H), 7.97 (dd, *J* = 9.1, 1.5 Hz, 1 H), 7.40 (d, *J* = 8.9 Hz, 1 H), 7.20 (d, *J* = 1.7 Hz, 1 H), 7.17 (d, *J* = 2.3 Hz, 1 H), 6.95 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.95 (dd, *J* = 10.6, 9.5 Hz, 1 H), 4.75-4.63 (m, 2 H), 4.19-4.09 (m, 2 H), 4.07 (t, *J* = 5.9 Hz, 2 H), 2.67 (t, *J* = 5.9 Hz, 2 H), 2.25 (s, 6 H); ^{13}C NMR δ 160.5, 152.9, 146.2, 142.1, 133.0, 131.9, 130.5, 129.6, 128.5, 127.9, 127.3, 124.9, 122.8, 118.2, 117.3, 116.4, 113.2, 111.0, 106.2, 103.1, 65.9, 57.6, 54.7, 47.9, 45.3, 41.2. Anal. ($C_{27}H_{24}ClN_5O_4$) C, H, N.

Synthesis of 17 and 34.



7-Bromo-2-naphthalenesulfonyl chloride (75). n-BuLi (1.50 mL, 3.50 mmol, 2.3 M solution in hexanes) was added to a solution of **68** (1.00 g, 3.50 mmol) in THF (15 mL) under nitrogen at -78 °C. After 20 min, SO_2(g) was bubbled into the solvent and the resulting mixture was allowed to warm to room temperature and stirred for 12 h. The THF was evaporated, the resulting solid was suspended in CH_2Cl_2 (25 mL) at 0 °C, and NCS (0.47 g, 3.50 mmol) was added. After 1 h the mixture was filtered through Celite and purified by chromatography on silica gel, eluting with petroleum ether/EtOAc (95:5), followed by recrystallization (petroleum ether/Et_2O) to give **75** (1.86 g, 87%) as colorless crystals: mp 100-101 °C; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, *J* = 1.3 Hz, 1 H), 8.21 (d, *J* = 1.2 Hz, 1 H), 8.04 (d, *J* = 8.8 Hz, 1 H), 8.01 (dd, *J* = 8.8, 1.8 Hz, 1 H), 7.84 (d, *J* = 8.8 Hz, 1 H), 7.81 (dd, *J* = 8.8, 1.8 Hz, 1 H). Anal. ($C_{10}H_6BrClO_2S$) C, H.

***N,N*-Dibenzyl-7-bromo-2-naphthalenesulfonamide (76).** A mixture of **75** (1.50 g, 4.92 mmol), dibenzylamine (1.45 g, 7.38 mmol), and Et_3N (0.75 g, 7.38 mmol) in THF (15 mL) was stirred at room temperature for 48 h. The solvents were evaporated under reduced pressure and the residue was extracted with EtOAc. The EtOAc extracts were washed with water and brine, then dried and evaporated. The residue was purified by chromatography on silica gel eluting with petroleum ether/EtOAc (95:5 then 1:1) to give **76** (2.11 g, 92%). A sample was recrystallized from petroleum ether/EtOAc as colorless crystals: mp 127-129°C; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, *J* = 1.4 Hz, 1 H), 8.05 (d, *J* = 1.6 Hz, 1 H), 7.91 (d, *J* = 8.7 Hz, 1 H), 7.79 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.77 (d, *J* = 8.5 Hz, 1 H), 7.71 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.22-7.15 (m, 6 H), 7.09-7.04 (m, 4 H), 4.39 (s, 4 H); ^{13}C NMR δ 138.9, 135.4, 133.3, 133.0, 132.1, 131.2, 129.4, 129.3, 128.6, 128.5, 127.8, 127.3, 123.0, 121.6, 50.6. Anal. ($C_{24}H_{20}BrNO_2S\cdot{}^1/_{10}Bn_2NH$) C, H, N.

Methyl 7-[(dibenzylamino)sulfonyl]-2-naphthoate (77). A mixture of **76** (2.10 g, 4.51 mmol), $Pd(OAc)_2$ (101 mg, 0.45 mmol), 1,3-bis(diphenylphosphino)propane (186 mg, 0.45 mmol), MeOH (30 mL), Et_3N (10 mL), and DMSO (5 mL) were placed in a pressure vessel and purged with CO(g) for 5 min. The reactor was then pressurized with CO(g) (50 bar) and heated at 70 °C for 12 h. After cooling EtOAc was added and the mixture was filtered through Celite. Solvents were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and brine. The CH_2Cl_2 layer was dried and evaporated, and the residue was purified by chromatography on silica gel, eluting with petroleum ther/EtOAc/CH_2Cl_2 (7:1:2) to give **77** (1.75 g, 87%). A sample was recrystallized from petroleum ether/EtOAc as colorless crystals: mp 141-142 °C; ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1 H), 8.45 (s, 1 H), 8.22 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 7.0 Hz, 1 H), 7.88 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.22-7.15 (m, 6 H), 7.10-7.04 (m, 4 H), 4.40 (s, 4 H), 4.01 (s, 3H); ^{13}C NMR δ 166.5, 138.7, 136.6, 135.4, 132.0, 131.5, 129.6, 129.2, 129.1, 128.6, 128.5, 128.2, 128.1, 127.8, 124.8, 52.5, 50.6. Anal. ($C_{26}H_{23}NO_4S$) C, H, N.

7-[(Dibenzylamino)sulfonyl]-2-naphthoic acid (78). A solution of KOH (720 mg, 12.8 mmol) in MeOH (5 mL) and H_2O (2 mL) was added dropwise to a solution of **77** (1.90 g, 4.27 mmol) in MeOH (10 mL) and CH_2Cl_2 (15 mL). After 48 h at room temperature CH_2Cl_2 and H_2O were added. The aqueous layer was separated and acidified to pH 2 with 2 M HCl. The resulting white precipitate was collected, dissolved in CH_2Cl_2, and the solution was washed with H_2O and brine. The CH_2Cl_2 layer was dried, the solvent was evaporated, and the residue was dried in a vacuum desiccator. Recrystallization from CH_2Cl_2/petroleum ether gave **78** (2.00 g, 99%) as colorless crystals: mp 189-190 °C; ^{1}H NMR ($CDCl_3$) δ (CO_2H not observed) 8.76 (s, 1 H), 8.47 (s, 1 H), 8.29 (dd, *J* = 8.6, 1.5 Hz, 1 H), 8.01 (d, *J* = 8.8 Hz, 1 H), 7.92 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.23-7.15 (m, 6 H), 7.12-7.05 (m, 4 H), 5.29 (s, 1 H), 4.42 (s, 4 H); ^{13}C NMR δ 170.8, 139.0, 137.0, 135.4, 133.1, 131.4, 129.7, 129.3, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 125.3, 50.7. Anal. ($C_{25}H_{21}NO_4S$) C, H, N.

***tert*-Butyl 7-[(dibenzylamino)sulfonyl]-2-naphthylcarbamate (138).** A solution of **78** (1.95 g, 4.52 mmol), DPPA (1.49 g, 5.43 mmol) and Et_3N (1.01 g, 9.95 mmol) in t-BuOH (40 mL) was heated at reflux for 15 h. The solvents were removed under reduced pressure and the residue purified by chromatography on silica gel, eluting with petroleum ether/EtOAc (4:1), to give **138** (1.37 g, 62%). A sample was recrystallized from Et_2O/petroleum ether as colorless needles: mp 139-140 °C; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, *J* = 1.2 Hz, 1 H), 8.03 (d, *J* = 1.3 Hz, 1 H), 7.86 (d, *J* = 8.7 Hz, 1 H), 7.82 (d, *J* = 8.9 Hz, 1 H), 7.68 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.57 (dd, *J* = 8.8, 2.1 Hz, 1 H), 7.22-7.12 (m, 6 H), 7.08-7.01 (m, 4 H), 6.75 (s, 1 H), 4.37 (s, 4 H), 1.56 (s, 9 H); ^{13}C NMR δ 152.1, 137.7, 137.0, 135.1, 132.5, 130.6, 128.5, 128.2, 128.1, 127.9, 127.2, 127.1, 121.3, 120.6, 114.9, 80.6, 50.1, 27.8. Anal. ($C_{29}H_{30}N_2O_4S$) C, H, N.

***tert*-Butyl 1-bromo-7-[(dibenzylamino)sulfonyl]-2-naphthylcarbamate (139).** A mixture of **138** (1.15 g, 2.29 mmol), NBS (450 mg, 2.52 mmol), and K_2CO_3 (380 mg, 2.75 mmol) in MeCN (25 mL) was stirred at 40 °C under nitrogen for 30 min. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and H_2O. The EtOAc layer was washed with H_2O, brine, then dried and evaporated. The residue was recrystallized from EtOAc/Et_2O/petroleum ether to give **139** (1.33 g, 100%) as colorless crystals: mp 150-151 °C; ^{1}H NMR ($CDCl_3$) δ 8.69 (d, *J* = 1.6 Hz,

1 H), 8.57 (d, *J* = 9.1 Hz, 1 H), 7.89 (d, *J* = 8.6 Hz, 1 H), 7.85 (d, *J* = 9.1 Hz, 1 H), 7.74 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.38 (s, 1 H), 7.22-7.15 (m, 6 H), 7.12-7.05 (m, 4 H), 4.40 (s, 4 H), 1.58 (s, 9 H); ^{13}C NMR δ 152.4, 139.6, 136.5, 135.5, 132.0, 131.5, 129.7, 128.6, 128.5, 128.1, 127.7, 126.8, 122.1, 121.8, 110.4, 81.8, 50.6, 28.3. Anal. ($C_{29}H_{29}BrN_2O_4S$) C, H, N.

***tert*-Butyl 1-bromo-7-[(dibenzylamino)sulfonyl]-2-naphthyl(3-chloro-2-propen-1-yl)carbamate (140).** NaH (107 mg, 2.69 mmol, 60% in oil) was added to a solution of **139** (1.3 g, 2.24 mmol) in DMF (15 mL) at 0 °C. 1,3-Dichloropropene (414 mg, 3.36 mmol, mixed isomers) was added and the mixture was allowed to warm to room temperature over 12 h. The DMF was evaporated under reduced pressure and the residue was partitioned between EtOAc and H_2O. The EtOAc layer was washed with H_2O, brine, then dried and evaporated. The residue was purified by chromatography on silica gel, eluting with petroleum ether/EtOAc (4:1) to give **140** (1.39 g, 95%) as a yellow foam: ^{1}H NMR ($CDCl_3$) (mixture of rotamers and E and Z forms) δ 8.86 (s, 1 H), 7.97-7.91 (m, 1 H), 7.89-7.82 (m, 2 H), 7.51-7.31, 7.26-7.16 (2 m, 7 H), 7.13-7.06 (m, 4 H), 6.14-6.01 (m, 2 H), 4.64-4.48, 4.02-3.90 (2 m, 2 H), 4.43 (s, 4 H), 1.56, 1.33 (2 s, 9 H). HRMS (FAB) calcd. for $C_{32}H_{32}{}^{79}Br^{35}ClN_2O_4S$ (MH^+) 655.1033, found 655.1032.

***tert*-Butyl 1-(chloromethyl)-8-[(dibenzylamino)sulfonyl]-1,2-dihydro-3*H*-benzo[*e*]indole-3-carboxylate (141).** A mixture of **140** (1.00 g, 1.53 mmol), Bu_3SnH (550 mg, 1.83 mmol), and AIBN (50 mg, 0.31 mmol) in benzene (25 mL) was heated at reflux for 15 min, then concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O and the EtOAc layer was washed with H_2O, brine and dried and evaporated. The residue was purified by chromatography on silica gel, eluting with petroleum ether/EtOAc (9:1) to give **141** (850 mg, 97%). A sample was recrystallized from Et_2O/petroleum ether as colorless needles: mp 131-133 °C; ^{1}H NMR ($CDCl_3$) δ 8.30 (br s, 1 H), 8.29 (d, *J* = 1.5 Hz, 1 H), 7.93 (d, *J* = 8.7 Hz, 1 H), 7.84 (d, *J* = 9.0 Hz, 1 H), 7.66 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.23-7.15 (m, 6 H), 7.09-7.03 (m, 4 H), 4.41 (s, 4 H), 4.28 (d, *J* = 11.5 Hz, 1 H), 4.15 (dd, *J* = 11.6, 9.0 Hz, 1 H), 4.02 (tt, *J* = 9.0, 2.9 Hz, 1 H), 3.75 (dd, *J* = 11.3, 3.5 Hz, 1 H), 3.48 (dd, *J* = 11.2, 9.3 Hz, 1 H), 1.61 (s, 9 H); ^{13}C NMR δ 152.4, 142.7, 138.9, 135.5, 131.3, 130.5, 129.8, 128.9, 128.50, 128.46, 127.7, 124.3, 122.4, 120.3, 118.4, 81.8, 52.7, 50.5, 46.4, 41.4, 28.4. Anal. ($C_{32}H_{33}ClN_2O_4S$) C, H, N.

***N*,*N*-Dibenzyl-1-(chloromethyl)-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-sulfonamide (142).** A solution of **141** (850 mg, 1.48 mmol) in HCl(g)-saturated dioxane (10 mL) was stirred for 4 h at room temperature. The dioxane was evaporated under reduced pressure and the resulting pale yellow solid was dissolved in pyridine (10 mL) at 0 °C. Trifluoroacetic anhydride (470 mg, 2.23 mmol) was added and the mixture was stirred at 0 °C for 30 min, then poured into ice water and extracted with EtOAc (×3). The combined EtOAc extracts were washed with 1 M HCl (×3), H_2O, and brine, then dried and evaporated. The residue was purified by chromatography on silica gel, eluting with petroleum ether/EtOAc (9:1) to give **142** (840 mg, 99%). A sample was recrystallized from EtOAc/Et_2O/petroleum ether as colorless crystals: mp 119-121 °C; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, *J* = 9.0 Hz, 1 H), 8.25 (d, *J* = 1.7 Hz, 1 H), 8.02 (d, *J* = 8.7 Hz, 1 H), 7.95 (d, *J* = 9.0 Hz, 1 H), 7.78 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.23-7.16 (m, 6 H), 7.10-7.04 (m, 4 H), 4.65 (d, *J* = 11.6 Hz, 1 H), 4.48-4.37 (m, 5

H), 4.22-4.16 (m, 1 H), 3.78 (dd, *J* = 11.5, 3.5 Hz, 1 H), 3.54 (dd, *J* = 11.5, 8.5 Hz, 1 H). Anal. ($C_{29}H_{24}ClF_3N_2O_3S$) C, H, N.

1-(Chloromethyl)-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-sulfonamide (143). Sulfonamide **142** (750 mg, 1.31 mmol) was cooled to 0 °C, dissolved in cH_2SO_4 (20 mL) at 0 °C, and the solution was stirred at this temperature for 2 h. Ice water and EtOAc were added and the mixture was extracted with EtOAc (×3). The combined extracts were washed with brine (×3), dried, and evaporated to give **143** (490 mg, 96%). A sample was recrystallized from CH_2Cl_2/EtOAc as yellow crystals: mp 229-231 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.45 (d, *J* = 9.0 Hz, 1 H), 8.42 (s, 1 H), 8.21 (d, *J* = 8.7 Hz, 1 H), 8.11 (d, *J* = 9.0 Hz, 1 H), 7.87 (dd, *J* = 8.7, 1.7 Hz, 1 H), 7.51 (s, 2 H), 4.65-4.57 (m, 1 H), 4.57-4.50 (m, 1 H), 4.44 (d, *J* = 10.8 Hz, 1 H), 4.18 (dd, *J* = 11.3, 3.1 Hz, 1 H), 4.05 (dd, *J* = 11.3, 5.9 Hz, 1 H). Anal. ($C_{15}H_{12}ClF_3N_2O_3S{\cdot}½H_2O$) C, H, N.

1-(Chloromethyl)-5-nitro-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-sulfonamide (145). Ice-cold cH_2SO_4 (14 mL) was added to **143** (450 mg, 1.15 mmol) at 0 °C with stirring. A solution of KNO_3 (128 mg, 1.26 mmol) in cH_2SO_4 (1 mL) at 0 °C was then added dropwise. After 15 min the mixture was poured into ice water and extracted with EtOAc (×3). The combined extracts were washed with H_2O, brine, dried, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with petroleum ether/EtOAc (3:2) to give 1-(chloromethyl)-7-nitro-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-sulfonamide (**144**) (76 mg, 15%). A sample was recrystallized from petroleum ether/EtOAc as yellow crystals: mp 192-195 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.79 (s, 1 H), 8.65 (s, 1 H), 8.59 (d, *J* = 9.0 Hz, 1 H), 8.31 (d, *J* = 9.1 Hz, 1 H), 7.88 (s, 2 H), 4.66 (dd, *J* = 10.5, 9.3 Hz, 1 H), 4.58-4.51 (m, 1 H), 4.47 (d, *J* = 11.1 Hz, 1 H), 4.19 (dd, *J* = 11.3, 3.3 Hz, 1 H), 4.08 (dd, *J* = 11.3, 5.9 Hz, 1 H). Anal. ($C_{15}H_{11}ClF_3N_3O_5S$) C, H, N.

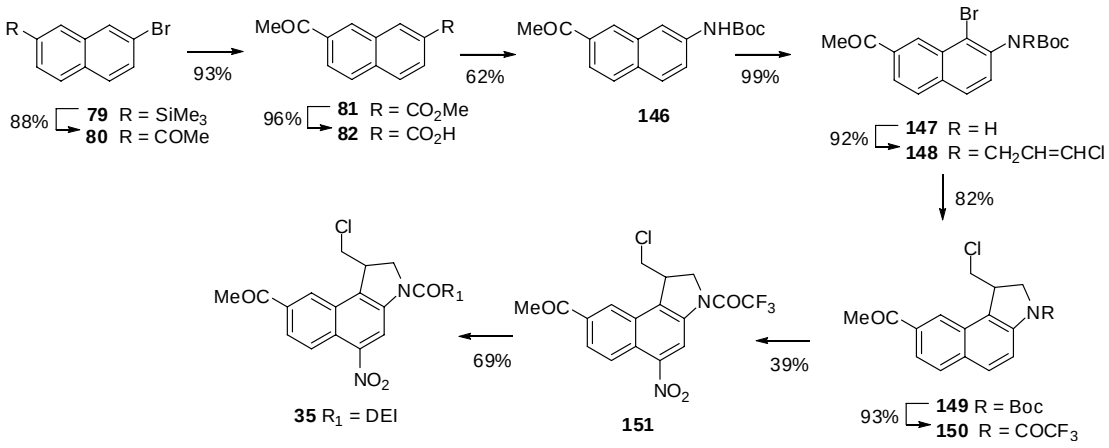
Further elution gave **145** (383 mg, 77%). A sample was recrystallized from petroleum ether/EtOAc as orange crystals: mp 251-254 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.09 (s, 1 H), 8.58 (d, *J* = 8.9 Hz, 1 H), 8.57 (d, *J* = 2.0 Hz, 1 H), 8.11 (dd, *J* = 9.4, 1.6 Hz, 1 H), 7.66 (s, 2 H), 4.76-4.63 (m, 2 H), 4.52 (d, *J* = 10.5 Hz, 1 H), 4.22 (dd, *J* = 11.3, 3.1 Hz, 1 H), 4.11 (dd, *J* = 11.4, 5.3 Hz, 1 H). Anal. ($C_{15}H_{11}ClF_3N_3O_5S$) C, H, N.

