Supporting Information

Tricyclic [1,2,4]triazine 1,4-dioxides as hypoxia selective cytotoxins

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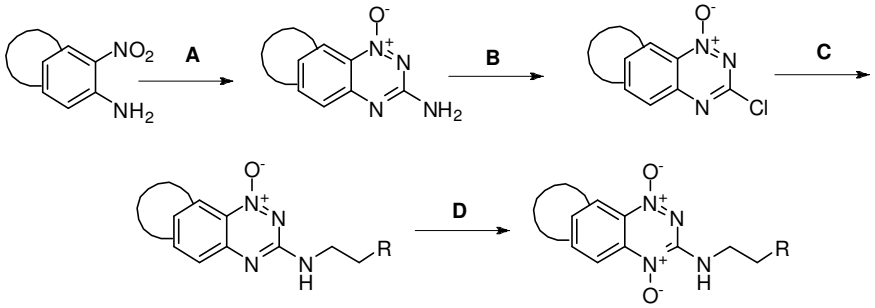
Experimental Section

Analyses were carried out in The Campbell Microanalytical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. NMR spectra were obtained on a Bruker Avance 400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C spectra. Spectra were obtained in $CDCl_3$ unless otherwise specified, and are referenced to Me_4Si. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Assignments were determined using COSY, HSQC, and HMBC two-dimensional experiments. Low resolution mass spectra were gathered by direct injection of methanolic solutions into a Surveyor MSQ mass spectrometer using an atmospheric pressure chemical ionization (APCI) mode with a corona voltage of 50 V and a source temperature of 400 °C. Mass spectra were determined on a VG-70SE mass spectrometer using an ionizing potential of 70 eV at a nominal resolution of 1000. High-resolution spectra were obtained at nominal resolutions of 3000, 5000, or 10000 as appropriate. All spectra were obtained using fast atom bombardment with positive ionization (FAB^+) unless otherwise stated. Solutions in organic solvents were dried with anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure on a rotary evaporator. Thin-layer chromatography was carried out on aluminum-backed silica gel plates (Merck 60 F_{254}) with visualization of components by UV light (254 nm) or exposure to I_2. Column chromatography was carried out on silica gel, (Merck 230–400 mesh). DCM refers to dichloromethane; DME refers to dimethoxyethane; DMF refers to dry dimethylformamide; Et_2O refers to diethyl ether; EtOAc refers to ethyl acetate; EtOH refers to ethanol; MeOH refers to methanol; pet. ether refers to petroleum ether, boiling range 40–60 °C; THF refers to tetrahydrofuran dried over sodium benzophenone ketyl. All solvents were freshly distilled.

TPZ[1] and BTO **2**[2] were synthesized as previously described.



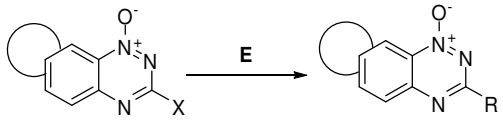
Preparation of 3-Aminotriazine 1-Oxides. General Method A. A mixture of nitroaniline (20 mmol) and cyanamide (80 mmol) were mixed together at 100 °C, cooled to 50 °C, cHCl (10 mL) added dropwise (CAUTION: Exotherm) and the mixture heated at 100 °C for 4 h. The mixture was cooled to 50 °C, 7.5 M NaOH solution added until the mixture was strongly basic and the mixture stirred at 100 °C for 3 h. The mixture was cooled, diluted with water (100 mL), filtered, washed with water (3 × 30 mL), washed with ether (2 × 5 mL) and dried. If necessary, the residue was purified by chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give the 1-oxide.

Preparation of 3-chlorotriazine 1-Oxides. General Method B. Sodium nitrite (10 mmol) was added in small portions to a stirred solution of 1-oxide (5 mmol) in trifluoroacetic acid (20 mL) at 0 °C and the solution stirred at 20 °C for 3 h. The solution was poured into ice/water, stirred 30 minutes, filtered, washed with water (3 × 10 mL)

and dried. The solid was suspended in $POCl_3$ (20 mL) and DMF (0.2 mL) and stirred at 100 °C for 1 h. The solution was cooled, poured into ice/water, stirred for 30 minutes, filtered, washed with water (3 × 30 mL) and dried. The solid was suspended in DCM (150 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with 5% EtOAc/DCM, to give the chloride.

Preparation of 1-Oxides. General Method C. Amine (3.0 mmol) was added to a stirred solution of chloride (1.0 mmol) in DME (50 mL) and the solution stirred at reflux temperature for 8 h. The solution was cooled to 20 °C, the solvent evaporated and the residue partitioned between aqueous NH_4OH solution (100 mL) and EtOAc (100 mL). The organic fraction was dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give the 1-oxide.

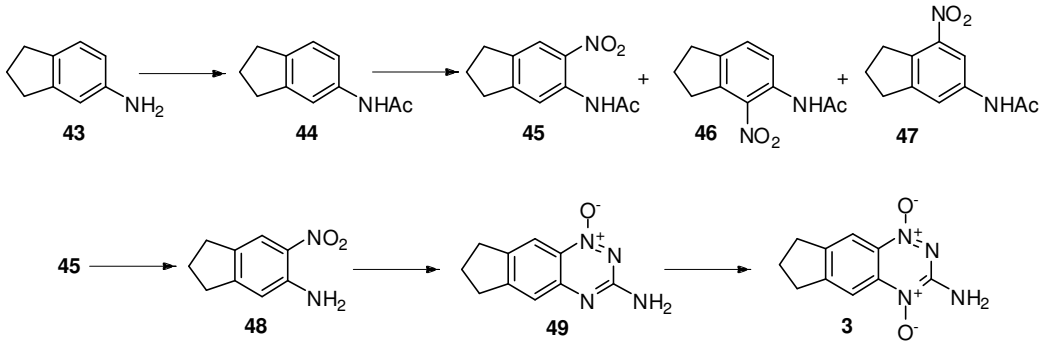
Preparation of 1,4-Dioxides 3–42. General Method D. Hydrogen peroxide (70%, 10 mmol) was added dropwise to a stirred solution of trifluoroacetic anhydride (10 mmol) in DCM (20 mL) at 0 °C. The mixture was stirred at 0 °C for 5 min, warmed to 20 °C, stirred for 10 min, and cooled to 5 °C. The mixture was added to a stirred solution of 1-oxide (1.0 mmol) [and where aliphatic amine side chains are present, TFA (5.0 mmol)] in DCM (15 ml) at 0 °C and the mixture stirred at 20 °C for 4–16 h. The solution was carefully diluted with water (20 mL) and the mixture made basic with aqueous NH_4OH solution, the mixture was stirred for 15 min and then extracted with $CHCl_3$ (5 × 50 mL). The organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–15%) of MeOH/DCM, to give 1,4-dioxides.



X = Cl, I

Preparation of 1-Oxides. General Method E. $Pd(PPh_3)_4$ (0.1 mmol) was added to a stirred, degassed solution of halide (2.0 mmol) and stannane (2.4 mmol) in DME (20 mL) and the solution stirred under N_2 at reflux temperature for 16 h. The solvent was evaporated, the residue dissolved in DCM (10 mL) and stirred with saturated aqueous KF solution (10 mL) for 30 min. The mixture was filtered through Celite, the Celite washed with DCM and the combined organic filtrate washed with water. The organic fraction was dried, the solvent evaporated and the residue purified by chromatography, eluting with DCM to give product, which was, if necessary, further purified by chromatography, eluting with 20% EtOAc/pet. ether, to give the 3-alkyl 1-oxide.

7,8-Dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (3).



***N*-(2,3-Dihydro-1*H*-inden-5-yl)acetamide (44).** Ac_2O (44.6 mL, 473 mmol) was added dropwise to a stirred solution of 5-indanamine (**43**) (30 g, 225 mmol) in dioxane (120 mL) at 0 °C and the solution stirred at 20 °C for 48 h. The solution was diluted with water (500 mL), stirred 20 min and the precipitate filtered. The solid was washed with water (3 × 30 mL) and air-dried to give acetamide **44** (37.4 g, 95%) as a tan solid: mp 99–101 °C (lit.[3] mp 106–107 °C); ^{1}H NMR ($CDCl_3$) δ 7.38–7.43 (m, 2 H, H-4, NH), 7.10–7.16 (m, 2 H, H-6, H-7), 2.85 (br q, *J* = 7.7 Hz, 4 H, H-1, H-3), 2.13 (s, 3 H, CH_3), 2.06 (br, p, *J* = 7.4 Hz, 2 H, H-2); ^{13}C NMR δ 168.3, 145.1, 140.3, 136.0, 124.4, 118.2, 116.6, 33.0, 32.3, 25.6, 24.4.

***N*-(6-Nitro-2,3-dihydro-1*H*-inden-5-yl)acetamide (45).** Acetamide (**44**) was dissolved in cH_2SO_4 (100 mL) and cooled to 5 °C. A solution of KNO_3 (8.35 g, 82.6 mmol) in cH_2SO_4 (15 mL) was added dropwise and the solution stirred at 5 °C for 2 h, then at 20 °C for 2 h. The solution was poured into ice/water (500 mL) and the suspension stirred for 2 h. The precipitate was filtered, washed with water (2 × 20 mL) and dried. The solid was purified by chromatography, eluting with a gradient (20–40%) of EtOAc/pet. ether, to give (i) *N*-(6-nitro-2,3-dihydro-1*H*-inden-5-yl)acetamide (**45**) (3.97 g, 24%) as a colourless solid: mp (EtOAc/pet. ether) 105–108 °C (lit.[3] mp 108–109 °C); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1 H, NHCO), 8.57 (s, 1 H, H-7), 8.03 (s, 1 H, H-4), 2.98 (br t, *J* = 7.5 Hz, 2 H, H-1), 2.93 (br t, *J* = 7.4 Hz, 2 H, H-3), 2.27 (s, 3 H, CH_3), 2.10–2.17 (m, 2 H, H-2); (ii) *N*-(4-nitro-2,3-dihydro-1*H*-inden-5-yl)acetamide (**46**) (0.92 g, 5%) as a white solid: mp 126–129 °C (lit.[3] mp 128.5 °C); ^{1}H NMR ($CDCl_3$) δ 9.51 (br s, 1 H, NHCO), 8.28 (d, *J* = 8.3 Hz, 1 H, H-7), 7.41 (d, *J* = 8.3 Hz, 1 H, H-6), 3.25 (br t, *J* = 7.5 Hz, 2 H, H-1), 2.96 (br t, *J* = 7.6 Hz, 2 H, H-3), 2.22 (s, 3 H, CH_3), 2.07–2.13 (m, 2 H, H-2); and (iii) *N*-(7-nitro-2,3-dihydro-1*H*-inden-5-yl)acetamide (**47**) (6.48 g, 39%) as a white solid: mp 174–176 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1 H, H-5), 7.89 (s, 1 H, H-7), 7.44 (br s, 1 H, NHCO), 3.36 (br t, *J* = 7.5 Hz, 2 H, H-3), 2.92 (br t, *J* = 7.6 Hz, 2 H, H-1), 2.20 (s, 3 H, CH_3), 2.09–2.18 (m, 2 H, H-2).

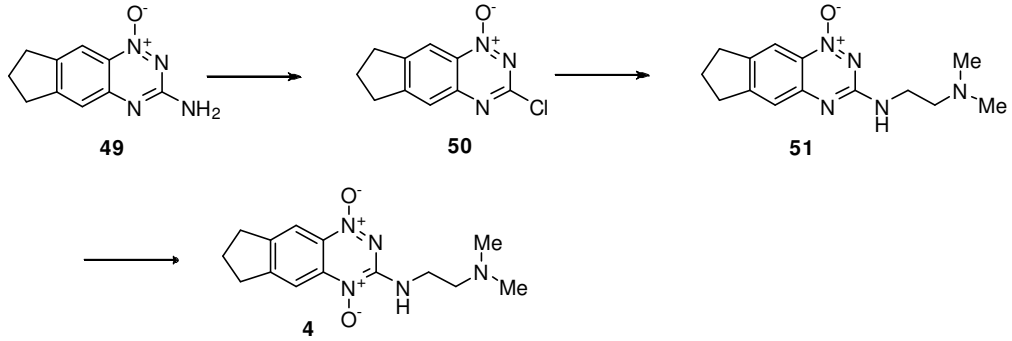
6-Nitro-5-indanamine (48). A suspension of nitroacetamide **45** (0.90 g, 4.1 mmol) in 5 M HCl was heated at 100 °C for 16 h. The suspension was cooled to 20 °C, diluted with water (100 mL), filtered, washed with water (3 × 15 mL) and dried to give indanamine **48** (0.69 g, 95%) as an orange solid: mp 129–131 °C [lit.[3] mp (EtOH) 128.5–129.5 °C]; ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1 H, H-7), 6.55 (s, 1 H, H-4), 5.99 (br s, 2 H, NH_2), 2.79–2.88

(m, 4 H, H-1, H-3), 2.02–2.10 (m, 2 H, H-2); ^{13}C NMR ($CDCl_3$) δ 154.3, 144.2, 134.0, 131.3, 120.8, 113.5, 33.0, 31.4, 25.7.

7,8-Dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1-Oxide (49). Method A. Reaction of nitroaniline **48** (21.67 g, 121.6 mmol) and cyanamide (20.45 g, 486 mmol) gave crude material (20.93 g, 85%), which can be used without further purification. The material was purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give 1-oxide **49** (16.72 g, 68%) as a yellow powder: mp (MeOH/DCM) 270–272 °C; ^{1}H NMR δ 7.92 (s, 1 H, H-9), 7.33 (s, 1 H, H-5), 7.11 (br s, 2 H, NH_2), 2.91–2.99 (m, 4 H, H-6, H-8), 2.01–2.09 (m, 2 H, H-7); ^{13}C NMR δ 159.9, 154.0, 148.5, 142.5, 128.7, 119.8, 113.8, 32.4, 31.6, 25.2. Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.4; H, 5.0; N, 27.7. Found: C, 59.4; H, 5.1; N, 27.8%.

7,8-Dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (3). Reaction D. Reaction of 1-oxide **49** (2.0 g, 9.9 mmol) and CH_3CO_3H (ca. 99 mmol) in HOAc (20 mL) gave 1,4-dioxide **3** (317 mg, 15%) as a red solid: mp (MeOH/EtOAc) 190–195 °C; ^{1}H NMR δ 8.01 (s, 1 H, H-9), 7.98 (s, 1 H, H-5), 7.87 (br s, 2 H, NH_2), 3.07 (br t, J = 7.4 Hz, 2 H, H-6), 3.01 (br t, J = 7.4 Hz, 2 H, H-8), 2.10 (p, J = 7.4 Hz, 2 H, H-7); ^{13}C NMR δ 154.3, 150.8, 144.7, 137.8, 129.6, 115.1, 111.2, 32.6, 31.7, 25.1. Anal. Calcd for $C_{10}H_{10}N_4O_2 \cdot ½CH_3OH$: C, 53.8; H, 5.2; N, 23.9. Found: C, 53.6; H, 5.2; N, 23.9%.

N^1-(1,4-Dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-N^2,N^2-dimethyl-1,2-ethanediamine (4).



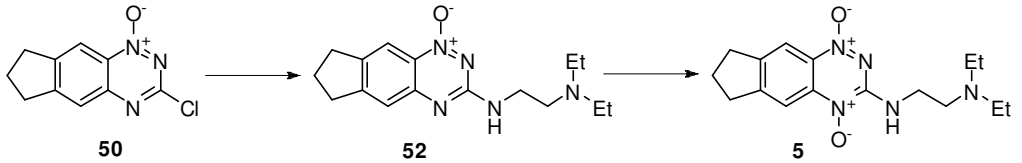
3-Chloro-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (50). Method B. Reaction of 1-oxide **49** (837 mg, 4.1 mmol) and $NaNO_2$ (570 mg, 8.3 mmol) gave chloride **50** (696 mg, 76%) as a pale yellow solid: mp (DCM) 162–164 °C; ^{1}H NMR ($CDCl_3$) δ 8.21 (s, 1 H, H-9), 7.75 (s, 1 H, H-5), 3.11–3.18 (m, 4 H, H-6, H-8), 2.21–2.28 (m, 2 H, H-7); ^{13}C NMR ($CDCl_3$) δ 156.4, 156.0, 150.1, 147.3, 132.8, 122.5, 114.5, 33.3, 32.9, 25.7. Anal. Calcd for $C_{10}H_8ClN_3O$: C, 54.2; H, 3.6; N, 19.0. Found: C, 54.1; H, 3.8; N, 18.7%.

N^1,N^1-Dimethyl-N^2-(1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (51). Method C. Reaction of chloride **50** (305 mg, 1.4 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (0.45 mL, 4.1 mmol) in DME (30 mL) gave 1-oxide **51** (334 mg, 88%) as a yellow solid: mp (MeOH/EtOAc) 122–124 °C; ^{1}H NMR δ 8.06 (s, 1 H, H-9), 7.38 (s, 1 H, H-5), 5.80 (br s, 1 H, NH), 3.50–3.55 (m, 2 H, CH_2N), 2.96–3.03 (m, 4

H, H-6, H-8), 2.55 (t, J = 6.0 Hz, 2 H, CH_2N), 2.27 [s, 6 H, $N(CH_3)_2$], 2.09–2.18 (m, 2 H, H-7); ^{13}C NMR δ 158.8, 154.5, 148.8, 143.2, 129.8, 120.5, 114.6, 57.6, 45.1 (2), 38.8, 33.1, 32.3, 25.7. Anal. Calcd for $C_{14}H_{19}N_5O·¼H_2O$: C, 60.5; H, 7.1; N, 25.2. Found: C, 60.6; H, 6.8; N, 25.2%.

N^1-(1,4-Dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-N^2,N^2-dimethyl-1,2-ethanediamine (4). Method D. Reaction of 1-oxide **51** (294 mg, 1.1 mmol) with CF_3CO_3H (ca. 11 mmol) gave 1,4-dioxide **4** (173 mg, 55%) as a red solid: mp (MeOH/EtOAc) 150–153 °C; ^1H NMR δ 8.12 (s, 1 H, H-9), 8.10 (s, 1 H, H-5), 7.40 (br s, 1 H, NH), 3.62–3.67 (m, 2 H, CH_2N), 3.03–3.13 (m, 4 H, H-6, H-8), 2.63 (t, J = 6.0 Hz, 2 H, CH_2N), 2.31 [s, 6 H, $N(CH_3)_2$], 2.17–2.23 (m, 2 H, H-7); ^{13}C NMR δ 155.6, 149.5, 145.8, 138.0, 129.7, 115.7, 111.6, 57.5, 45.2 (2), 38.8, 33.6, 32.4, 25.6; MS *m/z* 289 (M^+, 0.5%), 272 (5), 58 (100); HRMS (EI^+) calcd for $C_{14}H_{19}N_5O_2$ (M^+) *m/z* 289.1539, found 289.1536. The hydrochloride salt was crystallised from MeOH/EtOAc. Anal. Calcd for $C_{14}H_{20}ClN_5O_2·¼CH_3OH$: C, 49.7; H, 6.8; N, 19.3. Found: C, 49.4; H, 7.0; N, 19.8%.

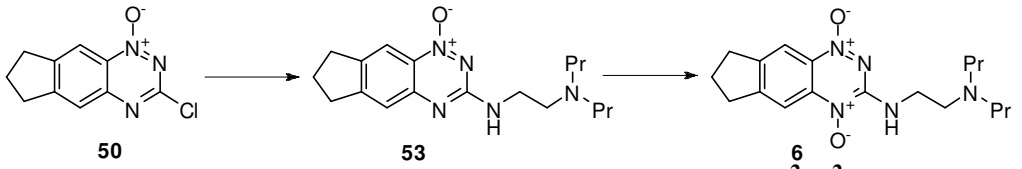
N^1-(1,4-Dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-N^2,N^2-diethyl-1,2-ethanediamine (5).



N^1-(1-Oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-N^2,N^2-diethyl-1,2-ethanediamine (52). Method C. Reaction of chloride **50** (314 mg, 1.4 mmol) and N^1,N^1-diethyl-1,2-ethanediamine (0.50 mL, 3.5 mmol) in DME (50 mL) gave 1-oxide **52** (406 mg, 95%) as a yellow solid: mp (MeOH/EtOAc) 109–112 °C; ^1H NMR δ 7.93 (s, 1 H, H-9), 7.31 (s, 1 H, H-5), 7.14 (br s, 1 H, NH), 3.97–4.03 (m, 2 H, CH_2N), 3.42–3.46 (m, 2 H, CH_2N), 3.25–3.33 (m, 4 H, 2 × CH_2N), 2.19–2.29 (m, 4 H, H-6, H-8), 2.08–2.14 (m, 2 H, H-7), 1.45 (t, J = 7.3 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 158.2, 154.6, 148.4, 143.7, 129.8, 120.7, 114.4, 50.8, 47.7 (2), 36.3, 33.1, 32.3, 25.7, 8.8 (2). Anal. Calcd for $C_{16}H_{23}N_5O$: C, 63.8; H, 7.7; N, 23.2. Found: C, 63.9; H, 7.7; N, 23.3%.

N^1-(1,4-Dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-N^2,N^2-diethyl-1,2-ethanediamine (5). Method D. Reaction of 1-oxide **52** (312 mg, 1.0 mmol) with CF_3CO_3H (ca. 10 mmol) gave 1,4-dioxide **5** (179 mg, 54%) as a red gum: ^1H NMR δ 8.11 (br s, 2 H, H-5, H-9), 7.73 (br s, 1 H, NH), 3.64–3.69 (m, 2 H, CH_2N), 3.01–3.10 (m, 4 H, H-6, H-8), 2.81–2.85 (m, 2 H, CH_2N), 2.64–2.73 (m, 4 H, 2 × CH_2N), 2.14–2.22 (m, 2 H, H-7), 1.09 (t, J = 7.1 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 156.0, 149.5, 145.8, 138.1, 129.8, 115.7, 111.7, 51.1, 46.6 (2), 38.5, 33.4, 32.3, 25.6, 11.0 (2); MS (FAB^+) *m/z* 318 (MH^+, 70%), 302 (20); HRMS calcd for $C_{16}H_{24}N_5O_2$ (MH^+) *m/z* 318.1930, found 318.1933.

N^1-(1,4-Dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-N^2,N^2-dipropyl-1,2-ethanediamine (6).

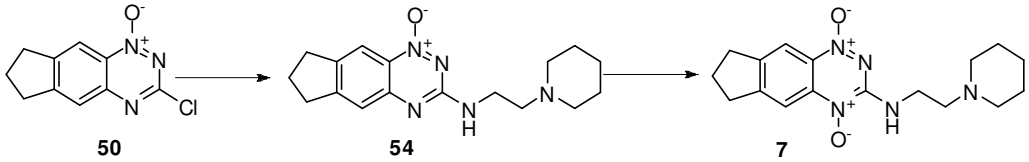


50 **53** **6**

***N*^{1}-(1-Oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dipropyl-1,2-ethanediamine (53). Method C.** Reaction of chloride **50** (298 mg, 1.3 mmol) and *N*^{1},*N*^{1}-dipropyl-1,2-ethanediamine[2] (0.27 g, 1.9 mmol) in DME (50 mL) gave 1-oxide **53** (325 mg, 74%) as a yellow powder: mp (MeOH/EtOAc) 95–97 °C; ^{1}H NMR δ 8.07 (s, 1 H, H-9), 7.39 (s, 1 H, H-5), 5.80 (br s, 1 H, NH), 3.46–3.53 (m, 2 H, CH_2N), 2.96–3.03 (m, 4 H, 2 × CH_2N), 2.68 (dd, *J* = 6.0, 5.8 Hz, 2 H, CH_2N), 2.38–2.45 (m, 4 H, H-6, H-8), 2.10–2.18 (m, 2 H, H-7), 1.41–1.51 (m, 4 H, 2 × CH_2), 0.87 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 158.7, 154.4, 148.8, 143.0, 129.8, 120.5, 114.7, 55.9 (2), 52.6, 38.9, 31.1, 32.3, 25.7, 20.3 (2), 11.9 (2). Anal. Calcd for $C_{18}H_{27}N_5O$: C, 65.6; H, 8.3; N, 21.3. Found: C, 65.4; H, 8.4; N, 21.3%.

***N*^{1}-(1,4-Dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dipropyl-1,2-ethanediamine (6). Method D.** Reaction of 1-oxide **53** (253 mg, 0.8 mmol) with CF_3CO_3H (ca. 8 mmol) gave 1,4-dioxide **6** (134 mg, 50%) as a red solid: mp (MeOH/EtOAc) 142–145 °C; ^{1}H NMR δ 8.12 (s, 1 H, H-9), 8.10 (s, 1 H, H-5), 7.46 (br s, 1 H, NH), 3.54–3.60 (m, 2 H, CH_2N), 3.03–3.11 (m, 4 H, H-6, H-8), 2.74 (dd, *J* = 6.1, 5.9 Hz, 2 H, CH_2N), 2.43–2.47 (m, 4 H, 2 × CH_2N), 2.16–2.24 (m, 2 H, H-7), 1.45–1.54 (m, 4 H, 2 × CH_2), 0.91 (t, *J* = 7.4 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 155.5, 149.5, 145.7, 138.0, 129.6, 115.7, 111.6, 56.0 (2), 52.5, 39.1, 33.4, 32.4, 25.6, 20.4 (2), 11.8 (2). Anal. Calcd for $C_{18}H_{27}N_5O_2$: C, 62.6; H, 7.9; N, 20.3. Found: C, 62.3; H, 8.0; N, 20.2%.

***N*-[2-(1-Piperidinyl)ethyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (7).**



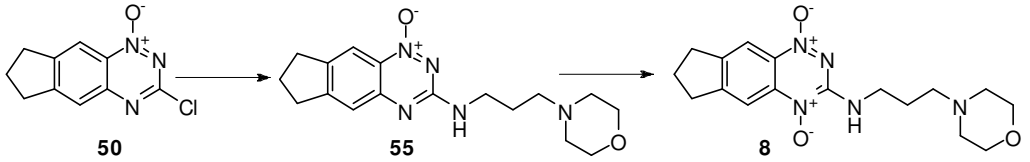
50 **54** **7**

***N*-[2-(1-Piperidinyl)ethyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1-Oxide (52). Method C.** Reaction of chloride **50** (348 mg, 1.6 mmol) and 2-(1-piperidinyl)ethylamine (0.67 mL, 4.7 mmol) in DME (50 mL) gave 1-oxide **54** (465 mg, 95%) as a yellow solid: mp (MeOH/EtOAc) 151–153 °C; ^{1}H NMR δ 8.06 (s, 1 H, H-9), 7.39 (s, 1 H, H-5), 5.91 (br s, 1 H, NH), 3.52–3.57 (m, 2 H, CH_2N), 2.97–3.03 (m, 4 H, H-6, H-8), 2.58 (t, *J* = 6.0 Hz, 2 H, CH_2N), 2.40–2.47 (m, 4 H, 2 × CH_2N), 2.10–2.18 (m, 2 H, H-7), 1.55–1.63 (m, 4 H, 2 × CH_2), 1.42–1.48 (m, 2 H, CH_2); ^{13}C NMR δ 158.7, 154.5, 148.8, 143.1, 129.7, 120.5, 114.6, 57.0, 54.3 (2), 37.9, 33.1, 32.3, 25.9 (2), 25.7, 24.4. Anal. Calcd for $C_{17}H_{23}N_5O·¼H_2O$: C, 64.2; H, 7.5; N, 22.0. Found: C, 64.6; H, 6.9; N, 22.1%.

***N*-[2-(1-Piperidinyl)ethyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (7). Method D.** Reaction of 1-oxide **54** (397 mg, 1.3 mmol) with CF_3CO_3H (ca. 13 mmol) gave 1,4-dioxide **7** (241 mg, 57%) as a red solid: mp (MeOH/EtOAc) 165–168

°C; ^{1}H NMR δ 8.11 (s, 1 H, H-9), 8.08 (s, 1 H, H-5), 7.43 (br s, 1 H, NH), 3.60–3.64 (m, 2 H, CH_2N), 3.03–3.11 (m, 4 H, H-6, H-8), 2.62 (t, *J* = 6.0 Hz, 2 H, CH_2N), 2.42–2.47 (m, 4 H, 2 × CH_2), 2.15–2.22 (m, 2 H, H-7), 1.57–1.63 (m, 4 H, 2 × CH_2), 1.41–1.47 (m, 2 H, CH_2); ^{13}C NMR δ 155.6, 149.5, 145.7, 138.0, 129.7, 115.8, 111.6, 56.9, 54.4 (2), 38.2, 33.4, 32.4, 25.9 (2), 25.6, 24.3. Anal. Calcd for $C_{17}H_{23}N_5O_2$·¼H_2O: C, 61.2; H, 7.1; N, 21.0. Found: C, 60.7; H, 7.0; N, 21.0%.