1-(Chloromethyl)-5-nitro-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-sulfonamide (17). A solution of **145** (50 mg, 0.114 mmol) and Cs_2CO_3 (58 mg, 0.172 mmol) in MeOH (2 mL), THF (2 mL), and CH_2Cl_2 (2 mL) was stirred at room temperature for 15 min. Water was added and the mixture was extracted with EtOAc (×3). The combined EtOAc extracts were washed with H_2O (×2), brine (×3), then dried and evaporated under reduced pressure. The resulting red solid was stirred in HCl(g)-saturated dioxane (5 mL) for 30 min then evaporated under reduced pressure. 5,6,7-Trimethoxyindole-2-carboxylic acid (34 mg, 0.137 mmol), EDCI (87 mg, 0.456 mmol), and DMA (3 mL) were added and the mixture was stirred at room temperature under nitrogen for 15 h. The mixture was partitioned between EtOAc and ice-cold 5% aq $KHCO_3$. The aqueous portion was extracted with cold EtOAc (×4) and the combined extracts were washed with H_2O (×3), brine (×2) and dried. Addition of Et_2O gave a precipitate of **17** (43 mg, 66%) as a red powder: mp 264-266 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.60 (s, 1 H), 9.21 (s, 1 H), 8.54 (d, *J* = 9.4 Hz, 1 H), 8.53 (d, *J* = 2.3 Hz, 1 H), 8.04 (dd, *J* = 9.2, 1.8 Hz, 1 H), 7.64 (s, 2 H), 7.19 (d, *J* = 1.9 Hz, 1 H), 6.98 (s, 1

H), 4.94 (dd, *J* = 11.1, 9.9 Hz, 1 H), 4.70-4.60 (m, 2 H), 4.17 (dd, *J* = 11.4, 3.4 Hz, 1 H), 4.08 (dd, *J* = 11.4, 5.8 Hz, 1 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H). HRMS (FAB) calcd. for $C_{25}H_{23}{}^{35}ClN_4O_8S$ (MH^+) 575.1003, found 575.0989. Anal. ($C_{25}H_{23}ClN_4O_8S \cdot ½EtOAc$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-sulfonamide (34). A solution of **145** (50 mg, 0.114 mmol) and Cs_2CO_3 (58 mg, 0.172 mmol) in MeOH (2 mL), THF (2 mL), and CH_2Cl_2 (2 mL) was stirred at room temperature for 15 min. Water was added and the mixture was extracted with EtOAc (×3). The combined EtOAc extracts were washed with H_2O (×2), brine (×3), then dried and evaporated under reduced pressure. The resulting red solid was stirred in HCl(g)-saturated dioxane (5 mL) for 30 min then evaporated under reduced pressure. 5-[2-(Dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (39 mg, 0.137 mmol), EDCI (87 mg, 0.456 mmol), and DMA (3 mL) were added and the mixture was stirred at room temperature under nitrogen for 15 h. The mixture was partitioned between CH_2Cl_2 and ice-cold 5% aq $KHCO_3$. The aqueous portion was extracted with cold CH_2Cl_2 (×4) and the combined extracts were washed with H_2O (×3), brine (×2) and dried. Addition of Et_2O gave a precipitate of **34** (43 mg, 66%) as an orange powder: mp 260-265 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.71 (d, *J* = 1.7 Hz, 1 H), 9.26 (s, 1 H), 8.55 (d, *J* = 8.9 Hz, 1 H), 8.53 (d, *J* = 2.1 Hz, 1 H), 8.04 (dd, *J* = 9.3, 1.7 Hz, 1 H), 7.64 (s, 2 H), 7.42 (d, *J* = 8.9 Hz, 1 H), 7.19 (dd, *J* = 10.2, 1.7 Hz, 2 H), 6.95 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.98 (dd, *J* = 10.1, 9.6 Hz, 1 H), 4.72 (dd, *J* = 11.0, 2.4 Hz, 1 H), 4.71-4.63 (m, 1 H), 4.18 (dd, *J* = 11.5, 3.4 Hz, 1 H), 4.10 (dd, *J* = 11.4, 5.9 Hz, 1 H), 4.08 (t, *J* = 5.9 Hz, 2 H), 2.66 (t, *J* = 5.8 Hz, 2 H), 2.24 (s, 6 H). HRMS (FAB) calcd. for $C_{26}H_{26}{}^{35}ClN_5O_6S$ (MH^+) m/z 572.1371, found 572.1362. Anal. ($C_{26}H_{26}ClN_5O_6S \cdot ½H_2O$) C, H, N.

Synthesis of 35.



2-Acetyl-7-bromonaphthalene (80). A solution of Ac_2O (340 mg, 3.35 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise to a suspension of $AlCl_3$ (490 mg, 3.66 mmol, 99.99%) in CH_2Cl_2 (15 mL) at 0 °C. A solution of 7-bromo-2-(trimethylsilyl)naphthalene (**79**)[5] (850 mg, 3.05 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise. After 15 min, the mixture was poured into ice water and extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine and dried. Filtration through Celite followed by chromatography eluting with petroleum ether/EtOAc (95:5 then 4:1) gave **80** (120 mg, 88%) as a colorless solid; ^{1}H NMR ($CDCl_3$) δ 8.36 (d, *J* = 0.9 Hz, 1 H), 8.13 (d, *J* = 1.7 Hz, 1 H), 8.04 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.87 (d, *J* = 8.6 Hz, 1 H), 7.75 (d, *J* = 8.7 Hz, 1 H), 7.67 (dd, *J* = 8.7, 1.9 Hz, 1 H), 2.72 (s, 3 H) (identical to that reported[6]).

Methyl 7-acetyl-2-naphthoate (81). A mixture of **80** (750 mg, 3.01 mmol), $Pd(OAc)_2$ (68 mg, 0.30 mmol), 1,3-bis(diphenylphosphino)propane (124 mg, 0.30 mmol), MeOH (10 mL), Et_3N (5 mL) and DMSO (5 mL) were placed in a Berghof reactor (HR-200) and purged with CO(g) for 5 min. The reactor was then pressurized with CO(g) (25 bar) and heated at 70 °C for 15 h. After cooling, EtOAc was added and the mixture was filtered through Celite/silica gel. Solvents were removed under reduced pressure, and CH_2Cl_2 and water were added. The mixture was extracted with CH_2Cl_2 (×3) and the combined organic extracts were washed with brine and dried. Filtration through silica gel, followed by chromatography eluting with petroleum ether/EtOAc (4:1 then 1:1 then 2:3) gave **81** (640 mg, 93%) as a white solid. A sample was recrystallized from petroleum ether/CH_2Cl_2: mp 103-105 °C; ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1 H), 8.55 (s, 1 H), 8.18 (dd, *J* = 8.6, 1.7 Hz, 1 H), 8.13 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.93 (d, *J* = 8.6 Hz, 1 H), 7.92 (d, *J* = 8.6 Hz, 1 H), 4.00 (s, 3 H), 2.74 (s, 3 H); ^{13}C NMR δ 197.5, 166.7, 137.5, 135.2, 132.4, 131.8, 131.3, 128.5, 128.3, 128.1, 127.8, 126.2, 52.4, 26.6. Anal. ($C_{14}H_{12}O_3$) C, H.

7-Acetyl-2-naphthoic acid (82). A solution of KOH (570 mg, 10 mmol) in water (3.5 mL) was added dropwise to a cooled solution of **81** (640 mg, 2.81 mmol) in MeOH (10 mL) and CH_2Cl_2 (10 mL) at 0 °C. After allowing the mixture to warm to room temperature and stirring for 96 h, excess CH_2Cl_2 and water were added. The aqueous portion was acidified (pH 2) with 2N HCl and the resulting white precipitate was extracted with EtOAc (×2). The combined EtOAc extracts were washed with

water, brine, and dried, to give **82** (575 mg, 96%) as a colorless solid. A sample was recrystallized from petroleum ether/CH_2Cl_2/Et_2O: mp 224-228 °C; ^{1}H NMR ($CDCl_3$) δ (CO_2H not observed) 8.82 (s, 1 H), 8.60 (s, 1 H), 8.23 (dd, *J* = 8.6, 1.6 Hz, 1 H), 8.18 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 2 H), 2.76 (s, 3 H). Anal. ($C_{13}H_{10}O_3$) C, H.

***tert*-Butyl 7-acetyl-2-naphthylcarbamate (146).** A solution of **82** (550 mg, 2.57 mmol), DPPA (850 mg, 3.08 mmol) and Et_3N (570 mg, 5.65 mmol) in *t*-BuOH (20 mL) was heated under reflux for 15 h. The mixture was poured into EtOAc and filtered through Celite. Chromatography on silica gel eluting with petroleum ether/CH_2Cl_2/EtOAc (8:1:1) gave **146** (451 mg, 62%) as a colorless solid: mp (EtOAc) 161-163 °C; ^{1}H NMR ($CDCl_3$) δ 8.38 (br s, 1 H), 8.16 (br s, 1 H), 7.91 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.80 (d, *J* = 8.6 Hz, 1 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 7.43 (dd, *J* = 8.8, 2.2 Hz, 1 H), 6.68 (br s, 1 H), 2.70 (s, 3 H), 1.55 (s, 9 H); ^{13}C NMR δ 198.2, 152.7, 136.7, 135.0, 133.2, 132.0, 129.7, 128.5, 128.0, 122.4, 121.6, 115.8, 81.0, 28.3, 26.6. Anal. ($C_{17}H_{19}NO_3$) C, H, N.

***tert*-Butyl 7-acetyl-1-bromo-2-naphthylcarbamate (147).** A mixture of **146** (420 mg, 1.47 mmol), NBS (292 mg, 1.62 mmol) and K_2CO_3 (244 mg, 1.77 mmol) in MeCN (10 mL) was heated at 40 °C under N_2 for 30 min then concentrated under reduced pressure. EtOAc and water were added to the residue, and the EtOAc portion was washed with water, brine and dried to give **147** (530 mg, 99%) as a colorless solid: mp (petroleum ether/EtOAc) 114-117 °C; ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1 H), 8.50 (d, *J* = 9.0 Hz, 1 H), 7.97 (dd, *J* = 8.5, 1.6 Hz, 1 H), 7.84 (d, *J* = 8.8 Hz, 1 H), 7.81 (d, *J* = 9.6 Hz, 1 H), 7.34 (br s, 1 H), 2.76 (s, 3 H), 1.58 (s, 9 H); ^{13}C NMR δ 197.9, 152.4, 136.0, 135.8, 133.0, 131.5, 128.7, 128.5, 128.0, 123.1, 122.0, 111.0, 81.6, 28.3, 26.7. Anal. ($C_{17}H_{18}BrNO_3$) C, H, N.

***tert*-Butyl 7-acetyl-1-bromo-2-naphthyl-(3-chloro-2-propen-1-yl)carbamate (148).** NaH (7 mg, 0.17 mmol, 60% in oil) was added to a solution of **147** (50 mg, 0.14 mmol) in DMF (3 mL) at -40 °C. 1,3-Dichloropropene (25 mg, 0.21 mmol) was added and the mixture was allowed to warm to room temperature over 1 h, then concentrated under reduced pressure. CH_2Cl_2 and water were added and the organic layer was washed with water, brine and dried. Chromatography eluting with petroleum ether/EtOAc (4:1) gave **148** (55 mg, 92%) as a yellow oil; ^{1}H NMR ($CDCl_3$) (mixture of rotamers and E and Z forms) δ 8.94 (s, 1 H), 8.13-8.07 (m, 1 H), 7.94-7.79 (m, 2 H), 7.50-7.35 (m, 1 H), 6.15-6.02 (m, 2 H), 4.66-4.28, 4.02-3.91 (2 m, 2 H), 2.78 (s, 3 H), 1.34 (s, 9 H). HRMS (CI) calcd. for $C_{20}H_{21}{}^{79}Br^{35}ClNO_3$ (MH^+) m/z 438.0472, found 438.0460.

***tert*-Butyl 8-acetyl-1-(chloromethyl)-1,2-dihydro-3*H*-benzo[*e*]indole-3-carboxylate (149).** A mixture of **148** (470 mg, 1.07 mmol), Bu_3SnH (380 mg, 1.29 mmol) and AIBN (18 mg, 0.11 mmol) in benzene (10 mL) was heated under reflux for 15 h, then concentrated under reduced pressure. EtOAc and water were added and the EtOAc portion was washed with water (×2), brine, and dried. Chromatography eluting with petroleum ether/EtOAc (4:1) followed by recrystallization (MeOH) gave **149** (320 mg, 82%) as colorless needles: mp 98-100 °C; ^{1}H NMR ($CDCl_3$) δ 8.34 (s, 1 H), 8.26 (br s, 1 H), 7.91-7.84 (m, 2 H), 7.81 (d, *J* = 8.9 Hz, 1 H), 4.36-4.28 (m, 1 H), 4.21-4.09 (m, 2 H), 3.97-3.90 (m, 1 H), 3.59-3.51 (m, 1 H), 2.72 (s, 3 H), 1.61 (s, 9 H); ^{13}C NMR δ (one C not observed) 198.0, 142.4, 135.4, 132.2, 129.7, 129.5, 129.2, 123.6, 122.2, 119.1, 118.2, 68.2, 52.7, 46.5, 28.5, 26.9, 25.2. Anal. ($C_{20}H_{22}ClNO_3$) C, H, N.

8-Acetyl-1-(chloromethyl)-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole (150). A solution of **149** (100 mg, 0.28 mmol) in HCl(g) saturated dioxane (10 mL) was stirred for 4 h. The solvent was removed under reduced pressure to give the crude amine hydrochloride (82 mg, 0.26 mmol, 100%). This was immediately dissolved in pyridine (5 mL), cooled (0 °C) and treated with TFAA (88 mg, 0.42 mmol). After 1 h, the mixture was poured into ice water and extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with aqueous HCl (1N, ×3), water, brine, and dried. Chromatography eluting with petroleum ether/EtOAc (1:1) gave **150** (92 mg, 93%) as a colorless solid: mp (petroleum ether/Et_2O) 161-163 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, *J* = 9.0 Hz, 1 H), 8.41 (s, 1 H), 8.02-7.95 (m, 2 H), 7.92 (d, *J* = 9.0 Hz, 1 H), 4.68 (dt, *J* = 11.5, 1.4 Hz, 1 H), 4.47 (dd, *J* = 11.4, 8.6 Hz, 1 H), 4.34-4.26 (m, 1 H), 3.98 (dd, *J* = 11.5, 3.5 Hz, 1 H), 3.63 (dd, *J* = 11.5, 8.9 Hz, 1 H), 2.74 (s, 3 H); ^{13}C NMR δ 197.7, 154.6 (q, $J_{C\text{-}F}$ 37.8 Hz), 140.9, 135.8, 134.0, 130.2, 129.7, 128.6, 127.1, 124.0, 123.8, 119.5, 116.1 (q, $J_{C\text{-}F}$ 288 Hz), 52.6 (q, $J_{C\text{-}F}$ 4.1 Hz), 45.7, 42.7, 26.9. Anal. ($C_{17}H_{13}ClF_3NO_2$) C, H, N.

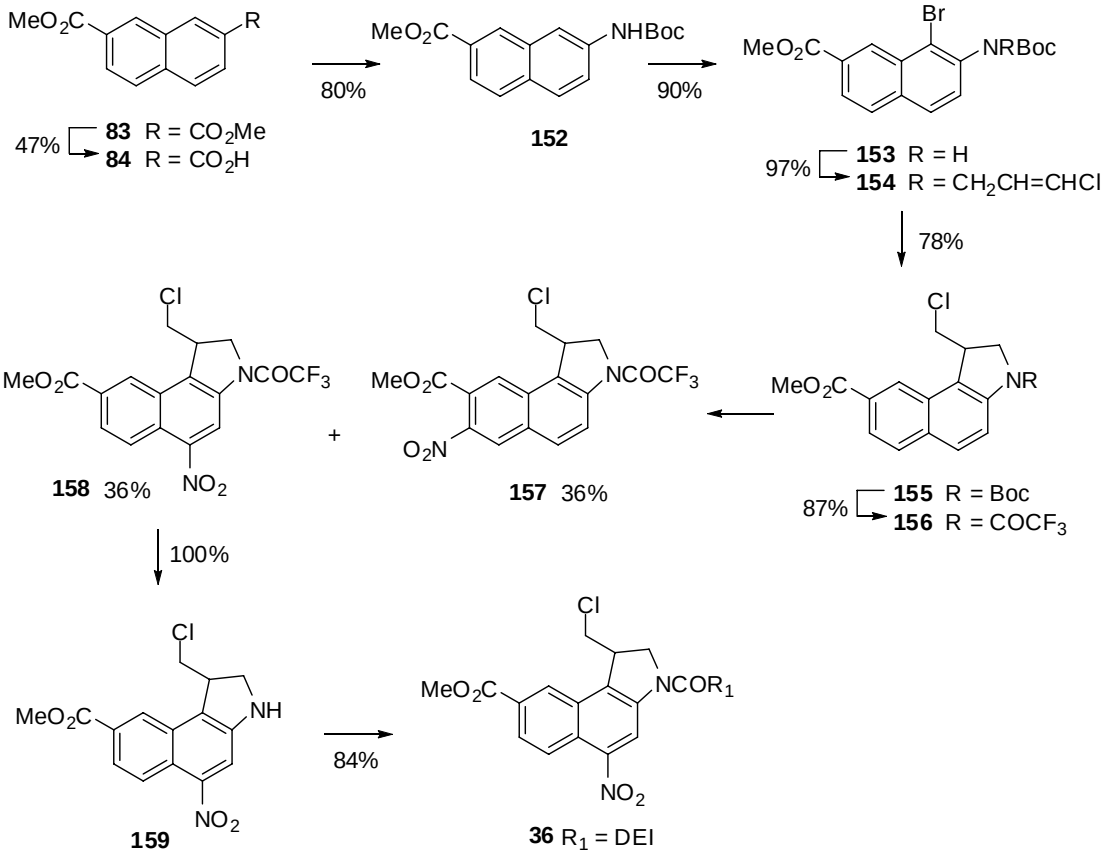
8-Acetyl-1-(chloromethyl)-5-nitro-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole (151). Solid **150** (57 mg, 0.16 mmol) was dissolved in cH_2SO_4 (5 mL) at 0 °C, then treated dropwise with a cold (0 °C) solution of KNO_3 (16 mg, 0.16 mmol) in cH_2SO_4 (0.5 mL). After 15 min, the mixture was poured into ice water and extracted with CH_2Cl_2 (×6). The combined organic extracts were washed with water (×2), brine, and dried. Chromatography eluting with petroleum ether/EtOAc (7:3) gave **151** (25 mg, 39%) as an orange powder: mp (petroleum ether/EtOAc) 196-198 °C; ^{1}H NMR ($CDCl_3$) δ 9.23 (s, 1H), 8.58 (d, *J* = 9.1 Hz, 1 H), 8.49 (d, *J* = 1.3 Hz, 1 H), 8.17 (dd, *J* = 9.1, 1.6 Hz, 1 H), 4.73 (d, *J* = 11.5 Hz, 1 H), 4.56 (dd, *J* = 11.4, 8.8 Hz, 1 H), 4.47-4.39 (m, 1 H), 3.98 (dd, *J* = 11.6, 3.6 Hz, 1 H), 3.77 (dd, *J* = 11.6, 7.8 Hz, 1 H), 2.78 (s, 3 H). Anal. ($C_{17}H_{12}ClF_3N_2O_4$) C, H, N.

8-Acetyl-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (35). A solution of **151** (45 mg, 0.11 mmol) and Cs_2CO_3 (38 mg, 0.11 mmol) in MeOH (3 mL) and CH_2Cl_2 (6 mL) was stirred for 15 min. Water was added and the mixture was extracted with EtOAc (×3). The combined EtOAc extracts were washed with water (×2), brine (×3), dried, and evaporated. The residue was dissolved in HCl(g) saturated dioxane (5 mL) and stirred for 1 h. The dioxane was evaporated to give 8-acetyl-1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole hydrochloride (38 mg, 100%): mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ (two H not observed) 8.42 (d, *J* = 1.3 Hz, 1 H), 8.19 (d, *J* = 9.1 Hz, 1 H), 7.80 (dd, *J* = 9.1, 1.7 Hz, 1 H), 7.77 (s, 1 H), 4.41-4.33 (m, 1 H), 3.96 (dd, *J* = 11.0, 4.1 Hz, 1 H), 3.85 (t, *J* = 10.1 Hz, 1 H), 3.77 (dd, *J* = 11.0, 2.6 Hz, 1 H), 3.73 (dd, *J* = 10.3, 2.7 Hz, 1 H), 2.74 (s, 3 H); ^{13}C NMR δ 197.9, 150.0, 147.1, 135.3, 130.0, 127.1, 124.3, 123.6, 121.6, 119.8, 111.0, 50.8, 46.6, 42.7, 26.8. This material was used directly in the next step.

A mixture of the amine hydrochloride (35 mg, 0.10 mmol), 5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (35 mg, 0.12 mmol) and EDCI (79 mg, 0.41 mmol) in DMA (3 mL) was stirred under a N_2 atmosphere for 15 h. The mixture was then partitioned between CH_2Cl_2 and cold (0 °C) 5% aq $KHCO_3$. The aqueous portion was extracted with cold CH_2Cl_2 (×4) and the combined extracts were washed with water (×3), brine (×2) and dried. The

solvent was evaporated and the residue was dissolved in CH_2Cl_2/MeOH and solvents were evaporated until precipitation began. The precipitate was filtered off and washed with MeOH to give **35** (38 mg, 69%) as an orange powder: mp 210-215°C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.71 (s, 1 H), 9.26 (s, 1 H), 8.73 (s, 1 H), 8.45 (d, *J* = 9.1 Hz, 1 H), 8.12 (dd, *J* = 9.1, 1.5 Hz, 1 H), 7.41 (d, *J* = 8.9 Hz, 1 H), 7.22 (d, *J* = 1.4 Hz, 1 H), 7.18 (d, *J* = 2.2 Hz, 1 H), 6.95 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.97 (t, *J* = 10.1 Hz, 1 H), 4.87-4.78 (m, 1 H), 4.74 (dd, *J* = 10.8, 2.0 Hz, 1 H), 4.22-4.12 (m, 2 H), 4.08 (t, *J* = 5.9 Hz, 2 H), 2.81 (s, 3 H), 2.66 (t, *J* = 5.8 Hz, 2 H), 2.25 (s, 6 H); ^{13}C NMR δ 197.7, 160.5, 153.0, 146.3, 141.5, 135.6, 133.9, 131.9, 129.8, 129.0, 127.4, 125.7, 125.2, 123.9, 123.4, 116.4, 116.3, 113.2, 106.1, 103.2, 66.1, 57.6, 54.7, 48.1, 45.3, 41.2, 27.0. Anal. ($C_{28}H_{27}ClN_4O_5 \cdot ½H_2O$) C, H, N.

Synthesis of 36.



7-(Methoxycarbonyl)-2-naphthoic acid (84). A solution of KOH (340 mg, 6.17 mmol) in MeOH (8 mL) and water (1 mL) was added dropwise to a solution of dimethyl 2,7-naphthalenedicarboxylate (**83**)[7] (1.52 g, 6.23 mmol) in MeOH (8 mL) and CH_2Cl_2 (8 mL). After 20 h, more CH_2Cl_2 and water were added, and the separated aqueous phase was acidified (pH 2) with 2N HCl. The resulting white precipitate was filtered off, washed with water, and dried in a vacuum desiccator. Chromatography eluting with CH_2Cl_2/MeOH (9:1 then 4:1) gave recovered **83** (0.50 g, 33%) and **84** (672 mg, 47%) as colorless crystals: mp (MeOH) 262-264 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.0 (br s, 1 H), 8.802 (s, 1 H), 8.796 (s, 1 H), 8.17-8.05 (m, 4 H), 3.95 (s, 3 H); ^{13}C NMR δ (one C not observed) 167.0, 166.0, 136.8, 131.8, 131.3, 129.2, 128.3, 128.1, 127.7, 127.6, 126.9, 52.3. Anal. ($C_{13}H_{10}O_4$) C, H.

Methyl 7-[(*tert*-butoxycarbonyl)amino]-2-naphthoate (152). A solution of acid **84** (50 mg, 0.22 mmol), DPPA (72 mg, 0.26 mmol) and Et_3N (48 mg, 0.48 mmol) in *t*-BuOH (5 mL) was heated under reflux for 20 h. The solvents were removed under reduced pressure and the residue was purified by chromatography eluting with CH_2Cl_2/MeOH (49:1) followed by recrystallization (EtOAc/petroleum ether) to give **152** (52 mg, 80%) as colorless needles. A sample was recrystallized: mp (CH_2Cl_2/*n*-hexane) 181-183 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (br s, 1 H), 8.05 (br s, 1 H), 7.94 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.79 (d, *J* = 8.7 Hz, 2 H), 7.51 (dd, *J* = 8.8, 2.1 Hz, 1 H), 6.67 (br s, 1 H), 3.97 (s, 3 H), 1.56 (s, 9

H); ^{13}C NMR δ 167.3, 152.7, 136.6, 133.1, 132.0, 130.4, 128.6, 127.9, 127.8, 123.8, 121.5, 115.6, 80.9, 52.2, 28.3. Anal. ($C_{17}H_{19}NO_4$) C, H, N.

Methyl 8-bromo-7-[(*tert*-butoxycarbonyl)amino]-2-naphthoate (153). A mixture of **152**(50 mg, 0.17 mmol), NBS (33 mg, 0.18 mmol) and K_2CO_3 (28 mg, 0.20 mmol) in MeCN (3 mL) was heated at 60 °C under N_2 for 30 min. The solvent was removed under reduced pressure and the residue was purified by chromatography eluting with petroleum ether/EtOAc (9:1) followed by recrystallization (petroleum ether) to give **153** (57 mg, 90%) as colorless crystals: mp 137-140 °C; ^{1}H NMR ($CDCl_3$) δ 8.89 (d, *J* = 1.2 Hz, 1 H), 8.49 (d, *J* = 9.1 Hz, 1 H), 8.01 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.83 (d, *J* = 8.6 Hz, 1 H), 7.82 (d, *J* = 9.0 Hz, 1 H), 7.35 (br s, 1 H), 4.00 (s, 3 H), 1.57 (s, 9 H). Anal. ($C_{17}H_{18}BrNO_4$) C, H, N, Br.

Methyl 8-bromo-7-[(*tert*-butoxycarbonyl)(3-chloro-2-propen-1-yl)amino]-2-naphthoate (154). NaH (57 mg, 1.42 mmol, 60% in oil) was added to a solution of **153** (450 mg, 1.18 mmol) in DMF (5 mL) at 0 °C. 1,3-Dichloropropene (260 mg, 2.37 mmol) was added and the mixture was allowed to warm to room temperature over 1 h, then concentrated under reduced pressure. CH_2Cl_2 and water were added and the organic phase was washed with water (×2), brine (×2), dried, and filtered through silica gel to give **154** (520 mg, 97%) as a yellow oil; ^{1}H NMR ($CDCl_3$) (mixture of rotamers and E and Z forms) δ 9.07 (s, 1 H), 8.18-8.08 (m, 1 H), 7.93-7.78 (m, 2 H), 7.42-7.32 (m, 1 H), 6.15-5.98 (m, 2 H), 4.01 (s, 3 H), 4.63-4.48 (m, 2 H), 1.26, 1.24 (2s, 9 H). HRMS (FAB) calcd. for $C_{20}H_{21}{}^{79}Br^{35}ClNO_4$ (MH^+) m/z 454.0421, found 454.0421.

8-Methyl 3-(*tert*-butoxycarbonyl)-1-(chloromethyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxylate (155). A mixture of **154** (500 mg, 1.10 mmol), Bu_3SnH (350 mg, 1.21 mmol) and AIBN (19 mg, 0.11 mmol) in benzene (8 mL) was heated under reflux for 1.5 h. The benzene was removed under reduced pressure, the residue was triturated with pentane, and the solid obtained was recrystallized (MeOH) to give **155** (369 mg, 78%) as colorless needles: mp 143-145 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1 H), 8.31 (br s, 1 H), 7.93 (dd, *J* = 8.6, 1.5 Hz, 1 H), 7.87 (d, *J* = 8.6 Hz, 1 H), 7.82 (d, *J* = 8.9 Hz, 1 H), 4.36-4.27 (m, 1 H), 4.20-4.08 (m, 2 H), 4.00 (s, 3 H), 3.99-3.92 (m, 1 H), 3.57-3.48 (m, 1 H), 1.61 (s, 9 H); ^{13}C NMR δ 167.1, 152.4, 142.0, 132.1, 129.6, 129.2, 129.0, 128.4, 124.9, 124.1, 123.2, 118.0, 81.4, 52.6, 52.3, 46.5, 41.6, 28.4. Anal. ($C_{20}H_{22}ClNO_4$) C, H, N, Cl.

Methyl 1-(chloromethyl)-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxylate (156). A solution of **155** (200 mg, 0.53 mmol) in HCl(g) saturated dioxane (10 mL) was stirred for 4 h, then evaporated, to give the amine hydrochloride (169 mg, 100%). A cold (0 ^{o}C) solution of this (85 mg, 0.27 mmol) in pyridine (4 mL) was treated with TFAA (66 mg, 0.32 mmol). After 30 min at 0 ^{o}C, the mixture was poured into ice water and extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with HCl (1N, ×2), water, brine, and dried. Chromatography eluting with petroleum ether/EtOAc/CH_2Cl_2 (7:2:1 then 8:1:1) followed by trituration with *n*-hexane gave **156** (88 mg, 87%) as colorless crystals: mp 161-163 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, *J* = 9.0 Hz, 1 H), 8.52 (s, 1 H), 8.07 (dd, *J* = 8.6, 1.5 Hz, 1 H), 7.95 (d, *J* = 8.6 Hz, 1 H), 7.92 (d, *J* = 9.0 Hz, 1 H), 4.68 (dt, *J* = 11.5, 1.4 Hz, 1 H), 4.45 (dd, *J* = 11.4, 8.6 Hz, 1 H), 4.32-4.27 (m, 1 H), 4.02 (s, 3 H), 4.00 (dd, *J* = 11.6, 3.3 Hz, 1 H), 3.62 (dd, *J* = 11.5, 9.2 Hz, 1 H); ^{13}C NMR δ 166.7, 154.8 (q, $J_{C\text{-}F}$ 37.4 Hz),

140.7, 134.0, 130.2, 129.4, 129.1, 128.4, 126.8, 125.4, 125.0, 119.4, 116.0 (q, $J_{C\text{-}F}$ 288 Hz), 76.7, 52.6 (q, $J_{C\text{-}F}$ 4.0 Hz), 45.7, 42.6. Anal. ($C_{17}H_{13}ClF_3NO_3$) C, H, N.

Methyl 1-(chloromethyl)-5-nitro-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxylate (158). Cold (0 °C) cH_2SO_4 (8 mL) was added to cooled (0 °C) **156** (350 mg, 0.94 mmol). A cooled (0 °C) solution of KNO_3 (95 mg, 0.94 mmol) in 98% H_2SO_4 (0.5 mL) was then added dropwise. After 15 min, the mixture was poured into ice water and extracted with CH_2Cl_2 (×3). The combined CH_2Cl_2 extracts were washed with water (×2), brine and dried. Chromatography eluting with EtOAc/petroleum ether (4:1) gave methyl 1-(chloromethyl)-7-nitro-3-(trifluoroacetyl)-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxylate (**157**) (136 mg, 36%) as a brown powder: mp (CH_2Cl_2/MeOH) 165-168 °C; ^{1}H NMR ($CDCl_3$) δ 8.69 (d, *J* = 9.0 Hz, 1 H), 8.53 (s, 1 H), 8.13 (s, 1 H), 8.07 (d, *J* = 9.0 Hz, 1 H), 4.69 (d, *J* = 11.5 Hz, 1 H), 4.52 (dd, *J* = 11.5, 8.6 Hz, 1 H), 4.32-4.25 (m, 1 H), 3.99 (s, 3 H), 3.95 (dd, *J* = 11.6, 3.5 Hz, 1 H), 3.66 (dd, *J* = 11.6, 8.5 Hz, 1 H); ^{13}C NMR δ 165.9, 154.9 (q, $J_{C\text{-}F}$ 38.4 Hz), 144.8, 143.8, 132.1, 131.0, 130.0, 126.7, 126.11, 126.05, 125.7, 120.7, 115.8 (q, $J_{C\text{-}F}$ 288 Hz), 53.5, 52.8, 45.6, 42.3. Anal ($C_{17}H_{12}ClF_3N_2O_5$.¼EtOAc) C, H, N.

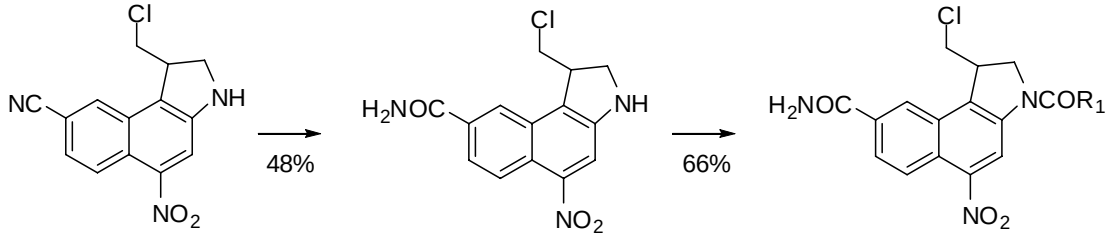
Further elution gave **158** (140 mg, 36%) as a cream powder. A sample was triturated with MeOH to give colorless crystals: mp 243-245 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.09 (s, 1 H), 8.75 (d, *J* = 1.2 Hz, 1 H), 8.51 (d, *J* = 9.2 Hz, 1 H), 8.22 (dd, *J* = 9.1, 1.6 Hz, 1 H), 4.86-4.79 (m, 1 H), 4.68-4.61 (m, 1 H), 4.55-4.49 (m, 1 H), 4.19 (dd, *J* = 11.5, 3.5 Hz, 1 H), 4.08 (dd, *J* = 11.5, 5.5 Hz, 1 H), 3.97 (s, 3 H); ^{13}C NMR δ 165.5, 150.3, 146.6, 139.3, 139.2, 134.8, 129.6, 128.7, 127.5, 126.3, 124.5, 123.0, 116.0, 52.8, 52.7, 47.6, 40.9. Anal. ($C_{17}H_{12}ClF_3N_2O_5$) C, H, N.

Methyl 1-(chloromethyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxylate (159). A solution of **158** (100 mg, 0.24 mmol) and Cs_2CO_3 (312 mg, 0.96 mmol) in MeOH (10 mL) and CH_2Cl_2 (15 mL) was stirred for 1.5 h. Water was added and the mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with water, brine and dried. The solvent was evaporated and the residue was dissolved in CH_2Cl_2/MeOH and solvents were evaporated under reduced pressure until precipitation began. The precipitate was filtered off and washed with MeOH to give **159** (76 mg, 100%): mp 161-163 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.40 (dd, *J* = 1.6, 0.6 Hz, 1 H), 8.22 (dd, *J* = 9.1, 0.4 Hz, 1 H), 7.82 (dd, *J* = 9.1, 1.7 Hz, 1 H), 7.78 (s, 1 H), 6.49 (d, *J* = 1.6 Hz, 1 H), 4.35-4.28 (m, 1 H), 3.93 (s, 3 H), 3.89-3.82 (m, 2 H), 3.79-3.69 (m, 2 H). HRMS (CI) calcd. for $C_{15}H_{13}{}^{35}ClN_2O_4$ (M^+) m/z 320.0534, found 320.0563.

Methyl 1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxylate (36). A solution of **159** (70 mg, 0.22 mmol) in HCl(g) saturated dioxane (5 mL) was stirred for 2 h. The dioxane was removed under reduced pressure to give the hydrochloride salt (78 mg, 100%). 5-[2-(Dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (75 mg, 0.26 mmol), EDCI (126 mg, 0.66 mmol), and DMA (5 mL) were added and the mixture was stirred under a N_2 atmosphere for 5 h. The mixture was partitioned between CH_2Cl_2 and ice-cold 5% aq $KHCO_3$. The aqueous portion was extracted with cold CH_2Cl_2 (×3) and the combined extracts were washed with water, brine and dried. The solvent was evaporated and the residue was dissolved in CH_2Cl_2/MeOH and solvents were concentrated under reduced pressure until precipitation began. The precipitate was filtered off and washed with MeOH to give crude **36** (101 mg, 84%) as an

orange powder: HRMS (FAB) calcd. for $C_{28}H_{27}{}^{35}ClN_4O_6$ (MH^+) m/z 551.1697, found 551.1696. ^1H NMR analysis showed that this sample contained 8% of the corresponding exomethylene compound (methyl 3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-1-methylene-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxylate). The sample was purified by HPLC (Synergi MAX column, CH_3CN/H_2O/TFA, pH 2.5) to give **36**·TFA (38 mg, 99% purity by HPLC analysis) as an orange powder: mp >320 °C; ^1H NMR [$(CD_3)_2SO$] δ 11.80 (d, *J* = 1.8 Hz, 1 H), 9.63 (br s, 1 H), 9.26 (s, 1 H), 8.74 (d, *J* = 1.1 Hz, 1 H), 8.49 (d, *J* = 9.4 Hz, 1 H), 8.17 (dd, *J* = 9.1, 1.7 Hz, 1 H), 7.48 (d, *J* = 8.9 Hz, 1 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 7.25 (d, *J* = 1.6 Hz, 1 H), 7.05 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.96 (dd, *J* = 10.6, 9.4 Hz, 1 H), 4.83-4.74 (m, 1 H), 4.70 (dd, *J* = 10.8, 2.3 Hz, 1 H), 4.35 (t, *J* = 4.8 Hz, 2 H), 4.14 (dd, *J* = 11.4, 3.4 Hz, 1 H), 4.05 (dd, *J* = 11.4, 5.8 Hz, 1 H), 3.98 (s, 3 H), 3.57 (br s, 2 H), 2.91 (br s, 6 H); ^{13}C NMR δ 165.5, 160.5, 152.0, 146.3, 141.5, 133.5, 132.3, 130.1, 129.1, 128.9, 127.3, 126.5, 125.9, 124.3, 123.5, 116.6, 116.1, 113.3, 106.2, 104.0, 62.6, 55.6, 54.8, 52.6, 47.8, 42.8, 41.4.