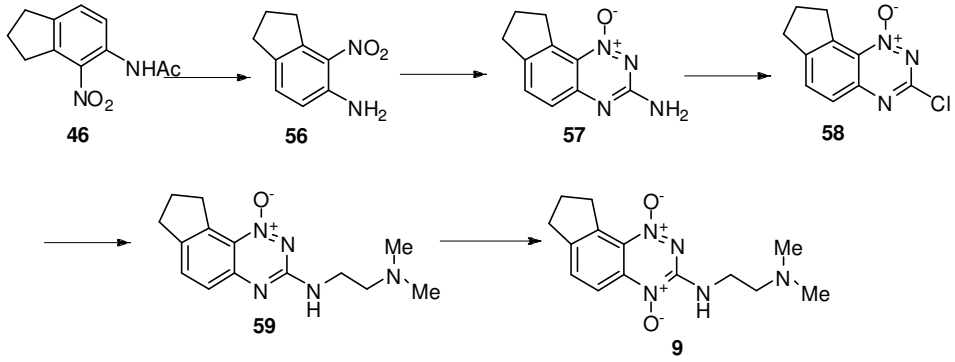
***N*-[3-(4-Morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (8).**



***N*-[3-(4-Morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1-Oxide (54). Method C.** Reaction of chloride **50** (382 mg, 1.7 mmol) and 3-(1-morpholinyl)propylamine (0.76 mL, 5.2 mmol) in DME (50 mL) gave 1-oxide **55** (553 mg, 98%) as a yellow solid: mp (MeOH/EtOAc) 139–141 °C; ^{1}H NMR δ 8.06 (s, 1 H, H-9), 7.38 (s, 1 H, H-5), 6.10 (br s, 1 H, NH), 3.72–3.77 (m, 4 H, 2 × CH_2O), 3.55–3.60 (m, 2 H, CH_2N), 2.95–3.02 (m, 4 H, H-6, H-8), 2.45–2.52 (m, 6 H, 3 × CH_2N), 2.09–2.17 (m, 2 H, CH_2), 1.79–1.86 (m, 2 H, CH_2); ^{13}C NMR δ 158.8, 154.5, 148.8, 143.2, 129.8, 120.5, 114.7, 67.0 (2), 57.3, 53.8 (2), 40.8, 33.1, 32.3, 25.7, 25.3. Anal. Calcd for $C_{17}H_{23}N_5O_2$: C, 62.0; H, 7.0; N, 21.3. Found: C, 62.2; H, 6.9; N, 21.3%.

***N*-[3-(4-Morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (8). Method D.** Reaction of 1-oxide **55** (412 mg, 1.2 mmol) with CF_3CO_3H (ca. 12 mmol) gave (i) starting material **55** (208 mg, 50%) and (ii) 1,4-dioxide **8** (122 mg, 30%) as a red solid: mp (MeOH) 158–160 °C; ^{1}H NMR δ 8.37 (br s, 1 H, NH), 8.11 (s, 1 H, H-5), 8.09 (s, 1 H, H-9), 3.80–3.84 (m, 4 H, 2 × CH_2O), 3.64–3.69 (m, 2 H, CH_2N), 3.02–3.10 (m, 4 H, H-6, H-8), 2.56 (dd, *J* = 6.2, 6.1 Hz, 2 H, CH_2N), 2.48–2.52 (m, 4 H, 2 × CH_2N), 2.15–2.22 (m, 2 H, H-7), 1.85–1.91 (m, 2 H, CH_2); ^{13}C NMR δ 155.5, 149.5, 145.6, 138.0, 129.6, 115.8, 111.6, 66.9 (2), 57.7, 53.8 (2), 41.6, 33.3, 32.3, 25.5, 24.5. Anal. Calcd for $C_{17}H_{23}N_5O_3$·¼CH_3OH: C, 58.6; H, 6.9; N, 19.8. Found: C, 58.4; H, 6.7; N, 19.9%.

7,8-Dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (9).



4-Nitro-5-indanamine (56). A suspension of acetamide **46** (0.90 g, 4.1 mmol) in 5 M HCl was heated at 100 °C for 16 h. The suspension was cooled to 20 °C, diluted with water (100 mL), filtered, washed with water (3 × 15 mL) and dried to give amine **56** (0.69 g, 95%) as an orange solid: mp (H_2O) 105–107 °C (lit.[3] mp 115 °C); ^{1}H NMR δ 7.17 (d, *J* = 8.2 Hz, 1 H, H-7), 6.62 (d, *J* = 8.2 Hz, 1 H, H-6), 5.73 (br s, 2 H, NH_2), 3.32 (br t, *J* = 7.5 Hz, 2 H, H-3), 2.80–2.85 (m, 2 H, H-1), 2.02–2.11 (m, 2 H, H-2). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.7; H, 5.7; N, 15.7. Found: C, 60.5; H, 5.5; N, 15.8%.

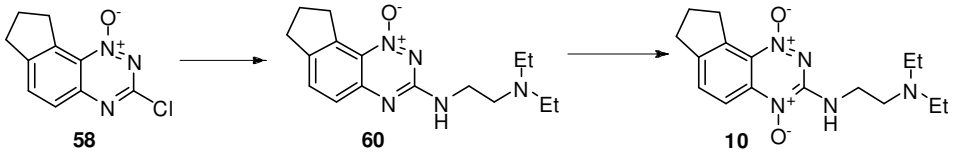
8,9-Dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-amine 1-Oxide (57). Method A. Reaction of amine **56** (0.67 g, 3.8 mmol) and cyanamide (0.63 g, 15.0 mmol) gave 1-oxide **57** (279 mg, 37%) as a yellow powder: mp (MeOH/DCM) 270–274 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.56 (d, *J* = 8.4 Hz, 1 H, H-6), 7.31 (d, *J* = 8.4 Hz, 1 H, H-5), 6.79 (br s, 2 H, NH_2), 3.55 (br t, *J* = 7.5 Hz, 2 H, H-9), 2.95 (br t, *J* = 7.7 Hz, 2 H, H-7), 2.09–2.20 (m, 2 H, H-8); ^{13}C NMR [$(CD_3)_2SO$] δ 159.4, 148.7, 140.9, 136.0, 131.6, 128.1, 123.9, 34.6, 32.1, 24.1. Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.4; H, 5.0; N, 27.7. Found: C, 59.5; H, 5.0; N, 27.7%.

3-Chloro-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazine 1-Oxide (58). Method B. Reaction of 1-oxide **57** (244 mg, 1.2 mmol) and $NaNO_2$ (167 mg, 2.4 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **58** (215 mg, 80%) as a pale yellow solid: mp (DCM/EtOAc) 162–164 °C; ^{1}H NMR δ 7.81 (d, *J* = 8.4 Hz, 1 H, H-6), 7.74 (d, *J* = 8.4 Hz, 1 H, H-5), 3.70 (dd, *J* = 8.0, 7.3 Hz, 2 H, H-9), 3.11 (dd, *J* = 8.0, 7.6 Hz, 2 H, H-7), 2.22–2.30 (m, 2 H, H-8); ^{13}C NMR δ 155.0, 148.4, 146.8, 137.0, 132.8, 131.5, 126.1, 34.4, 32.9, 24.3. Anal. Calcd for $C_{10}H_8ClN_3O$: C, 54.2; H, 3.6; N, 19.0. Found: C, 54.2; H, 3.8; N, 18.9%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (59). Method C.** Reaction of chloride **58** (187 mg, 0.8 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (0.28 mL, 2.5 mmol) in DME (30 mL) gave 1-oxide **59** (201 mg, 88%) as a pale yellow solid: mp (MeOH/EtOAc) 186–190 °C; ^{1}H NMR δ 7.54 (d, *J* = 8.4 Hz, 1 H, H-6), 7.37 (d, *J* = 8.4 Hz, 1 H, H-5), 5.80 (br s, 1 H, NH), 3.63 (br t, *J* = 7.3 Hz, 2 H, H-9), 3.52–3.57 (m, 2 H, CH_2N), 2.96 (br t, *J* = 7 Hz, 2 H, H-7), 2.57 (t, *J* = 6.0 Hz, 2 H, CH_2N), 2.29 [s, 6 H, $N(CH_3)_2$], 2.12–2.21 (m, 2 H, H-8); ^{13}C NMR δ 158.5, 149.0, 142.0, 137.3, 132.2, 129.2, 124.7, 57.6, 45.0 (2), 38.7, 35.3, 32.9, 24.8. Anal. Calcd for $C_{14}H_{19}N_5O{\cdot}¼H_2O$: C, 60.5; H, 7.1; N, 25.2. Found: C, 60.6; H, 6.6; N, 25.4%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1,4-dioxido-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (9). Method D.** Oxidation of 1-oxide **59** (182 mg, 0.7 mmol) with CF_3CO_3H (ca. 7 mmol) gave 1,4-dioxide **9** (60 mg, 31%) as a red solid: mp (MeOH/EtOAc) 153–156 °C; ^{1}H NMR δ 8.12 (d, *J* = 8.7 Hz, 1 H, H-5), 7.70 (d, *J* = 8.7 Hz, 1 H, H-6), 7.37 (br s, 1 H, NH), 3.71 (br t, *J* = 7.4 Hz, 2 H, H-9), 3.60–3.64 (m, 2 H, CH_2N), 3.03 (br t, *J* = 7.8 Hz, 2 H, H-7), 2.61 (t, *J* = 6.0 Hz, 2 H, CH_2N), 2.30 [s, 6 H, $N(CH_3)_2$], 2.17–2.26 (m, 2 H, H-8); ^{13}C NMR δ 149.1, 144.7, 138.6, 138.4, 132.7, 129.1, 115.8, 57.6, 45.2 (2), 38.8, 35.1, 32.9, 24.6; MS (EI$^+$) *m/z* 289 (M^+, 0.5%), 273 (2), 256 (3), 58 (100); HRMS (EI$^+$) calcd for $C_{14}H_{19}N_5O_2$ (M^+) *m/z* 289.1539, found 289.1536.

N^1,N^1-Diethyl-N^2-(1,4-dioxido-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (10).

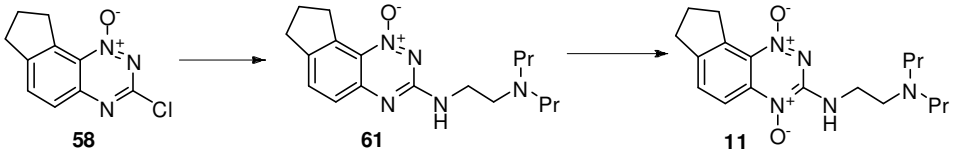


58 **60** **10**

N^1,N^1-Diethyl-N^2-(1-oxido-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (60). Method C. Reaction of chloride **58** (215 mg, 1.0 mmol) and *N*,*N*-diethyl-1,2-ethanediamine (0.41 mL, 2.9 mmol) in DME (30 mL) gave 1-oxide **60** (271 mg, 93%) as a pale yellow solid: mp (MeOH/EtOAc) 126–130 °C; ^{1}H NMR δ 7.54 (d, *J* = 8.4 Hz, 1 H, H-6), 7.39 (d, *J* = 8.4 Hz, 1 H, H-5), 5.93 (br s, 1 H, NH), 3.63 (br dd, *J* = 7.5, 7.4 Hz, 2 H, H-9), 3.52–3.57 (m, 2 H, CH_2N), 2.97 (br dd, *J* = 7.8, 7.6 Hz, 2 H, H-7), 2.74 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.63 (q, *J* = 7.4 Hz, 4 H, 2 × CH_2N), 2.16 (br p, *J* = 7.6 Hz, 2 H, H-8), 1.07 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 158.4, 149.0, 142.0, 137.3, 132.2, 129.2, 124.6, 51.2, 46.6 (2), 38.5, 35.3, 32.8, 24.8, 11.5 (2). Anal. Calcd for $C_{16}H_{23}N_5O·¼H_2O$: C, 62.8; H, 7.7; N, 22.9. Found: C, 63.0; H, 7.6; N, 22.9%.

N^1,N^1-Diethyl-N^2-(1,4-dioxido-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (10). Method D. Oxidation of 1-oxide **60** (219 mg, 0.7 mmol) with CF_3CO_3H (ca. 7 mmol) gave 1,4-dioxide **10** (91 mg, 31%) as a red solid: mp (MeOH) 138–141 °C; ^{1}H NMR δ 8.11 (d, *J* = 8.7 Hz, 1 H, H-5), 7.70 (d, *J* = 8.7 Hz, 1 H, H-6), 7.44 (br s, 1 H, NH), 3.70 (br t, *J* = 7.4 Hz, 2 H, H-9), 3.58–3.63 (m, 2 H, CH_2N), 3.03 (br t, *J* = 7.7 Hz, 2 H, H-7), 2.77 (br dd, *J* = 6.0, 5.8 Hz, 2 H, CH_2N), 2.63 (q, *J* = 7.1 Hz, 4 H, 2 × CH_2N), 2.22 (br p, *J* = 7.7 Hz, 2 H, H-8), 1.08 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 149.0, 144.7, 138.6, 138.3, 132.7, 129.0, 115.7, 51.2, 46.8 (2), 38.8, 35.1, 32.9, 25.6, 11.7 (2). Anal. Calcd for $C_{16}H_{23}N_5O_2·½H_2O$: C, 58.9; H, 7.4; N, 21.5. Found: C, 59.2; H, 7.2; N, 21.5%.

N^1-(1-Oxido-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-yl)-N^2,N^2-dipropyl-1,2-ethanediamine (11).

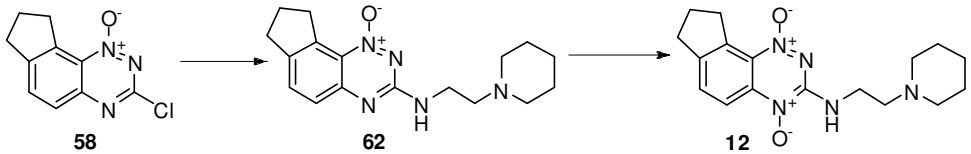


58 **61** **11**

N^1-(1-Oxido-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-yl)-N^2,N^2-dipropyl-1,2-ethanediamine (61). Method C. Reaction of chloride **58** (325 mg, 1.5 mmol) *N*,*N*-dipropyl-1,2-ethanediamine[2] (0.53 g, 3.7 mmol) in DME (30 mL) gave 1-oxide **61** (454 mg, 94%) as a pale yellow solid: mp (MeOH) 148–151 °C; ^{1}H NMR δ 7.54 (d, *J* = 8.4 Hz, 1 H, H-6), 7.40 (d, *J* = 8.4 Hz, 1 H, H-5), 5.77 (br s, 1 H, NH), 3.63–3.68 (m, 2 H, H-9), 3.48–3.52 (m, 2 H, CH_2N), 2.95–3.00 (m, 2 H, H-7), 2.68 (dd, *J* = 6.0, 5.8 Hz, 2 H, CH_2N), 2.40–2.45 (m, 4 H, 2 × CH_2N), 2.16–2.23 (m, 2 H, H-8), 1.43–1.52 (m, 4 H, 2 × CH_2), 0.90 (t, *J* = 7.3 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 158.5, 149.0, 142.0, 137.3, 132.2, 129.2, 124.7, 55.9 (2), 52.6, 38.9, 35.3, 32.9, 24.8, 20.3 (2), 11.9 (2). Anal. Calcd for $C_{18}H_{27}N_5O$: C, 65.6; H, 8.3; N, 21.3. Found: C, 65.7; H, 8.6; N, 21.5%.

***N*^{1}-(1-Oxido-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dipropyl-1,2-ethanediamine (11). Method D.** Oxidation of 1-oxide **61** (364 mg, 1.1 mmol) with CF_3CO_3H (ca. 11 mmol) gave 1,4-dioxide **11** (207 mg, 57%) as a red solid: mp (MeOH/EtOAc) 133–135 °C; ^{1}H NMR δ 8.11 (d, *J* = 8.7 Hz, 1 H, H-5), 7.68 (d, *J* = 8.7 Hz, 1 H, H-6), 7.48 (br s, 1 H, NH), 3.68 (t, *J* = 7.5 Hz, 2 H, H-9), 3.58–3.64 (m, 2 H, CH_2N), 3.02 (t, *J* = 7.8 Hz, 2 H, H-7), 2.76–2.81 (m, 2 H, CH_2N), 2.46–2.55 (m, 4 H, 2 × CH_2N), 2.17–2.25 (m, 2 H, H-8), 1.47–1.58 (m, 4 H, 2 × CH_2), 0.92 (t, 6 H, *J* = 7.4 Hz, 2 × CH_3); ^{13}C NMR δ 149.1, 144.7, 138.6, 138.4, 132.6, 129.0, 115.8, 55.9 (2), 52.5, 38.8, 35.1, 32.9, 24.6, 20.0 (2), 11.8 (2). Anal. calcd for $C_{18}H_{27}N_5O_2$: C, 62.6; H, 7.9; N, 20.3. Found: C, 62.7; H, 8.0; N, 20.4%.

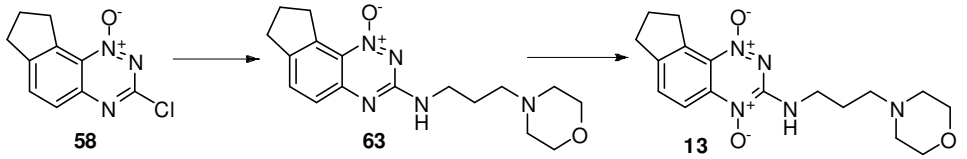
***N*-[2-(1-Piperidinyl)ethyl]-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (12).**



***N*-[2-(1-Piperidinyl)ethyl]-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-amine 1-Oxide (62). Method C.** Reaction of chloride **58** (165 mg, 0.7 mmol) and 2-(1-piperidinyl)ethylamine (0.32 mL, 2.2 mmol) in DME (30 mL) gave 1-oxide **62** (205 mg, 88%) as a pale yellow solid: mp (MeOH) 152–155 °C; ^{1}H NMR δ 7.53 (d, *J* = 8.4 Hz, 1 H, H-5), 7.38 (d, *J* = 8.4 Hz, 1 H, H-6), 5.90 (br s, 1 H, NH), 3.60–3.66 (m, 2 H, H-9), 3.48–3.54 (m, 2 H, CH_2N), 2.97 (br t, *J* = 7.7 Hz, 2 H, H-7), 2.57 (dd, *J* = 6.1, 5.9 Hz, 2 H, CH_2N), 2.38–2.45 (m, 4 H, 2 × CH_2N), 2.17 (br p, *J* = 7.7 Hz, 2 H, H-8), 1.55–1.61 (m, 4 H, 2 × CH_2), 1.41–1.48 (m, 2 H, CH_2); ^{13}C NMR δ 158.4, 149.0, 142.0, 137.3, 132.2, 129.1, 124.6, 56.9, 54.2 (2), 37.9, 35.3, 32.8, 25.9 (2), 24.8, 24.4. Anal. Calcd for $C_{17}H_{23}N_5O$: C, 65.2; H, 7.4; N, 22.4. Found: C, 65.1; H, 7.2; N, 22.5%.

***N*-[2-(1-Piperidinyl)ethyl]-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (12). Method D.** Oxidation of 1-oxide **62** (170 mg, 0.5 mmol) with CF_3CO_3H (ca. 5.4 mmol) gave 1,4-dioxide **12** (89 mg, 50%) as a red solid: mp (MeOH/EtOAc) 138–141 °C; ^{1}H NMR δ 8.12 (d, *J* = 8.7 Hz, 1 H, H-5), 7.70 (d, *J* = 8.7 Hz, 1 H, H-6), 7.44 (br s, 1 H, NH), 3.70 (br t, *J* = 7.6 Hz, 2 H, H-9), 3.60–3.64 (m, 2 H, CH_2N), 3.04 (br t, *J* = 7.7 Hz, 2 H, H-7), 2.64 (br t, *J* = 6.1 Hz, 2 H, CH_2N), 2.43–2.50 (m, 4 H, 2 × CH_2), 2.21 (br p, *J* = 7.7 Hz, 2 H, H-8), 1.59–1.65 (m, 4 H, 2 × CH_2), 1.42–1.48 (m, 2 H, CH_2); ^{13}C NMR δ 149.1, 144.7, 138.6, 138.4, 132.7, 129.0, 115.7, 56.9, 54.4 (2), 38.1, 35.1, 32.9, 25.9 (2), 24.6, 24.3. Anal. Calcd for $C_{17}H_{23}N_5O_2 \cdot ½H_2O$: C, 60.3; H, 7.2; N, 20.7. Found: C, 59.9; H, 7.0; N, 20.3%.

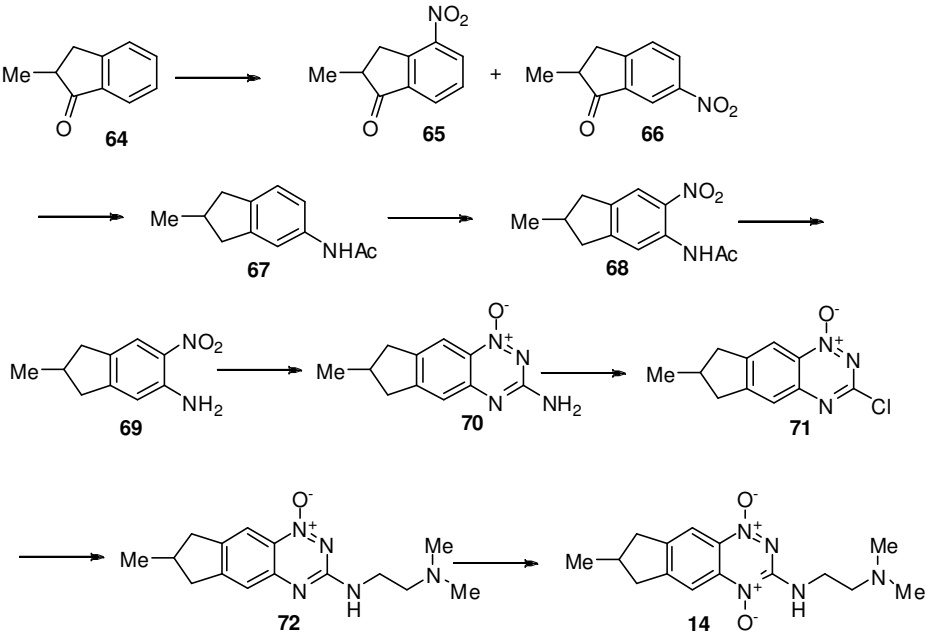
***N*-[3-(1-Morpholinyl)propyl]-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (13).**



***N*-[3-(1-Morpholinyl)propyl]-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-amine 1-Oxide (63). Method C.** Reaction of chloride **58** (158 mg, 0.7 mmol) and 3-(1-morpholinyl)propylamine (0.31 mL, 2.1 mmol) in DME (30 mL) gave 1-oxide **63** (212 mg, 91%) as a pale yellow solid: mp (MeOH/EtOAc) 179–181 °C; ^{1}H NMR δ 7.54 (d, *J* = 8.4 Hz, 1 H, H-5), 7.37 (d, *J* = 8.4 Hz, 1 H, H-6), 6.11 (br s, 1 H, NH), 3.73–3.78 (m, 4 H, 2 × CH_2O), 3.63 (br t, *J* = 7.6 Hz, 2 H, H-9), 3.55–3.60 (m, 2 H, CH_2N), 2.97 (br t, *J* = 7.7 Hz, 2 H, H-7), 2.43–2.52 (m, 6 H, 3 × CH_2N), 2.18 (br p, *J* = 7.7 Hz, 2 H, H-8), 1.90–1.96 (m, 2 H, CH_2); ^{13}C NMR δ 158.5, 149.0, 142.0, 137.3, 132.2, 129.1, 124.6, 67.0 (2), 57.2, 53.7 (2), 40.7, 35.3, 32.8, 25.3, 24.8. Anal. Calcd for $C_{17}H_{23}N_5O{\cdot}¼H_2O$: C, 61.2; H, 7.1; N, 21.0. Found: C, 61.2; H, 7.0; N, 21.0%.

***N*-[3-(1-Morpholinyl)propyl]-8,9-dihydro-7*H*-indeno[5,4-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (13). Method D.** Oxidation of 1-oxide **63** (173 mg, 0.5 mmol) with CF_3CO_3H (ca. 5 mmol) gave 1,4-dioxide **13** (42 mg, 23%) as a red solid: mp (MeOH) 172–175 °C; ^{1}H NMR δ 8.28 (br s, 1 H, NH), 8.12 (d, *J* = 8.7 Hz, 1 H, H-5), 7.69 (d, *J* = 8.7 Hz, 1 H, H-6), 3.81–3.85 (m, 4 H, 2 × CH_2O), 3.64–3.72 (m, 4 H, CH_2N, H-9), 3.03 (br t, *J* = 7.7 Hz, 2 H, H-7), 2.49–2.57 (m, 6 H, 3 × CH_2N), 2.22 (br p, *J* = 7.7 Hz, 2 H, H-8), 1.84–1.91 (m, 2 H, CH_2); ^{13}C NMR δ 149.2, 144.6, 138.6, 138.4, 132.6, 128.9, 115.8, 66.9 (2), 57.6, 53.9 (2), 41.4, 35.1, 32.9, 24.6, 24.3. Anal. Calcd for $C_{17}H_{23}N_5O_3{\cdot}¼CH_3OH$: C, 58.6; H, 6.9; N, 19.8. Found: C, 58.6; H, 6.7; N, 19.9%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(7-methyl-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (14).**



Nitration of 2-Methyl-1-indanone (64). 2-Methyl-1-indanone (**64**) (18.74 g, 128 mmol) was added dropwise to stirred fuming HNO_3 (100 mL) at –10 °C over 1 h. The mixture was stirred at –10 °C for 10 min then poured into ice/water (1 L) and the mixture stirred for 1 h. The precipitate was filtered and the filtrate extracted with DCM (4 × 80 mL). The combined organic fraction was dried and the solvent evaporated. The combined residue was purified by chromatography, eluting with a gradient (10–20%) of EtOAc/pet. ether, to give (i) 2-methyl-4-nitro-1-indanone (**65**) (1.89 g, 8%) as a tan solid: mp 61–63 °C [lit.[4] mp (Et_2O/pet. ether) 74–75 °C]; ^{1}H NMR δ 8.46 (dd, *J* = 8.0, 1.1 Hz, 1 H, H-5), 8.08 (br d, *J* = 7.5 Hz, 1 H, H-7), 7.60 (br dd, *J* = 8.0, 7.5 Hz, 1 H, H-6), 3.93 (dd, *J* = 19.2, 8.0 Hz, 1 H, H-3), 3.20 (dd, *J* = 19.2, 4.0 Hz, 1 H, H-3), 2.76–2.85 (m, 1 H, H-2), 1.37 (d, *J* = 7.5 Hz, 3 H, CH_3); and (ii) 2-methyl-6-nitro-1-indanone (**66**) (10.76 g, 44%) as a tan solid: mp 60–61 °C; ^{1}H NMR δ 8.56 (d, *J* = 2.0 Hz, 1 H, H-7), 8.44 (dd, *J* = 8.4, 2.2 Hz, 1 H, H-5), 7.63 (d, *J* = 8.4 Hz, 1 H, H-4), 3.48–3.54 (m, 1 H, H-2), 2.81–2.90 (m, 2 H, H-3), 1.36 (d, *J* = 7.3 Hz, 3 H, CH_3). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.8; H, 4.7; N, 7.3. Found: C, 62.7; H, 4.8; N, 7.4%.

***N*-(2-Methyl-2,3-dihydro-1*H*-inden-5-yl)acetamide (67).** A solution of nitroindanone **66** (2.08 g, 10.9 mmol) in EtOH (100 mL), water (10 mL) and cHCl (1 mL) with Pd/C (200 mg) was vigorously stirred under H_2 (60 psi) for 16 h. The mixture was filtered through Celite and the solvent was evaporated. The residue was partitioned between dilute aqueous NH_3 solution and DCM, and the organic fraction dried and the solvent evaporated. The residue was suspended in dioxane (30 mL), and Ac_2O (1.6 mL, 17.0 mmol) added dropwise. The mixture was stirred at 20 °C for 16 h, and then quenched with MeOH (20 mL) and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give acetamide **67** (1.03 g, 50%) as a white solid: mp (EtOAc/pet. ether) 90–91 °C; ^{1}H NMR δ 7.41 (br d, *J* = 1.7 Hz, 1 H, H-4), 7.35 (br s, 1 H, NH), 7.15 (br dd, *J* = 8.0, 1.7 Hz, 1 H, H-6), 7.10 (br d, *J* = 8.0 Hz, 1 H, H-7), 2.97–3.05 (m, 2 H, CH_2), 2.45–2.61 (m, 3 H, H-2, CH_2), 2.16 (s, 3 H, $COCH_3$), 1.13 (d, *J* = 6.4 Hz, 3 H, CH_3); ^{13}C NMR δ 168.3, 144.7, 139.9, 136.0, 124.5, 118.2, 116.7, 41.2, 40.6, 34.7, 24.5, 20.7. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.2; H, 8.0; N, 7.4. Found: C, 76.3; H, 7.9; N, 7.4%.