Synthesis of 37.



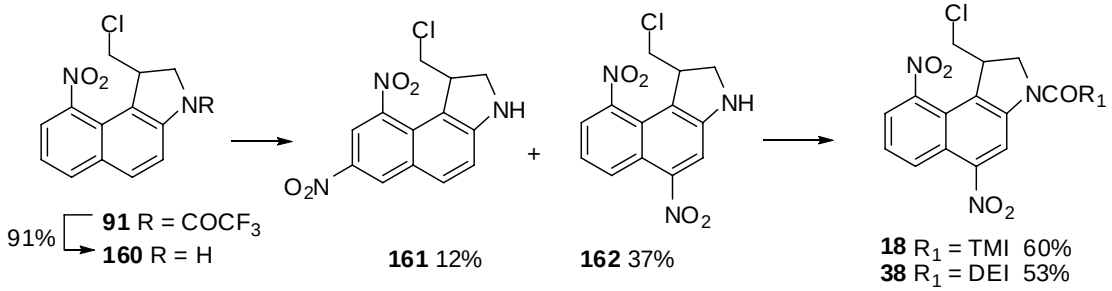
100 **102** **37** R_1 = DEI

1-(Chloromethyl)-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxamide (102). A solution of **100**·HCl (81 mg, 0.25 mmol) in cH_2SO_4 (9 mL) and water (1 mL) was heated at 60 °C for 1 h, then poured into cold water. Conc. aq NH_3 was carefully added until the pH of the mixture was 3, followed by careful addition of solid $KHCO_3$ until the pH of the mixture was 8. The mixture was extracted with cold CH_2Cl_2 (×3), and the combined organic extracts were washed with water, brine, and dried. The solvent was evaporated and the residue was dissolved in CH_2Cl_2/MeOH. The solvents were concentrated until precipitation began. The precipitate was filtered off and washed with MeOH to give crude **102** (37 mg, 48%) as red crystals: mp >300 °C; ^{1}H NMR [$(CD_3)_2SO$] δ (two H not observed) 8.32 (d, *J* = 1.3 Hz, 1 H), 8.17 (d, *J* = 9.1 Hz, 1 H), 7.80 (dd, *J* = 9.1, 1.7 Hz, 1 H), 7.72 (s, 1 H), 7.53 (br s, 1 H), 4.26-4.18 (m, 1 H), 3.99 (dd, *J* = 10.9, 3.8 Hz, 1 H), 3.83 (t, *J* = 10.1 Hz, 1 H), 3.77-3.69 (m, 2 H). ^{1}H NMR also showed the presence of an unidentified impurity (ca. 10%) which was not removed by chromatography. HRMS (CI) calcd. for $C_{14}H_{12}{}^{35}ClN_3O_3$ (M^+) m/z 305.0567, found 305.0564.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxamide (37). A solution of **102** (30 mg, 0.098 mmol) in HCl(g) saturated dioxane (5 mL) was stirred for 1 h, then evaporated to give the amine hydrochloride (34 mg, 0.098 mmol, 100%). 5-[2-(Dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (34 mg, 0.098 mmol), EDCI (57 mg, 0.30 mmol), and DMA (4 mL) were added and the mixture was stirred under a N_2 atmosphere for 15 h. The mixture was partitioned between EtOAc and cold (0 °C) 5% aq $KHCO_3$. The aqueous portion was extracted with cold EtOAc (×3) and the combined extracts were washed with water, brine and dried. The solvent was evaporated and the residue was dissolved in CH_2Cl_2/MeOH, and solvents were concentrated until precipitation began. The precipitate was filtered off and washed with MeOH to give crude **37** (35 mg, 66%) as an orange powder: HRMS (FAB) calcd. for $C_{27}H_{26}{}^{35}ClN_5O_5$ (MH^+) m/z 536.1701, found 536.1710. ^{1}H NMR analysis showed that this sample contained 13% of the corresponding exomethylene compound (3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-1-methylene-5-nitro-1,2-dihydro-3*H*-benzo[*e*]indole-8-carboxamide). The sample was purified by HPLC (Synergi MAX column, CH_3CN/H_2O/TFA, pH 2.5) to give **37**·TFA (38 mg) as an orange powder: mp >320 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.71 (d, *J* = 1.7 Hz, 1 H), 9.60 (br s, 1 H), 9.21 (s, 1 H), 8.62 (d, *J* = 1.2 Hz, 1 H), 8.43 (d, *J* = 9.1 Hz, 1 H), 8.40 (s, 1 H), 8.14 (dd, *J* = 7.3, 1.7 Hz, 1 H), 7.70 (br s, 1 H), 7.47 (d, *J* = 8.9 Hz, 1 H), 7.27 (d, *J* = 2.4 Hz, 1 H), 7.23 (d, *J* = 1.7 Hz, 1 H), 7.04 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.97 (dd, *J* = 10.8, 9.5 Hz, 1 H), 4.72 (dd, *J* = 10.8, 2.2 Hz, 1 H), 4.68-4.61

(m, 1 H), 4.33 (t, *J* = 5.0 Hz, 2 H), 4.21 (dd, *J* = 11.3, 3.2 Hz, 1 H), 4.13 (dd, *J* = 11.1, 6.1 Hz, 1 H), 3.48 (br s, 2 H), 2.85 (s, 6 H); ^{13}C NMR δ 166.9, 160.5, 152.1, 146.3, 141.1, 133.6, 133.2, 132.2, 130.2, 129.0, 127.3, 126.5, 123.6, 123.0, 122.8, 116.1, 115.8, 113.3, 106.0, 104.0, 63.0, 55.8, 54.7, 47.7, 43.0, 41.5. Anal. ($C_{27}H_{26}ClN_5O_6$·TFA·1½H_2O) C, H.

Synthesis of 18 and 38.



1-(Chloromethyl)-9-nitro-1,2-dihydro-3*H*-benzo[*e*]indole (160). A solution of **91** (1.54 g, 4.29 mmol) in dioxane (10 mL) was treated with a solution of Cs_2CO_3 (3.26 g, 10 mmol) in water (3 mL) and MeOH (7 mL) and the mixture was stirred at room temperature for 10 min. The mixture was treated with AcOH (1.2 mL), then concentrated under reduced pressure to a small volume and partitioned between water and CH_2Cl_2. The organic phase was washed with water (×2), dried, and filtered through a column of silica gel. The resulting oil was crystallized from EtOAc/petroleum ether to give **160** (1.03 g, 91%) as a red solid: mp 100 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.07 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.94 (dd, *J* = 7.6, 1.3 Hz, 1 H), 7.87 (d, *J* = 8.7 Hz, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 7.13 (d, *J* = 8.7 Hz, 1 H), 6.63 (s, 1 H), 3.81-3.71 (m, 1 H), 3.71-3.62 (m, 1 H), 3.62-3.54 (m, 1 H), 3.33-3.25 (m, 2 H). Anal. ($C_{13}H_{11}ClN_2O_2$) C, H, N.

1-(Chloromethyl)-5,9-dinitro-1,2-dihydro-3*H*-benzo[*e*]indole (162). A stirred solution of **160** (900 mg, 3.43 mmol) in cH_2SO_4 (9 mL) was cooled to –5 °C and treated with powdered KNO_3 (520 mg, 5.14 mmol). The mixture was stirred at 0 °C for a further 15 min, then poured into ice-water and the solid was collected. Chromatography on silica gel, eluting with petroleum ether/EtOAc (3:1), followed by two recrystallizations from CH_2Cl_2/iPr_2O gave **162** (394 mg, 37%) as a red solid: mp 130-131 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.21 (dd, *J* = 8.6, 1.1 Hz, 1 H), 8.10 (dd, *J* = 7.6, 1.1 Hz, 1 H), 7.75 (s, 1 H), 7.44 (dd, *J* = 8.6, 7.6 Hz, 1 H), 7.02 (s, 1 H), 3.89-3.81 (m, 1 H), 3.72-3.62 (m, 2 H), 3.41-3.35 (m, 2 H). Anal. ($C_{13}H_{10}ClN_3O_4$) C, H, N, Cl.

Further elution with petroleum ether/EtOAc (2:1) gave 1-(chloromethyl)-7,9-dinitro-1,2-dihydro-3*H*-benzo[*e*]indole (**161**) (122 mg, 12%) as a red solid: mp (EtOAc/iPr_2O) 216-218 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.00 (d, *J* = 2.4 Hz, 1 H), 8.65 (d, *J* = 2.5 Hz, 1 H), 8.19 (d, *J* = 8.9 Hz, 1 H), 7.74 (s, 1 H), 7.24 (d, *J* = 8.9 Hz, 1 H), 3.93 (dd, *J* = 10.8, 9.0 Hz, 1 H), 3.76-3.68 (m, 1 H), 3.67 (dd, *J* = 11.0, 2.4 Hz, 1 H), 3.38-3.24 (after D_2O exchange, m, 2 H). Anal. ($C_{13}H_{10}ClN_3O_4$) C, H, N, Cl.

1-(Chloromethyl)-5,9-dinitro-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (18). A suspension of 5,6,7-trimethoxyindole-2-carboxylic acid (122 mg, 0.49 mmol) in dry CH_2Cl_2 (10 mL) was treated with oxalyl chloride (0.13 mL, 1.49 mmol) followed by DMF (10 μL). The mixture was stirred at room temperature for 15 min, then evaporated under reduced pressure and azeotroped dry with benzene. The resulting acid chloride was cooled to –5 °C and treated with an ice-cold solution of **162** (100 mg, 0.33 mmol) in dry pyridine (2 mL) containing DMAP (5 mg). The stirred mixture was warmed to room temperature for 30 min, then poured into dilute aqueous $KHCO_3$.

The precipitate was collected, purified by chromatography on silica gel eluting with CH_2Cl_2/EtOAc (19:1), then crystallized from CH_2Cl_2/EtOAc to give **18** (106 mg, 60%) as a yellow solid: mp 270-271 ^oC; ^1H NMR [$(CD_3)_2SO$] δ 11.67 (d, *J* = 1.0 Hz, 1 H), 9.22 (s, 1 H), 8.53 (dd, *J* = 8.8, 0.9 Hz, 1 H), 8.34 (dd, *J* = 7.4, 0.9 Hz, 1 H), 7.84 (dd, *J* = 8.7, 7.6 Hz, 1 H), 7.17 (d, *J* = 2.1 Hz, 1 H), 6.99 (s, 1 H), 4.93 (dd, *J* = 10.9, 9.0 Hz, 1 H), 4.53 (dd, *J* = 11.0, 1.8 Hz, 1 H), 3.99-3.89 (m, 4 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.70 (dd, *J* = 11.5, 3.3 Hz, 1 H), 3.55 (dd, *J* = 11.5, 7.0 Hz, 1 H). HRMS (FAB) calcd. for $C_{25}H_{21}{}^{35}ClN_4O_8$ (M+) m/z 540.1048, found 540.1034. Anal. ($C_{25}H_{21}ClN_4O_8$) C, H, N.

1-(Chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-5,9-dinitro-1,2-dihydro-3*H*-benzo[*e*]indole (38). A mixture of **162** (100 mg, 0.33 mmol), 5-[2-(dimethylamino)ethoxy]indole-2-carboxylic acid hydrochloride (111 mg, 0.39 mmol), EDCI (249 mg, 1.30 mmol) and anhydrous TsOH (40 mg, 0.23 mmol) in dry DMA (6 mL) was stirred at room temperature under N_2 for 6 h, then poured into dilute aq NH_3. The solid was collected, dissolved in CH_2Cl_2 at room temperature, dried, and concentrated under reduced pressure below 30 ^oC to a small volume and diluted with EtOAc/iPr2O to give **38**. Treatment of a solution of the free base in CH_2Cl_2 with HCl(g)/EtOAc/hexane, followed by crystallization from MeOH/Me_2CO/EtOAc, gave **38**·HCl (99 mg, 53%) as a yellow solid: mp 187-191 ^oC; ^1H NMR [$(CD_3)_2SO$] δ 11.87 (d, *J* = 1.6 Hz, 1 H), 10.01 (br s, 1 H), 9.28 (s, 1 H), 8.53 (dd, *J* = 8.8, 1.0 Hz, 1 H), 8.36 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.85 (dd, *J* = 8.7, 7.6 Hz, 1 H), 7.46 (d, *J* = 8.9 Hz, 1 H), 7.28 (d, *J* = 2.3 Hz, 1 H), 7.21 (d, *J* = 1.6 Hz, 1 H), 7.04 (dd, *J* = 8.9, 2.4 Hz, 1 H), 4.99 (dd, *J* = 10.8, 9.0 Hz, 1 H), 4.60 (dd, *J* = 10.9, 1.7 Hz, 1 H), 4.35 (t, *J* = 5.0 Hz, 2 H), 4.02-3.92 (m, 1 H), 3.70 (dd, *J* = 11.4, 3.3 Hz, 1 H), 3.58 (dd, *J* = 11.4, 7.2 Hz, 1 H), 3.52 (t, *J* = 4.8 Hz, 2 H), 2.87 (s, 6 H). Anal. ($C_{26}H_{24}ClN_5O_6$·HCl) C, H, N.

Synthesis of anilines 41-44 and 47-52.

5-Amino-1-(chloromethyl)-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole-7-carbonitrile (41). Compound **11** was hydrogenated as described in the general method (50 psi for 30 min) and the crude product purified by chromatography on silica gel, eluting with EtOAc/petroleum ether (1:1), to give **41** (60%) as a yellow solid: mp 280-285 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.42 (d, *J* = 1.6 Hz, 1 H), 8.67 (d, *J* = 1.3 Hz, 1 H), 7.88 (d, *J* = 8.7 Hz, 1 H), 7.72 (s, 1 H), 7.63 (dd, *J* = 8.7, 1.5 Hz, 1 H), 7.06 (d, *J* = 2.2 Hz, 1 H), 6.96 (s, 1 H), 6.41 (s, 2 H), 4.69 (dd, *J* = 10.9, 9.0 Hz, 1 H), 4.42 (dd, *J* = 11.0, 1.8 Hz, 1 H), 4.15-4.08 (m, 1 H), 3.97-3.92 (m, 1 H), 3.93 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.76 (dd, *J* = 11.0, 7.7 Hz, 1 H). ^{1}H NMR and HPLC analysis showed the presence of an impurity (7%), presumably formed by over-reduction of the 7-CN substituent. HRMS (FAB) calcd. for $C_{26}H_{23}{}^{35}ClN_4O_4$ (MH^+) m/z 490.1408, found 490.1400.

5-Amino-1-(chloromethyl)-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole-7-sulfonamide (42). Compound **10** was hydrogenated as described in the general method (50 psi for 60 min) to give **42** (65%) as a yellow powder: mp 240-245 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.40 (s, 1 H), 8.55 (d, *J* = 1.6 Hz, 1 H), 7.92 (d, *J* = 8.9 Hz, 1 H), 7.80 (dd, *J* = 8.9, 1.7 Hz, 1 H), 7.73 (s, 1 H), 7.24 (s, 2 H), 7.06 (s, 1 H), 6.97 (s, 1 H), 6.21 (s, 2 H), 4.70 (dd, *J* = 10.9, 9.0 Hz, 1 H), 4.43 (dd, *J* = 11.0, 1.8 Hz, 1 H), 4.16-4.09 (m, 1 H), 3.98 (dd, *J* = 11.0, 3.1 Hz, 1 H), 3.94 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.76 (dd, *J* = 11.0, 7.9 Hz, 1 H). Anal. ($C_{25}H_{25}ClN_4O_6S$) C, H, N.

5-Amino-1-(chloromethyl)-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxamide (43). Compound **15** was hydrogenated as described (50 psi for 45 min) to give **43** (71%) as a pale yellow-green solid: mp 260-265 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.39 (d, *J* = 1.4 Hz, 1 H), 8.65 (d, *J* = 0.9 Hz, 1 H), 7.91 (dd, *J* = 8.7, 1.4 Hz, 1 H), 7.84 (s, 1 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 7.66 (s, 1 H), 7.33 (s, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 6.96 (s, 1 H), 6.10 (s, 2 H), 4.68 (dd, *J* = 10.9, 9.0 Hz, 1 H), 4.41 (dd, *J* = 11.0, 1.7 Hz, 1 H), 4.14-4.08 (m, 1 H), 3.97 (dd, *J* = 11.1, 3.2 Hz, 1 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.75 (dd, *J* = 11.0, 8.0 Hz, 1 H). Anal. ($C_{26}H_{25}ClN_4O_5$) C, H, N.

5-Amino-1-(chloromethyl)-8-(methylsulfonyl)-3-(5,6,7-trimethoxyindol-2-carbonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (44). Compound **16** was hydrogenated as described in the general method (45 psi for 90 min) to give **44** (84%) as a yellow solid: mp (*i*Pr_2O/THF) 165-170 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.41 (d, *J* = 2.0 Hz, 1 H), 8.33 (d, *J* = 8.9 Hz, 1 H), 8.26 (d, *J* = 1.8 Hz, 1 H), 7.81 (s, 1 H), 7.66 (dd, *J* = 8.9, 1.8 Hz, 1 H), 7.08 (d, *J* = 2.2 Hz, 1 H), 6.96 (s, 1 H), 6.26 (s, 2 H), 4.71 (dd, *J* = 10.9, 8.8 Hz, 1 H), 4.45 (dd, *J* = 11.0, 1.6 Hz, 1 H), 4.24-4.17 (m, 1 H), 4.00 (dd, *J* = 11.0, 3.3 Hz, 1 H), 3.95 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.74 (dd, *J* = 11.0, 7.9 Hz, 1 H), 3.32 (s, 3 H). Anal. ($C_{26}H_{26}ClN_3O_6S\cdot½H_2O$) C, H, N.

5-Amino-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-7-(methylsulfonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (46). Compound **26** (as the free base) was hydrogenated as described in the general method (45 psi for 60 min) to give **46** (81%) as a yellow solid: mp (*i*Pr_2O/THF) 280-285 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.57 (s, 1 H), 8.70 (d, *J* = 1.6 Hz, 1 H), 7.97 (d, *J* = 8.9 Hz, 1 H), 7.85-7.79 (m, 2 H), 7.40 (d, *J* = 8.9 Hz, 1 H), 7.17 (d, *J* = 2.3 Hz, 1 H), 7.10 (d, *J* = 1.7 Hz, 1 H), 6.93 (dd, *J* = 8.9, 2.4 Hz, 1 H), 6.40 (s, 2 H), 4.77 (dd, *J* = 10.8, 9.0 Hz, 1 H), 4.54

(dd, *J* = 10.9, 1.8 Hz, 1 H), 4.24-4.16 (m, 1 H), 4.06 (t, *J* = 5.9 Hz, 2 H), 3.99 (dd, *J* = 11.0, 3.0 Hz, 1 H), 3.81 (dd, *J* = 11.0, 7.5 Hz, 1 H), 3.26 (s, 3 H), 2.65 (t, *J* = 5.9 Hz, 2 H), 2.24 (s, 6 H). Anal. ($C_{27}H_{29}ClN_4O_4S$) C, H, N, Cl.

5-Amino-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-1,2-dihydro-3*H*-benzo[*e*]indole-7-carbonitrile (47). Compound **27** (as the free base) was hydrogenated as described in the general method (50 psi for 60 min) to give **47** (48%) as a yellow solid: mp 250-255 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.57 (d, *J* = 1.5 Hz, 1 H), 8.67 (s, 1 H), 7.89 (d, *J* = 8.7 Hz, 1 H), 7.80 (s, 1 H), 7.64 (dd, *J* = 8.7, 1.5 Hz, 1 H), 7.39 (d, *J* = 8.9 Hz, 1 H), 7.17 (d, *J* = 2.3 Hz, 1 H), 7.09 (s, 1 H), 6.91 (dd, *J* = 8.9, 2.4 Hz, 1 H), 6.40 (s, 2 H), 4.75 (dd, *J* = 10.7, 9.1 Hz, 1 H), 4.52 (dd, *J* = 10.9, 1.8 Hz, 1 H), 4.20-4.14 (m, 1 H), 4.06 (t, *J* = 5.9 Hz, 2 H), 3.96 (dd, *J* = 11.0, 3.1 Hz, 1 H), 3.77 (dd, *J* = 11.0, 7.6 Hz, 1 H), 2.65 (t, *J* = 5.9 Hz, 2 H), 2.24 (s, 6 H). HRMS (FAB) calcd. for $C_{27}H_{27}{}^{35}ClN_5O_2$ (MH^+) m/z 488.1853, found 488.1847.

5-Amino-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-1,2-dihydro-3*H*-benzo[*e*]indole-7-sulfonamide (48). Compound **28** (as the free base) was hydrogenated as described in the general method (50 psi for 60 min) to give **48** (43%) as a yellow solid: mp 260-266 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1 H), 8.56 (d, *J* = 1.5 Hz, 1 H), 7.93 (d, *J* = 8.9 Hz, 1 H), 7.81 (s, 1 H), 7.80 (dd, *J* = 8.8, 1.7 Hz, 1 H), 7.40 (d, *J* = 8.9 Hz, 1 H), 7.24 (s, 2 H), 7.17 (d, *J* = 2.3 Hz, 1 H), 7.08 (s, 1 H), 6.91 (dd, *J* = 8.9, 2.4 Hz, 1 H), 6.22 (s, 2 H), 4.77 (dd, *J* = 10.8, 9.1 Hz, 1 H), 4.53 (dd, *J* = 10.9, 1.8 Hz, 1 H), 4.22-4.14 (m, 1 H), 4.06 (t, *J* = 5.9 Hz, 2 H), 3.99 (dd, *J* = 11.0, 3.0 Hz, 1 H), 3.80 (dd, *J* = 10.9, 7.7 Hz, 1 H), 2.65 (t, *J* = 5.8 Hz, 2 H), 2.24 (s, 6 H). HRMS (FAB) calcd. for $C_{26}H_{29}{}^{35}ClN_5O_4S$ (MH^+) m/z 542.1629, found 542.1625.

7-Acetyl-5-amino-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-1,2-dihydro-3*H*-benzo[*e*]indole (49). Compound **29** (as the free base) was hydrogenated as described in the general method (50 psi for 20 min). The crude product purified by chromatography on silica gel, eluting with EtOAc/MeOH (4:1), followed by trituration with EtOAc to give **49** (31%) as a yellow solid: mp 220-224 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1 H), 8.78 (d, *J* = 1.2 Hz, 1 H), 7.88 (dd, *J* = 8.8, 1.5 Hz, 1 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 7.75 (s, 1 H), 7.38 (d, *J* = 8.9 Hz, 1 H), 7.16 (d, *J* = 2.3 Hz, 1 H), 7.08 (d, *J* = 1.5 Hz, 1 H), 6.92 (dd, *J* = 8.9, 2.4 Hz, 1 H), 6.43 (s, 2 H), 4.75 (dd, *J* = 10.8, 9.0 Hz, 1 H), 4.51 (dd, *J* = 10.9, 1.9 Hz, 1 H), 4.19-4.13 (m, 1 H), 4.07 (t, *J* = 5.9 Hz, 2 H), 3.97 (dd, *J* = 10.9, 3.1 Hz, 1 H), 3.81-3.75 (m, 1 H), 2.68 (s, 3 H), 2.65 (t, *J* = 5.9 Hz, 2 H), 2.24 (s, 6 H). HRMS (FAB) calcd. for $C_{28}H_{30}{}^{35}ClN_4O_3$ (MH^+) m/z 505.2006, found 505.1999.

Methyl 5-amino-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxylate (50). Compound **30** (as the free base) was hydrogenated as described in the general method (50 psi for 45 min) to give **50** (82%) as a yellow solid: mp 225-230 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.57 (d, *J* = 1.6 Hz, 1 H), 8.80 (d, *J* = 1.4 Hz, 1 H), 7.90 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.76 (s, 1 H), 7.40 (d, *J* = 8.9 Hz, 1 H), 7.17 (d, *J* = 2.4 Hz, 1 H), 7.08 (d, *J* = 1.5 Hz, 1 H), 6.91 (dd, *J* = 8.9, 2.4 Hz, 1 H), 6.34 (s, 2 H), 4.75 (dd, *J* = 10.8, 8.9 Hz, 1 H), 4.52 (dd, *J* = 10.9, 1.8 Hz, 1 H), 4.18-4.11 (m, 1 H), 4.06 (t, *J* = 5.9 Hz, 2 H), 3.98 (dd, *J* = 11.0, 3.1 Hz, 1 H), 3.90 (s, 3 H), 3.78 (dd, *J* = 11.0, 7.9 Hz, 1 H), 2.65 (t, *J* = 5.9 Hz, 2 H), 2.23 (s, 6 H). Anal. ($C_{28}H_{29}ClN_4O_4$) C, H, N.

5-Amino-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-1,2-dihydro-3*H*-benzo[*e*]indole-7-carboxamide (51). Compound **31** (as the free base) was hydrogenated as described in the general method (50 psi for 45 min) to give **51** (70%) as a green solid: mp 232-236 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (d, *J* = 1.6 Hz, 1 H), 8.66 (s, 1 H), 7.90 (dd, *J* = 8.7, 1.5 Hz, 1 H), 7.83 (br s, 1 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 7.73 (s, 1 H), 7.39 (d, *J* = 8.9 Hz, 1 H), 7.32 (br s, 1 H), 7.17 (d, *J* = 2.3 Hz, 1 H), 7.07 (d, *J* = 1.4 Hz, 1 H), 6.91 (dd, *J* = 8.9, 2.4 Hz, 1 H), 6.11 (s, 2 H), 4.75 (dd, *J* = 10.8, 9.0 Hz, 1 H), 4.51 (dd, *J* = 10.9, 1.8 Hz, 1 H), 4.18-4.12 (m, 1 H), 4.06 (t, *J* = 5.9 Hz, 2 H), 3.98 (dd, *J* = 10.9, 3.1 Hz, 1 H), 3.78 (dd, *J* = 11.0, 7.9 Hz, 1 H), 2.65 (t, *J* = 5.9 Hz, 2 H), 2.24 (s, 6 H). Anal. ($C_{27}H_{28}ClN_5O_3 \cdot ½H_2O$) C, H, N.

5-Amino-1-(chloromethyl)-3-{5-[2-(dimethylamino)ethoxy]indol-2-carbonyl}-8-(methylsulfonyl)-1,2-dihydro-3*H*-benzo[*e*]indole (52). Compound **32** (as the free base) was hydrogenated as described in the general method (50 psi for 60 min) to give **52** as a pale yellow solid: mp (*i*-Pr_2O/THF) 235-240 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (d, *J* = 1.6 Hz, 1 H), 8.33 (d, *J* = 8.9 Hz, 1 H), 8.26 (d, *J* = 1.8 Hz, 1 H), 7.88 (s, 1 H), 7.67 (dd, *J* = 8.9, 1.8 Hz, 1 H), 7.40 (d, *J* = 8.9 Hz, 1 H), 7.17 (d, *J* = 2.3 Hz, 1 H), 7.10 (d, *J* = 1.4 Hz, 1 H), 6.92 (dd, *J* = 8.9, 2.4 Hz, 1 H), 6.26 (s, 2 H), 4.76 (dd, *J* = 10.8, 8.9 Hz, 1 H), 4.55 (dd, *J* = 10.9, 1.6 Hz, 1 H), 4.28-4.21 (m, 1 H), 4.06 (t, *J* = 5.9 Hz, 2 H), 4.01 (dd, *J* = 11.0, 3.3 Hz, 1 H), 3.78 (dd, *J* = 11.1, 7.8 Hz, 1 H), 3.32 (s, 3 H), 2.65 (t, *J* = 5.9 Hz, 2 H), 2.23 (s, 6 H). Anal. ($C_{27}H_{29}ClN_4O_4S \cdot ½H_2O$) C, H, N.

Combustion analyses for the new compounds of Tables 1 - 3

No	Found				Calculated			
	C	H	N	Other	C	H	N	Other
7	55.60	4.02	10.44		55.51	3.91	10.36	
8	59.48	4.35	7.50		59.29	4.57	7.68	
9	55.76	4.17	10.29		55.51	3.91	10.36	
10	53.57	4.46	7.30		53.56	4.32	7.21	
11	59.94	3.83	10.71		59.94	4.06	10.76	
12	52.00	4.28	9.35		52.22	4.03	9.74	
13	60.35	4.47	7.52		60.28	4.50	7.81	
14	58.30	4.23	7.38		58.54	4.37	7.59	
15	58.07	4.36	9.89		57.94	4.30	10.40	
16	54.41	4.31	7.39		54.40	4.21	7.32	
17	52.54	4.42	9.16		52.39	4.40	9.05	
18	55.52	3.90	10.22		55.51	3.91	10.36	
20	51.87	4.74	11.69		51.92	4.69	11.65	
21	62.09	4.71	13.12		62.09	4.69	13.41	
22	54.39	4.60	12.12	6.37 (Cl)	54.59	4.58	12.24	6.20 (Cl)
23	61.80	5.10	10.49	6.65 (Cl)	61.86	5.09	10.47	6.65 (Cl)
24	60.30	4.86	12.91	6.67 (Cl)	60.50	4.89	13.07	6.61 (Cl)
25	54.26	4.54	11.92		54.37	4.39	12.19	
26	53.35	4.66	8.97		53.38	4.65	9.22	
27	57.57	4.39	12.24		57.56	4.65	12.43	
28	50.63	4.83	11.25		50.57	4.57	11.34	
29	60.88	5.17	10.16	5.75 (Cl)	60.82	5.24	10.13	6.40 (Cl)
30	56.23	4.75	9.31		56.38	4.90	9.40	
31	54.87	4.79	11.86		54.92	4.95	11.86	
32	53.05	4.51	9.27		53.38	4.65	9.22	
33	62.35	4.67	13.21		62.61	4.67	13.52	
34	53.61	4.67	11.75		53.75	4.68	12.05	
35	60.87	4.90	9.72		60.81	5.29	10.13	
37	51.65	3.90	10.03		51.79	4.42	10.41	
38	52.95	4.57	11.91		52.71	4.59	11.82	
40	57.59	4.81	7.59		57.40	4.82	7.73	
42	54.93	4.84	9.88		55.10	4.62	10.28	
43	61.26	5.04	10.80		61.36	4.95	11.01	
44	56.78	4.88	7.48		56.46	4.92	7.60	
46	59.91	5.60	10.22	6.33 (Cl)	59.93	5.40	10.36	6.55 (Cl)
50	64.31	5.70	10.46		64.55	5.61	10.75	

51	63.08	5.70	13.46		62.97	5.68	13.60	
52	58.93	5.61	10.00		58.96	5.50	10.19	

Combustion analyses for new intermediate compounds.

No	Found				Calculated			
	C	H	N	Other	C	H	N	other
59 EWG=6-COMe	50.96	2.75	6.71		50.95	3.02	6.99	
59 EWG=6-SO_2Cl	39.22	1.76	6.13		39.41	1.98	6.13	
59 EWG=6-CN	50.01	2.15	10.68		50.08	2.36	10.95	
59 EWG=6-$CONH_2$	48.23	3.28	9.98	8.48 (Cl)	47.84	2.76	10.46	8.83 (Cl)
64	62.32	5.49	4.92		62.26	5.23	4.84	
65	62.74	5.35	5.15		62.26	5.23	4.84	
66	66.25	4.39			66.03	4.62		
67	57.67	3.79			57.59	4.03		
69	52.28	3.53		12.45 (S)	52.19	3.58		12.66 (S)
70	66.34	4.40			66.03	4.62		
71	57.36	3.99			57.59	4.03		
72	56.80	2.39	5.91	34.32 (Br)	56.93	2.61	6.04	34.43 (Br)
75	39.45	1.94			39.11	1.98		
76	62.82	4.26	2.90		62.76	4.46	3.17	
77	69.94	5.24	3.22		70.09	5.20	3.14	
78	69.47	4.66	3.47		69.59	4.91	3.25	
81	73.96	5.27			73.67	5.30		
82	72.60	4.60			72.89	4.71		
84	67.50	3.99			67.82	4.38		
86	56.10	5.11	4.38	24.66 (Br)	55.92	5.01	4.35	24.80 (Br)
88	68.02	6.15	4.48		68.02	6.34	4.41	
89	57.40	3.65	4.44		57.43	3.53	4.46	
90	50.12	3.00	7.54		50.22	2.81	7.81	
91	50.44	2.94	7.76		50.22	2.81	7.81	
92	57.48	3.44	3.83		57.40	3.68	3.94	
93	57.13	3.54	3.79		57.40	3.68	3.94	
94	43.81	2.16	3.28	17.10 (Cl)	43.71	2.45	3.40	17.20 (Cl)
95	43.85	2.15	3.27	17.27 (Cl)	43.71	2.45	3.40	17.20 (Cl)
96	41.20	1.99	2.97		40.98	2.29	3.19	

97	55.73	2.76	8.07		55.75	3.02	8.13	
98	54.03	3.27	7.87	9.95 (Cl)	53.87	3.39	7.85	9.94 (Cl)
99	58.74	3.44	14.53	12.13 (Cl)	58.44	3.50	14.61	12.32 (Cl)
100	57.99	3.39	14.42		58.45	3.50	14.61	
101	55.30	4.18	13.49		55.00	3.96	13.75	
104	59.59	4.17	10.47		59.44	4.22	10.66	
105	50.98	3.27	13.67		50.74	3.28	13.66	
107	59.72	4.25	10.76		59.44	4.22	10.67	
108	51.03	2.99	13.45	11.55 (Cl)	50.74	3.28	13.66	11.52 (Cl)
109	60.00	5.75	4.32		59.79	5.96	4.36	
110	48.05	4.32	3.67		48.01	4.53	3.50	
112	57.94	5.54	3.81		57.64	5.60	3.54	
113	49.63	3.56	8.14	10.45 (Cl)	49.34	3.84	8.22	10.40 (Cl)
115	71.47	5.93	10.16		71.62	6.01	10.44	
116	55.61	4.28	8.08	23.24 (Br)	55.35	4.36	8.07	23.01 (Br)
118	66.00	5.43	7.96		65.70	5.66	8.07	
119	39.63	1.74	6.16	15.96 (Cl)	39.41	1.98	6.13	15.51 (Cl)
120	45.95	3.80	12.15		45.69	3.54	12.30	
121	51.25	2.86	7.00		50.95	3.02	6.99	
123	68.04	6.38	4.64		67.76	6.36	4.65	
124	53.93	4.70	3.59	20.97 (Br)	53.70	4.77	3.68	21.01 (Br)
126	64.21	6.07	3.62		63.91	5.90	3.73	
128	56.37	3.83	8.67	10.98 (Cl)	56.18	4.09	8.73	11.05 (Cl)
129	59.49	6.08	4.27		59.79	5.96	4.36	
130	48.06	4.59	3.33		48.01	4.53	3.50	
132	59.23	6.01	3.34		59.11	6.54	3.13	
133	49.60	3.70	8.06		49.34	3.84	8.22	
134	71.38	6.05	10.34		71.62	6.01	10.44	
135	55.59	4.22	8.06	23.27 (Br)	55.35	4.36	8.07	23.01 (Br)
137	66.65	5.41	8.09		66.57	5.59	8.17	
138	69.47	6.13	5.55		69.30	6.02	5.57	
139	60.19	5.11	4.73		59.90	5.03	4.82	
141	66.81	5.86	4.95		66.60	5.76	4.85	
141	60.74	4.19	4.98		60.79	4.22	4.89	
143	44.92	3.16	6.76		44.84	3.26	6.97	
144	41.53	2.64	9.38		41.15	2.53	9.60	
145	41.16	2.64	9.26		41.15	2.53	9.60	
146	71.55	6.90	5.06		71.56	6.71	4.91	
147	56.37	5.15	3.98		56.06	4.98	3.85	

149	66.80	6.23	3.85		66.76	6.16	3.89	
150	57.61	3.65	3.91		57.40	3.68	3.94	
151	50.94	2.89	6.73		50.95	3.02	6.99	
152	68.03	6.37	4.57		67.76	6.36	4.65	
153	53.88	4.75	3.69	21.16 (Br)	53.70	4.77	3.69	21.01
155	64.18	6.01	3.61	9.20 (Cl)	63.91	5.90	3.73	9.43 (Cl)
156	54.98	3.73	3.67		54.93	3.52	3.77	
157	49.60	3.06	6.49		49.27	3.22	6.39	
158	49.26	2.73	6.59		49.00	2.90	6.73	
160	59.47	4.25	10.51		59.44	4.22	10.67	
161	50.86	3.20	13.39	11.83 (Cl)	50.74	3.28	13.66	11.52 (Cl)
162	50.67	3.56	13.86	11.62 (Cl)	50.74	3.28	13.66	11.52 (Cl)

2D NMR Spectra of **105**, **162**, **161**, **97**, **59** (EWG = 6-COMe), **92**, **119**, **144**

NMR data were collected on a Bruker Avance 400 spectrometer operating at frequencies of 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C) and equipped with a 5mm triple-resonance (^{1}H/^{13}C/^{15}N) inverse detection probe with a self-shielded z-gradient coil for 2D experiments (90° pulse width 7.6/15.8/40 μs). A 5mm ^{1}H/^{13}C dual probe (90° pulse width 12.0/7.56 μs) was used to observe standard 1D spectra, which were obtained in $(CD_3)_2SO$ at 300 K, and referenced to Me_4Si. Typical experimental parameters for one-dimensional ^{1}H/^{13}C spectra were as follows: spectral width 17/240 ppm, data points 32K/64K, spectral resolution 0.21/0.40 Hz, number of scans 32/2000, acquisition time 2.42/1.25 s, relaxation delay 0.1/0.75 s, flip angle 30/50°.