***N*-(2-Methyl-6-nitro-2,3-dihydro-1*H*-inden-5-yl)acetamide (68).** A solution of nitric acid (70%, 3.2 mL, 50.3 mmol) in TFA (5 mL) was added dropwise to a stirred solution of acetamide **67** (3.93 g, 16.8 mmol) in TFA (40 mL) and the solution stirred at 20 °C for 2 h. The solution was poured into ice/water (400 mL) and stirred for 30 min. The precipitate was filtered, washed with water (3 × 30 mL), and dried. The solid was purified by chromatography, eluting with 10% EtOAc/pet. ether, to give nitroacetamide **68** (3.79 g, 96%) as a red solid: mp (EtOAc/pet. ether) 99–100 °C; ^{1}H NMR δ 10.41 (br s, 1 H, NH), 8.50 (s, 1 H, H-7), 8.00 (s, 1 H, H-4), 3.03–3.13 (m, 2 H, CH_2), 2.51–2.67 (m, 3 H, H-2, CH_2), 2.29 (s, 3 H, $COCH_3$), 1.14 (d, *J* = 6.4 Hz, 3 H, CH_3); ^{13}C NMR δ 169.0, 153.9, 139.4, 135.3, 133.7, 121.1, 117.7, 41.6, 40.2, 34.7, 25.6, 20.4. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 6.0; N, 12.0. Found: C, 61.6; H, 6.2; N, 11.5%.

2-Methyl-6-nitro-5-indanamine (69). A suspension of nitroacetamide **68** (3.79 g, 16.2 mmol) in EtOH (100 mL) and cHCl (14 mL) was stirred at reflux temperature for 4 h.

The mixture was cooled and the EtOH evaporated. The mixture was diluted with water (100 mL) and the pH adjusted to 9 with cNH_3. The mixture was extracted with DCM (3 × 50 mL) and the combined organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with 20% EtOAc/pet. ether, to give nitroaniline **69** (3.01 g, 97%) as a red solid: mp (EtOAc/pet. ether) 100–101 °C; ^{1}H NMR δ 7.89 (s, 1 H, H-7), 6.61 (s, 1 H, H-4), 5.99 (br s, 2 H, NH_2), 2.92–2.99 (m, 2 H, CH_2), 2.40–2.58 (m, 3 H, H-2, CH_2), 1.12 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR δ 153.9, 144.3, 133.6, 131.3, 120.9, 113.6, 41.1, 39.6, 34.8, 20.4. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3; N, 14.6. Found: C, 62.6; H, 6.3; N, 14.5%.

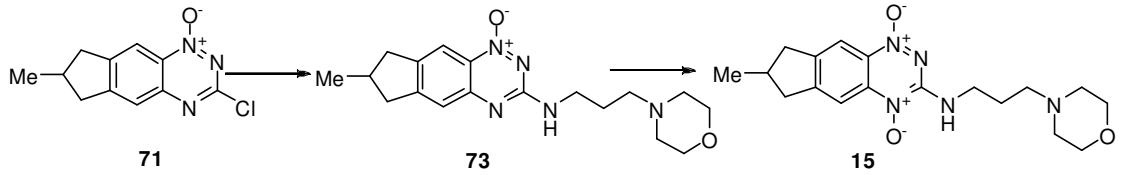
7-Methyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1-Oxide (70). Method A. Reaction of nitroaniline **69** (3.0 g, 15.7 mmol) and cyanamide (2.6 g, 62.6 mmol) gave 1-oxide **70** (3.06 g, 90%) as a yellow powder: mp (MeOH/DCM) 275–277 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.90 (s, 1 H, H-9), 7.31 (s, 1 H, H-5), 7.10 (br s, 2 H, NH_2), 3.05–3.14 (m, 2 H, CH_2), 2.48–2.62 (m, 3 H, H-7, CH_2), 1.09 (d, J = 6.3 Hz, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 159.9, 153.7, 148.6, 142.1, 128.7, 120.0, 113.9, 41.4, 39.6, 34.3, 19.9. Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.1; H, 5.6; N, 25.9. Found: C, 61.3; H, 5.6; N, 26.2%.

3-Chloro-7-methyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (71). Method B. Reaction of 1-oxide **70** (1.23 g, 5.7 mmol) and $NaNO_2$ (0.43 g, 6.2 mmol) in TFA (50 mL), followed by chlorination with $POCl_3$/DMF, gave chloride **71** (1.06 g, 79%) as a pale yellow solid: mp (DCM/pet. ether) 121–122 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.18 (s, 1 H, H-9), 7.71 (s, 1 H, H-5), 3.21–3.30 (m, 2 H, CH_2), 2.65–2.80 (m, 3 H, H-7, CH_2), 1.20 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 156.0, 155.9, 149.8, 147.4, 132.8, 122.6, 114.6, 41.3, 40.9, 35.0, 20.2. Anal. Calcd for $C_{11}H_{10}ClN_3O$: C, 56.1; H, 4.3; N, 17.8. Found: C, 56.0; H, 4.2; N, 17.8%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(7-methyl-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (72). Method C.** Reaction of chloride **71** (240 mg, 0.9 mmol), *N*^{1},*N*^{1}-dimethyl-1,2-ethanediamine (0.26 mL, 2.4 mmol) and Et_3N (0.33 mL, 2.4 mmol) in DME (50 mL) gave 1-oxide **72** (389 mg, 86%) as a yellow solid: mp (MeOH/EtOAc) 119–121 °C; ^{1}H NMR δ 8.03 (s, 1 H, H-9), 7.35 (s, 1 H, H-5), 5.82 (br s, 1 H, NH), 3.52–3.58 (m, 2 H, CH_2N), 3.07–3.17 (m, 2 H, CH_2), 2.55–2.67 (m, 5 H, CH, CH_2, CH_2N), 2.28 [s, 6 H, $N(CH_3)_2$], 1.15 (d, J = 6.1 Hz, 3 H, CH_3); ^{13}C NMR δ 158.7, 154.2, 148.9, 142.9, 129.8, 120.7, 114.8, 57.6, 45.1 (2), 41.2, 40.4, 38.7, 34.9, 20.2. Anal. Calcd for $C_{15}H_{21}N_5O$: C, 62.7; H, 7.4; N, 24.4. Found: C, 62.4; H, 7.1; N, 24.1%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(7-methyl-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (14). Method D.** Oxidation of 1-oxide **72** (371 mg, 1.3 mmol) with CF_3CO_3H (ca. 13 mmol) gave (i) starting material **72** (181 mg, 49%) and (ii) 1,4-dioxide **14** (103 mg, 26%) as a red solid: mp (MeOH/DCM) 149–151 °C; ^{1}H NMR δ 8.09 (s, 1 H, H-9), 8.07 (s, 1 H, H-5), 7.52 (br s, 1 H, NH), 3.58–3.64 (m, 2 H, CH_2N), 3.14–3.27 (m, 2 H, CH_2), 2.63–2.75 (m, 3 H, CH, CH_2), 2.59 (br t, J = 6.0 Hz, 2 H, CH_2), 2.28 [s, 6 H, $N(CH_3)_2$], 1.18 (d, J = 6.2 Hz, 3 H, CH_3); ^{13}C NMR δ 155.6, 149.4, 145.5, 138.0, 128.9, 115.8, 111.8, 57.4, 45.0 (2), 41.4, 40.4, 38.7, 34.8, 20.1. Anal. Calcd for $C_{15}H_{21}N_5O_2 \cdot ½CH_2Cl_2$: C, 54.6; H, 6.3; N, 19.9. Found: C, 54.4; H, 6.0; N, 19.8%.

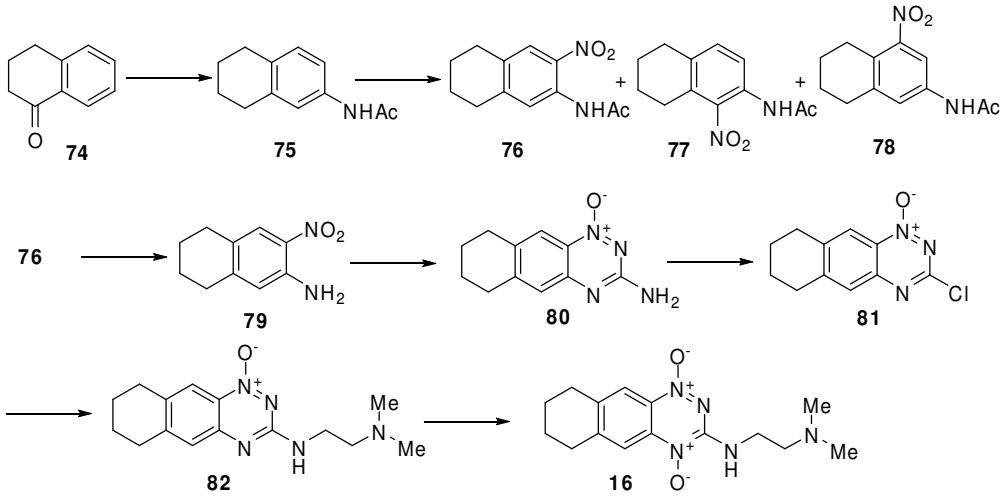
7-Methyl-*N*-[3-(4-morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (15).



7-Methyl-*N*-[3-(4-morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1-Oxide (73). Method C. Reaction of chloride **71** (367 mg, 1.6 mmol), 3-(4-morpholinyl)propylamine (0.34 mL, 2.3 mmol) and Et_3N (0.33 mL, 2.3 mmol) in DME (50 mL) gave 1-oxide **73** (525 mg, 98%) as a yellow solid: mp (MeOH/DCM) 138–140 °C; ^{1}H NMR δ 8.04 (s, 1 H, H-9), 7.35 (s, 1 H, H-5), 6.10 (br t, *J* = 5.0 Hz, 1 H, NH), 3.75 (br t, *J* = 4.7 Hz, 4 H, 2 × CH_2O), 3.56–3.61 (m, 2 H, CH_2N), 3.08–3.18 (m, 2 H, CH_2), 2.56–2.65 (m, 3 H, CH, CH_2), 2.44–2.52 (m, 6 H, 3 × CH_2N), 1.83 (br p, *J* = 6.5 Hz, 2 H, CH_2), 1.15 (d, *J* = 6.1 Hz, 3 H, CH_3); ^{13}C NMR δ 158.8, 154.2, 148.9, 142.8, 129.8, 120.7, 114.8, 67.0 (2), 57.3, 53.8 (2), 41.2, 40.8, 40.4, 34.9, 25.3, 20.4. Anal. Calcd for $C_{18}H_{25}N_5O_2$: C, 63.0; H, 7.3; N, 20.4. Found: C, 63.2; H, 7.2; N, 20.4%.

7-Methyl-*N*-[3-(4-morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (15). Method D. Oxidation of 1-oxide **73** (490 mg, 1.4 mmol) with CF_3CO_3H (ca. 14 mmol) gave (i) starting material **73** (280 mg, 57%) and (ii) 1,4-dioxide **15** (88 mg, 17%) as a red solid: mp (MeOH/DCM) 161–163 °C; ^{1}H NMR δ 8.30 (br s, 1 H, NH), 8.08 (br s, 2 H, H-5, H-9), 3.82 (br t, *J* = 4.5 Hz, 4 H, 2 × CH_2O), 3.58–3.63 (m, 2 H, CH_2N), 3.15–3.25 (m, 2 H, CH_2), 2.61–2.74 (m, 3 H, CH, CH_2), 2.57 (br t, *J* = 6.1 Hz, 2 H, CH_2N), 2.47–2.53 (m, 4 H, 2 × CH_2N), 1.83–1.90 (m, 2 H, CH_2), 1.18 (d, *J* = 6.2 Hz, 3 H, CH_3); ^{13}C NMR δ 155.2, 149.5, 145.2, 138.1, 129.5, 115.8, 111.7, 66.9 (2), 57.7, 53.8 (2), 41.6, 41.4, 40.4, 34.9, 24.5, 20.2; MS *m/z* 360 (MH^+, 5%); HRMS calcd for $C_{18}H_{26}N_5O_3$ (MH^+) *m/z* 360.2036, found 360.2041. Anal. Calcd for $C_{18}H_{25}N_5O_3$: C, 60.2; H, 7.0. Found: C, 60.6; H, 7.0%. Also Calcd for N, 19.5. Found: 18.3%.

***N*^{1}-(1,4-Dioxido-6,7,8,9-tetrahydronaphtho[2,3-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (16).**



***N*-(5,6,7,8-Tetrahydro-2-naphthalenyl)acetamide (75).** $fHNO_3$ (8.6 mL, 144 mmol) in cH_2SO_4 (50 mL) was added dropwise to a stirred solution of α-tetralone (**74**) (20 g, 137 mmol) in cH_2SO_4 (300 mL) at 0 °C and the solution stirred for 1 h. The solution was poured into ice/water (2 L), stirred for 30 min, filtered and washed with water. The solid was dried and purified by chromatography, eluting with 20% EtOAc/pet. ether, to give (i) 5-nitro-3,4-dihydro-1(2*H*)-naphthalenone (4.1 g, 16%) as a white solid: ^{1}H NMR δ 8.35 (dd, *J* = 7.8, 1.4 Hz, 1 H, H-6), 8.09 (dd, *J* = 8.0, 1.4 Hz, 1 H, H-8), 7.48 (br t, *J* = 7.9 Hz, 1 H, H-7), 3.22 (t, *J* = 6.1 Hz, 2 H, H-4), 2.74 (dd, *J* = 6.8, 6.4 Hz, 2 H, H-2), 2.13–2.21 (m, 2 H, H-3); and (ii) 7-nitro-3,4-dihydro-1(2*H*)-naphthalenone (20.1 g, 77%) as a white solid: ^{1}H NMR δ 8.86 (d, *J* = 2.5 Hz, 1 H, H-4), 8.30 (dd, *J* = 8.4, 2.5 Hz, 1 H, H-6), 7.46 (d, *J* = 8.4 Hz, 1 H, H-5), 3.09 (t, *J* = 6.1 Hz, 2 H, H-4), 2.74 (dd, *J* = 7.0, 6.2 Hz, 2 H, H-2), 2.17–2.25 (m, 2 H, H-3).

A solution of 7-nitro-3,4-dihydro-1(2*H*)-naphthalenone (1.67 g, 8.7 mmol) in EtOAc/EtOH (1:1, 150 mL), water (15 mL) and cHCl (2 mL) with Pd/C (5%, 500 mg) was stirred vigorously under H_2 (60 psi) for 16 h. The suspension was filtered through Celite, washed with EtOH (4 × 10 mL) and the organic solvent evaporated. The aqueous residue was partitioned between DCM and dilute aqueous NH_3 solution and the organic fraction dried and the solvent evaporated. The residue was dissolved in dioxane (20 mL), and Ac_2O (1.8 mL, 19.2 mmol) was added dropwise to the solution at 0 °C. The solution was stirred at 20 °C for 16 h, diluted with water (50 mL), and partitioned between EtOAc and dilute aqueous NH_3 solution. The organic fraction was washed with water (3 × 20 mL), dried and the solvent evaporated to give acetamide **75** (1.57 g, 95%) as a white solid: mp 98–101 °C (lit.[5] mp 104–105 °C); ^{1}H NMR δ 7.18–7.25 (m, 2 H, H-1, NH), 7.15 (dd, *J* = 8.2, 2.1 Hz, 1 H, H-3), 7.00 (d, *J* = 8.2 Hz, 1 H, H-4), 2.69–2.77 (m, 4 H, 2 × CH_2), 2.15 (s, 3 H, CH_3), 1.74–1.80 (m, 4 H, 2 × CH_2). The procedure was repeated a number of times to give acetamide **75** (10.21 g, 88% overall).

Nitration of *N*-(5,6,7,8-Tetrahydro-2-naphthalenyl)acetamide (75). A solution of KNO_3 (5.73 g, 56.6 mmol) in cH_2SO_4 (25 mL) was added dropwise to a stirred solution of acetamide **75** (10.21 g, 53.9 mmol) in cH_2SO_4 (150 mL) at 0 °C and the mixture stirred at 0 °C for 2 h. The mixture was poured into ice/water (1.5 L) and the suspension stirred for 30 min. The precipitate was filtered, washed with water and dried. The solid was purified by chromatography, eluting with a gradient (20–70%) of EtOAc/pet. ether, to give (i) *N*-(3-nitro-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide (**76**) (840 mg, 7%) as a white solid: mp 129–130 °C [lit.[6] mp (EtOH) 135–135 °C]; ^{1}H NMR δ 10.24 (br s, 1 H, NH), 8.44 (s, 1 H, H-4), 7.93 (s, 1 H, H-1), 2.82–2.86 (m, 2 H, CH_2), 2.75–2.79 (m, 2 H, CH_2), 2.27 (s, 3 H, CH_3), 1.78–1.83 (m, 4 H, 2 × CH_2); and (ii) *N*-(1-nitro-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide (**77**) (1.65, g, 13%) as a white solid: mp 118–120 °C (lit.[7] mp 127 °C); ^{1}H NMR δ 8.04 (br s, 1 H, NH), 7.91 (br d, *J* = 8.4 Hz, 1 H, H-3), 7.24 (d, *J* = 8.4 Hz, 1 H, H-4), 2.78–2.82 (m, 2 H, CH_2), 2.72–2.76 (m, 2 H, CH_2), 2.18 (s, 3 H, CH_3), 1.76–1.83 (m, 4 H, 2 × CH_2); and (iii) *N*-(4-nitro-5,6,7,8-tetrahydro-2-naphthalenyl)acetamide (**78**) (7.58 g, 60%) as a white solid: mp 196–198 °C; ^{1}H NMR δ 7.79 (d, *J* = 2.0 Hz, 1 H, H-3), 7.56 (d, *J* = 2.0 Hz, 1 H, H-1), 7.22 (br s, 1 H, NH), 2.87–2.93 (m, 2 H, CH_2), 2.80–2.84 (m, 2 H, CH_2), 2.20 (s, 3 H, CH_3), 1.76–1.83 (m, 4 H, 2 × CH_2).

3-Nitro-5,6,7,8-tetrahydro-2-naphthalenamine (79). A suspension of nitroacetamide **76** (151 mg, 0.65 mmol) in 6 M HCl (30 mL) was stirred at 100 °C for 6 h. The suspension was cooled to 20 °C, diluted with water (50 mL) and the pH adjusted to 8 with aqueous NH_3 solution. The mixture was extracted with DCM (3 × 50 mL), the combined organic fraction dried, and the solvent evaporated to give amine **79** (113 mg, 100%) as an orange solid: mp 120–122 °C (lit.[6] mp 124–127 °C); ^{1}H NMR δ 7.83 (s, 1 H, H-4), 7.50 (s, 1 H, H-1), 5.79 (s, 2 H, NH_2), 2.67–2.73 (m, 4 H, 2 × CH_2), 1.78–1.83 (m, 4 H, 2 × CH_2).

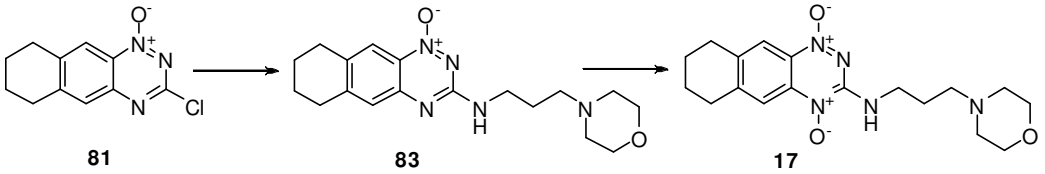
6,7,8,9-Tetrahydronaphtho[2,3-*e*][1,2,4]triazin-3-amine 1-Oxide (80). Method A. Reaction of nitroaniline **79** (0.77 g, 4.0 mmol) and cyanamide (0.68 g, 16.0 mmol) gave amine **80** (0.30 g, 35%) as a yellow powder: mp (MeOH/DCM) 270–274 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.83 (s, 1 H, H-10), 7.23 (s, 1 H, H-5), 7.11 (br s, 2 H, NH_2), 2.82–2.89 (m, 4 H, H-6, H-9), 1.72–1.77 (m, 4 H, H-7, H-8); ^{13}C NMR [$(CD_3)_2SO$] δ 159.8, 146.9, 146.8, 136.2, 128.0, 124.0, 118.1, 29.1, 28.5, 22.0, 21.8. Anal. Calcd for $C_{11}H_{12}N_4O·¼H_2O$: C, 59.9; H, 5.7; N, 25.4. Found: C, 60.4; H, 5.5; N, 25.5%.

3-Chloro-6,7,8,9-tetrahydronaphtho[2,3-*e*][1,2,4]triazine 1-Oxide (81). Method B. Reaction of 1-oxide **80** (284 mg, 1.3 mmol) and $NaNO_2$ (181 mg, 2.6 mmol), followed by chlorination with $POCl_3$/DMF, gave chloride **81** (173 mg, 56%) as a pale yellow solid: mp (EtOAc/DCM) 104–106 °C; ^{1}H NMR δ 8.10 (s, 1 H, H-10), 7.65 (s, 1 H, H-5), 2.98–3.05 (m, 4 H, H-6, H-9), 1.86–1.93 (m, 4 H, H-7, H-8); ^{13}C NMR δ 155.9, 149.5, 145.5, 143.1, 131.8, 126.9, 118.8, 30.2, 29.9, 22.2, 22.0. Anal. Calcd for $C_{11}H_{10}ClN_3O$: C, 56.0; H, 4.3; N, 17.8. Found: C, 56.2; H, 4.3; N, 17.8%.

***N*^{1}-(1-Oxido-6,7,8,9-tetrahydronaphtho[2,3-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (82). Reaction C.** Reaction of chloride **81** (157 mg, 0.7 mmol) and *N*,*N*-dimethylethanediamine (0.22 mL, 2.0 mmol) in DME (30 mL) gave 1-oxide **82** (167 mg, 87%) as a yellow solid: mp (MeOH) 149–151 °C; ^{1}H NMR δ 7.96 (s, 1 H, H-10), 7.29 (s, 1 H, H-5), 5.81 (br s, 1 H, NH), 3.50–3.55 (m, 2 H, CH_2N), 2.85–2.92 (m, 4 H, H-6, H-9), 2.56 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.28 [s, 6 H, $N(CH_3)_2$], 1.81–1.85 (m, 4 H, H-7, H-8); ^{13}C NMR δ 158.7, 147.5, 147.0, 136.0, 129.1, 124.9, 119.0, 57.6, 45.1 (2), 38.7, 30.0, 29.3, 22.7, 22.5. Anal. Calcd for $C_{15}H_{21}N_5O$: C, 62.7; H, 7.4; N, 24.4. Found: C, 62.5; H, 7.2; N, 24.3%.

***N*^{1}-(1,4-Dioxido-6,7,8,9-tetrahydronaphtho[2,3-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (16). Method D.** Oxidation of 1-oxide **82** (153 mg, 0.5 mmol) with CF_3CO_3H (ca. 5 mmol) gave (i) starting material **82** (37 mg, 24%) and (ii) 1,4-dioxide **16** (47 mg, 29%) as a red solid: mp (MeOH) 148–151 °C; ^{1}H NMR δ 8.02 (s, 1 H, H-10), 7.98 (s, 1 H, H-5), 7.35 (br s, 1 H, NH), 3.63 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.98–3.04 (m, 2 H, CH_2), 2.91–2.96 (m, 2 H, CH_2), 2.61 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.30 [s, 6 H, $N(CH_3)_2$], 1.83–1.92 (m, 4 H, H-7, H-8); ^{13}C NMR δ 149.4, 148.7, 138.8, 136.5, 128.9, 120.1, 115.8, 57.6, 45.2 (2), 38.9, 30.3, 29.4, 22.3, 22.0; HRMS calcd for $C_{15}H_{22}N_5O_2$ (MH^+) *m/z* 304.1774, found 304.1768. Anal. Calcd for $C_{15}H_{21}N_5O_2·1½H_2O$: C, 54.5; H, 7.3; N, 21.2. Found: C, 54.4; H, 6.3; N, 20.7%.

***N*-[3-(4-Morpholinyl)propyl]-6,7,8,9-tetrahydronaphtho[2,3-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (17).**

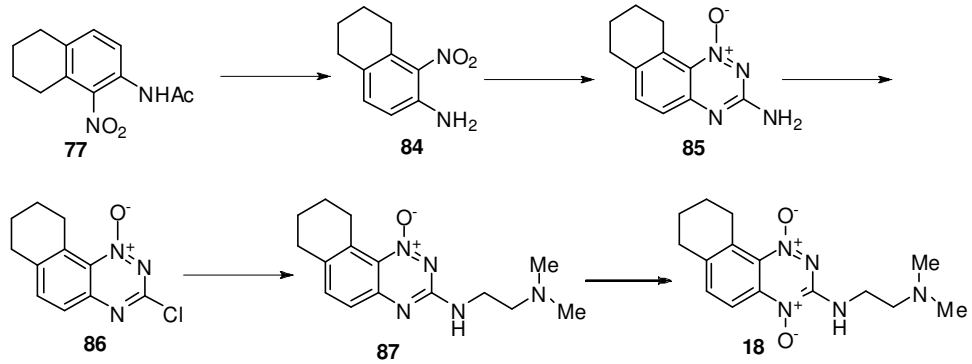


81 **83** **17**

***N*-[3-(4-Morpholinyl)propyl]-6,7,8,9-tetrahydronaphtho[2,3-*e*][1,2,4]triazin-3-amine 1-Oxide (83). Method C.** Reaction of chloride **81** (171 mg, 0.7 mmol) and 3-(4-morpholinyl)propylamine (314 mg, 2.2 mmol) in DME (8 mL) gave 1-oxide **83** (250 mg, 100%) as an orange solid: mp (EtOAc) 115–116 °C; ^{1}H NMR δ 7.97 (s, 1 H, H-10), 7.29 (s, 1 H, H-5), 6.14 (br s, 1 H, NH), 3.75 (t, J = 4.6 Hz, 4 H, 2 × CH_2O), 3.60 (q, J = 6.2 Hz, 2 H, CH_2N), 2.86–2.95 (m, 4 H, H-6, H-9), 2.45–2.56 (m, 6 H, 3 × CH_2N), 1.80–1.88 (m, 6 H, H-7, H-8, CH_2); ^{13}C NMR δ 158.7, 147.5 147.0, 136.0, 129.1, 124.9, 119.0, 67.0 (2), 57.3, 53.8 (2), 40.8, 30.0, 29.3, 25.3, 22.7, 22.5. Anal. Calcd for $C_{18}H_{25}N_5O_2$: C, 63.0; H, 7.3; N, 20.4. Found: C, 62.8; H, 7.4; N, 20.3%.

***N*-[3-(4-Morpholinyl)propyl]-6,7,8,9-tetrahydronaphtho[2,3-*e*][1,2,4]triazin-3-amine 1,4-Dioxide (17). Method D.** Oxidation of 1-oxide **83** (204 mg, 0.6 mmol) with CF_3CO_3H (ca. 6 mmol) gave 1,4-dioxide **17** (28 mg, 13%) as a red solid which was converted to the hydrochloride salt: mp (MeOH/DCM) 182–185 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.29 (s, 1 H, HCl), 8.35 (br s, 1 H, NH), 7.95 (s, 1 H, H-10), 7.87 (s, 1 H, H-5), 3.92–4.01 (m, 2 H, CH_2O), 3.37 (m, 4 H, CH_2N, CH_2O), 2.88–3.22 (m, 8 H, 2 × CH_2N, H-6, H-9), 2.53 (t, J = 5.6 Hz, 2 H, CH_2N), 2.00–2.09 (m, 2 H, CH_2N), 1.74–1.83 (m, 4 H, H-7, H-8); ^{13}C NMR [$(CD_3)_2SO$] δ 149.2, 147.8, 138.0, 136.1, 128.5, 119.4, 115.0, 63.0 (2), 53.5, 50.9 (2), 37.9, 29.4, 28.5, 22.7, 21.7, 21.6. Anal. Calcd for $C_{18}H_{25}N_5O_3 \cdot 2HCl \cdot 2H_2O$: C, 46.2; H, 6.7; N, 15.0. Found: C, 46.3; H, 6.4; N, 15.0%.