Assignments were determined using ^{1}H-^{1}H gs-COSY, ^{1}H-^{1}H ROESY, ^{1}H-^{13}C gs-HSQC and gs-HMBC two-dimensional experiments using standard pulse sequences from the Bruker pulse library. The pulse conditions are as follows:

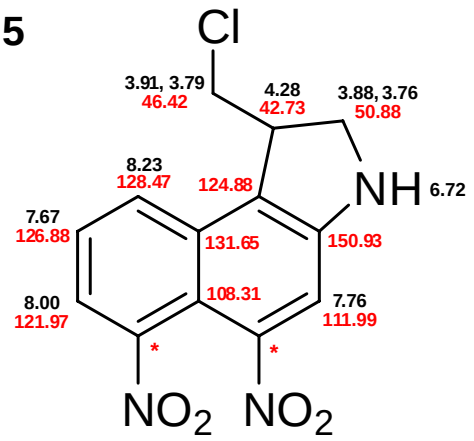
^{1}H-^{1}H gs-COSY: Spectral width of 10ppm was used in both dimensions and the acquisition data size was 2048 points. One transient was acquired per increment, with a 1.5 s relaxation delay, for a total of 256 experiments.

^{1}H-^{1}H ROESY: Spectral width of 10 ppm was used in both dimensions and the acquisition data size was 2048 points. Eight transients were acquired per increment, with a 2 s relaxation delay, for a total of 256 experiments. Mixing time was 250ms.

^{1}H-^{13}C gs-HSQC and gs-HMBC: Spectral width of 10 ppm in F_2 and 200 ppm (10-210 ppm) in F_1 was used and the HSQC/HMBC experiments optimized for C-H coupling of 140/8.3 Hz. Typically, acquisition data size was 2048 points and the number of increments for time evolution was 256. The number of scans per increment was 2/4 with 0.5/1 s delays between transients. Gradient ratios were 40:10 and 50:30:40% for the ^{1}H-^{13}C gs-HSQC and gs-HMBC experiments respectively.

The following compounds were analysed by 2D NMR experiments (COSY, ROESY, HSQC, HMBC) in d_6-DMSO solution. The deduced assignments and key interactions are shown below:

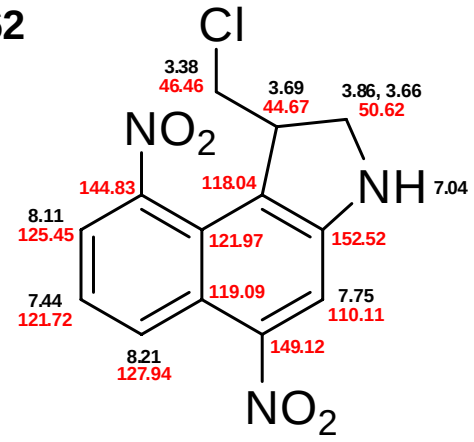
105



NOEs observed between:
6.72 and 7.76
8.23 and aliphatic protons,
confirming 5,6-diNO_2
substitution pattern.

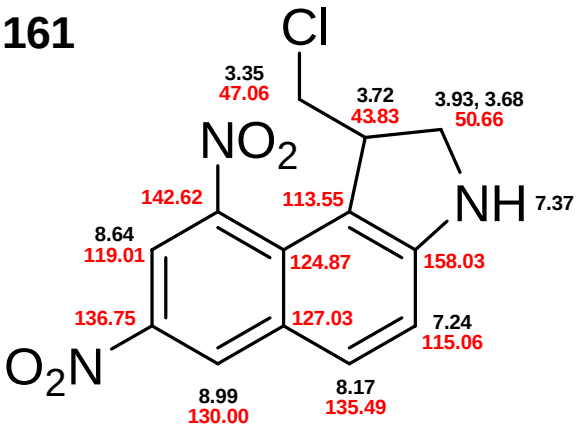
* Two signals at δ
145.92 and 145.84
could not be assigned.

162



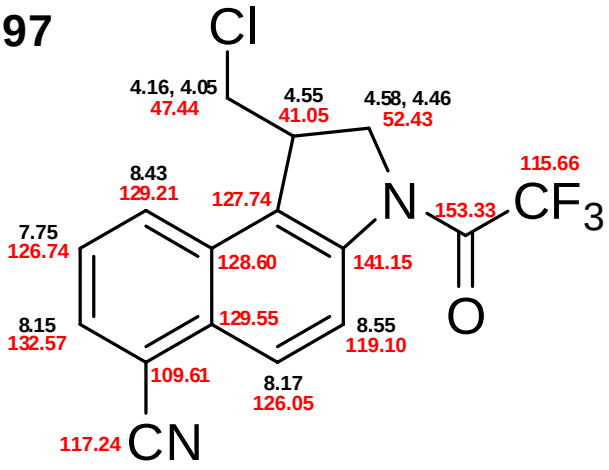
NOE observed between:
7.75 and 7.04
but none from aromatic to
aliphatic protons,
HMBC link from:
7.75 to 149.12
8.21 to 149.12
confirming 5,9-diNO_2
substitution pattern.

161



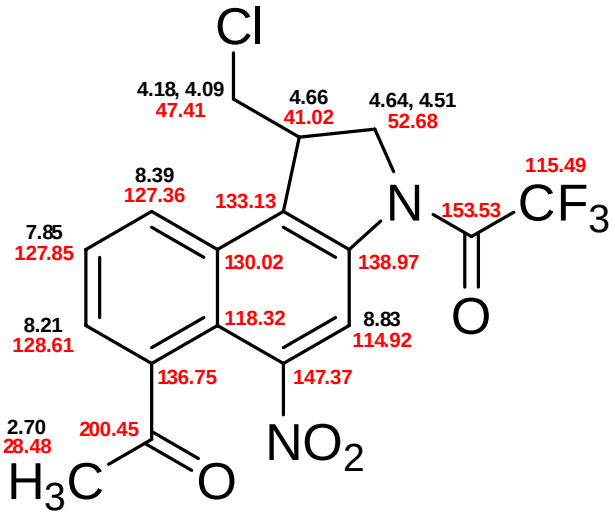
HMBC links:
consistent with 7,9-diNO_2 substitution pattern.
(NOESY experiment not performed)

97



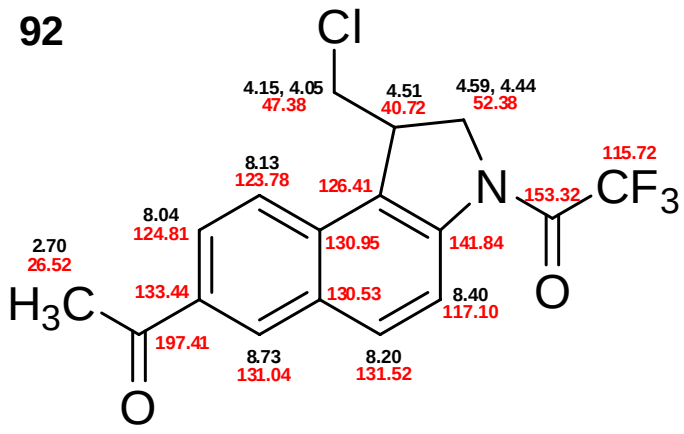
NOE observed between:
8.43 and aliphatic protons, confirming 6- and not 9-CN substitution pattern.

59 (EWG = 6-COMe)



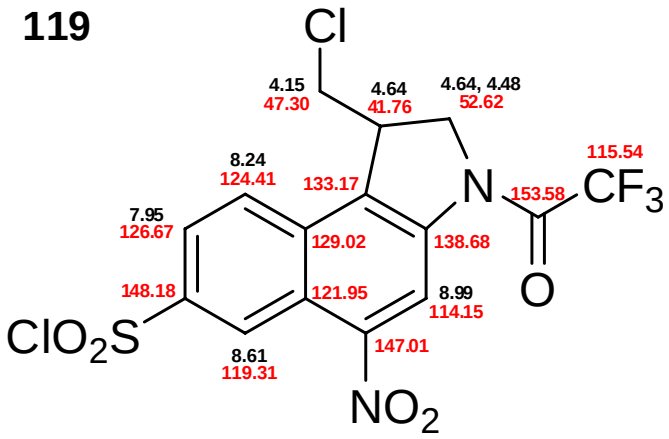
NOE observed between:
8.39 and aliphatic protons, confirming 6- and not 9-COMe,
HMBC link from:
8.83 only to 147.37, 138.97, 118.32, and 133.13, confirms 5-NO_2 substitution pattern.

92



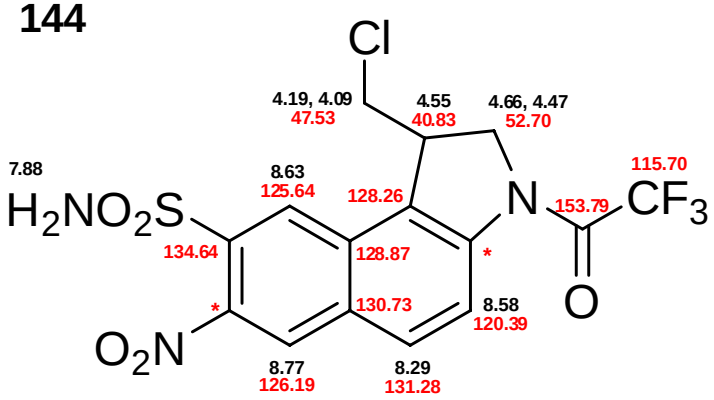
NOE observed between:
8.13 and aliphatic protons
8.73 and 8.20,
confirms 7-COMe substitution.

119



NOE observed between:
8.24 and aliphatic protons,
HMBC link from:
8.99 only to 147.01, 138.68, 133.17, and 121.95,
confirms 5-NO_2, 7-SO_2Cl substitution pattern.

144



NOE observed between:
8.63 and aliphatic protons
8.63 and 7.88
8.77 and 8.29,
confirming 7,8-substitution pattern.

***** Two signals at δ 143.58 and 143.53 could not be assigned.

X-ray Crystallographic Data for 133 and 105

Note: **133** is numbered as **60** (EWG = 8-SO_2Me) in the accompanying paper.

133 was crystallized from CH_2Cl_2/*i*-Pr_2O followed by EtOAc and **105** was crystallized from benzene.

Intensity data (λ_{Mo} = 0.71073 Å) were collected on a Seimens SMART diffractometer. Absorption corrections were applied to the raw intensity data using the SADABS program.[8,9] Structures were solved by direct methods using WINGX[10] with SHELXS-97.[9] Structures were refined using SHELXL-97.[9] The crystal data and structural refinement details are given in the tables below. Figures were created using The Cambridge Crystallographic Database Mercury visualization software.[11]

Crystal data and structure refinement for 133.

Empirical formula	C14 H13 Cl N2 O4 S	
Formula weight	340.77	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 8.428 Å	α= 90°.
	b = 14.8189(3) Å	β= 97.472(1)°.
	c = 11.3830(2) Å	γ = 90°.
Volume	1409.56(4) $Å^3$	
Z	4	
Density (calculated)	1.606 Mg/m^3	
Absorption coefficient	0.439 mm^{-1}	
F(000)	704	
Crystal size	0.42 x 0.38 x 0.36 mm^3	
Theta range for data collection	2.27 to 25.40°.	
Index ranges	-7<=h<=10, -13<=k<=17, -13<=l<=13	
Reflections collected	7607	
Independent reflections	2578 [R(int) = 0.0183]	
Completeness to theta = 25.40°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.883036 and 0.818036	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2578 / 0 / 200	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0290, wR2 = 0.0809	
R indices (all data)	R1 = 0.0322, wR2 = 0.0825	
Extinction coefficient	0.0076(14)	
Largest diff. peak and hole	0.476 and -0.516 e.$Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 133. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1956(2)	-2019(1)	10906(1)	22(1)
C(2)	1100(2)	-2695(1)	11658(2)	29(1)
C(3)	-754(2)	-2201(1)	10118(1)	21(1)
C(4)	-2205(2)	-2053(1)	9387(1)	22(1)
C(5)	-2251(2)	-1389(1)	8550(1)	19(1)
C(6)	-998(2)	-85(1)	7586(2)	23(1)
C(7)	324(2)	422(1)	7477(2)	25(1)
C(8)	1788(2)	219(1)	8187(1)	21(1)
C(9)	1904(2)	-441(1)	9030(1)	19(1)
C(10)	535(2)	-980(1)	9174(1)	18(1)
C(11)	-934(2)	-812(1)	8405(1)	19(1)
C(12)	584(2)	-1679(1)	10015(1)	19(1)
C(13)	3333(2)	-2443(1)	10360(2)	25(1)
C(14)	3661(2)	529(1)	6412(2)	34(1)
S(1)	3501(1)	832(1)	7893(1)	23(1)
Cl(1)	2686(1)	-3415(1)	9469(1)	39(1)
O(1)	-5006(1)	-1529(1)	8089(1)	31(1)
O(2)	-3655(1)	-1150(1)	6676(1)	28(1)
O(3)	4890(2)	507(1)	8641(1)	35(1)
O(4)	3142(2)	1783(1)	7917(1)	32(1)
N(1)	-452(2)	-2876(1)	10943(1)	28(1)
N(2)	-3741(2)	-1340(1)	7723(1)	22(1)

Bond lengths [Å] and angles [°] for 133.

C(1)-C(13)	1.521(2)
C(1)-C(12)	1.521(2)
C(1)-C(2)	1.555(2)
C(1)-H(1)	0.9800
C(2)-N(1)	1.472(2)
C(2)-H(2)	0.9700
C(2)-H(3)	0.9700
C(3)-N(1)	1.372(2)
C(3)-C(12)	1.384(2)
C(3)-C(4)	1.405(2)
C(4)-C(5)	1.367(2)
C(4)-H(4)	0.9300
C(5)-C(11)	1.427(2)
C(5)-N(2)	1.470(2)
C(6)-C(7)	1.363(2)
C(6)-C(11)	1.421(2)
C(6)-H(5)	0.9300
C(7)-C(8)	1.416(2)
C(7)-H(6)	0.9300
C(8)-C(9)	1.366(2)
C(8)-S(1)	1.7736(16)
C(9)-C(10)	1.430(2)
C(9)-H(7)	0.9300
C(10)-C(12)	1.408(2)
C(10)-C(11)	1.441(2)
C(13)-Cl(1)	1.8048(18)
C(13)-H(8)	0.9700
C(13)-H(9)	0.9700
C(14)-S(1)	1.7669(19)
C(14)-H(10)	0.9600
C(14)-H(11)	0.9600
C(14)-H(12)	0.9600
S(1)-O(3)	1.4383(13)
S(1)-O(4)	1.4417(13)
O(1)-N(2)	1.2271(18)
O(2)-N(2)	1.2360(19)
N(1)-H(13)	0.8600
C(13)-C(1)-C(12)	114.77(13)
C(13)-C(1)-C(2)	113.09(14)
C(12)-C(1)-C(2)	102.31(13)
C(13)-C(1)-H(1)	108.8
C(12)-C(1)-H(1)	108.8
C(2)-C(1)-H(1)	108.8
N(1)-C(2)-C(1)	104.77(13)
N(1)-C(2)-H(2)	110.8
C(1)-C(2)-H(2)	110.8
N(1)-C(2)-H(3)	110.8
C(1)-C(2)-H(3)	110.8
H(2)-C(2)-H(3)	108.9
N(1)-C(3)-C(12)	112.59(14)
N(1)-C(3)-C(4)	126.11(15)
C(12)-C(3)-C(4)	121.21(15)
C(5)-C(4)-C(3)	118.01(15)
C(5)-C(4)-H(4)	121.0
C(3)-C(4)-H(4)	121.0
C(4)-C(5)-C(11)	124.02(15)
C(4)-C(5)-N(2)	115.24(14)

C(11)-C(5)-N(2)	120.59(14)
C(7)-C(6)-C(11)	121.02(15)
C(7)-C(6)-H(5)	119.5
C(11)-C(6)-H(5)	119.5
C(6)-C(7)-C(8)	119.57(15)
C(6)-C(7)-H(6)	120.2
C(8)-C(7)-H(6)	120.2
C(9)-C(8)-C(7)	122.00(15)
C(9)-C(8)-S(1)	120.94(13)
C(7)-C(8)-S(1)	117.01(12)
C(8)-C(9)-C(10)	119.72(15)
C(8)-C(9)-H(7)	120.1
C(10)-C(9)-H(7)	120.1
C(12)-C(10)-C(9)	122.40(14)
C(12)-C(10)-C(11)	119.15(14)
C(9)-C(10)-C(11)	118.43(14)
C(6)-C(11)-C(5)	124.43(15)
C(6)-C(11)-C(10)	119.07(14)
C(5)-C(11)-C(10)	116.47(14)
C(3)-C(12)-C(10)	121.09(15)
C(3)-C(12)-C(1)	108.38(14)
C(10)-C(12)-C(1)	130.51(14)
C(1)-C(13)-Cl(1)	111.62(11)
C(1)-C(13)-H(8)	109.3
Cl(1)-C(13)-H(8)	109.3
C(1)-C(13)-H(9)	109.3
Cl(1)-C(13)-H(9)	109.3
H(8)-C(13)-H(9)	108.0
S(1)-C(14)-H(10)	109.5
S(1)-C(14)-H(11)	109.5
H(10)-C(14)-H(11)	109.5
S(1)-C(14)-H(12)	109.5
H(10)-C(14)-H(12)	109.5
H(11)-C(14)-H(12)	109.5
O(3)-S(1)-O(4)	118.24(8)
O(3)-S(1)-C(14)	108.80(9)
O(4)-S(1)-C(14)	107.98(9)
O(3)-S(1)-C(8)	109.66(8)
O(4)-S(1)-C(8)	108.59(8)
C(14)-S(1)-C(8)	102.40(8)
C(3)-N(1)-C(2)	108.57(13)
C(3)-N(1)-H(13)	125.7
C(2)-N(1)-H(13)	125.7
O(1)-N(2)-O(2)	122.82(14)
O(1)-N(2)-C(5)	118.63(14)
O(2)-N(2)-C(5)	118.46(13)