***N*^{1}-(1,4-Dioxido-7,8,9,10-tetrahydronaphtho[2,1-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (18).**



77 **84** **85**

86 **87** **18**

1-Nitro-5,6,7,8-tetrahydro-2-naphthalenamine (84). A suspension of acetamide **77** (835 mg, 4.4 mmol) in 6 M HCl (50 mL) was stirred at 100 °C for 16 h. The suspension was cooled to 20 °C, diluted with water (50 mL) and the pH adjusted to 8 with dilute aqueous NH_3 solution. The mixture was extracted with DCM (3 × 50 mL), the combined organic fraction dried and the solvent evaporated. The residue was purified by

chromatography, eluting with 20% EtOAc/pet. ether, to give amine **84** (755 mg, 56%) as an orange solid: mp (EtOAc/pet. ether) 76–78 °C; ^{1}H NMR δ 6.98 (d, *J* = 8.4 Hz, 1 H, H-4), 6.58 (d, *J* = 8.4 Hz, 1 H, H-3), 4.73 (br s, 2 H, NH_2), 2.76–2.81 (m, 2 H, CH_2), 2.65–2.69 (m, 2 H, CH_2), 1.69–1.78 (m, 4 H, 2 × CH_2). Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3; N, 14.6. Found: C, 62.8; H, 6.1; N, 14.6%.

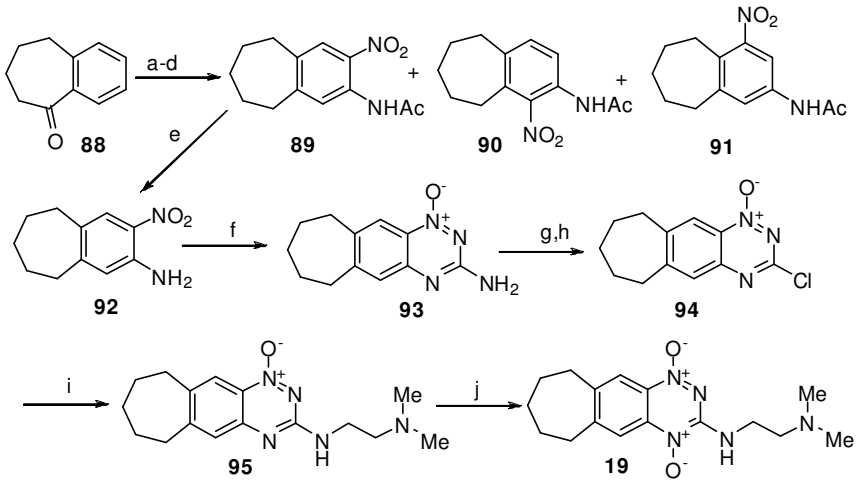
7,8,9,10-Tetrahydronaphtho[2,1-*e*][1,2,4]triazin-3-amine 1-Oxide (85). Method A. Reaction of nitroaniline **84** (0.73 g, 3.8 mmol) and cyanamide (0.63 g, 15.1 mmol) gave 1-oxide **85** (124 mg, 15%) as a yellow powder: mp (MeOH) 271 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 7.43 (d, *J* = 8.6 Hz, 1 H, H-6), 7.26 (d, *J* = 8.6 Hz, 1 H, H-5), 7.00 (br s, 2 H, NH_2), 3.36–3.40 (m, 2 H, CH_2), 2.75–2.80 (m, 2 H, CH_2), 1.67–1.75 (m, 4 H, 2 × CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 159.5, 149.5, 137.3, 133.8, 131.1, 129.9, 123.0, 29.8, 28.7, 22.5, 21.0. Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.1; H, 5.6; N, 25.9. Found: C, 61.0; H, 5.6; N, 26.0%.

3-Chloro-7,8,9,10-tetrahydronaphtho[2,1-*e*][1,2,4]triazine 1-Oxide (86). Method B. Reaction of 1-oxide **85** (114 mg, 0.5 mmol) and $NaNO_2$ (73 mg, 1.0 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **86** (95 mg, 76%) as a pale yellow solid: mp (MeOH) 165–167 °C; ^{1}H NMR δ 7.68 (d, *J* = 8.6 Hz, 1 H, H-5), 7.63 (d, *J* = 8.6 Hz, 1 H, H-6), 3.48–3.53 (m, 2 H, CH_2), 2.92–2.97 (m, 2 H, CH_2), 1.80–1.88 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 155.6, 148.3, 141.3, 138.6, 133.9, 132.8, 125.0, 31.1, 29.0, 22.6, 21.1. Anal. Calcd for $C_{11}H_{10}ClN_3O_2$: C, 56.0; H, 4.3; N, 17.8. Found: C, 56.3; H, 4.4; N, 17.6%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido-7,8,9,10-tetrahydronaphtho[2,1-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (87). Method C.** Reaction of chloride **86** (83 mg, 0.4 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (0.12 mL, 1.0 mmol) in DME (20 mL) gave 1-oxide **87** (84 mg, 84%) as a yellow solid: mp (MeOH) 151–153 °C; ^{1}H NMR δ 7.31–7.36 (m, 2 H, H-5, H-6), 5.75 (br s, 1 H, NH), 3.51–3.55 (m, 2 H, CH_2N), 3.45–3.49 (m, 2 H, CH_2), 2.72–2.83 (m, 2 H, CH_2), 2.57 (br dd, *J* = 6.0, 5.8 Hz, 2 H, CH_2N), 2.29 [s, 6 H, $N(CH_3)_2$], 1.75–1.82 (m, 4 H, 2 × CH_2); ^{13}C NMR δ 158.4, 149.8, 137.4, 134.7, 132.4, 129.1, 123.5, 57.7, 45.0 (2), 38.6, 30.7, 29.3, 23.1, 21.6. Anal. Calcd for $C_{15}H_{21}N_5O·½CH_3OH$: C, 61.4; H, 7.6; N, 23.1. Found: C, 61.2; H, 7.4; N, 23.4%.

***N*^{1}-(1,4-Dioxido-7,8,9,10-tetrahydronaphtho[2,1-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (18). Method D.** Oxidation of 1-oxide **87** (70 mg, 0.2 mmol) with CF_3CO_3H (ca. 2 mmol) gave 1,4-dioxide **18** (38 mg, 52%) as a red solid: mp (MeOH/EtOAc) 139–142 °C; ^{1}H NMR δ 8.06 (d, *J* = 8.9 Hz, 1 H, H-5), 7.51 (d, *J* = 8.9 Hz, 1 H, H-6), 7.38 (br s, 1 H, NH), 3.59–3.66 (m, 2 H, CH_2N), 3.49–3.55 (m, 2 H, CH_2), 2.83–2.92 (m, 2 H, CH_2), 2.61–2.65 (m, 2 H, CH_2N), 2.32 [s, 6 H, $N(CH_3)_2$], 1.80–1.88 (m, 4 H, 2 × CH_2). HRMS calcd for $C_{15}H_{22}N_5O_2$ (MH^+) *m/z* 304.1774, found 304.1772.

***N*^{1}-(1,4-Dioxido-7,8,9,10-tetrahydro-6*H*-cyclohepta[*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (19).**



3-Nitro-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-amine (92). A solution of $fHNO_3$ (7.5 mL) in cH_2SO_4 (50 mL) was added dropwise to a stirred suspension of 1-benzosuberone (**88**) (20 g, 125 mmol) in cH_2SO_4 (400 mL) at 0 °C. The mixture was stirred a further 30 min and poured into ice/water. The slurry was extracted with ether (2 × 200 mL), the combined organic fraction dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (10–30%) of EtOAc/pet. ether, to give 3-nitro-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (14.75 g, 58%) as a tan powder: mp (EtOAc/pet. ether) 81–82 °C; ^{1}H NMR δ 8.56 (d, *J* = 2.5 Hz, 1 H, H-4), 8.26 (dd, *J* = 8.3, 2.5 Hz, 1 H, H-2), 7.40 (d, *J* = 8.3 Hz, 1 H, H-1), 3.02–3.08 (m, 2 H, H-9), 2.78–2.82 (m, 2 H, H-6), 1.92–1.99 (m, 2 H, H-8), 1.83–1.90 (m, 2 H, H-7). A solution of the ketone (14.7 g, 71.6 mmol) in EtOAc/EtOH (1:1, 100 mL) and 20% HCl (50 mL) was stirred vigorously under H_2 (60 psi) for 5 days. The suspension was filtered through Celite, washed with EtOH (4 × 20 mL) and the solvent evaporated. The residue was dissolved in DCM, washed with dilute NH_3, dried, and the solvent evaporated. The residue was dissolved in dioxane (300 mL), cooled to 0 °C, and Ac_2O (13.5 mL, 143.2 mmol) added dropwise. The solution was stirred at 20 °C for 16 h, diluted with water (500 mL) and the suspension filtered. The filtrate was extracted with EtOAc (2 × 100 mL); the combined organic fraction washed with water (50 mL) and dilute aqueous NH_3 solution (2 × 50 mL), dried, and the solvent evaporated. The combined solids were purified by chromatography, eluting with 50% EtOAc/pet. ether, to give *N*-(6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-yl)acetamide (10.89 g, 75%) as a tan powder: mp 112–114 °C; ^{1}H NMR δ 7.20 (d, *J* = 2.2 Hz, 1 H, H-1), 7.15–7.21 (m, 2 H, H-3, NH), 7.02 (d, *J* = 8.0 Hz, 1 H, H-4), 2.71–2.77 (m, 4 H, H-5, H-9), 2.15 (s, 3 H, CH_3), 1.78–1.86 (m, 2 H, H-7), 1.56–1.66 (m, 4 H, H-6, H-8). A solution of KNO_3 (5.96 g, 58.9 mmol) in cH_2SO_4 (25 mL) was added dropwise to a stirred suspension of amide (10.89 g, 53.6 mmol) in cH_2SO_4 (160 mL) at 0 °C and the mixture stirred at 0–5 °C for 2 h. The mixture was poured into ice/water, stirred 30 min, filtered, washed with water (3 × 30 mL) and dried. The solid was purified by chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give (i) *N*-(3-nitro-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-yl)acetamide (**89**) (2.62 g, 20%) as a white solid: ^{1}H NMR δ 10.32 (br s, 1 H, NH), 8.52 (s, 1 H, H-4), 7.94 (s, 1 H, H-1), 2.84–2.88 (m, 2 H, H-5), 2.78–2.82 (m, 2 H, H-9), 2.27 (s, 3 H, CH_3), 1.80–1.87 (m, 2 H, H-7), 1.61–1.69 (m, 4 H, H-6, H-8); (ii) *N*-(1-nitro-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-yl)acetamide

(**90**) (0.85 g, 6%) as a white solid: ^{1}H NMR δ 7.81 (br d, *J* = 8.4 Hz, 1 H, H-4), 7.77 (br s, 1 H, NH), 7.23 (d, *J* = 8.4 Hz, 1 H, H-3), 2.82–2.86 (m, 2 H, H-5), 2.65–2.69 (m, 2 H, H-9), 2.27 (s, 3 H, CH_3), 1.80–1.88 (m, 2 H, H-7), 1.61–1.73 (m, 4 H, H-6, H-8); and (iii) *N*-(4-nitro-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-yl)acetamide (**91**) (6.91 g, 52%) as a white solid: ^{1}H NMR δ 7.69 (br d, *J* = 1.9 Hz, 1 H, H-3), 7.45 (d, *J* = 1.9 Hz, 1 H, H-1), 7.24 (br s, 1 H, NH), 2.84–2.88 (m, 2 H, H-5), 2.78–2.81 (m, 2 H, H-9), 2.19 (s, 3 H, CH_3), 1.81–1.87 (m, 2 H, H-7), 1.61–1.72 (m, 4 H, H-6, H-8).

A suspension of 3-nitroacetamide **89** (2.62 g, 10.6 mmol) in 5 M HCl (100 mL) was stirred at reflux temperature for 16 h. The suspension was cooled, diluted with water (100 mL), filtered, washed with water (3 × 10 mL) and dried to give nitroaniline **92** (1.96 g, 90%) as a yellow powder: mp 137–139 °C; ^{1}H NMR δ 7.83 (s, 1 H, H-4), 6.55 (s, 1 H, H-1), 5.96 (br s, 2 H, NH_2), 2.67–2.73 (m, 4 H, H-5, H-9), 1.76–1.81 (m, 2 H, H-7), 1.59–1.67 (m, 4 H, H-6, H-8); ^{13}C NMR δ 153.1, 143.2, 133.0, 129.8, 125.1, 118.5, 36.6, 35.4, 32.1, 28.8, 28.2. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.8; N, 13.6. Found: C, 64.0; H, 6.5; N, 13.5%.

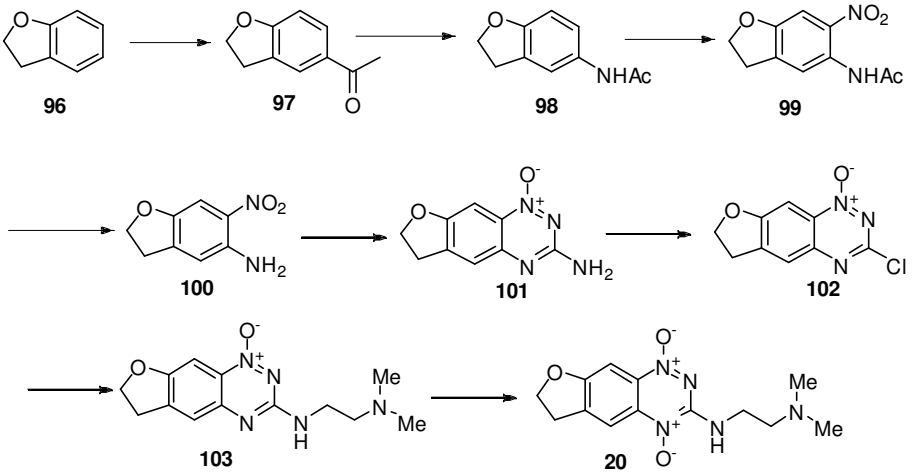
7,8,9,10-Tetrahydro-6*H*-cyclohepta[*g*][1,2,4]benzotriazin-3-amine 1-Oxide (93). Method A. Reaction of nitroaniline **92** (2.26 g, 11.0 mmol) and cyanamide (1.84 g, 43.8 mmol) gave 1-oxide **93** (0.26 g, 10%) as a yellow powder: mp (MeOH) 261–265 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.86 (s, 1 H, H-11), 7.29 (s, 1 H, H-5), 7.13 (br s, 2 H, NH_2), 2.84–2.90 (m, 4 H, H-6, H-10), 1.74–1.80 (m, 2 H, H-8), 1.58–1.67 (m, 4 H, H-7, H-9); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2, 152.8, 147.8, 141.2, 127.9, 124.3, 117.8, 35.6, 35.1, 31.3, 29.3, 28.0. Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.6; H, 6.1; N, 24.3. Found: C, 62.9; H, 6.2; N, 24.6%.

3-Chloro-7,8,9,10-tetrahydro-6*H*-cyclohepta[*g*][1,2,4]benzotriazine 1-Oxide (94). Method B. Reaction of 1-oxide **93** (252 mg, 1.1 mmol) and $NaNO_2$ (151 mg, 2.2 mmol), with subsequent reaction with DMF/$POCl_3$, gave chloride **94** (204 mg, 75%) as a pale yellow solid: mp (EtOAc/DCM) 146–148 °C; ^{1}H NMR δ 8.11 (s, 1 H, H-11), 7.67 (s, 1 H, H-5), 2.97–3.03 (m, 4 H, H-6, H-10), 1.85–1.91 (m, 2 H, H-8), 1.70–1.76 (m, 4 H, H-7, H-9); ^{13}C NMR δ 156.3, 155.2, 148.9, 146.7, 132.0, 126.8, 118.5, 36.9, 36.7, 31.9, 28.2, 28.1. Anal. Calcd for $C_{12}H_{12}ClN_3O$: C, 57.7; H, 4.8; N, 16.8. Found: C, 57.6; H, 4.9; N, 16.9%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido-7,8,9,10-tetrahydro-6*H*-cyclohepta[*g*][1,2,4]benzotriazin-3-yl)-1,2-ethanediamine (95). Method C.** Reaction of chloride **94** (178 mg, 0.7 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (0.23 mL, 2.1 mmol) in DME (30 mL) gave 1-oxide **95** (204 mg, 95%) as a yellow solid: mp (MeOH) 149–152 °C; ^{1}H NMR δ 7.96 (s, 1 H, H-11), 7.31 (s, 1 H, H-5), 5.84 (br s, 1 H, NH), 3.52–3.57 (m, 2 H, CH_2N), 2.85–2.90 (m, 4 H, H-6, H-10), 2.58 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.28 [s, 6 H, $N(CH_3)_2$], 1.79–1.85 (m, 2 H, H-8), 1.65–1.74 (m, 4 H, H-7, H-9); ^{13}C NMR δ 159.0, 153.4, 148.0, 142.1, 129.0, 125.0, 118.8, 57.6, 45.1 (2), 38.7, 36.8, 36.2, 32.0, 28.7, 28.4. Anal. Calcd for $C_{16}H_{23}N_5O·½H_2O$: C, 61.9; H, 7.8; N, 22.6. Found: C, 62.0; H, 7.8; N, 22.4%.

***N*^{1}-(1,4-Dioxido-7,8,9,10-tetrahydro-6*H*-cyclohepta[*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (19). Method D.** Oxidation of 1-oxide **95** (186 mg, 0.6 mmol) with CF_3CO_3H (6 mmol) gave (i) starting material **95** (43 mg, 23%) and (ii) 1,4-dioxide **19** (82 mg, 42%) as a red solid: mp (MeOH) 131–133 °C; ^{1}H NMR δ 8.03 (s, 1 H, H-11), 7.99 (s, 1 H, H-5), 7.36 (br s, 1 H, NH), 3.63 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.98–3.03 (m, 2 H, CH_2), 2.91–2.95 (m, 2 H, CH_2), 2.60 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.30 [s, 6 H, $N(CH_3)_2$], 1.82–1.89 (m, 2 H, H-8), 1.68–1.76 (m, 4 H, H-7, H-9); ^{13}C NMR δ 154.4, 149.7, 144.7, 137.1, 128.7, 119.8, 115.9, 57.5, 45.2 (2), 38.9, 37.0, 36.2, 31.8, 28.4, 28.2. Anal. Calcd for $C_{16}H_{23}N_5O_2 \cdot ¼CH_3OH$: C, 60.0; H, 7.4; N, 21.5. Found: C, 59.9; H, 7.0; N, 21.5%.

***N*^{1}-(1,4-Dioxido-6,7-dihydrofuro[3,2-*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (20).**



1-(2,3-Dihydro-1-benzofuran-5-yl)ethanone (97). $AlCl_3$ (12.4 g, 93 mmol) was added in small portions to a stirred solution of AcCl (12.6 mL, 178 mmol) in dry DCM (100 mL) at –10 °C and the mixture stirred until homogeneous (15 min). The solution was added, via a cannula, to a stirred solution of 2,3-dihydro-1-benzofuran (**96**) (11.2 g, 93 mmol) in dry DCM (100 mL) at –10 °C and the solution stirred for 30 min at –10 °C, and then poured into ice/cHCl (5:1 v/v, 1 L). The mixture was stirred for 2 h, extracted with DCM (3 × 100 mL), the combined organic fraction dried, and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (10–20%) of EtOAc/pet. ether, to give ketone **97** (14.23 g, 94%) as a white solid: mp 59–60 °C (lit.[8] mp 60 °C); ^{1}H NMR δ 7.85 (d, *J* = 1.9 Hz, 1 H, H-4), 7.79 (dd, *J* = 8.5, 1.9 Hz, 1 H, H-6), 6.80 (d, *J* = 8.5 Hz, 1 H, H-7), 4.65 (t, *J* = 8.7 Hz, 2 H, H-2), 3.18 (br t, *J* = 8.7 Hz, 2 H, H-3), 2.13 (s, 3 H, CH_3).

***N*-(2,3-Dihydro-1-benzofuran-5-yl)acetamide (98).** $NH_2OH \cdot HCl$ (7.3 g, 105 mmol) was added to a stirred solution of ketone **97** (14.2 g, 88 mmol) and pyridine (9.2 mL, 114 mmol) in MeOH (100 mL) and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between brine and EtOAc. The organic fraction was dried and the solvent evaporated to give crude 1-(2,3-dihydro-1-benzofuran-5-yl)ethanone oxime (15.3 g, 99%). HCl gas was bubbled through a solution of the oxime

(15.3 g, 86.5 mmol) in Ac_2O (16.3 mL, 173 mmol) and HOAc (54 mL, 865 mmol), and the solution stood at 20 °C for 24 h. The precipitate was poured into ice/water, stirred for 2 h, the solid filtered and washed with water and dried. The aqueous fraction was extracted with DCM (2 × 50 mL), the combined organic extract dried and the solvent evaporated. The slurry was treated with water (20 mL) and evaporated several times to remove Ac_2O. The combined solids were purified by chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give acetamide **98** (7.94 g, 52%) as a white solid: mp 92–93 °C (lit.[9] mp 93 °C); ^{1}H NMR δ 7.47 (br s, 1 H, H-4), 7.21 (br s, 1 H, NH), 6.99 (dd, *J* = 8.5, 2.1 Hz, 1 H, H-6), 6.69 (d, *J* = 8.5 Hz, 1 H, H-7), 4.55 (t, *J* = 8.7 Hz, 2 H, H-2), 3.18 (br t, *J* = 8.7 Hz, 2 H, H-3), 2.13 (s, 3 H, CH_3).

***N*-(6-Nitro-2,3-dihydro-1-benzofuran-5-yl)acetamide (99).** A solution of $fHNO_3$ (2.1 mL, 52 mmol) in HOAc (10 mL) was added dropwise to a stirred solution of acetamide **98** (6.58 g, 37 mmol) in HOAc (100 mL) at 15 °C. The mixture was stirred at 15 °C for 1 h, then poured into ice/water (800 mL) and stirred for 30 min. The precipitate was filtered, washed with water (3 × 30 mL) and dried. The solid was purified by chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give acetamide **99** (7.52 g, 91%) as a white solid: mp (EtOAc) 139–140 °C (lit.[10] mp 141–142 °C); ^{1}H NMR δ 10.19 (br s, 1 H, NH), 8.56 (s, 1 H, H-7), 7.53 (s, 1 H, H-4), 4.65 (t, *J* = 8.7 Hz, 2 H, H-2), 3.30 (dt, *J* = 8.7, 1.1 Hz, 2 H, H-3), 2.26 (s, 3 H, CH_3). Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.0; H, 4.5; N, 12.6. Found: C, 54.2; H, 4.6; N, 12.6%.

6-Nitro-2,3-dihydro-1-benzofuran-5-ylamine (100). A suspension of acetamide **99** (8.98 g, 40.4 mmol) and cHCl (50 mL) in EtOH (100 mL) was heated at reflux temperature for 2 h. The solution was cooled, carefully neutralized with aqueous NH_3 solution, and the resulting precipitate filtered and dried to give nitroaniline **100** (7.27 g, 100%) as an orange solid: mp (H_2O) 148–149 °C; ^{1}H NMR δ 7.44 (s, 1 H, H-7), 6.68 (t, *J* = 1.2 Hz, 1 H, H-4), 5.92 (br s, 2 H, NH_2), 4.54 (t, *J* = 8.4 Hz, 2 H, H-2), 3.18 (dt, *J* = 8.4, 1.2 Hz, 2 H, H-3); ^{13}C NMR δ 151.8, 140.8, 139.0, 131.2, 114.4, 103.4, 71.2, 30.0. Anal. Calcd for $C_8H_8N_2O_3$: C, 53.3; H, 4.5; N, 15.6. Found: C, 53.2; H, 4.5; N, 15.6%.

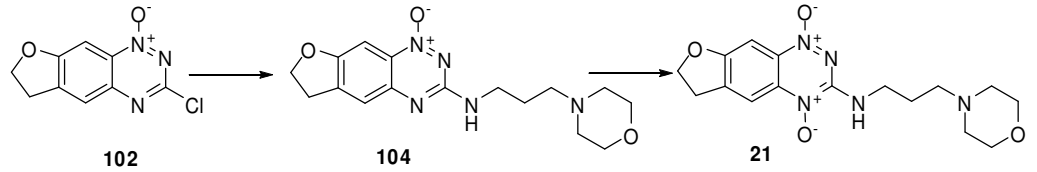
6,7-Dihydrofuro[3,2-*g*][1,2,4]benzotriazin-3-amine 1-Oxide (101). Method A. Reaction of nitroaniline **100** (7.27 g, 40.4 mmol) and cyanamide (6.79 g, 162 mmol) gave crude 1-oxide **101** (1.87 g, 23%) as a yellow powder: mp (MeOH/DCM) 241–246 °C. Anal. Calcd for $C_9H_8N_4O_2$: C, 52.9; H, 4.0. Found: C, 53.3; H, 3.8%. Also calcd for N, 26.4; found 27.4%.

3-Chloro-6,7-dihydrofuro[3,2-*g*][1,2,4]benzotriazine 1-Oxide (102). Method B. Reaction of 1-oxide **101** (825 mg, 4.0 mmol) and $NaNO_2$ (310 mg, 4.4 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **102** (283 mg, 31%) as a pale yellow solid: mp (EtOAc/DCM) 223–224 °C; ^{1}H NMR δ 7.75 (br t, *J* = 1.4 Hz, 1 H, H-5), 7.58 (s, 1 H, H-9), 4.81 (t, *J* = 8.4 Hz, 2 H, H-7), 3.49 (dt, *J* = 8.4, 1.4 Hz, 2 H, H-6); ^{13}C NMR δ 162.8, 154.9, 154.3, 144.4, 142.3, 123.8, 96.4, 72.9, 29.5. Anal. Calcd for $C_9H_6ClN_3O_2$: C, 48.3; H, 2.7; N, 18.8. Found: C, 48.5; H, 2.7; N, 18.9%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido-6,7-dihydrofuro[3,2-*g*][1,2,4]benzotriazin-3-yl)-1,2-ethanediamine (103). Method C.** Reaction of chloride **102** (270 mg, 1.2 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (0.40 mL, 3.6 mmol) in DME (30 mL) gave 1-oxide **103** (216 mg, 65%) as a yellow solid: mp (MeOH/EtOAc) 153–157 °C; ^{1}H NMR δ 7.50 (s, 1 H, H-9), 7.40 (t, *J* = 1.4 Hz, 1 H, H-5), 5.73 (br s, 1 H, NH), 4.67 (t, *J* = 8.3 Hz, 2 H, H-7), 3.48–3.53 (m, 2 H, CH_2N), 3.53 (dt, *J* = 8.3, 1.4 Hz, 2 H, H-6), 2.55 (dd, *J* = 6.1, 5.9 Hz, 2 H, CH_2N), 2.28 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 158.3, 158.2, 146.1, 140.6, 130.6, 121.8, 96.6, 71.9, 57.7, 45.1 (2), 38.8, 29.7. Anal. Calcd for $C_{13}H_{17}N_5O_2 \cdot ¼CH_3OH$: C, 56.2; H, 6.4; N, 24.7. Found: C, 56.1; H, 6.2; N, 25.0%.

***N*^{1}-(1,4-Dioxido-6,7-dihydrofuro[3,2-*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (20). Method D.** Oxidation of 1-oxide **103** (363 mg, 1.3 mmol) with CF_3CO_3H (ca. 13 mmol) gave 1,4-dioxide **20** (98 mg, 25%) as a red solid: mp (MeOH/EtOAc) 149–151 °C; ^{1}H NMR δ 8.12 (s, 1 H, H-5), 7.54 (s, 1 H, H-9), 7.27 (br s, 1 H, NH), 4.75 (t, *J* = 8.3 Hz, 2 H, H-7), 3.58–3.64 (m, 2 H, CH_2N), 3.43 (t, *J* = 8.2 Hz, 2 H, H-6), 2.62 (t, *J* = 6.0 Hz, 2 H, CH_2N), 2.31 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 159.9, 148.9, 141.6, 135.2, 130.9, 113.1, 97.4, 72.4, 57.5, 45.1 (2), 38.8, 29.7. Anal. Calcd for $C_{13}H_{17}N_5O_3 \cdot ¼H_2O$: C, 52.8; H, 6.0; N, 23.7. Found: C, 52.8; H, 5.7; N, 23.5%.

***N*-[3-(4-Morpholinyl)propyl]-6,7-dihydrofuro[3,2-*g*][1,2,4]benzotriazin-3-amine 1,4-Dioxide (21).**

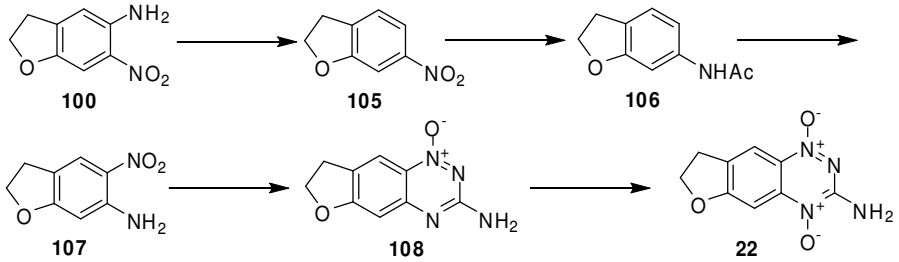


***N*-[3-(4-Morpholinyl)propyl]-6,7-dihydrofuro[3,2-*g*][1,2,4]benzotriazin-3-amine 1-Oxide (104). Method C.** Reaction of chloride **102** (850 mg, 3.8 mmol) and 3-(4-morpholinyl)propylamine (1.7 mL, 11.5 mmol) in DME (30 mL) gave 1-oxide **104** (1.08 g, 85%) as a yellow solid: mp 142–144 °C; ^{1}H NMR δ 7.52 (s, 1 H, H-9), 7.41 (s, 1 H, H-5), 5.97 (br s, 1 H, NH), 4.67 (t, *J* = 8.3 Hz, 2 H, H-7), 3.75 (t, *J* = 4.7 Hz, 4 H, 2 × CH_2O), 3.56 (dt, *J* = 6.4, 5.9 Hz, 2 H, CH_2N), 3.35 (dt, *J* = 8.3, 1.2 Hz, 2 H, H-6), 2.42–2.53 (m, 6 H, 2 × CH_2N, CH_2), 1.83 (p, *J* = 6.5 Hz, 2 H, CH_2); ^{13}C NMR δ 158.3, 151.4, 146.1, 140.5, 128.7, 121.8, 96.7, 71.9, 67.0 (2), 57.3, 53.8 (2), 40.8, 29.7, 25.4; MS (APCI) *m/z* 332 (MH^+, 100%). Anal. Calcd for $C_{16}H_{21}N_5O_3$: C, 58.0; H, 6.4; N, 21.1. Found: C, 58.0; H, 6.0; N, 21.2%.

***N*-[3-(4-Morpholinyl)propyl]-6,7-dihydrofuro[3,2-*g*][1,2,4]benzotriazin-3-amine 1,4-Dioxide (21). Method D.** Oxidation of 1-oxide **104** (1.06 g, 3.2 mmol) with CF_3CO_3H (ca. 32 mmol) gave 1,4-dioxide **21** (150 mg, 14%) as a red solid: mp 145–148 °C; ^{1}H NMR δ 8.26 (br s, 1 H, NH), 8.14 (s, 1 H, H-9), 7.53 (s, 1 H, H-5), 4.74 (t, *J* = 8.3 Hz, 2 H, H-7), 3.83 (t, *J* = 4.6 Hz, 4 H, 2 × CH_2O), 3.65 (br q, *J* = 5.9 Hz, 2 H, CH_2N), 3.43 (dt, *J* = 8.3, 1.2 Hz, 2 H, H-6), 2.58 (br t, *J* = 6.1 Hz, 2 H, CH_2), 2.53 (br s, 4 H, 2 × CH_2N), 1.88 (p, *J* = 6.2 Hz, 2 H, CH_2); ^{13}C NMR δ 159.8, 149.0, 141.5, 135.2, 130.8, 113.1, 97.4, 72.4, 66.8 (2), 57.7, 53.8 (2), 41.6, 29.7, 24.5; MS (APCI) *m/z* 348 (MH^+, 100%); HRMS

calcd for $C_{16}H_{22}N_5O_4$ (MH^+) *m/z* 348.1672, found 348.1666. Anal. Calcd for $C_{16}H_{21}N_5O_4 \cdot 0.4CH_2Cl_2$: C, 51.7; H, 5.8; N, 18.4. Found: C, 51.7; H, 5.4; N, 18.1%.

7,8-Dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-amine 1,4-Dioxide (22).



6-Nitro-2,3-dihydro-1-benzofuran (105). $NaNO_2$ (2.66 g, 39 mmol) was added in portions to a solution of nitroaniline **100** (6.5 g, 36 mmol) in water (150 mL) and cH_2SO_4 (60 mL) at 0 °C. The solution was stirred at 0 °C for 3 h, aqueous H_3PO_2 solution (50%, 13 mL) was added, and the mixture stood at 0 °C for 16 h and then at 20 °C for 4 days. The mixture was extracted with ether (3 × 300 mL), the combined organic layer washed with water (3 × 200 mL), dried and the solvent evaporated to yield dihydrobenzofuran **105** (4.34 g, 73%) as a red-brown solid: mp 71–72 °C; ^{1}H NMR δ 7.76 (dd, *J* = 8.1, 2.1 Hz, 1 H, H-5), 7.57 (d, *J* = 2.1 Hz, 1 H, H-7), 7.29 (d, *J* = 8.1 Hz, 1 H, H-4), 4.70 (t, *J* = 8.1 Hz, 2 H, H-2), 3.30 (t, *J* = 8.1 Hz, 2 H, H-3). Anal. Calcd for $C_8H_7NO_3$: C, 58.2; H, 4.3; N, 8.5. Found: C, 58.5; H, 4.3; N, 8.5%.

***N*-(2,3-Dihydro-1-benzofuran-6-yl)acetamide (106).** A mixture of dihydrobenzofuran **105** (4.34 g, 26.3 mmol) and PtO_2 (420 mg, 1.9 mmol) in THF (40 mL) and EtOH (200 mL) was stirred vigorously under H_2 (30 psi) for 16 h. The mixture was filtered through Celite, washed with THF and the solvent evaporated. The residue was purified by chromatography, eluting with 2% MeOH/DCM, to give 6-amino-2,3-dihydrobenzofuran (2.89 g, 81%), which was dissolved in dioxane (95 mL), Ac_2O (4.3 mL, 45.6 mmol) was added dropwise, and the solution stirred at 20 °C for 16 h. Water (200 mL) was added and the mixture extracted with DCM (3 × 120 mL). The combined organic layer was dried and the solvent evaporated to give acetamide **106** (3.56 g, 97%) as a yellow solid: mp 115–118 °C; ^{1}H NMR δ 7.26 (br s, 1 H, NH), 7.09 (d, *J* = 7.9 Hz, 1 H, H-4), 7.04 (s, 1 H, H-7), 6.91 (d, *J* = 7.9 Hz, 1 H, H-5), 4.56 (t, *J* = 8.6 Hz, 2 H, H-2), 3.15 (t, *J* = 8.1 Hz, 2 H, H-3), 2.14 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.3; N, 7.9. Found: C, 67.7; H, 6.4; N, 8.0%.

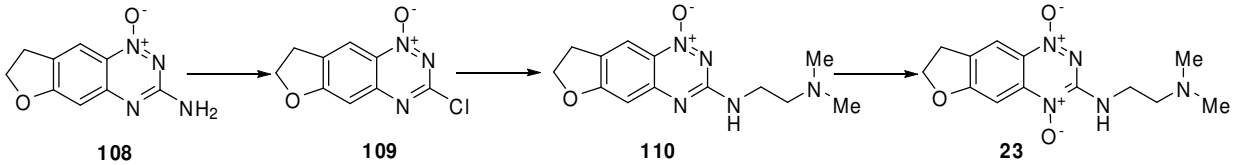
5-Nitro-2,3-dihydro-1-benzofuran-6-ylamine (107). A solution of $cHNO_3$ (70%, 1.3 mL, 21 mmol) in HOAc (5 mL) was added dropwise to a stirred solution of acetamide **106** (3.56 g, 20 mmol) in HOAc (15 mL) at 20 °C and the solution stirred at 20 °C for 2 h. The solution was poured into ice/water (150 mL) and the mixture stirred for 30 min. The precipitate was filtered, washed with water, and dried to give a pale-brown solid, which was dissolved in a mixture of EtOH (35 mL) and cHCl (16 mL) and stirred at reflux temperature for 2 h. The resulting solution was cooled, the solvent evaporated, the residue diluted with water (40 mL), and then made basic with dilute aqueous NH_3 solution. The precipitate was filtered, washed with water, and dried to give nitroaniline

107 (2.08 g, 90%) as a yellow solid, mp 140–142 °C; ^{1}H NMR δ 7.98 (s, 1 H, H-4), 6.25 (br s, 2 H, NH_2), 6.11 (s, 1 H, H-7), 4.64 (t, *J* = 8.0 Hz, 2 H, H-2), 3.13 (t, *J* = 7.8 Hz, 2 H, H-3); ^{13}C NMR δ 166.6, 147.7, 126.9, 122.8, 118.9, 96.1, 73.2, 27.9. Anal. Calcd for $C_8H_8N_2O_3$: C, 53.3; H, 4.5; N, 15.6. Found: C, 53.1; H, 4.6; N, 15.5%.

7,8-Dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-amine 1-Oxide (108). Method A. Reaction of nitroaniline **107** (4.0 g, 22.2 mmol) and cyanamide (7.2 g, 171 mmol) gave 1-oxide **108** (8.60 g, 96%) as a yellow powder: mp (DCM) 293–296 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.71 (s, 1 H, H-9), 6.23 (s, 1 H, H-5), 4.59 (t, *J* = 8.5 Hz, 2 H, H-7), 3.12 (t, *J* = 8.5 Hz, 2 H, H-8), NH_2 not observed; HRMS calcd for $C_9H_9N_4O_2$ (MH^+) *m/z* 205.0726, found 205.0725.

7,8-Dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-amine 1,4-Dioxide (22). Method D. Oxidation of 1-oxide **108** (500 mg, 2.45 mmol) with CH_3CO_3H (ca. 25 mmol) in HOAc (10 mL) gave 1,4-dioxide **22** (199 mg, 37%) as a red solid: mp > 300 °C (235–240 °C dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 8.06 (t, *J* = 1.6 Hz, 1 H, H-9), 7.86 (br s, 2 H, NH_2), 7.23 (s, 1 H, H-5), 4.77 (t, *J* = 8.3 Hz, 2 H, H-8), 3.30–3.60 (m, 2 H, H-7); HRMS (EI^+) calcd for $C_9H_8N_4O_3$ (M^+) *m/z* 220.0596, found 220.0601.

***N*^{1}-(1,4-Dioxido-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (23).**

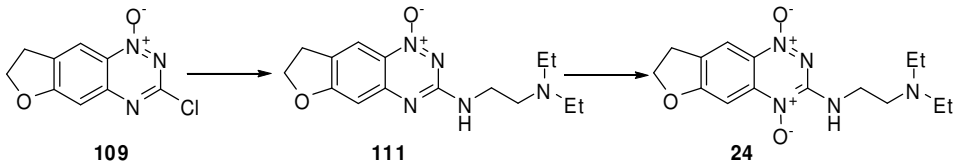


3-Chloro-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazine 1-Oxide (109). Method B. Reaction of 1-oxide **108** (5.0 g, 24.5 mmol) and $NaNO_2$ (3.38 g, 49.0 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **109** (3.76 g, 69%) as a yellow solid: mp (DCM) 203–205 °C; ^{1}H; ^{1}H NMR δ 8.23 (t, *J* = 1.6 Hz, 1 H, H-9), 7.20 (s, 1 H, H-5), 4.23 (t, *J* = 8.4 Hz, 2 H, H-7), 3.45 (dt, *J* = 8.4, 1.6 Hz, 2 H, H-8); ^{13}C NMR δ 167.2, 155.3, 150.0, 137.4, 129.1, 116.0, 102.7, 73.9, 28.3; HRMS calcd for $C_9H_7{}^{35}ClN_3O_2$ (MH^+) m/z 224.0227, found 224.0221.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-yl)-1,2-ethanediamine (110). Method C.** Reaction of chloride **109** (100 mg, 0.45 mmol) and *N*^{1},*N*^{1}-dimethylethane-1,2-diamine (0.2 mL, 1.8 mmol) in DME (10 mL) gave 1-oxide **110** (108 mg, 88%) as a yellow solid: mp 163–165 °C; ^{1}H NMR δ 8.09 (t, *J* = 1.4 Hz, 1 H, H-9), 6.79 (s, 1 H, H-5), 5.83 (br s, 1 H, NH), 4.72 (t, *J* = 8.3 Hz, 2 H, H-7), 3.52–3.56 (m, 2 H, CH_2N), 3.31 (dt, *J* = 8.3, 1.4 Hz, 2 H, H-8), 2.57 (t, *J* = 8.3 Hz, 2 H, CH_2N), 2.29 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 166.5, 159.3, 151.8, 129.3, 126.4, 116.6, 102.0, 72.9, 57.6, 45.0 (2), 38.6, 28.6. HRMS calcd for $C_{13}H_{18}N_5O_2$ (MH^+) *m/z* 276.1461, found 276.1461.

***N*^{1}-(1,4-Dioxido-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (23). Method D.** Oxidation of 1-oxide **110** (100 mg, 0.36 mmol) with CF_3CO_3H (ca. 4 mmol) gave 1,4-dioxide **23** (56 mg, 53%) as an orange solid: mp 186–189 °C; ^{1}H NMR δ 8.13 (t, *J* = 1.6 Hz, 1 H, H-9), 7.48 (br s, 2 H, H-5, NH), 4.81 (t, *J* = 8.3 Hz, 2 H, H-7), 3.62 (t, *J* = 6.0 Hz, 2 H, CH_2N), 3.37 (dt, *J* = 8.3, 1.6 Hz, 2 H, H-8), 2.62 (t, *J* = 8.3 Hz, 2 H, CH_2N), 2.30 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 167.2, 149.9, 140.6, 132.0, 117.9, 93.8, 87.9, 73.4, 57.5, 45.2 (2), 38.8, 28.5. HRMS calcd for $C_{13}H_{18}N_5O_3$ (MH^+) *m/z* 292.1410, found 292.1409.

***N*^{1}-(1,4-Dioxido-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-diethyl-1,2-ethanediamine (24).**

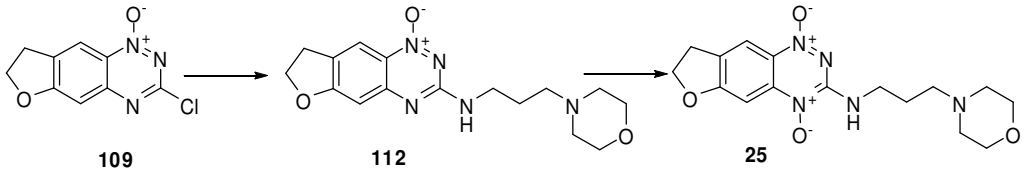


109 **111** **24**

***N*^{1},*N*^{1}-Diethyl-*N*^{2}-(1-oxido-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-yl)-1,2-ethanediamine (111). Method C.** Reaction of chloride **109** (250 mg, 1.12 mmol) and *N*^{1},*N*^{1}-diethylethane-1,2-diamine (0.63 mL, 4.48 mmol) in DME (25 mL) gave 1-oxide **111** (255 mg, 75%) as a yellow solid: mp (MeOH/EtOAc) 150–151 °C; ^{1}H NMR δ 8.09 (t, *J* = 1.6 Hz, 1 H, H-9), 6.79 (s, 1 H, H-5), 5.90 (br s, 1 H, NH), 4.72 (t, *J* = 8.3 Hz, 2 H, H-7), 3.48–3.54 (m, 2 H, CH_2N), 3.30 (dt, *J* = 8.3, 1.4 Hz, 2 H, H-8), 2.69–2.72 (m, 2 H, CH_2N), 2.59 (q, *J* = 7.1 Hz, 4 H, 2 × CH_2), 1.05 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3); ^{13}C NMR δ 166.5, 159.3, 151.8, 129.3, 126.3, 116.6, 102.1, 72.9, 51.3, 46.7 (2), 38.7, 28.6, 11.7 (2). Anal. Calcd for $C_{15}H_{21}N_5O_2 \cdot ¼CH_3OH$: C, 58.8; H, 7.1; N, 22.5. Found: C, 58.8; H, 6.7; N, 22.8%.

***N*^{1}-(1,4-Dioxido-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-diethyl-1,2-ethanediamine (24). Method D.** Oxidation of 1-oxide **111** (235 mg, 0.78 mmol) with CF_3CO_3H (ca. 2.8 mmol) gave 1,4-dioxide **24** (95 mg, 38%) as a red solid: mp 187–190 °C; ^{1}H NMR (CD_3OD) δ 8.16 (t, *J* = 1.7 Hz, 1 H, H-9), 7.30 (s, 1 H, H-5), 4.85 (t, *J* = 8.4 Hz, 2 H, H-7), 3.90–3.94 (m, 2 H, CH_2), 3.40–3.49 (m, 4 H, H-8, CH_2), 3.36 (q, *J* = 7.3 Hz, 4 H, CH_2), 1.37 (t, *J* = 7.3 Hz, 6 H, CH_3), NH not observed; ^{13}C NMR δ 169.8, 151.5, 142.3, 135.5, 128.2, 119.0, 93.7, 75.6, 51.7, 49.0 (2), 37.3, 29.4, 9.1 (2); HRMS calcd for $C_{15}H_{22}N_5O_3$ (MH^+) *m/z* 320.1723, found 320.1726.

***N*-[3-(4-Morpholinyl)propyl]-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-amine 1,4-Dioxide (25).**



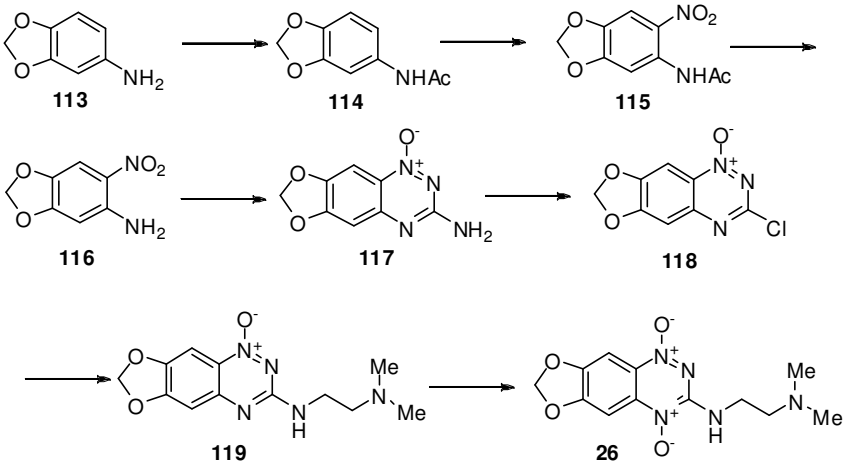
109 **112** **25**

***N*-[3-(4-Morpholinyl)propyl]-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-amine 1-Oxide (112). Method C.** Reaction of chloride **109** (250 mg, 1.1 mmol) and 3-(4-morpholinyl)propylamine (0.65 mL, 4.5 mmol) in DME (25 mL) gave 1-oxide **112** (340 mg, 92%) as a yellow solid: mp 152–154 °C; ^{1}H NMR δ 8.10 (t, *J* = 1.6 Hz, 1 H, H-9),

6.79 (s, 1 H, H-5), 6.09 (br s, 1 H, NH), 4.42 (t, J = 8.3 Hz, 2 H, H-7), 3.75 (t, J = 4.7 Hz, 4 H, 2 × CH_2O), 3.55–3.60 (m, 2 H, CH_2), 3.30 (dt, J = 8.3, 1.6 Hz, 2 H, H-7), 2.46–2.52 (m, 6 H, 2 × CH_2N, CH_2), 1.82 (p, J = 6.5 Hz, 2 H, CH_2); ^{13}C NMR δ 166.5, 159.4, 151.8, 129.2, 126.4, 116.6, 102.1, 72.9, 67.0 (2), 57.3, 53.8 (2), 40.8, 28.6, 25.3. Anal. Calcd for $C_{16}H_{21}N_5O_3$: C, 58.0; H, 6.4; N, 21.1. Found: C, 57.8; H, 6.2; N, 21.1%.

***N*-[3-(4-Morpholinyl)propyl]-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-amine 1,4-Dioxide (25). Method D.** Oxidation of 1-oxide **112** (313 mg, 0.95 mmol) with CF_3CO_3H (ca. 9.5 mmol) gave (i) starting material **112** (120 mg, 38%) and (ii) 1,4-dioxide **25** (68 mg, 21%) as a dark orange solid: mp 186–189 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.45 (t, J = 1.4 Hz, 1 H, H-9), 8.05 (s, 1 H, H-5), 7.21 (s, 1 H, NH), 4.77 (t, J = 8.3 Hz, 2 H, H-7), 3.33–3.64 (m, 8 H, 2 × CH_2O, H-8, CH_2), 2.36–2.45 (m, 6 H, 2 × CH_2N, CH_2), 1.77 (p, J = 6.6 Hz, 2 H, CH_2); HRMS calcd for $C_{16}H_{22}N_5O_4$ (MH^+) *m/z* 348.1672, found 348.1671.

***N*^{1}-(1,4-Dioxido[1,3]dioxolo[4,5-*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (26).**



***N*-(1,3-Benzodioxol-5-yl)acetamide (114).** Ac_2O (21.4 mL, 226 mmol) was added dropwise to a stirred solution of 3,4-methylendioxyaniline (**113**) (25.87 g, 189 mmol) in dioxane (200 mL) at 0 °C and the mixture was stirred at 16 °C for 16 h. MeOH (10 mL) was added to decompose excess Ac_2O and the solvent evaporated. The residue was dissolved in EtOAc (200 mL), dried and the solvent evaporated. The residue was filtered through a short column of silica, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give acetamide **114** (29.17 g, 86%) as a white solid: mp (EtOAc/pet. ether) 133–135 °C [lit.[11] mp (toluene) 138–139 °C]; ^{1}H NMR δ 7.09 (d, J = 1.8 Hz, 1 H, H-4), 7.06 (br s, 1 H, NH), 6.77 (dd, J = 8.3, 1.8 Hz, 1 H, H-6), 6.72 (d, J = 8.3 Hz, 1 H, H-7), 5.94 (s, 2 H, H-2), 2.14 (s, 3 H, CH_3).

***N*-(6-Nitro-1,3-benzodioxol-5-yl)acetamide (115).** A solution of 70% HNO_3 (15.5 mL, 244 mmol) in HOAc (40 mL) was added dropwise to a stirred solution of acetamide **114** (29.17 g, 163 mmol) in HOAc (150 mL) at 15–20 °C and the mixture stirred at 20 °C for 16 h. The precipitate was filtered, washed with water and dried to give nitroacetamide **115** (36.0 g, 99%) as a yellow powder: mp 207–208 °C (lit.[11] mp 212–213 °C); ^{1}H NMR

δ 10.78 (br s, 1 H, NH), 8.36 (s, 1 H, H-7), 7.66 (s, 1 H, H-4), 6.10 (s, 2 H, H-2), 2.27 (s, 3 H, CH_3).

6-Nitro-1,3-benzodioxol-5-amine (116). NaOMe (4.82 g, 89.2 mmol) was added to a stirred solution of nitroacetamide **115** (5.0 g, 22.3 mmol) in MeOH (100 mL) at reflux temperature and the mixture stirred at reflux temperature for 15 min. HOAc (25 mL, 446 mmol) was added to quench the reaction and the solvent evaporated. Toluene (2 × 50 mL) was added and the azeotrope evaporated. The residue was dissolved in DCM (100 mL) and filtered through a short column of silica to give nitroaniline **116** (3.25 g, 80%) as an orange solid: mp 199–201 °C [lit.[11] mp (*i*PrOH) 203–204 °C]; ^{1}H NMR δ 7.53 (s, 1 H, H-7), 6.30 (br s, 2 H, NH_2), 6.22 (s, 1 H, H-4), 5.98 (s, 2 H, H-2).

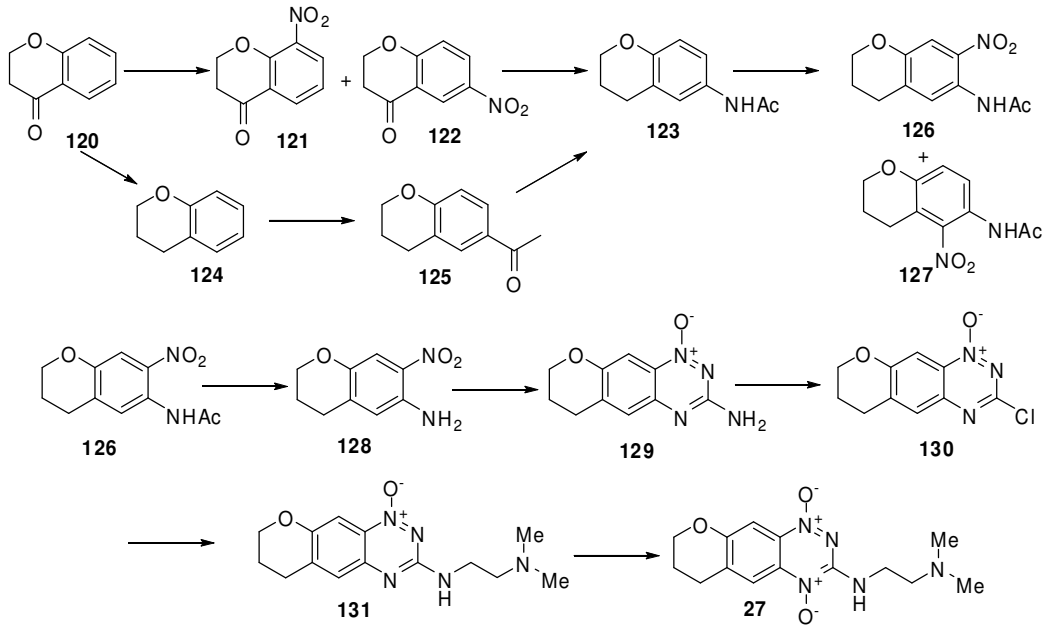
[1,3]Dioxolo[4,5-*g*][1,2,4]benzotriazin-3-amine 1-Oxide (117). Method A. Reaction of nitroaniline **116** (5.55 g, 30.5 mmol) and cyanamide (5.37 g, 122 mmol) gave 1-oxide **117** (3.24 g, 51%) as a yellow powder: mp (MeOH/DCM) 290–295 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.45 (s, 1 H, H-9), 7.00 (br s, 2 H, NH_2), 6.94 (s, 1 H, H-5), 6.23 (s, 2 H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 160.0, 155.1, 149.0, 147.0, 125.3, 103.1, 101.3, 95.8. Anal. Calcd for $C_8H_6N_4O_3$: C, 46.6; H, 2.9; N, 27.2. Found: C, 46.7; H, 2.9; N, 27.3%.

3-Chloro[1,3]dioxolo[4,5-*g*][1,2,4]benzotriazine 1-Oxide (118). Method B. Reaction of 1-oxide **117** (1.75 g, 8.5 mmol) with $NaNO_2$ (620 mg, 8.9 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **118** (753 mg, 39%) as a pale yellow solid: mp (DCM) 253–255 °C; ^{1}H NMR δ 7.69 (s, 1 H, H-9), 7.45 (s, 1 H, H-5), 6.42 (s, 2 H, H-7); ^{13}C NMR δ 156.6, 154.2, 152.0, 147.8, 130.6, 104.7, 103.1, 95.7. Anal. Calcd for $C_8H_4ClN_3O_3$: C, 42.6; H, 1.8; N, 18.6. Found: C, 42.7; H, 1.7; N, 18.5%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido[1,3]dioxolo[4,5-*g*][1,2,4]benzotriazin-3-yl)-1,2-ethanediamine (119). Method C.** Reaction of chloride **118** (359 mg, 1.6 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (0.52 mL, 4.8 mmol) gave 1-oxide **119** (390 mg, 88%) as a yellow solid: mp (MeOH/DCM) 192–194 °C; ^{1}H NMR δ 7.45 (s, 1 H, H-9), 7.35 (br s, 1 H, NH), 6.96 (s, 1 H, H-5), 6.23 (s, 2 H, H-7), 3.35–3.39 (m, 2 H, CH_2N), 2.42 (t, *J* = 6.7 Hz, 2 H, CH_2N), 2.18 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 158.9, 155.2, 148.7, 146.9, 125.3, 103.2, 101.6, 95.9, 57.8, 45.2 (2), 38.6. Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 52.0; H, 5.5; N, 25.3. Found: C, 52.1; H, 5.5; N, 25.3%.