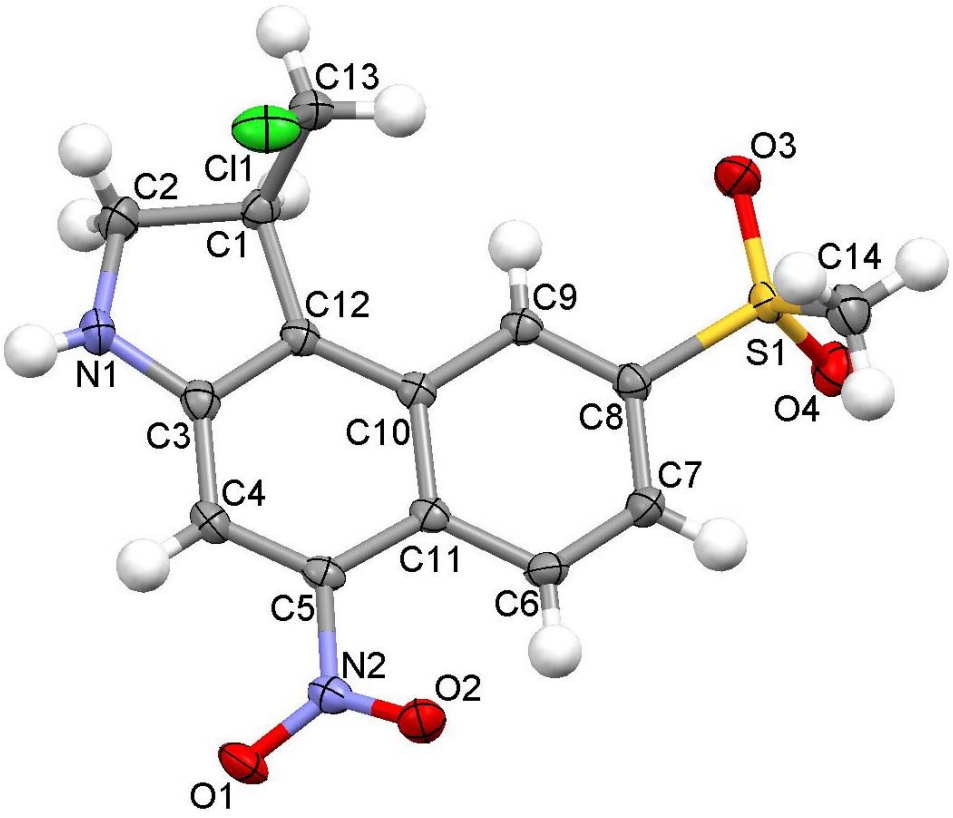
Anisotropic displacement parameters ($Å^2$x 10^3)for 133. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	23(1)	23(1)	18(1)	2(1)	1(1)	-1(1)
C(2)	29(1)	35(1)	22(1)	7(1)	3(1)	-1(1)
C(3)	23(1)	22(1)	21(1)	0(1)	7(1)	1(1)
C(4)	18(1)	24(1)	25(1)	-2(1)	7(1)	-3(1)
C(5)	16(1)	22(1)	20(1)	-5(1)	3(1)	1(1)
C(6)	18(1)	24(1)	26(1)	3(1)	-2(1)	2(1)
C(7)	24(1)	22(1)	28(1)	7(1)	0(1)	1(1)
C(8)	18(1)	19(1)	26(1)	0(1)	2(1)	-3(1)
C(9)	18(1)	19(1)	21(1)	-2(1)	1(1)	0(1)
C(10)	18(1)	18(1)	17(1)	-3(1)	3(1)	1(1)
C(11)	17(1)	18(1)	20(1)	-3(1)	4(1)	2(1)
C(12)	19(1)	21(1)	18(1)	-2(1)	4(1)	1(1)
C(13)	21(1)	27(1)	27(1)	3(1)	0(1)	1(1)
C(14)	32(1)	37(1)	34(1)	2(1)	11(1)	-2(1)
S(1)	20(1)	21(1)	28(1)	4(1)	2(1)	-5(1)
Cl(1)	35(1)	39(1)	40(1)	-13(1)	-2(1)	10(1)
O(1)	16(1)	42(1)	38(1)	-1(1)	6(1)	-2(1)
O(2)	26(1)	35(1)	23(1)	1(1)	-2(1)	-3(1)
O(3)	22(1)	36(1)	44(1)	11(1)	-5(1)	-7(1)
O(4)	36(1)	21(1)	39(1)	3(1)	7(1)	-5(1)
N(1)	24(1)	31(1)	31(1)	12(1)	5(1)	-5(1)
N(2)	17(1)	21(1)	28(1)	-3(1)	2(1)	-1(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 133.

	x	y	z	U(eq)
H(1)	2371	-1515	11413	26
H(2)	1716	-3247	11796	35
H(3)	949	-2432	12416	35
H(4)	-3107	-2396	9469	26
H(5)	-1958	47	7118	28
H(6)	265	898	6941	30
H(7)	2868	-540	9510	23
H(8)	4165	-2623	10986	30
H(9)	3783	-1999	9871	30
H(10)	2738	742	5905	50
H(11)	3726	-116	6352	50
H(12)	4607	796	6175	50
H(13)	-1066	-3328	11027	34

Structure of 133 showing 50% probability displacement ellipsoids for non-hydrogen atoms and hydrogen atoms as arbitrary spheres.



Crystal data and structure refinement for 105.

Empirical formula	C13 H10 Cl N3 O4	
Formula weight	307.69	
Temperature	87(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 16.7427(4) Å	α= 90°.
	b = 8.8730(2) Å	β= 93.8820(10)°.
	c = 17.28940(10) Å	γ = 90°.
Volume	2562.59(9) $Å^3$	
Z	8	
Density (calculated)	1.595 Mg/m^3	
Absorption coefficient	0.319 mm^{-1}	
F(000)	1264	
Crystal size	0.36 x 0.22 x 0.1 mm^3	
Theta range for data collection	2.36 to 26.38°.	
Index ranges	-20<=h<=14, -10<=k<=11, -21<=l<=21	
Reflections collected	7407	
Independent reflections	2602 [R(int) = 0.0416]	
Completeness to theta = 26.38°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9488 and 0.6825	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2602 / 0 / 194	
Goodness-of-fit on F^2	1.070	
Final R indices [I>2sigma(I)]	R1 = 0.0416, wR2 = 0.0988	
R indices (all data)	R1 = 0.0569, wR2 = 0.1074	
Largest diff. peak and hole	0.349 and -0.401 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 105. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	9577(1)	6950(1)	3379(1)	31(1)
O(2)	9224(1)	123(2)	6898(1)	25(1)
O(4)	9144(1)	-2062(2)	5373(1)	31(1)
O(3)	8078(1)	-1238(2)	5892(1)	30(1)
O(1)	8123(1)	556(2)	7455(1)	34(1)
N(3)	9302(1)	2062(2)	3302(1)	25(1)
N(2)	8677(1)	-1052(2)	5518(1)	25(1)
N(1)	8578(1)	779(2)	6940(1)	23(1)
C(5)	8516(1)	3138(2)	5117(1)	17(1)
C(1)	8367(1)	1950(2)	6360(1)	19(1)
C(6)	8562(1)	1784(2)	5575(1)	18(1)
C(7)	8805(1)	458(2)	5189(1)	20(1)
C(11)	8798(1)	4362(2)	3767(1)	19(1)
C(4)	8222(1)	4488(2)	5440(1)	18(1)
C(2)	8079(1)	3256(2)	6656(1)	21(1)
C(3)	7991(1)	4544(2)	6183(1)	21(1)
C(10)	8756(1)	3095(2)	4353(1)	18(1)
C(8)	9069(1)	444(2)	4453(1)	23(1)
C(9)	9057(1)	1803(2)	4036(1)	20(1)
C(12)	8926(1)	3473(2)	3016(1)	23(1)
C(13)	9516(1)	5355(2)	4013(1)	22(1)

Bond lengths [Å] and angles [°] for 105.

Cl(1)-C(13)	1.797(2)
O(2)-N(1)	1.234(2)
O(4)-N(2)	1.227(2)
O(3)-N(2)	1.240(2)
O(1)-N(1)	1.227(2)
N(3)-C(9)	1.380(3)
N(3)-C(12)	1.471(3)
N(3)-HN1	0.83(3)
N(2)-C(7)	1.477(3)
N(1)-C(1)	1.471(3)
C(5)-C(10)	1.407(3)
C(5)-C(4)	1.424(3)
C(5)-C(6)	1.438(3)
C(1)-C(2)	1.369(3)
C(1)-C(6)	1.425(3)
C(6)-C(7)	1.425(3)
C(7)-C(8)	1.374(3)
C(11)-C(10)	1.518(3)
C(11)-C(13)	1.527(3)
C(11)-C(12)	1.547(3)
C(11)-H(11)	0.9800
C(4)-C(3)	1.367(3)
C(4)-H(4)	0.9300
C(2)-C(3)	1.407(3)
C(2)-H(2)	0.9300
C(3)-H(3)	0.9300
C(10)-C(9)	1.381(3)
C(8)-C(9)	1.405(3)
C(8)-H(8)	0.9300
C(12)-H(12A)	0.9700
C(12)-H(12B)	0.9700
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(9)-N(3)-C(12)	107.68(17)
C(9)-N(3)-HN1	119.8(18)
C(12)-N(3)-HN1	119.3(17)
O(4)-N(2)-O(3)	123.99(18)
O(4)-N(2)-C(7)	118.20(18)
O(3)-N(2)-C(7)	117.71(17)
O(1)-N(1)-O(2)	123.78(17)
O(1)-N(1)-C(1)	118.48(17)
O(2)-N(1)-C(1)	117.66(16)
C(10)-C(5)-C(4)	121.31(18)
C(10)-C(5)-C(6)	119.10(17)
C(4)-C(5)-C(6)	119.59(17)
C(2)-C(1)-C(6)	123.65(18)
C(2)-C(1)-N(1)	114.65(17)
C(6)-C(1)-N(1)	121.11(18)
C(7)-C(6)-C(1)	128.45(18)
C(7)-C(6)-C(5)	116.03(17)
C(1)-C(6)-C(5)	115.52(17)
C(8)-C(7)-C(6)	124.05(18)
C(8)-C(7)-N(2)	114.36(18)
C(6)-C(7)-N(2)	121.02(18)
C(10)-C(11)-C(13)	108.25(16)
C(10)-C(11)-C(12)	101.41(16)
C(13)-C(11)-C(12)	112.14(17)

C(10)-C(11)-H(11)	111.5
C(13)-C(11)-H(11)	111.5
C(12)-C(11)-H(11)	111.5
C(3)-C(4)-C(5)	121.81(18)
C(3)-C(4)-H(4)	119.1
C(5)-C(4)-H(4)	119.1
C(1)-C(2)-C(3)	119.70(18)
C(1)-C(2)-H(2)	120.1
C(3)-C(2)-H(2)	120.1
C(4)-C(3)-C(2)	119.43(19)
C(4)-C(3)-H(3)	120.3
C(2)-C(3)-H(3)	120.3
C(9)-C(10)-C(5)	122.01(18)
C(9)-C(10)-C(11)	108.36(17)
C(5)-C(10)-C(11)	129.49(18)
C(7)-C(8)-C(9)	118.30(19)
C(7)-C(8)-H(8)	120.9
C(9)-C(8)-H(8)	120.9
N(3)-C(9)-C(10)	111.48(18)
N(3)-C(9)-C(8)	128.42(19)
C(10)-C(9)-C(8)	120.08(18)
N(3)-C(12)-C(11)	103.44(16)
N(3)-C(12)-H(12A)	111.1
C(11)-C(12)-H(12A)	111.1
N(3)-C(12)-H(12B)	111.1
C(11)-C(12)-H(12B)	111.1
H(12A)-C(12)-H(12B)	109.0
C(11)-C(13)-Cl(1)	111.14(14)
C(11)-C(13)-H(13A)	109.4
Cl(1)-C(13)-H(13A)	109.4
C(11)-C(13)-H(13B)	109.4
Cl(1)-C(13)-H(13B)	109.4
H(13A)-C(13)-H(13B)	108.0

Anisotropic displacement parameters ($Å^2$x 10^3)for 105. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	41(1)	30(1)	22(1)	5(1)	4(1)	-12(1)
O(2)	21(1)	25(1)	29(1)	8(1)	1(1)	4(1)
O(4)	34(1)	17(1)	40(1)	-1(1)	-1(1)	6(1)
O(3)	25(1)	23(1)	43(1)	7(1)	2(1)	-4(1)
O(1)	33(1)	39(1)	32(1)	16(1)	16(1)	5(1)
N(3)	31(1)	24(1)	20(1)	-7(1)	4(1)	2(1)
N(2)	24(1)	18(1)	31(1)	0(1)	-4(1)	-1(1)
N(1)	23(1)	23(1)	24(1)	6(1)	4(1)	0(1)
C(5)	14(1)	18(1)	19(1)	-1(1)	0(1)	-2(1)
C(1)	16(1)	20(1)	21(1)	7(1)	1(1)	0(1)
C(6)	14(1)	17(1)	22(1)	1(1)	1(1)	-1(1)
C(7)	19(1)	15(1)	26(1)	1(1)	-2(1)	-2(1)
C(11)	21(1)	20(1)	17(1)	0(1)	4(1)	0(1)
C(4)	20(1)	16(1)	19(1)	1(1)	1(1)	-1(1)
C(2)	19(1)	26(1)	19(1)	1(1)	4(1)	1(1)
C(3)	19(1)	22(1)	22(1)	-2(1)	4(1)	2(1)
C(10)	17(1)	18(1)	18(1)	-2(1)	0(1)	-2(1)
C(8)	20(1)	18(1)	29(1)	-7(1)	-1(1)	0(1)
C(9)	17(1)	22(1)	21(1)	-5(1)	-1(1)	0(1)
C(12)	26(1)	25(1)	17(1)	-2(1)	2(1)	-1(1)
C(13)	26(1)	24(1)	17(1)	1(1)	3(1)	-3(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 105.

	x	y	z	U(eq)
H(11)	8300	4946	3721	23
H(4)	8185	5355	5138	22
H(2)	7941	3292	7168	25
H(3)	7778	5426	6375	25
H(8)	9250	-442	4237	27
H(12A)	8420	3276	2726	27
H(12B)	9274	4017	2687	27
H(13A)	10004	4766	4004	27
H(13B)	9469	5704	4539	27
HN1	9341(15)	1350(30)	2998(15)	30(7)

Structure of 105 showing 50% probability displacement ellipsoids for non-hydrogen atoms and hydrogen atoms as arbitrary spheres.

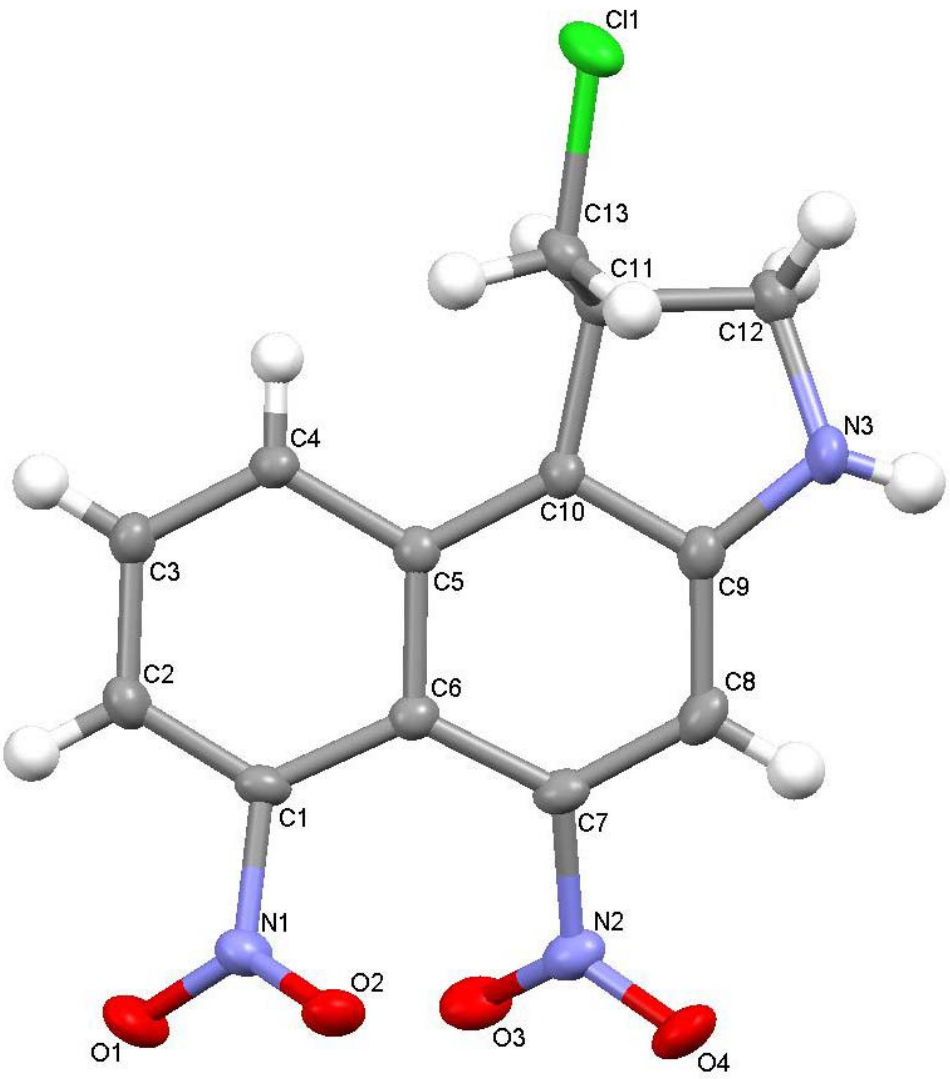


Figure S1. Relationship between one-electron reduction potential [*E*(1)] and cytotoxicity (IC_{50}) for the nitroCBIs of Table 2.