***N*^{1}-(1,4-Dioxido[1,3]dioxolo[4,5-*g*][1,2,4]benzotriazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (26). Method D.** Oxidation of 1-oxide **119** (374 mg, 1.4 mmol) with CF_3CO_3H (ca. 14 mmol) gave 1,4-dioxide **26** (52 mg, 13%) as a red solid: mp (MeOH/EtOAc) 175–179 °C; ^{1}H NMR δ 7.60 (s, 1 H, H-9), 7.59 (s, 1 H, H-5), 7.35 (br s, 1 H, NH), 6.21 (s, 2 H, H-7), 3.61 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.62 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.31 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 155.9, 149.7, 148.9, 137.8, 126.7, 103.5, 97.9, 94.1, 57.4, 45.1 (2), 38.8. Anal. Calcd for $C_{12}H_{15}N_5O_4 \cdot ½CH_3OH$: C, 48.5; H, 5.5; N, 22.6. Found: C, 48.7; H, 5.3; N, 22.6%.

***N*^{1}-(1,4-Dioxido-7,8-dihydro-6*H*-chromeno[6,7-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (27).**



6-Nitro-2,3-dihydro-4*H*-chromen-4-one (122). A solution of KNO_3 (2.25 g, 22.3 mmol) in cH_2SO_4 (10 mL) was added dropwise to a stirred solution of 4-chromanone (**120**) (3.0 g, 20.2 mmol) in cH_2SO_4 (50 mL) at 0 °C and the mixture stirred at 0 °C for 2 h. The mixture was poured into ice/water (500 mL), stirred 30 min and the precipitate filtered. The solid was washed with water (3 × 10 mL) and dried. The solid was purified by chromatography, eluting with 20% EtOAc/pet. ether, to give (i) 8-nitro-2,3-dihydro-4*H*-chromen-4-one (**121**) (369 mg, 9%) as a white solid: mp (EtOAc/pet. ether) 120–121 °C; ^{1}H NMR δ 8.17 (dd, *J* = 7.8, 1.8 Hz, 1 H, H-7), 8.10 (dd, *J* = 8.0, 1.8 Hz, 1 H, H-5), 7.12 (dd, *J* = 8.0, 7.8 Hz, 1 H, H-6), 4.73 (dd, *J* = 6.5, 6.4 Hz, 2 H, H-2), 2.95 (br t, *J* = 6.5 Hz, 2 H, H-3). Anal. Calcd for $C_9H_7NO_4$: C, 56.0; H, 3.7; N, 7.3. Found: C, 56.1; H, 3.7; N, 7.3%; and (ii) 6-nitro-2,3-dihydro-4*H*-chromen-4-one (**122**) (3.17 g, 81%) as a white solid: mp (EtOAc/pet. ether) 169–171 °C; ^{1}H NMR δ 8.78 (d, *J* = 2.8 Hz, 1 H, H-5), 8.32 (dd, *J* = 9.1, 2.8 Hz, 1 H, H-7), 7.11 (d, *J* = 9.1 Hz, 1 H, H-8), 4.67 (dd, *J* = 6.6, 6.4 Hz, 2 H, H-2), 2.91 (dd, *J* = 6.6, 6.4 Hz, 2 H, H-3); ^{13}C NMR δ 189.4, 165.7, 142.1, 130.3, 123.7, 120.8, 119.3, 67.6, 37.1. Anal. Calcd for $C_9H_7NO_4$: C, 56.0; H, 3.7; N, 7.3. Found: C, 56.1; H, 3.7; N, 7.4%.

***N*-(3,4-Dihydro-2*H*-chromen-6-yl)acetamide (123).** A mixture of nitrochromanone **122** (2.0 g, 13.4 mmol) and Pd/C (5%, 100 mg) in EtOH/EtOAc (4:1, 150 mL), water (10 mL), and cHCl (1 mL) was stirred under H_2 (60 psi) for 16 h. The mixture was filtered through Celite, washed with EtOH (3 × 25 mL) and the solvent evaporated. The residue was partitioned between dilute aqueous NH_3 solution and DCM, the organic fraction was dried, and the solvent was evaporated. The residue was dissolved in dry dioxane (100 mL) and Ac_2O (2.8 mL, 29.4 mmol) added dropwise. The solution was stirred at 20 °C for 16 h, diluted with water and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give acetamide **123** (2.09 g, 70%) as a white solid: mp (EtOAc/pet. ether) 111–113 °C [lit.[12] mp (EtOH) 118 °C]; ^{1}H NMR δ 7.28 (d, *J* = 2.2 Hz, 1 H, H-5), 7.02 (dd, *J* = 8.6, 2.2 Hz,

1 H, H-7), 6.72 (d, *J* = 8.6 Hz, 1 H, H-8), 4.15 (br dd, *J* = 5.2, 5.0 Hz, 2 H, H-2), 2.77 (br t, *J* = 6.5 Hz, 2 H, H-4), 2.13 (s, 3 H, CH_3), 1.95–2.02 (m, 2 H, H-3).

Alternative Preparation of *N*-(3,4-Dihydro-2*H*-chromen-6-yl)acetamide (123). A solution of 4-chromanone (**120**) (14.82 g, 100 mmol) in HOAc (50 mL) was added to a stirred suspension of Zn dust (10 eq. w/w, 148 g) in HOAc (200 mL) and the mixture stirred at 100 °C for 16 h. The mixture was cooled, filtered, washed with HOAc (3 × 100 mL) and the solvent from the combined filtrate evaporated. The residue was suspended in water (200 mL) and the suspension made basic with NaOH, extracted with EtOAc (3 × 100 mL), the combined extracts dried and the solvent evaporated to give chroman (**124**) (11.83 g, 88%) as a white solid.

$AlCl_3$ (11.8 g, 88.2 mmol) was added in small portions to a stirred solution of AcCl (11.9 mL, 167.5 mmol) in dry DCM (250 mL) at –10 °C and the mixture stirred until homogeneous (15 min). The solution was added, via a cannula, to a stirred solution of chroman (**124**) (11.8 g, 88.2 mmol) in dry DCM (200 mL) at –10 °C and the solution stirred for 30 min at –10 °C and then poured into ice/cHCl (5:1 v/v, 1.5 L). The mixture was stirred for 2 h, extracted with DCM (3 × 100 mL), the combined organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (10–20%) of EtOAc/pet. ether, to give 1-(3,4-dihydro-2*H*-chromen-6-yl)ethanone (**125**) (12.45 g, 80%) as a white solid: ^{1}H NMR δ 7.68–7.22 (m, 2 H, H-5, H-7), 6.82 (d, *J* = 9.2 Hz, 1 H, H-8), 4.24 (br dd, *J* = 5.3, 5.2 Hz, 2 H, H 2), 2.83 (br t, *J* = 6.5 Hz, 2 H, H-4), 2.53 (s, 3 H, CH_3), 2.00–2.06 (m, 2 H, H-3).

Hydroxylamine·HCl (2.9 g, 41.9 mmol) was added to a stirred solution of ketone 230 (6.15 g, 34.9 mmol) and pyridine (3.7 mL, 45.4 mmol) in MeOH (30 mL) and the mixture stirred at 20 °C for 16 h. The solvent was evaporated and the residue partitioned between brine and EtOAc. The organic fraction was dried and the solvent evaporated to give crude 1-(3,4-dihydro-2*H*-chromen-6-yl)ethanone oxime (6.3 g, 94%). HCl gas was bubbled through a solution of oxime (6.3 g, 32.5 mmol) in Ac_2O (6.1 mL, 65 mmol) and HOAc (40 mL, 650 mmol), and the solution stood at 20 °C for 24 h. The precipitate was poured into ice/water, stirred for 2 h, the solid filtered and washed with water and dried. The aqueous fraction was extracted with DCM (2 × 50 mL), the combined extract dried and the solvent evaporated. The slurry was treated with water (20 mL) and evaporated several times to remove Ac_2O. The combined solids were purified by chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give acetamide **123** (3.74 g, 59%) as a white solid: spectroscopically identical to the sample prepared above.

Nitration of *N*-(3,4-Dihydro-2*H*-chromen-6-yl)acetamide (123). A solution of $fHNO_3$ (2.5 mL, 63.2 mmol) in HOAc (10 mL) was added dropwise to a stirred solution of acetamide **123** (8.63 g, 45.1 mmol) in HOAc (100 mL) at 15 °C. The mixture was stirred at 15 °C for 1 h, then poured into ice/water (800 mL) and stirred for 30 min. The precipitate was filtered, washed with water (3 × 30 mL) and dried. The solid was purified by chromatography, eluting with a gradient (30–100%) of EtOAc/pet. ether, to give (i) *N*-(7-nitro-3,4-dihydro-2*H*-chromen-6-yl)acetamide (**126**) (2.49 g, 23%) as a white solid: mp (EtOAc) 141–143 °C [lit.[13] mp (EtOH) 139–142 °C]; ^{1}H NMR δ 10.0 (br s, 1 H, NH), 8.40 (s, 1 H, H-8), 7.61 (s, 1 H, H-5), 4.21 (br t, *J* = 5.2 Hz, 2 H, H-2), 2.87 (br t, *J* = 6.5 Hz, 2 H, H-4), 2.24 (s, 3 H, CH_3), 2.00–2.06 (m, 2 H, H-3); and (ii) *N*-(5-nitro-3,4-

dihydro-2*H*-chromen-6-yl)acetamide (**127**) (2.08 g, 19%) as a white solid: mp (EtOAc) 191–192 °C [lit.[13] mp (EtOH) 177–180 °C]; ^{1}H NMR δ 8.07 (br s, 1 H, NH), 7.83 (br d, *J* = 9.1 Hz, 1 H, H-7), 6.99 (d, *J* = 9.1 Hz, 1 H, H-8), 4.20 (br t, *J* = 5.2 Hz, 2 H, H-2), 2.80 (br t, *J* = 6.5 Hz, 2 H, H-4), 2.16 (s, 3 H, CH_3); 1.96–2.02 (m, 2 H, H-3); and (iii) *N*-(8-nitro-3,4-dihydro-2*H*-chromen-6-yl)acetamide (0.85g, 8%), as a white solid: mp (EtOAc) 200–201 °C [lit.[13] mp (EtOH) 188–191 °C]; ^{1}H NMR δ 7.67 (br s, 1 H, H-6), 7.61 (br s, 1 H, H-5), 7.16 (br s, 1 H, NH), 4.30 (br t, *J* = 5.2 Hz, 2 H, H-2), 2.86 (br t, *J* = 6.5 Hz, 2 H, H-4), 2.17 (s, 3 H, CH_3); 2.04–2.10 (m, 2 H, H-3).

7-Nitro-3,4-dihydro-2*H*-chromen-6-ylamine (128). A suspension of acetamide **126** (2.49 g, 10.5 mmol) and cHCl (10 mL) in EtOH (50 mL) was heated at reflux temperature for 16 h. The solution was cooled, carefully neutralized with aqueous NH_3 solution, extracted with EtOAc (2 × 50 mL), the combined organic fraction dried and the solvent evaporated to give nitroaniline **128** (2.05 g, 100%) as an orange solid: mp (EtOAc) 145–148 °C [lit.[13] mp (H_2O) 139–140 °C]; ^{1}H NMR δ 7.54 (s, 1 H, H-8), 6.50 (s, 1 H, H-5), 5.62 (br s, 2 H, NH_2), 4.14 (br t, *J* = 5.2 Hz, 2 H, H-2), 2.77 (br t, *J* = 6.5 Hz, 2 H, H-4), 1.95–2.02 (m, 2 H, H-3).

7,8-Dihydro-6*H*-chromeno[6,7-*e*][1,2,4]triazin-3-amine 1-Oxide (129). Method A. Reaction of nitroaniline **128** (2.05 g, 10.6 mmol) and cyanamide (1.78 g, 42.3 mmol) gave 1-oxide **129** (1.30 g, 56%) as a yellow powder: mp (MeOH/DCM) 280–283 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.32 (s, 1 H, H-10), 7.31 (s, 1 H, H-5), 6.96 (br s, 2 H, NH_2), 4.22 (dd, *J* = 5.3, 5.2 Hz, 2 H, H-8), 2.95 (br t, *J* = 6.3 Hz, 2 H, H-6), 1.92–1.98 (m, 2 H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 159.1, 152.2, 143.4, 135.8, 128.7, 125.7, 102.6, 66.5, 25.0, 21.0. Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.0; H, 4.6; N, 25.7. Found: C, 55.1; H, 4.6; N, 25.5%.

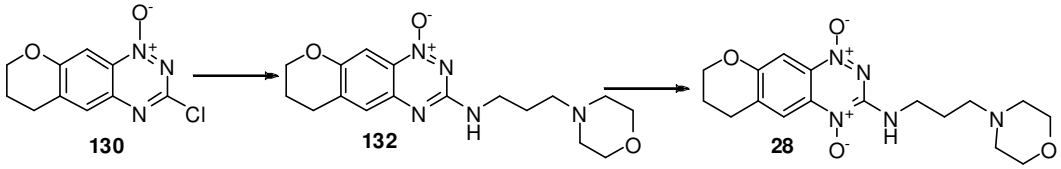
3-Chloro-7,8-dihydro-6*H*-chromeno[6,7-*e*][1,2,4]triazine 1-Oxide (130). Method B. Reaction of 1-oxide **129** (963 mg, 4.4 mmol) and $NaNO_2$ (320 mg, 4.6 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **130** (939 mg, 66%) as a pale yellow solid: mp (EtOAc/DCM) 192–195 °C; ^{1}H NMR δ 7.64–7.67 (m, 2 H, H-5, H-10), 4.34–4.39 (m, 2 H, H-8), 3.08 (br dd, *J* = 6.6, 6.1 Hz, 2 H, H-6), 2.09–2.15 (m, 2 H, H-7); ^{13}C NMR δ 157.6, 154.1, 141.9, 136.7, 133.2, 128.3, 104.0, 67.4, 26.0, 21.1. Anal. Calcd for $C_{10}H_8ClN_3O_2$: C, 50.5; H, 3.4; N, 17.7. Found: C, 50.8; H, 3.3; N, 17.7%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido-7,8-dihydro-6*H*-chromeno[6,7-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (131). Method C.** Reaction of chloride **130** (341 mg, 1.4 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (0.47 mL, 4.3 mmol) gave 1-oxide **131** (343 mg, 83%) as a yellow solid: mp (MeOH/EtOAc) 150–152 °C; ^{1}H NMR δ 7.58 (s, 1 H, H-10), 7.30 (s, 1 H, H-5), 5.79 (br s, 1 H, NH), 4.25 (br dd, *J* = 5.3, 5.2 Hz, 2 H, H-8), 3.51–3.56 (m, 2 H, CH_2N), 2.96 (br t, *J* = 6.0 Hz, 2 H, H-6), 2.60 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.31 [s, 6 H, $N(CH_3)_2$], 2.02–2.09 (m, 2 H, H-7); ^{13}C NMR δ 158.0, 152.9, 143.6, 135.1, 130.0, 126.1, 104.3, 66.9, 57.6, 45.0 (2), 38.7, 25.9, 21.7. Anal. Calcd for $C_{14}H_{19}N_5O_2 \cdot ¼H_2O$: C, 57.2; H, 6.7; N, 23.8. Found: C, 57.1; H, 6.5; N, 23.9%.

***N*^{1}-(1,4-Dioxido-7,8-dihydro-6*H*-chromeno[6,7-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (27). Method D.** Oxidation of 1-oxide **131** (270 mg, 0.9 mmol) with

CF_3CO_3H (ca. 9 mmol) gave 1,4-dioxide **27** (71 mg, 22%) as a red solid: mp (MeOH/EtOAc) 152–154 °C; ^{1}H NMR δ 7.99 (s, 1 H, H-5), 7.61 (s, 1 H, H-10), 7.27 (br s, 1 H, NH), 4.30 (br dd, *J* = 5.3, 5.2 Hz, 2 H, H-8), 3.62 (br t, *J* = 5.9 Hz, 2 H, CH_2N), 3.05 (br t, *J* = 6.3 Hz, 2 H, H-6), 2.62 (t, *J* = 6.0 Hz, 2 H, CH_2N), 2.31 [s, 6 H, $N(CH_3)_2$], 2.05–2.12 (m, 2 H, H-7); ^{13}C NMR δ 154.7, 148.7, 136.2, 133.2, 130.1, 117.4, 105.2, 67.1, 57.6, 45.1 (2), 38.8, 26.1, 21.3; HRMS calcd for $C_{14}H_{19}N_5O_3$ (MH^+) *m/z* 3060.1566, found 306.1569. Anal. Calcd for $C_{14}H_{19}N_5O_3 \cdot ¾H_2O$: C, 52.7; H, 6.5; N, 22.0. Found: C, 53.0; H, 5.9, N, 21.6%.

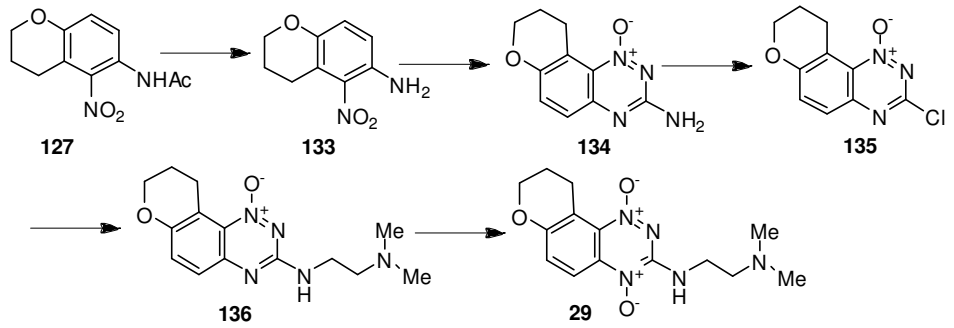
_N_-[3-(4-Morpholinyl)propyl]-7,8-dihydro-6_H_-chromeno[6,7-_e_][1,2,4]triazin-3-amine 1,4-Dioxide (28).



_N_-[3-(4-Morpholinyl)propyl]-7,8-dihydro-6_H_-chromeno[6,7-_e_][1,2,4]triazin-3-amine 1-Oxide (132). Method C. Reaction of chloride **130** (380 mg, 1.6 mmol) and 3-(4-morpholinyl)propylamine (0.71 mL, 4.8 mmol) gave 1-oxide **132** (514 mg, 93%) as a yellow solid: mp (MeOH/EtOAc) 151–152 °C; ^{1}H NMR δ 7.60 (s, 1 H, H-10), 7.30 (s, 1 H, H-5), 6.00 (br s, 1 H, NH), 4.26 (br dd, *J* = 5.3, 5.2 Hz, 2 H, H-8), 3.75 (br t, *J* = 4.7 Hz, 4 H, 2 × CH_2O), 3.55 (dt, *J* = 6.3, 5.9 Hz, 2 H, CH_2N), 2.97 (br t, *J* = 6.3 Hz, 2 H, H-6), 2.45–2.52 (m, 6 H, 3 × CH_2N), 2.02–2.08 (m, 2 H, H-7), 1.79–1.86 (m, 2 H, CH_2); ^{13}C NMR δ 158.1, 152.9, 143.6, 135.1, 130.0, 126.1, 104.4, 67.0 (2), 66.9, 57.3 (2), 53.8, 40.7, 25.9, 25.3, 21.7. Anal. Calcd for $C_{17}H_{23}N_5O_3$: C, 59.1; H, 6.7; N, 20.3. Found: C, 59.4; H, 6.6; N, 20.3%.

_N_-[3-(4-Morpholinyl)propyl]-7,8-dihydro-6_H_-chromeno[6,7-_e_][1,2,4]triazin-3-amine 1,4-Dioxide (28). Method D. Oxidation of 1-oxide **132** (509 mg, 1.5 mmol) with CF_3CO_3H (ca. 15 mmol) gave (i) starting material **132** (80 mg, 16%) and (ii) 1,4-dioxide **28** (75 mg, 16%) as a red solid: mp (MeOH/EtOAc) 173–176 °C; ^{1}H NMR δ 8.33 (br t, *J* = 4.9 Hz, 1 H, NH), 8.01 (s, 1 H, H-5), 7.62 (s, 1 H, H-10), 4.31 (br dd, *J* = 5.3, 5.2 Hz, 2 H, H-8), 3.83 (br t, *J* = 4.6 Hz, 4 H, 2 × CH_2O), 3.62–3.68 (m, 2 H, CH_2N), 3.03–3.08 (m, 2 H, H-6), 2.58 (br dd, *J* = 6.2, 6.0 Hz, 2 H, CH_2N), 2.50 (m, 4 H, 2 × CH_2N), 2.07–2.13 (m, 2 H, H-7), 1.84–1.91 (m, 2 H, CH_2); ^{13}C NMR δ 154.5, 148.7, 136.1, 133.2, 129.9, 117.3, 105.2, 67.1, 66.9 (2), 57.8, 53.8 (2), 41.6, 26.1, 24.4, 21.3. Anal. Calcd for $C_{17}H_{23}N_5O_3 \cdot ¼H_2O$: C, 55.8; H, 6.5; N, 19.1. Found: C, 55.8; H, 6.5, 18.8%.

_N_^{1}-(1,4-Dioxido-9,10-dihydro-8_H_-chromeno[6,5-_e_][1,2,4]triazin-3-yl)-_N_^{2},_N_^{2}-dimethyl-1,2-ethanediamine (29).



5-Nitro-3,4-dihydro-2*H*-chromen-6-ylamine (133). A solution of acetamide **127** (1.24 g, 5.3 mmol) in 95% EtOH (50 mL) and NaOH (0.63 g, 15.7 mmol) was stirred at reflux temperature for 16 h. The mixture was cooled and the solvent evaporated. The residue was partitioned between Et_2O and water, the organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with 20% EtOAc/pet. ether, to give nitroaniline[13] **133** (1.54 g, 85%) as red oil: ^{1}H NMR δ 6.85 (d, *J* = 9.0 Hz, 1 H, H-8), 6.60 (d, *J* = 9.0 Hz, 1 H, H-7), 4.90 (br s, 2 H, NH_2), 4.13 (dd, *J* = 5.3, 5.1 Hz, 2 H, H-2), 2.90 (br t, *J* = 6.5 Hz, 2 H, H-4), 1.91–1.96 (m, 2 H, H-3).

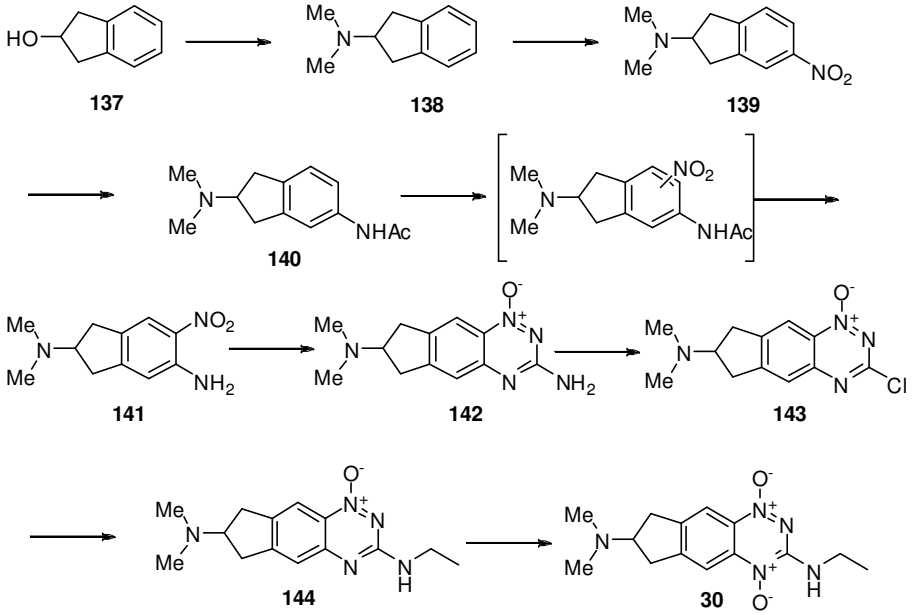
9,10-Dihydro-8*H*-chromeno[6,5-*e*][1,2,4]triazin-3-amine 1-Oxide (134). Method A. Reaction of nitroaniline **133** (1.52 g, 7.8 mmol) and cyanamide (1.32 g, 31.3 mmol) gave (i) starting nitroaniline **133** (470 mg, 31%) and (ii) amine **134** (246 mg, 14%) as a yellow powder: mp (MeOH/DCM) 275–279 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 7.26–7.31 (m, 2 H, H-5, H-6), 6.90 (br s, 2 H, NH_2), 4.12–4.17 (m, 2 H, H-8), 3.30–3.33 (m, 2 H, H-10), 1.87–1.93 (m, 2 H, H-9); ^{13}C NMR [$(CD_3)_2SO$] δ 159.0, 151.2, 146.3, 129.5, 128.0, 124.6, 113.5, 65.3, 24.4, 21.5. Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.0; H, 4.6; N, 25.6. Found: C, 55.0; H, 4.6; N, 25.6%.

3-Chloro-9,10-dihydro-8*H*-chromeno[6,5-*e*][1,2,4]triazine 1-Oxide (135). Method B. Reaction of 1-oxide **134** (231 mg, 1.0 mmol) and $NaNO_2$ (134 mg, 1.9 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **135** (63 mg, 27%) as a pale yellow solid: mp (EtOAc) 160–162 °C; ^{1}H NMR δ 7.70 (d, *J* = 9.2 Hz, 1 H, H-6), 7.47 (d, *J* = 9.2 Hz, 1 H, H-5), 4.29 (br dd, *J* = 5.2, 5.2 Hz, 2 H, H-8), 3.54 (t, *J* = 6.5 Hz, 2 H, H-10), 2.03–2.09 (m, 2 H, H-9); ^{13}C NMR δ 156.6, 154.0, 145.0, 133.9, 129.5, 126.9, 114.0, 66.4, 24.6, 21.6. Anal. Calcd for $C_{10}H_8ClN_3O_2$: C, 50.5; H, 3.4; N, 17.7. Found: C, 50.7; H, 3.4; N, 17.8%.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(1-oxido-9,10-dihydro-8*H*-chromeno[6,5-*e*][1,2,4]triazin-3-yl)-1,2-ethanediamine (136). Method C.** Reaction of chloride **135** (47 mg, 0.2 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (65 μL, 0.6 mmol) gave 1-oxide **136** (55 mg, 95%) as a pale yellow solid: mp (MeOH/EtOAc) 119–120 °C; ^{1}H NMR δ 7.35 (d, *J* = 9.2 Hz, 1 H, H-6), 7.23 (d, *J* = 9.2 Hz, 1 H, H-5), 5.66 (br s, 1 H, NH), 4.19 (br dd, *J* = 5.1, 5.0 Hz, 2 H, H-8), 3.47–3.53 (m, 4 H, H-10, CH_2N), 2.54 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.27 [s, 6 H, $N(CH_3)_2$], 1.97–2.04 (m, 2 H, H-9); ^{13}C NMR δ 158.0, 152.2, 146.7, 130.3, 128.4, 125.2, 114.0, 65.9, 57.7, 45.1 (2), 38.7, 24.9, 22.2. Anal. Calcd for $C_{14}H_{19}N_5O_2 \cdot ¼H_2O$: C, 57.2; H, 6.7; N, 23.8. Found: C, 57.5; H, 6.6; N, 23.8%.

***N*^{1}-(1,4-Dioxido-9,10-dihydro-8*H*-chromeno[6,5-*e*][1,2,4]triazin-3-yl)-*N*^{2},*N*^{2}-dimethyl-1,2-ethanediamine (29). Method D.** Oxidation of 1-oxide **136** (50 mg, 0.17 mmol) with CF_3CO_3H (ca. 3.2 mmol) gave 1,4-dioxide **29** (28 mg, 54%) as a red gum: ^{1}H NMR δ 8.11 (d, *J* = 9.5 Hz, 1 H, H-5), 7.36 (d, *J* = 9.5 Hz, 1 H, H-6), 7.23 (br s, 1 H, NH), 4.21–4.25 (m, 2 H, H-8), 3.61 (br t, *J* = 5.8 Hz, 2 H, CH_2N), 3.56 (br t, *J* = 6.5 Hz, 2 H, H-10), 2.62 (br t, *J* = 6.0 Hz, 2 H, CH_2N), 2.31 [s, 6 H, $N(CH_3)_2$], 2.00–2.07 (m, 2 H, H-9); ^{13}C NMR δ 154.0, 148.4, 135.8, 130.6, 128.9, 116.0, 114.9, 66.2, 57.5, 45.1 (2), 38.7, 24.5, 21.9; MS *m/z* 306 (MH^+, 60%), 290 (20), 176 (100); HRMS calcd for $C_{14}H_{20}N_5O_3$ (MH^+) *m/z* 306.1566, found 306.1568. Anal. Calcd for $C_{14}H_{19}N_5O_3 \cdot ½H_2O \cdot ½MeOH$: C, 52.7; H, 6.7; N, 21.2. Found: C, 52.8; H, 6.7; N, 21.2%.