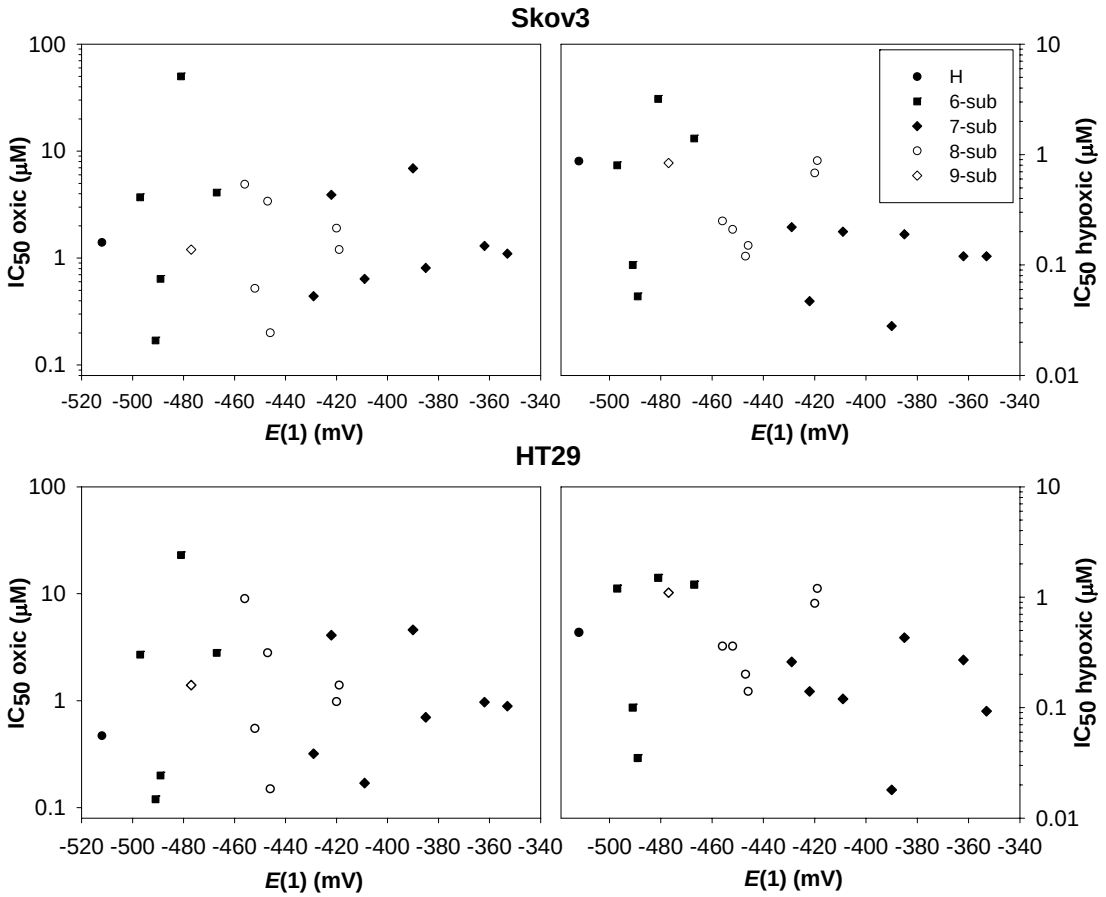


Figure S2. Relationship between hypoxic cytotoxicity ratio (HCR) in HT29 and one-electron reduction potential [*E*(1)] for the compounds of Table 2. The A-ring substituents are divided into two groups: (●) 6,7,8-SO_2NH_2 and 6,7,8-$CONH_2$ (linear regression gives $r^2 = 0.75$), and (○) all other substituents (linear regression $r^2 = 0.22$).

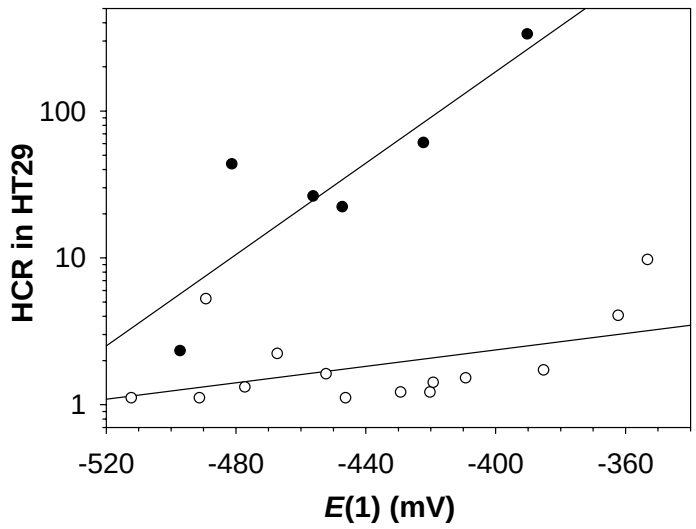
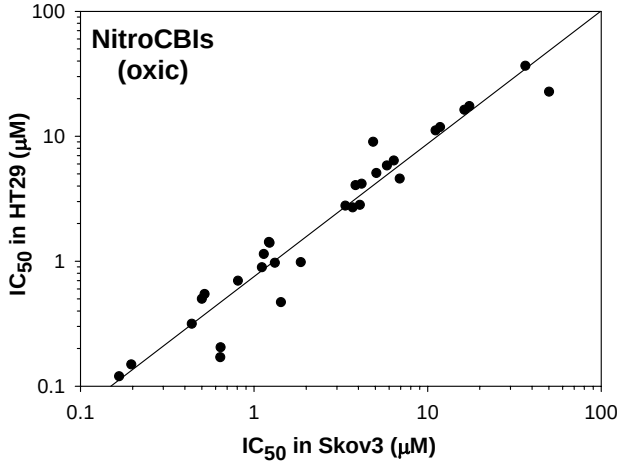
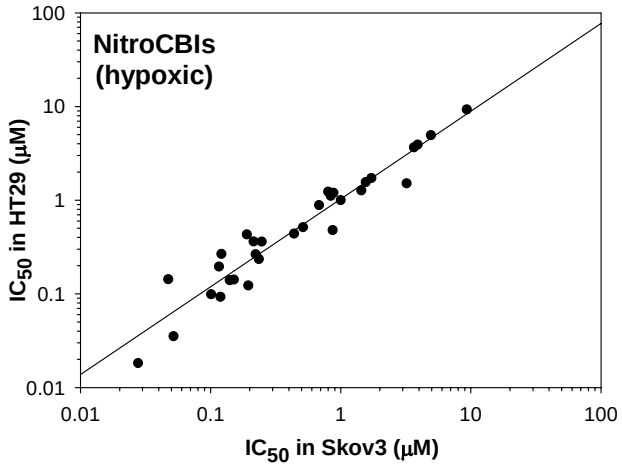


Figure S3. Correlation between cytotoxicity in HT29 and Skov3. Correlations are shown for the nitroCBIs of Tables 1 and 2 under oxic and hypoxic conditions, and for the aminoCBIs of Table 3 under hypoxic conditions.



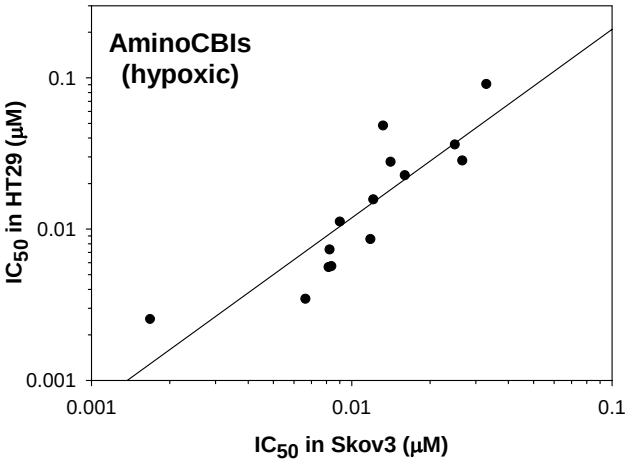
Regression analysis equation:

$\log IC_{50}$ (HT29) = -0.12 + 1.07[$\log IC_{50}$ (Skov3)]
(n = 31, r^2 = 0.95)



Regression analysis equation:

$\log IC_{50}$ (HT29) = 0.02 + 0.95[$\log IC_{50}$ (Skov3)]
(n = 31, r^2 = 0.95)



Regression analysis equation:

$\log IC_{50}$ (HT29) = 0.57 + 1.25[$\log IC_{50}$ (Skov3)]
(n = 14, r^2 = 0.75)

Figure S4. Comparison of hypoxic cytotoxicity and hypoxic selectivity of 28, PR-104A (3), and tirapazamine (1) across a cell line panel. Data for PR-104A and tirapazamine taken from ref[12]

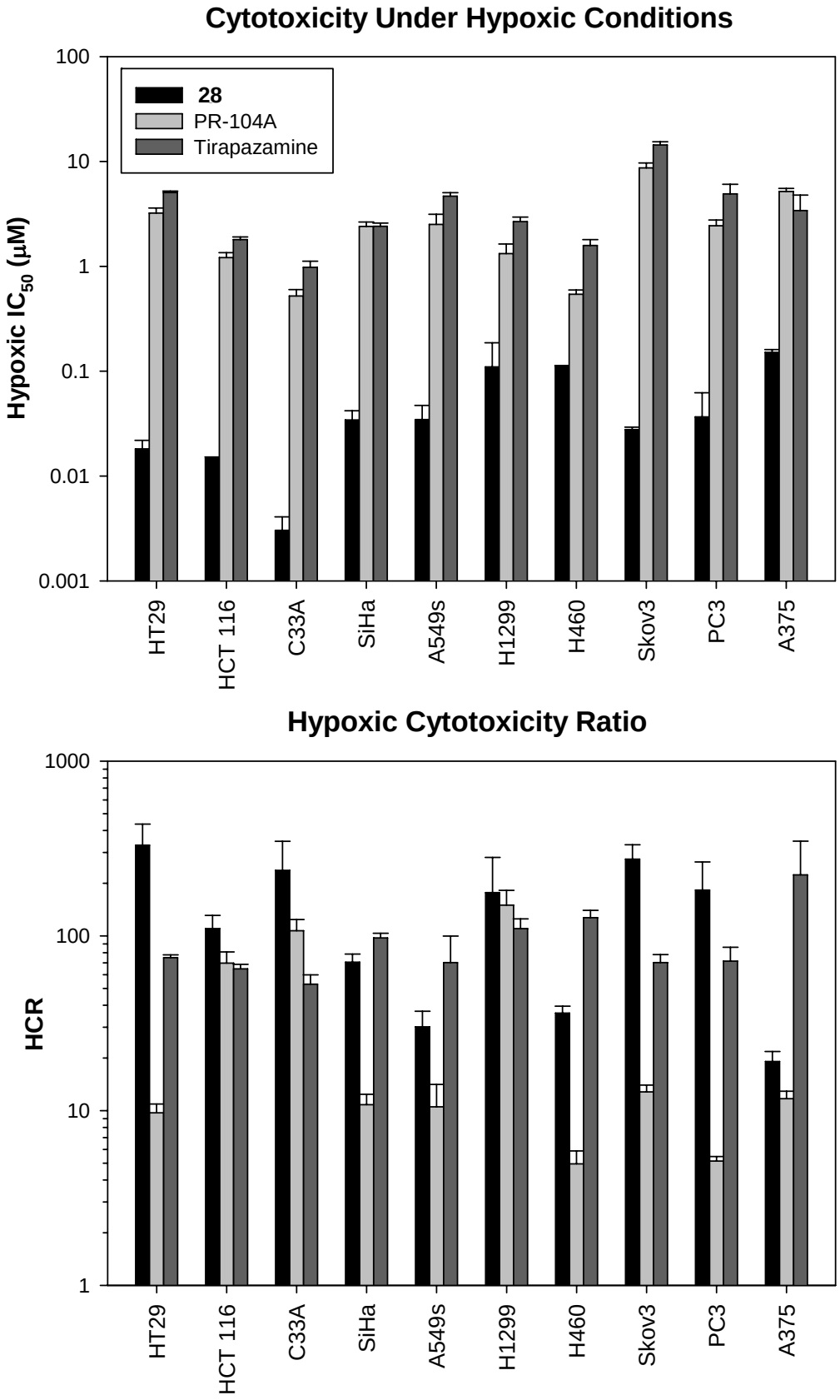
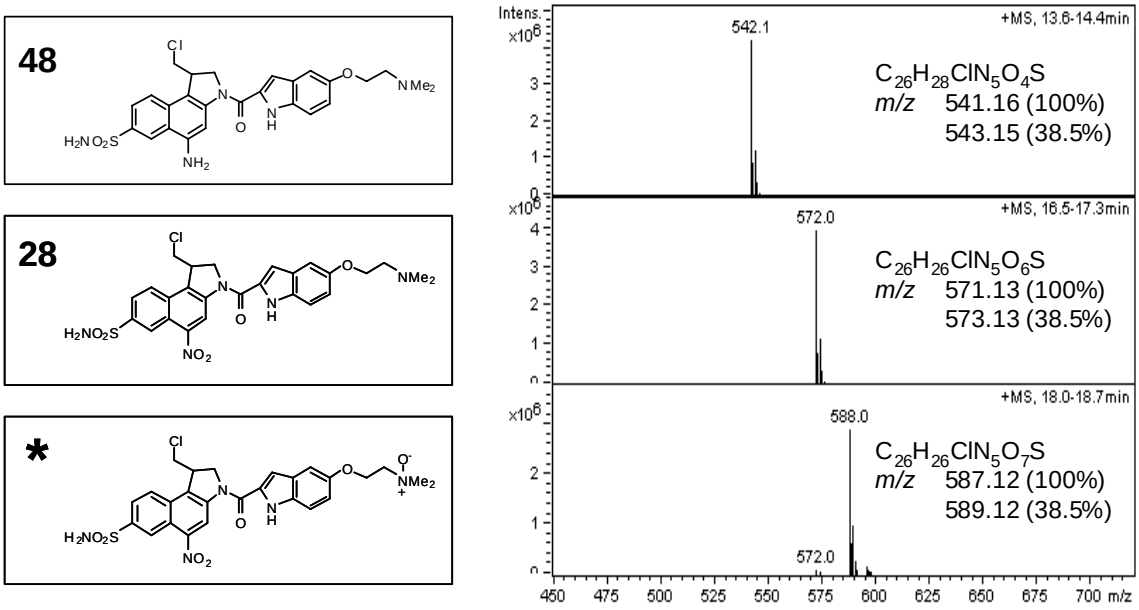
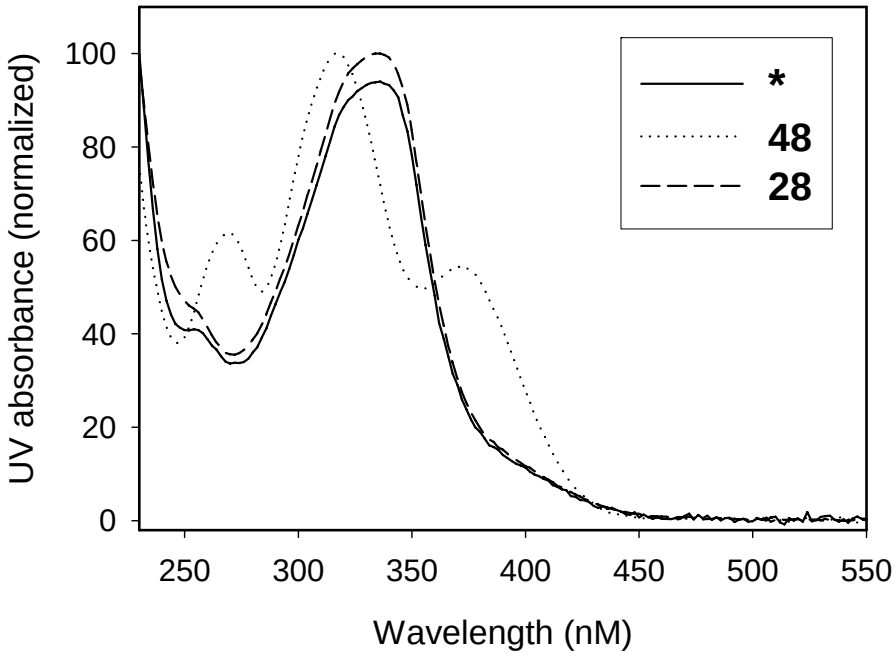


Figure S5. MS and UV-visible spectroscopy characterisation of 28 and its major S9 metabolites under oxic and hypoxic incubation conditions. The data shown correspond to the labelled peaks in the HPLC traces of Figure 8B,D. The compound labelled with an asterisk is tentatively identified as the N-oxide structure shown.





References

(1) Atwell, G. J.; Milbank, J. J.; Wilson, W. R.; Hogg, A.; Denny, W. A. 5-Amino-1-(chloromethyl)-1,2-dihydro-3H-benz[e]indoles: relationships between structure and cytotoxicity for analogues bearing different DNA minor groove binding subunits. *J. Med. Chem.* **1999**, *42*, 3400-3411.

(2) Gao, Y.; Voigt, J.; Zhao, H.; Pais, G. C.; Zhang, X.; Wu, L.; Zhang, Z. Y.; Burke, T. R., Jr. Utilization of a peptide lead for the discovery of a novel PTP1B-binding motif. *J. Med. Chem.* **2001**, *44*, 2869-2878.

(3) Wendt, M. D.; Rockway, T. W.; Geyer, A.; McClellan, W.; Weitzberg, M.; Zhao, X.; Mantei, R.; Nienaber, V. L.; Stewart, K.; Klinghofer, V.; Giranda, V. L. Identification of novel binding interactions in the development of potent, selective 2-naphthamidine inhibitors of urokinase. Synthesis, structural analysis, and SAR of N-phenyl amide 6-substitution. *J. Med. Chem.* **2004**, *47*, 303-324.

(4) Adcock, W.; Wells, P. R. Substituent effects in naphthalene. I. Syntheses of 4, 5, 6, 7, and 8-substituted 2-naphthoic acids. *Aust. J. Chem.* **1965**, *18*, 1351-1364.

(5) Katz, T. J.; Sudhakar, A.; Teasley, M. F.; Gilbert, A. M.; Geiger, W. E.; Robben, M. P.; Wuensch, M.; Ward, M. D. Synthesis and properties of optically active helical metallocene oligomers. *J. Am. Chem. Soc.* **1993**, *115*, 3182-3198.

(6) Yuho, T.; Masami, S.; Takahiro, F.; Yasuhide, Y. The substituent effect. 14. The solvolysis of 6- and 7-substituted 1-(2-naphthyl)ethyl chlorides. *Bull. Chem. Soc. Japan* **1979**, *52*, 3033-3042.

(7) Yao, Z. J.; Ye, B.; Wu, X. W.; Wang, S.; Wu, L.; Zhang, Z. Y.; Burke, T. R., Jr. Structure-based design and synthesis of small molecule protein-tyrosine phosphatase 1B inhibitors. *Bioorg. Med. Chem.* **1998**, *6*, 1799-1810.

(8) Sheldrick, G. M. SADABS: Program for semi-empirical absorption correction, **1997**. Institüt für Anorganische Chemie der Universität Göttingen, Germany.

(9) Sheldrick, G. M. SHELX97 [Includes SHELXS97, SHELXL97, CIFTAB] - Programs for Crystal Structure Analysis, **1997**. Institüt für Anorganische Chemie der Universität Göttingen, Germany.

(10) Farrugia, L. J. *WinGX* suite for small-molecule single-crystal crystallography. *J. Appl. Crystallog.* **1999**, *32*, 837-838.

(11) Bruno, I. J.; Cole, J. C.; Edgington, P. R.; Kessler, M.; Macrae, C. F.; McCabe, P.; Pearson, J.; Taylor, R. New software for searching the Cambridge Structural Database and visualizing crystal structures. *Acta Crystallog., Section B: Structural Science* **2002**, *B58*, 389-397.

(12) Patterson, A. V.; Ferry, D. M.; Edmunds, S. J.; Gu, Y.; Singleton, R. S.; Patel, K.; Pullen, S. M.; Syddall, S. P.; Atwell, G. J.; Yang, S.; Denny, W. A.; Wilson, W. R. Mechanism of action and preclinical antitumor activity of the novel hypoxia-activated DNA crosslinking agent PR-104. *Clin. Cancer Res.* **2007**, *13*, 3922-3932.