***N*^{3}-Ethyl-*N*^{7},*N*^{7}-dimethyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine-3,7-diamine 1,4-Dioxide (30).**



***N*,*N*-Dimethyl-2-indanamine (138).** Methanesulfonyl chloride (11.5 mL, 149 mmol) was added dropwise to a stirred solution of 2-indanol (**137**) (20 g, 149 mmol) and iPr_2NEt (28.6 mL, 164 mmol) in DCM (300 mL) at 0 °C, and the solution stirred at 20 °C for 16 h. The solution was washed with 1 M HCl (80 mL), aqueous saturated $NaHCO_3$ solution (80 mL) and brine (100 mL), dried and the solvent evaporated. The residue was recrystallised from EtOH to give 2,3-dihydro-1*H*-inden-2-yl methanesulfonate (31.14 g, 98%) as a white solid. Aqueous $HNMe_2$ (40%, 180 mL, 1.42 mol) was added slowly to a stirred solution of mesylate (30.25 g, 143 mmol) in DMF (200 mL) and the solution stirred at 20 °C for 16 h. The solution was partitioned between EtOAc (400 mL) and water (800 mL) and the organic fraction washed with water (3 × 80 mL), brine (100 mL), dried and the solvent evaporated. The residue was suspended in 1 M HCl (400 mL) and washed with DCM (3 × 80 mL). The pH of the aqueous fraction was adjusted to 14 with NaOH, the mixture chilled at 5 °C for 8 h and the precipitate filtered. The precipitate was washed with water (50 mL) and dried to give amine **138** (21.54 g, 93%) as a light gray solid: ^{1}H NMR δ 7.10–7.17 (m, 4 H, H_{arom}), 3.01–3.08 (m, 3 H, H-2, CH_2), 2.82–2.91 (m, 2 H, CH_2), 2.31 [s, 6 H, $N(CH_3)_2$].

***N*,*N*-Dimethyl-5-nitro-2-indanamine (139).** $cHNO_3$ (70%, 22.6 mL, 357 mmol) was added dropwise to a stirred solution of indane **138** (15.54 g, 95.8 mmol) in TFA (90 mL) and the solution stirred at 20 °C for 48 h. The solution was poured into ice/water (1 L) and the pH adjusted to 10 with cNH_3. The mixture was extracted with DCM (4 × 150 mL), the combined organic fraction dried and the solvent evaporated to give crude 5-nitroindanamine containing ca. 5% of the corresponding 4-nitro isomer. A small portion was purified by chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give 5-nitroindanamine **139** as an oil: ^{1}H NMR δ 8.03–8.06 (m, 2 H, H-4, H-6), 7.30 (d, *J* = 8.9 Hz, 1 H, H-7), 3.23–3.30 (m, 1 H, H-2), 3.12–3.20 (m, 2 H, CH_2), 2.97–3.03 (m, 2 H, CH_2), 2.38 [s, 6 H, $N(CH_3)_2$]. The hydrochloride salt crystallised as a tan powder, mp 223–227 °C. Anal. Calcd for $C_{11}H_{15}ClN_2O_2$: C, 54.4; H, 6.2; N, 11.5. Found: C, 55.0; H, 6.3; N, 11.4%.

***N*-[2-(Dimethylamino)-2,3-dihydro-1*H*-inden-5-yl]acetamide (140).** A solution of crude nitroindanamine **139** (19.82 g, 95.8 mmol) in EtOH (200 mL) and Pd/C (500 mg) was stirred in 2 × 100 mL batches under H_2 (60 psi) for 16 h. The combined batches were filtered through Celite, and washed with warm EtOH (1 L) and then DMF (100 mL). The solvent was evaporated and the residue suspended in dioxane (130 mL), and Ac_2O (19 mL, 190 mmol) added dropwise. The mixture was stirred at 20 °C for 16 h, diluted with water (200 mL), the pH adjusted to 10 with cNH_3, and the mixture stirred for 30 min. The precipitate was filtered, washed with water (50 mL) and dried to give pure 5-acetamide **140** (15.38 g, 73%) as tan powder: mp 94–96 °C; ^{1}H NMR δ 7.42 (br s, 1 H, NH), 7.08–7.14 (m, 3 H, H-4, H-6, H-7), 2.97–3.08 (m, 3 H, H-2, CH_2), 2.78–2.89 (m, 2 H, CH_2), 2.30 [s, 6 H, $N(CH_3)_2$], 2.15 (s, 3 H, $COCH_3$); ^{13}C NMR δ 168.3, 142.8, 137.9, 136.3, 124.5, 118.5, 116.6, 68.1, 43.8 (2), 37.7, 37.1, 24.5. Anal. Calcd for $C_{13}H_{18}N_2O{\cdot}H_2O$: C, 66.1; H, 8.5; N, 11.9. Found: C, 66.1; H, 8.5; N, 11.9%.

***N*^{2},*N*^{2}-Dimethyl-6-nitro-2,5-indanediamine (141).** A solution of $cHNO_3$ (70%, 13.4 mL, 211 mmol) in TFA (15 mL) was added dropwise to a stirred solution of acetamide **140** (15.38 g, 70.5 mmol) in TFA (120 mL) and the solution stirred at 20 °C for 16 h. The solution was poured into ice/water (1.2 L) and the pH adjusted to 10 with cNH_3. The mixture was extracted with DCM (4 × 150 mL), the combined organic fraction dried and the solvent evaporated. The residue was filtered through a short column of silica, eluting with a gradient (0–15%) of MeOH/DCM, to give a 6:1 mixture of *N*-[2-(dimethylamino)-6-nitro-2,3-dihydro-1*H*-inden-5-yl]acetamide and *N*-[2-(dimethylamino)-4-nitro-2,3-dihydro-1*H*-inden-5-yl]acetamide (16.7 g, 90%). A solution of the acetamide mixture (16.7 g, 63.4 mmol) in EtOH (300 mL) and cHCl (70 mL) was stirred at reflux temperature for 4 h. The mixture was cooled and the EtOH evaporated. The mixture was diluted with water (200 mL) and the pH adjusted to 9 with cNH_3. The precipitate was filtered, washed with water (40 mL), dried and recrystallised from EtOAc/pet. ether to give pure 6-nitroaniline **141** (8.12 g, 52%) as a red solid: mp 119–121 °C; ^{1}H NMR δ 7.91 (s, 1 H, H-7), 6.61 (s, 1 H, H-4), 6.00 (br s, 2 H, NH_2), 2.95–3.06 (m, 3 H, H-2, CH_2), 2.74–2.84 (m, 2 H, CH_2), 2.29 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 151.8, 144.4, 131.6, 131.4, 121.0, 113.6, 67.8, 43.8 (2), 37.9, 36.2. Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.7; H, 6.8; N, 19.0. Found: C, 59.5; H, 6.9; N, 18.9%.

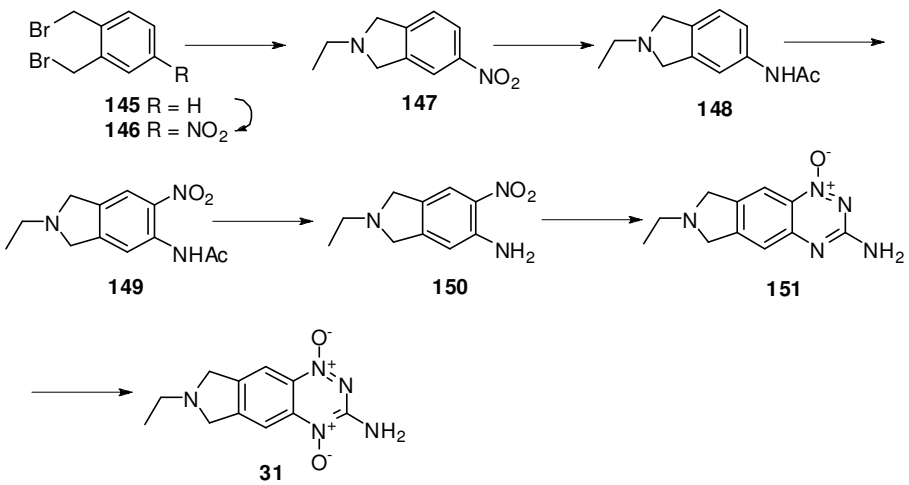
N^7,N^7-Dimethyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine-3,7-diamine 1-Oxide (142). Method A. Reaction of nitroaniline **141** (0.50 g, 2.3 mmol) and cyanamide (0.4 g, 9.0 mmol) gave 1-oxide **142** (246 mg, 44%) as a yellow powder: mp (MeOH/DCM) 212–216 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.93 (s, 1 H, H-9), 7.34 (s, 1 H, H-5), 7.11 (br s, 2 H, NH_2), 3.03–3.18 (m, 3 H, H-7, CH_2), 2.79–2.89 (m, 2 H, CH_2), 2.22 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 159.9, 152.0, 148.6, 140.5, 128.9, 120.0, 114.1, 67.0, 43.2 (2), 37.0, 36.1. Anal. Calcd for $C_{12}H_{15}N_5O{\cdot}½H_2O$: C, 56.7; H, 6.3; N, 27.5. Found: C, 56.9; H, 6.0; N, 27.4%.

3-Chloro-*N*,*N*-dimethyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-amine 1-Oxide (143). **Method B.** Reaction of 1-oxide **142** (320 mg, 1.3 mmol) and $NaNO_2$ (100 mg, 1.4 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **143** (245 mg, 71%) as a pale yellow solid: mp (DCM) 160–165 °C; ^{1}H NMR δ 8.19 (s, 1 H, H-9), 7.73 (s, 1 H, H-5), 3.25–3.34 (m, 2 H, CH_2), 3.15–3.23 (m, 1 H, H-7), 3.02–3.11 (m, 2 H, CH_2), 2.34 [s, 6 H, $N(CH_3)_2$]; ^{13}C NMR δ 156.1, 154.0, 147.8, 147.4, 133.0, 122.7, 114.8, 67.5, 43.8 (2), 38.1, 37.7. Anal. Calcd for $C_{12}H_{13}ClN_4O$: C, 54.5; H, 5.0; N, 21.2. Found: C, 54.6; H, 4.9; N, 21.3%.

N^3-Ethyl-N^7,N^7-dimethyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine-3,7-diamine 1-Oxide (144). Method C. Reaction of chloride **143** (240 mg, 0.9 mmol) and aqueous ethylamine (70%, 0.35 mL, 4.4 mmol) gave 1-oxide **144** (203 mg, 84%) as a yellow solid: mp (MeOH/EtOAc) 187–190 °C; ^{1}H NMR δ 8.05 (s, 1 H, H-9), 7.37 (s, 1 H, H-5), 5.14 (br s, 1 H, NH), 3.54 (dq, J = 7.2, 1.3 Hz, 2 H, CH_2N), 3.06–3.21 (m, 3 H, CH, CH_2), 2.89–2.99 (m, 2 H, CH_2), 2.32 [s, 6 H, $N(CH_3)_2$], 1.28 (t, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 158.7, 152.1, 148.9, 140.9, 130.0, 120.8, 115.0, 67.7, 43.9 (2), 38.0, 37.1, 36.3, 14.8. Anal. Calcd for $C_{14}H_{19}N_5O$: C, 61.5; H, 7.0; N, 25.6. Found: C, 61.3; H, 7.1; N, 25.5%.

N^3-Ethyl-N^7,N^7-dimethyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine-3,7-diamine 1,4-Dioxide (30). Method D. Oxidation of 1-oxide **144** (188 mg, 0.7 mmol) with CF_3CO_3H (ca. 6.9 mmol) gave (i) starting material **144** (175 mg, 93%) and (ii) 1,4-dioxide **30** (8 mg, 4%) as a red gum: ^{1}H NMR δ 8.11 (s, 1 H, H-9), 8.08 (s, 1 H, H-5), 6.98 (br s, 1 H, NH), 3.63 (dq, J = 7.2, 1.0 Hz, 2 H, CH_2N), 3.15–3.30 (m, 3 H, CH, CH_2), 2.95–3.07 (m, 2 H, CH_2), 2.33 [s, 6 H, $N(CH_3)_2$], 1.36 (t, J = 7.2 Hz, 3 H, CH_3); MS *m/z* 290 (MH^+, 20%), 274 (5); HRMS calcd for $C_{14}H_{20}N_5O_2$ (MH^+) *m/z* 290.1617, found 290.1607.

7-Ethyl-7,8-dihydro-6*H*-[1,2,4]triazino[5,6-*f*]isoindol-3-amine 1,4-Dioxide (31).



1,2-Bis(bromomethyl)-4-nitrobenzene (146). KNO_3 (33.0 g, 330 mmol) was added in small portions, over 1 h, to a stirred solution of 1,2-bis(bromomethyl)benzene (**145**) (72.2 g, 300 mmol) in cH_2SO_4 (600 mL) at 0 °C. After the addition was completed, the mixture was stirred at 0 °C for 3 h. The mixture was poured onto ice and stirred at 0 °C for 2 h. The solid was filtered, washed with water several times and dried to give nitrobenzene **146** (63.1 g, 68%) as a white solid: mp (EtOAc/pet. ether) 73–74 °C; (lit[14] mp 68–72 °C) ^{1}H NMR δ 8.25 (d, *J* = 2.3 Hz, 1 H, H-3), 8.15 (dd, *J* = 8.4, 2.3 Hz, 1 H, H-5), 7.56 (d, *J* = 8.4 Hz, 1 H, H-6), 4.67 (s, 2 H, CH_2Br), 4.66 (s, 2 H, CH_2Br); ^{13}C NMR δ 148.0, 143.4 138.3, 132.1, 125.9, 124.1, 28.0, 27.5. Anal. Calcd for $C_8H_7NBr_2O_2$: C, 31.1; H, 2.3; N, 4.5. Found: C, 31.1; H, 2.3; N, 4.5%.

2-Ethyl-5-nitroisoindoline (147). A mixture of dibromide **146** (9.27 g, 30.0 mmol), ethylamine hydrochloride (2.45 g, 30.0 mmol) and Et_3N (21 mL, 150 mmol) in DMF (100 mL) was stirred at 20 °C for 90 min. The mixture was partitioned between EtOAc and aqueous Na_2CO_3 solution. The organic fraction was washed with water, dried and the solvent evaporated to give isoindole **147** (3.21 g, 56%) as a dark oil: ^{1}H NMR δ 8.11 (dd, *J* = 8.1, 2.1 Hz, 1 H, H-6), 8.05 (d, *J* = 2.1 Hz, 1 H, H-4), 7.34 (d, *J* = 8.1 Hz, 1 H, H-7), 3.99 (s, 4 H, H-1, H-3), 2.82 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.22 (t, *J* = 7.2 Hz, 3 H, CH_3); HRMS calcd for $C_{10}H_{13}N_2O_2$ (MH^+) *m/z* 193.0977, found 193.0983.

***N*-(2-Ethyl-2,3-dihydro-1*H*-isoindol-5-yl)acetamide (148).** A solution of isoindole **147** (3.20 g, 16.7 mmol) in MeOH (100 mL) was stirred with Pd/C (5%, 300 mg) under H_2 (60 psi) for 16 h. The solution was filtered through Celite, washed with MeOH (3 × 20 mL) and the solvent evaporated. The residue was dissolved in DCM (130 mL) and Et_3N (13 mL, 93 mmol), Ac_2O (13 mL, 138 mmol) was added dropwise and the solution stirred at 20 °C for 15 h. The mixture was partitioned between DCM and aqueous Na_2CO_3 solution. The organic solution was washed with water, dried and the solvent was evaporated to give acetamide **148** (3.00 g, 88%) as a dark oil: ^{1}H NMR δ 7.45 (br s, 1 H, H-4), 7.30 (br s, 1 H, NH), 7.18 (br d, *J* = 8.0 Hz, 1 H, H-6), 7.12 (d, *J* = 8.0 Hz, 1 H, H-7), 3.90 (s, 2 H, H-1), 3.87 (s, 2 H, H-3), 2.76 (q, *J* = 7.2 Hz, 2 H, CH_2), 2.15 (s, 3 H, $COCH_3$) 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3); HRMS calcd for $C_{12}H_{17}N_2O$ (MH^+) *m/z* 203.1184, found 203.1188.

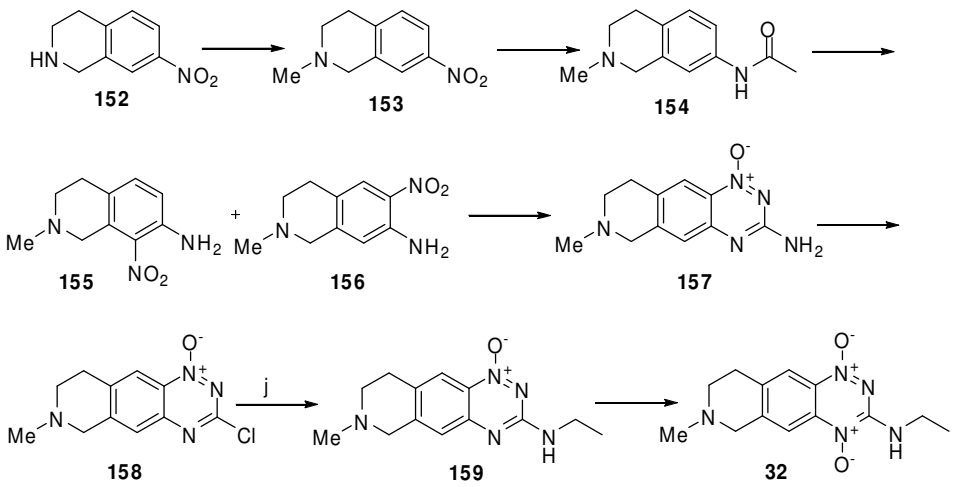
***N*-(2-Ethyl-6-nitro-2,3-dihydro-1*H*-isoindol-5-yl)acetamide (149).** KNO_3 (1.33 g, 13.2 mmol) was added in small portions, over 10 min, to a stirred solution of acetamide **148** (2.45 g, 12.0 mmol) in cH_2SO_4 (50 mL) at 0 °C and the reaction mixture was stirred at 0 °C for a further 45 min. The mixture was poured onto ice, made basic with cNH_3 and extracted with DCM (3 × 100 mL). The solvent was evaporated to give a brown oil which was purified by chromatography on neutral Al_2O_3, eluting with a gradient (0–20%) of EtOAc/pet. ether, to give nitroacetamide **149** (1.49 g, 50%) as a yellow solid: mp EtOAc/pet. ether) 85–87 °C; ^{1}H NMR δ 10.43 (br s, 1 H, NH), 8.62 (s, 1 H, H-7), 8.03 (s, 1 H, H-4), 3.96 (s, 2 H, CH_2N), 3.92 (s, 2 H, CH_2N), 2.79 (q, *J* = 7.2 Hz, 2 H, CH_2N), 2.28 (s, 3 H, $COCH_3$), 1.21 (t, *J* = 7.2 Hz, 3 H, CH_3); HRMS calcd for $C_{12}H_{16}N_3O_3$ (MH^+) *m/z* 250.1192, found 250.1195. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.8; H, 6.0; N, 16.9. Found: C, 57.9; H, 5.9; N, 16.7%.

2-Ethyl-6-nitro-5-isoindolinamine (150). A mixture of nitroacetamide **149** (1.52 g, 6.1 mmol) and 5 M HCl (12 mL) was stirred at reflux temperature for 20 min. The suspension was diluted with water (40 mL), cooled to 0 °C, and made basic with cNH_3. The precipitate was filtered, washed with water and dried to give nitroaniline **150** (1.13 g, 89%) as a tan solid: mp 121–123 °C; ^{1}H NMR δ 7.94 (s, 1 H, H-7), 6.64 (s, 1 H, H-4), 6.06 (br s, 2 H, NH_2), 3.83 (br s, 2 H, CH_2N), 3.81 (br s, 2 H, CH_2N), 2.75 (q, *J* = 7.2 Hz, 2 H, CH_2N), 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 149.7, 144.6, 131.5, 130.0, 119.3, 111.7, 58.4, 57.3, 49.9, 13.9. Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.2; N, 20.3. Found: C, 57.8; H, 6.2; N, 20.0%.

7-Ethyl-7,8-dihydro-6*H*-[1,2,4]triazino[5,6-*f*]isoindol-3-amine 1-Oxide (151). Method A. Reaction of nitroaniline **150** (414 mg, 2.0 mmol) and cyanamide (336 mg, 8.0 mmol) gave 1-oxide **151** (404 mg, 87%) as a greenish-yellow solid: mp 218 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.98 (s, 1 H, H-9), 7.38 (s, 1 H, H-5), 7.18 (s, 2 H, NH_2), 3.89 (s, 2 H, CH_2N), 3.86 (s, 2 H, CH_2N), 2.70 (q, *J* = 7.2 Hz, 2 H, CH_2N), 1.11 (t, *J* = 7.2 Hz, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 160.0, 149.8, 148.7, 138.5, 128.9, 118.2, 112.5, 57.5, 57.0, 49.0, 13.5. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.1; H, 5.7; N, 30.3. Found: C, 57.1; H, 5.6; N, 30.3%.

7-Ethyl-7,8-dihydro-6*H*-[1,2,4]triazino[5,6-*f*]isoindol-3-amine 1,4-Dioxide (31). Method D. Oxidation of 1-oxide **151** (328 mg, 1.4 mmol) with CF_3CO_3H (ca. 10 mmol) gave 1,4-dioxide **31** (68 mg, 19%) as a red solid which was crystallised as the hydrochloride salt: mp (MeOH/DCM) 230 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.84 (br s, 1 H, HCl), 8.27 (s, 1 H, H-9), 8.20 (s, 1 H, H-5), 8.14 (br s, 2 H, NH_2), 4.88–5.05 (m, 2 H, CH_2N), 4.50–4.73 (m, 2 H, CH_2N), 3.42 (q, *J* = 7.2 Hz, 2 H, CH_2N), 1.32 (t, *J* = 7.2 Hz, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 151.4, 143.0, 138.5, 134.0, 130.6, 115.6, 111.4, 56.5, 56.1, 49.1, 10.3; HRMS calcd for $C_{11}H_{14}N_5O_2$ (MH^+) *m/z* 248.1148, found 248.1154.

***N*-Ethyl-7-methyl-6,7,8,9-tetrahydro[1,2,4]triazino[6,5-*g*]isoquinolin-3-amine 1,4-Dioxide (32).**



2-Methyl-7-nitro-1,2,3,4-tetrahydroisoquinoline (153). Formic acid (9.4 mL, 250 mmol) was added dropwise to Ac_2O (19 mL, 202 mmol) at 0 °C. The solution was stirred at 50 °C for 45 min, then cooled to −18 °C, diluted with THF (100 mL) and a solution of 7-nitro-1,2,3,4-tetrahydroisoquinoline[15] (**152**) (13.8 g, 5.0 mmol) in THF (100 mL) was added and stirred at −15 to −18 °C for 30 min. The solution was warmed to 20 °C, the solvent was evaporated and the residue was partitioned between saturated aqueous $NaHCO_3$ solution (250 mL) and EtOAc (250 mL). The aqueous fraction was extracted with EtOAc (3 × 250 mL), dried and the solvent evaporated. The residue was dissolved in THF (200 mL), cooled to 10 °C and BH_3·DMS solution (10 M, 19.4 mL, 194 mmol) was added. The solution was stirred at 20 °C for 1 h, diluted with MeOH (30 mL) and acidified with HCl solution (1 M, 45 mL). The solution was stirred at 40 °C for 15 min, the solvent evaporated and the residue partitioned between saturated aqueous $NaHCO_3$ solution (250 mL) and EtOAc (250 mL). The aqueous fraction was extracted with EtOAc (3 × 250 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (2–5%) of MeOH/DCM, to give isoquinoline **153** (13.9 g, 94%) as an orange solid: mp 51–54 °C (lit.[16] mp 57 °C) ^{1}H NMR δ 8.09 (dd, *J* = 8.4, 2.3 Hz, 1 H, H-6), 7.95 (d, *J* = 2.3 Hz, 1 H, H-8), 7.37 (d, *J* = 8.4 Hz, 1 H, H-5), 4.27 (d, *J* = 16.1 Hz, 1 H, H-1), 3.94 (d, *J* = 16.1 Hz, 1 H, H-1), 3.23–3.34 (m, 2 H, CH_2), 2.99–3.18 (m, 2 H, CH_2), 2.17 (s, 3 H, NCH_3); MS (APCI) *m/z* 193 (MH^+, 100%).

***N*-(2-Methyl-1,2,3,4-tetrahydro-7-isoquinolinyl)acetamide (154).** A solution of isoquinoline **153** (2.5 g, 13.0 mmol) in EtOH (200 mL) was stirred with Pd/C (5%, 200 mg) under H_2 (35 psi) for 4 h. The solution was filtered through Celite, washed with EtOH (50 mL) and the solvent was evaporated. The residue was dissolved in dioxane (50 mL), Ac_2O (2.7 mL, 28.6 mmol) was added and the solution stirred at 20 °C for 16 h. The solvent was evaporated and the residue was partitioned between dilute aqueous NH_3 solution (50 mL) and DCM (50 mL). The aqueous layer was extracted with DCM (4 × 125 mL), the combined organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with 5% MeOH/DCM, to give acetamide **154** (2.10 g, 77%) as a brown solid: mp 157–159 °C; ^{1}H NMR δ 7.29 (br s, 1 H, H-8), 7.27 (br s, 1 H, H-6), 7.22 (br s, 1 H, NH), 7.12 (br d, *J* = 8.1 Hz, 1 H, H-5), 4.18 (d, *J* = 16.2 Hz, 1 H, H-1), 3.82 (d, *J* = 16.1 Hz, 1 H, H-1), 3.11–3.25 (m, 2 H, H-3), 2.91–3.00 (m, 2 H, H-4), 2.61 (s, 3 H, NCH_3), 2.16 (s, 3 H, $COCH_3$); ^{13}C NMR δ 168.3, 136.6, 131.0,

129.2, 126.6, 119.2, 118.1, 61.5, 56.6, 47.3, 24.5, 24.0; MS (APCI) *m/z* 205 (MH^+, 100%). Anal. Calcd for $C_{12}H_{16}N_2O·½CH_3OH·½H_2O$: C, 65.5; H, 8.4; N, 12.2. Found: C, 65.8; H, 8.8; N, 12.6%.

Nitration of *N*-(2-Methyl-1,2,3,4-tetrahydro-7-isoquinolinyl)acetamide (154). A solution of KNO_3 (7.9 g, 78.4 mmol) in cH_2SO_4 (30 mL) was added dropwise to a stirred solution of acetamide **154** (14.6 g, 71.3 mmol) in cH_2SO_4 (200 mL) at 0 °C. The solution was stirred at 0 °C for 90 min, then poured into ice/water (1 L), the pH adjusted to 10 with cNH_3 and the mixture extracted with DCM (4 × 250 mL). The solvent was evaporated, the residue dissolved in HCl (5 M, 150 mL) and heated at reflux temperature for 3 h. The solution was cooled and partitioned between cNH_3 (70 mL) and DCM (250 mL). The aqueous layer was extracted with DCM (3 × 250 mL), the combined organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (5–20%) of MeOH/DCM, to give (i) 2-methyl-8-nitro-1,2,3,4-tetrahydro-7-isoquinolinamine (**155**) (4.75 g, 30%) as an orange solid: mp 122–123 °C; ^{1}H NMR δ 7.05 (d, *J* = 8.5 Hz, 1 H, H-6), 6.64 (d, *J* = 8.5 Hz, 1 H, H-5), 5.24 (br s, 2 H, NH_2), 3.69 (s, 2 H, H-1), 2.84 (t, *J* = 6.0 Hz, 2 H, H-3), 2.66 (t, *J* = 6.0 Hz, 2 H, H-4), 2.46 (s, 3 H, NCH_3); ^{13}C NMR δ 141.5, 134.5, 134.0, 131.6, 124.6, 116.6, 56.3, 51.9, 46.0, 28.7; MS (APCI) *m/z* 208 (MH^+, 100%). Anal. Calcd for $C_{10}H_{13}N_3O_2·¼H_2O$: C, 56.7; H, 6.4; N, 19.9. Found: C, 56.5; H, 6.8; N, 20.0%; and (ii) 2-methyl-6-nitro-1,2,3,4-tetrahydro-7-isoquinolinamine (**156**) (6.07 g, 18%) as an orange solid: mp 171–172 °C; ^{1}H NMR δ 7.89 (s, 1 H, H-5), 6.46 (s, 1 H, H-8), 5.85 (br s, 2 H, NH_2), 3.50 (s, 2 H, H-1), 2.84 (t, *J* = 6.0 Hz, 2 H, H-3), 2.66 (t, *J* = 6.0 Hz, 2 H, H-4), 2.43 (s, 3 H, NCH_3); ^{13}C NMR δ 144.0, 142.5, 131.4, 125.5, 123.5, 115.4, 57.7, 52.8, 45.8, 28.0; MS (APCI) *m/z* 208 (MH^+, 100%). Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 58.0; H, 6.3; N, 20.3. Found: C, 57.9; H, 6.3; N, 20.4%.

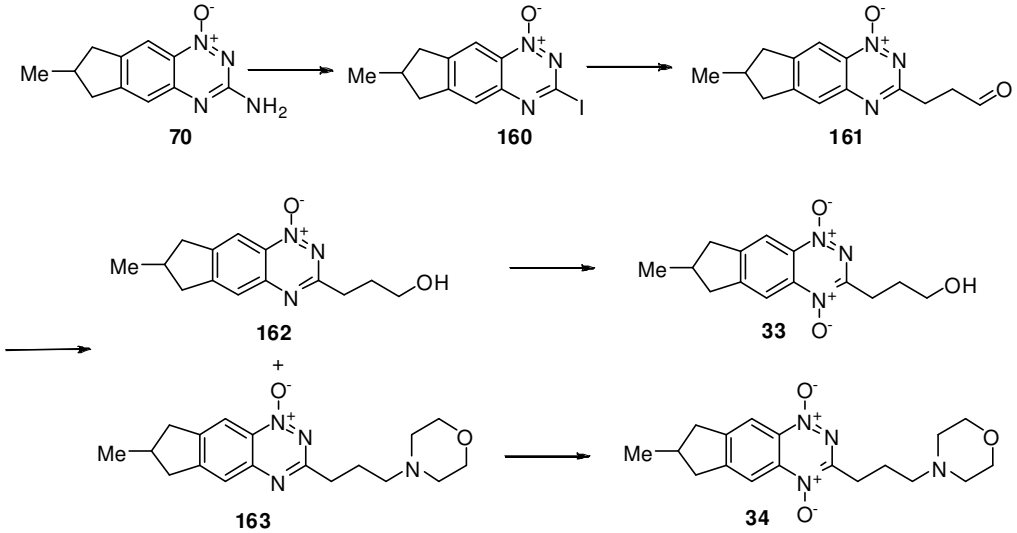
7-Methyl-6,7,8,9-tetrahydro[1,2,4]triazino[6,5-*g*]isoquinolin-3-amine 1-Oxide (157). Method A. Reaction of 6-nitroaniline **156** (2.30 g, 10.7 mmol) and cyanamide (2.00 g, 46.6 mmol) gave 1-oxide **157** (2.32 g, 90%) as a brown solid: mp 170–175 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.90 (s, 1 H, H-10), 7.25 (s, 1 H, H-5), 7.15 (br s, 2 H, NH_2), 3.62 (s, 2 H, H-6), 2.96 (t, *J* = 5.9 Hz, 2 H, H-8), 2.62 (t, *J* = 5.9 Hz, 2 H, H-9), 2.35 (s, 3 H, NCH_3); ^{13}C NMR δ 159.8, 146.8, 144.3, 132.0, 128.4, 121.9, 118.3, 57.3, 51.9, 45.4, 28.3; MS (APCI) *m/z* 232 (MH^+, 100%). Anal. Calcd for $C_{11}H_{13}N_5O·½H_2O$: C, 55.0; H, 5.9; N, 29.1. Found: C, 55.6; H, 5.5; N, 28.7%.

3-Chloro-7-methyl-6,7,8,9-tetrahydro[1,2,4]triazino[6,5-*g*]isoquinoline 1-Oxide (158). Method B. Reaction of 1-oxide **157** (1.8 g, 7.8 mmol) and $NaNO_2$ (570 mg, 8.2 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **158** (1.55 g, 79%) as a yellow solid: mp 179 °C (dec.); ^{1}H NMR δ 8.17 (s, 1 H, H-10), 7.63 (s, 1 H, H-5), 3.80 (s, 2 H, H-6), 3.17 (t, *J* = 6.0 Hz, 2 H, H-8), 2.77 (t, *J* = 5.9 Hz, 2 H, H-9), 2.51 (s, 3 H, NCH_3); ^{13}C NMR δ 156.2, 146.3, 145.5, 139.7, 128.0, 124.8, 119.0, 58.0, 52.0, 45.8, 29.7; MS (APCI) *m/z* 251 (MH^+, 100%), 253 (MH^+, 30%). Anal. Calcd for $C_{11}H_{11}ClN_4O$: C, 52.7; H, 4.4; N, 22.4; Cl, 14.1. Found: C, 52.7; H, 4.4; N, 22.3; Cl, 14.2%.

***N*-Ethyl-7-methyl-6,7,8,9-tetrahydro[1,2,4]triazino[6,5-*g*]isoquinolin-3-amine 1-Oxide (159). Method C.** Reaction of chloride **158** (500 mg, 2.0 mmol) and ethylamine (0.4 mL, 6.0 mmol) in DME (15 mL) gave 1-oxide **159** (460 mg, 88%) as a yellow solid: mp 193–196 °C; ^{1}H NMR δ 8.03 (s, 1 H, H-10), 7.27 (s, 1 H, H-5), 5.07 (br s, 1 H, NH), 3.69 (s, 2 H, H-6), 3.53 (dq, *J* = 7.2, 5.8 Hz, 2 H, CH_2N), 3.05 (t, *J* = 6.0 Hz, 2 H, H-8), 2.72 (t, *J* = 6.0 Hz, 2 H, H-9), 2.48 (s, 3 H, NCH_3), 1.29 (t, *J* = 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 158.6, 147.0, 144.4, 132.5, 129.6, 122.8, 119.3, 58.2, 52.6, 46.0, 36.3, 29.1, 14.8; MS (APCI) *m/z* 260 (MH^+, 100%). Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.2; H, 6.6; N, 27.0. Found: C, 59.9; H, 6.6; N, 26.9%.

***N*-Ethyl-7-methyl-6,7,8,9-tetrahydro[1,2,4]triazino[6,5-*g*]isoquinolin-3-amine 1,4-Dioxide (32). Method D.** Oxidation of 1-oxide **159** (440 mg, 1.7 mmol) with CF_3CO_3H (ca. 17 mmol) gave 1,4-dioxide **32** (35 mg, 8%) as a red solid: mp 120–124 °C; ^{1}H NMR δ 8.10 (s, 1 H, H-10), 7.96 (s, 1 H, H-5), 6.95 (br s, 1 H, NH), 3.78 (s, 2 H, H-6), 3.63 (dq, *J* = 7.2, 6.0 Hz, 2 H, CH_2N), 3.10 (t, *J* = 6.0 Hz, 2 H, H-8), 2.75 (t, *J* = 6.0 Hz, 2 H, H-9), 2.50 (s, 3 H, NCH_3), 1.36 (t, *J* = 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 149.3, 145.5, 136.5, 135.3, 129.3, 120.5, 113.9, 58.1, 52.1, 45.8, 36.5, 29.1, 14.8; MS (APCI) *m/z* 276 (MH^+, 100%); HRMS calcd for $C_{13}H_{18}N_5O_2$ (MH^+) *m/z* 276.1461, found 276.1456.

3-(7-Methyl-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-1-propanol (33).



3-Iodo-7-methyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (160). *tert*-Butyl nitrite (2.5 mL, 18.6 mmol) was added a stirred mixture of 1-oxide **70** (1.30 g, 6.0 mmol), diiodomethane (4.8 mL, 60 mmol) and CuI (1.2 g, 6.3 mmol) in THF (50 mL) and the mixture stirred at reflux temperature for 3 h. The solution was cooled and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give iodide **160** (1.31 g, 67%) as a pale yellow solid: mp (EtOAc/pet. ether) 140–142 °C; ^{1}H NMR δ 8.15 (s, 1 H, H-9), 7.70 (s, 1 H, H-5), 3.20–3.30 (m, 2 H, CH_2), 2.65–2.79 (m, 3 H, H-7, CH_2), 1.20 (d, *J* = 6.4 Hz, 3 H, CH_3); ^{13}C NMR δ 155.5, 149.9, 147.6, 133.4, 122.5, 121.7, 114.6, 41.3, 41.0, 35.0, 20.2. Anal. Calcd for $C_{11}H_{10}IN_3O$: C, 40.4; H, 3.1; N, 12.9. Found: C, 40.6; H, 3.0; N, 12.7%.

3-(7-Methyl-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)propanal (161). Iodide **160** (1.53 g, 4.7 mmol) was added to a degassed solution of allyl alcohol (0.89 mL, 13.1 mmol), $Pd(OAc)_2$ (52 mg, 0.23 mmol), nBu_4NBr (1.35 g, 4.2 mmol) and $NaHCO_3$ (0.86 g, 10.3 mmol) in DMF (40 mL) and the solution was stirred at 50 °C for 24 h under N_2. The mixture was quenched with saturated aqueous NH_4Cl solution (50 mL) and filtered. The filtrate was extracted with EtOAc (5 × 50 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give (i) starting material **160** (0.86 g, 56%) and (ii) aldehyde **161** (426 mg, 37%) as an orange gum: ^{1}H NMR δ 9.93 (s, 1 H, CHO), 8.21 (s, 1 H, H-9), 7.69 (s, 1 H, H-5), 3.35 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.20–3.27 (m, 2 H, CH_2), 3.19 (br dd, *J* = 7.2, 6.7 Hz, 2 H, CH_2), 2.64–2.76 (m, 3 H, H-7, CH_2), 1.19 (d, *J* = 6.4 Hz, 3 H, CH_3); ^{13}C NMR δ 200.5, 163.9, 154.5, 148.7, 147.3, 132.4, 122.8, 114.4, 41.2, 40.9, 40.5, 35.0, 29.4, 20.2; MS *m/z* 258 (MH^+, 60%), 242 (10); HRMS calcd for $C_{14}H_{16}N_3O_2$ (MH^+) *m/z* 258.1243, found 258.1242.

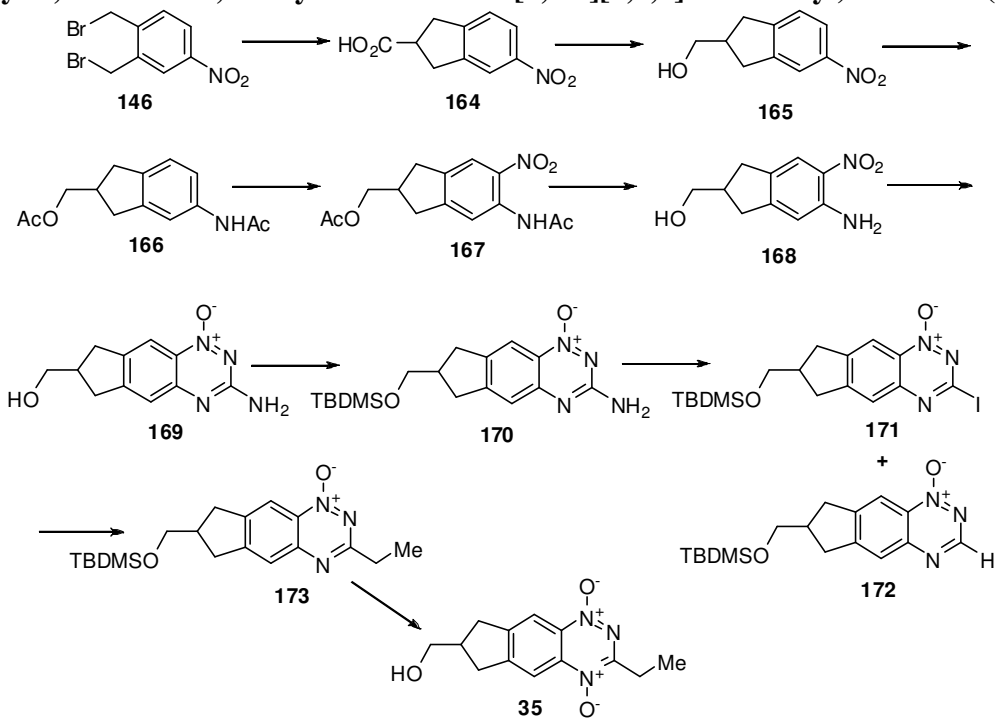
Reductive Amination of 3-(7-Methyl-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)propanal (161). Morpholine (0.64 mL, 7.3 mmol) was added to a solution of aldehyde **161** (0.47 g, 1.8 mmol) in EtOH (20 mL) at 0 °C and the solution stirred for 30 min. $NaCNBH_3$ (0.35 g, 5.5 mmol) was added and the mixture stirred at 0 °C for 30 min, then HOAc (0.5 mL) was added and the mixture stirred at 20 °C for 30 min. The solvent was evaporated and the residue partitioned between DCM and water, the organic phase was dried, the solvent evaporated and the residue purified by chromatography, eluting with a gradient (0–10%) of MeOH/EtOAc, to give (i) starting material **161** (83 mg, 17%) and (ii) 3-(7-methyl-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)propanol (**162**) (134 mg, 28%) as a white solid: mp (MeOH/EtOAc) 70–71 °C; ^{1}H NMR δ 8.21 (s, 1 H, H-9), 7.71 (s, 1 H, H-5), 3.78 (t, *J* = 6.1 Hz, 2 H, CH_2O), 3.20–3.28 (m, 2 H, CH_2), 3.15 (t, *J* = 7.2 Hz, 2 H, CH_2), 2.64–2.78 (m, 3 H, H-7, CH_2), 2.35 (br s, 1 H, OH), 2.12–2.19 (m, 2 H, CH_2), 1.19 (d, *J* = 6.4 Hz, 3 H, CH_3); ^{13}C NMR δ 165.7, 154.6, 148.7, 147.3, 132.3, 122.6, 114.4, 62.1, 41.2, 40.9, 35.0, 30.6, 24.7, 20.2. Anal. Calcd for $C_{14}H_{17}N_3O_2 \cdot ¼H_2O$: C, 63.7; H, 6.7; N, 15.9. Found: C, 63.7; H, 6.6; N, 15.9%; and (iii) 7-methyl-3-[3-(4-morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-oxide (**163**) (331 mg, 55%) as a yellow gum: ^{1}H NMR δ 8.22 (s, 1 H, H-9), 7.70 (s, 1 H, H-5), 3.60 (br t, *J* = 4.7 Hz, 4 H, 2 × CH_2O), 3.21–3.28 (m, 2 H, CH_2), 3.05 (br t, *J* = 7.4 Hz, 2 H, CH_2), 2.65–2.77 (m, 3 H, H-7, CH_2), 2.47–2.54 (m, 6 H, 3 × CH_2N), 2.11 (p, *J* = 7.3 Hz, 2 H, CH_2), 1.19 (d, *J* = 6.4 Hz, 3 H, CH_3); ^{13}C NMR δ 165.7, 154.4, 148.5, 147.5, 132.3, 122.7, 114.4, 66.7 (2), 55.1, 53.5 (2), 41.2, 40.9, 35.2, 35.0, 24.7, 20.2; MS *m/z* 392 (MH^+, 100%), 311 (20); HRMS calcd for $C_{18}H_{25}N_4O_2$ (MH^+) *m/z* 329.1978, found 329.1978.

3-(7-Methyl-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl)-1-propanol (33). Method D. Oxidation of 1-oxide **162** (130 mg, 0.5 mmol) with CF_3CO_3H (ca. 5 mmol) gave 1,4-dioxide **33** (68 mg, 49%) as a red solid: mp (EtOAc/pet. ether) 130–131 °C; ^{1}H NMR δ 8.30 (s, 1 H, H-9), 8.22 (s, 1 H, H-5), 3.69 (br t, *J* = 5.8 Hz, 2 H, CH_2O), 3.24–3.35 (m, 4 H, 2 × CH_2), 3.10 (br s, 1 H, OH), 2.68–2.83 (m, 3 H, H-7, CH_2), 2.10–2.17 (m, 2 H, CH_2), 1.21 (d, *J* = 6.5 Hz, 3 H, CH_3); ^{13}C NMR δ 155.2, 155.0, 150.5,

138.9, 134.0, 115.9, 114.2, 61.2, 41.4, 40.9, 34.9, 29.6, 26.8, 20.1. Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.1; H, 6.2; N, 15.3. Found: C, 61.4; H, 6.3; N, 15.0%.

7-Methyl-3-[3-(4-morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1,4-Dioxide (34). Method D. Oxidation of 1-oxide **163** (320 mg, 1.0 mmol) with CF_3CO_3H (ca. 10 mmol) gave 1,4-dioxide **34** (148 mg, 44%) as a red solid: mp (MeOH/DCM) 119–121 °C; ^{1}H NMR δ 8.27 (s, 1 H, H-9), 8.23 (s, 1 H, H-5), 3.45 (br t, *J* = 4.5 Hz, 4 H, 2 × CH_2O), 3.21–3.33 (m, 4 H, 2 × CH_2), 2.68–2.81 (m, 3 H, H-7, CH_2), 2.48 (t, *J* = 6.5 Hz, 2 H, CH_2N), 2.37 (br t, *J* = 4.5 Hz, 4 H, 2 × CH_2N), 2.06–2.13 (m, 2 H, CH_2), 1.20 (d, *J* = 6.4 Hz, 3 H, CH_3); ^{13}C NMR δ 155.2, 154.7, 150.2, 139.1, 133.8, 115.9, 113.9, 67.0 (2), 58.0, 53.5 (2), 41.4, 40.8, 35.0, 28.8, 21.8, 20.1. Anal. Calcd for $C_{18}H_{24}N_4O_3 \cdot ¼CH_3OH$: C, 62.2; H, 7.2; N, 15.9. Found: C, 62.3; H, 7.0; N, 16.0%.

3-Ethyl-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)methanol (35).



5-Nitro-2-indanecarboxylic Acid (164). Diethyl malonate (9.10 mL, 60 mmol) was added to a stirred suspension of NaH (60% in oil, 3.02 g, 126 mmol) in dry Et_2O (500 mL) at 20 °C under N_2 and the mixture was stirred for 30 min. 1,2-Bis(bromomethyl)-4-nitrobenzene (**146**) (18.5 g, 60 mmol) was added and the mixture was stirred at 20 °C for 24 h. The reaction was diluted with EtOAc (200 mL) and washed with 1 M HCl. The solvent was evaporated to give a brown oil that was treated with 2 M NaOH (100 mL) in EtOH (100 mL) at 20 °C for 15 h. Most of the solvent was evaporated and DCM (300 mL) was added and the mixture was acidified with 1 M HCl. The organic fraction was dried and the solvent evaporated to give a brown solid that was suspended in xylene (200 mL) and stirred at reflux temperature for 90 min. The solvent was evaporated to give a brown oil which was purified by chromatography, eluting with a gradient (0–20%) of EtOAc/pet. ether, to give acid **164** (2.44 g, 20%) as a pale yellow solid: mp (EtOAc/pet.

ether) 115–117 °C; ^{1}H NMR δ 9.10 (br s, 1 H, CO_2H), 8.06–8.11 (m, 2 H, H-4, H-6), 7.36 (d, *J* = 9.0 Hz, 1 H, H-7), 3.30–3.56 (m, 5 H, H-1, H-2, H-3); ^{13}C NMR δ 180.0, 149.0, 147.6, 143.1, 124.8, 122.7, 119.6, 43.3, 35.9, 35.7. Anal. Calcd for $C_{10}H_9NO_4$: C, 58.0; H, 4.4; N, 6.8. Found: C, 58.2; H, 4.5; N, 6.8%.

(5-Nitro-2,3-dihydro-1*H*-inden-2-yl)methanol (165). BH_3·DMS (10 M, 1.30 mL, 13.0 mmol) was added to a stirred solution of acid **164** (2.07 g, 10.0 mmol) in dry THF (30 mL) at 20 °C under N_2 and the mixture was stirred at 20 °C for 30 min. The reaction was quenched with MeOH and the solvent evaporated to give a brown oil which was purified by chromatography, eluting with a gradient (0–20%) of EtOAc/pet. ether, to give alcohol **165** (1.13 g, 59%) as an oil: ^{1}H NMR δ 8.01–8.07 (m, 2 H, H-4, H-6), 7.32 (d, *J* = 8.0 Hz, 1 H, H-7), 3.68 (d, *J* = 5.8 Hz, 2 H, CH_2O), 3.09–3.20 (m, 2 H, CH_2), 2.76–2.91 (m, 3 H, CH_2, CH), OH not observed; HRMS (EI$^+$) calcd for $C_{10}H_{11}NO_3$ (M^+) *m/z* 193.0739, found 193.0733.

[5-(Acetylamino)-2,3-dihydro-1*H*-inden-2-yl]methyl Acetate (166). A solution of nitroindane **165** (0.54 g, 2.77 mmol) in MeOH (70 mL) and 5% Pd/C (100 mg) was stirred under H_2 (60 psi) for 16 h. The mixture was filtered through Celite, washed with MeOH and the solvent evaporated to give the corresponding aniline derivative, which was treated with Ac_2O (5 mL, 53.0 mmol) and Et_3N (5 mL, 36.0 mmol) in DCM (50 mL) at 20 °C for 28 h. The mixture was partitioned between EtOAc and water, and the organic fraction was washed with water, dried and the solvent evaporated to give a brown oil which was purified by chromatography, eluting with a gradient (30–50%) of EtOAc/pet. ether, to give acetate **166** (0.38 g, 56%) as an oil: ^{1}H NMR δ 7.44 (s, 1 H, H-4), 7.26 (br s, 1 H, NH), 7.09–7.17 (m, 2 H, H-6, H-7), 4.08 (d, *J* = 7.0 Hz, 2 H, CH_2O), 2.99–3.09 (m, 2 H, CH_2), 2.65–2.87 (m, 3 H, CH, CH_2), 2.16 (s, 3 H, $COCH_3$) 2.06 (s, 3 H, CH_3); ^{13}C NMR δ 171.2, 168.2, 143.3, 138.4, 136.4, 124.7, 118.5, 116.7, 67.5, 38.5, 36.0, 35.4, 24.5, 20.9; HRMS (EI$^+$) calcd for $C_{14}H_{17}NO_3$ (M^+) *m/z* 247.1208, found 247.1204.

[5-(Acetylamino)-6-nitro-2,3-dihydro-1*H*-inden-2-yl]methyl Acetate (167). cHNO_3 (70%, 3.0 mL, 33 mmol) was added dropwise (over 20 min) to a stirred solution of **166** (1.45 g, 5.9 mmol) in TFA (30 mL) at 20 °C and the reaction mixture stirred for 15 min at 20 °C. The mixture was poured into ice/water (300 mL), stirred 30 min and extracted with DCM (3 × 100 mL). Evaporation of the solvent gave crude acetate **167** (1.60 g, 94%), containing ca. 8% of the 4-nitro isomer which was removed by recrystallisation from ether, to give acetate **167** as a tan solid: mp (ether) 106–107 °C; ^{1}H NMR δ 10.36 (br s, 1 H, NH), 8.58 (s, 1 H, H-7), 8.03 (s, 1 H, H-4), 4.05–4.13 (m, 2 H, CH_2O), 3.06–3.22 (m, 2 H, CH_2), 2.73–2.94 (m, 3 H, CH_2, CH), 2.27 (s, 3 H, $COCH_3$), 2.06 (s, 3 H, $COCH_3$); ^{13}C NMR δ 171.0, 169.0, 152.3, 137.9, 135.5, 134.0, 121.4, 117.8, 66.7, 38.5, 36.5, 35.1, 25.6, 20.8. Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.5; H, 5.5; N, 9.6. Found: C, 57.7; H, 5.4; N, 9.7%.

(5-Amino-6-nitro-2,3-dihydro-1*H*-inden-2-yl)methanol (168). A mixture of acetate **167** (5.60 g, 19.2 mmol) and 5 M HCl (80 mL) in MeOH (80 mL) was stirred at reflux temperature for 30 min. The solvent was evaporated to give the hydrochloride salt of **168**

(4.42 g, 94%) as an orange solid: mp (MeOH) 143–145 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.73 (s, 1 H, H-7), 7.43 (br s, 4 H, NH_2, OH, HCl), 6.84 (s, 1 H, H-4), 3.31–3.38 (m, 2 H, CH_2O), 2.77–2.90 (m, 2 H, CH_2), 2.44–2.64 (m, 3 H, CH_2, CH); ^{13}C NMR [$(CD_3)_2SO$] δ 153.2, 145.7 131.4, 129.1, 119.8, 113.7, 63.8, 41.5, 35.2, 33.6; HRMS (EI^+) calcd for $C_{10}H_{12}N_2O_3$ (M^+) *m/z* 208.0848, found 208.0850. Anal. Calcd for $C_{10}H_{12}N_2O_3$·HCl: C, 49.1; H, 5.4; N, 11.5. Found: C, 49.4; H, 5.4; N, 11.5%.

(3-Amino-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)methanol (169). Method A. Reaction of nitroaniline **168** (4.43 g, 17.8 mmol) and cyanamide (3.51 g, 83.6 mmol) gave 1-oxide **169** (3.67 g, 89%) as a green-yellow solid: mp (DCM/MeOH) 255–257 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.93 (s, 1 H, H-9), 7.33 (s, 1 H, H-5), 7.10 (s, 2 H, NH_2), 4.67 (t, *J* = 5.2 Hz, 1 H, OH), 3.40 (dd, *J* = 6.5 Hz, 5.2 Hz, 2 H, CH_2O), 2.99–3.10 (m, 2 H, CH_2), 2.73–2.85 (m, 2 H, CH_2), 2.52–2.63 (m, 1 H, CH); ^{13}C NMR [$(CD_3)_2SO$] δ 159.9, 153.5, 148.6, 141.9, 128.8, 120.1, 114.1, 63.7, 41.6, 35.3, 34.6. Anal. Calcd for $C_{11}H_{12}N_4O_2$·¼CH_3OH: C, 56.2; H, 5.5; N, 23.3. Found: C, 56.7; H, 5.4; N, 23.2%.

7-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-amine 1-Oxide (170). iPr_2NEt (22.1 mL, 127 mmol) was added dropwise (over 30 min) to a mixture of alcohol **169** (8.56 g, 37 mmol) and TBDMSCl (8.34 g, 55 mmol) in DMF (100 mL) at 20 °C and the mixture was stirred at 20 °C for 1 h. The solvent was evaporated, the residue suspended in water (400 mL) and stirred at 0 °C for 1 h. The solid was filtered, washed with water (3 × 50 mL) and dried to give silylether **170** (12.10 g, 94%): mp (MeOH/EtOAc) 169–171 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.93 (s, 1 H, H-9), 7.34 (s, 1 H, H-5), 7.10 (s, 2 H, NH_2), 3.55–3.63 (m, 2 H, CH_2O), 3.20–3.12 (m, 2 H, CH_2), 2.72–2.84 (m, 2 H, CH_2), 2.58–2.68 (m, 1 H, H-7), 0.83 [s, 9 H, $SiC(CH_3)_3$], 0.02 [s, 6 H, $Si(CH_3)_2$]; ^{13}C NMR [$(CD_3)_2SO$] δ 159.8, 153.2, 148.6, 141.6, 128.7, 120.1, 114.1, 65.2, 41.3, 35.1, 34.3, 25.6 (3), 17.8, -5.52 (2). Anal. Calcd for $C_{17}H_{26}N_4O_2Si$: C, 58.9; H, 7.6; N, 16.2. Found: C, 58.7; H, 7.6; N, 16.6%.

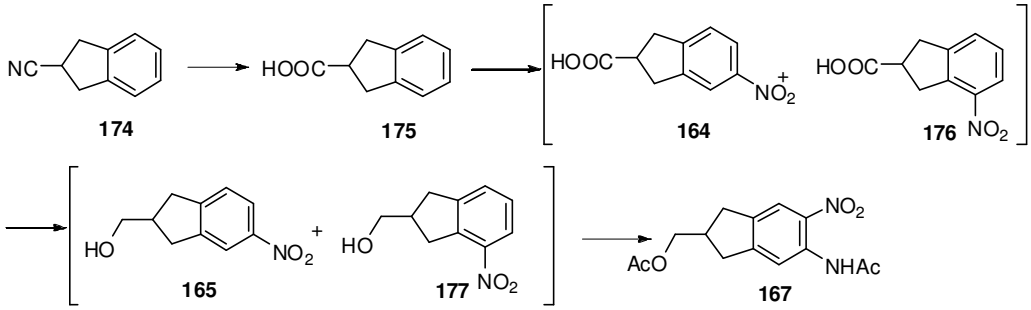
7-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-iodo-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (171) and 7-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (172). *tert*-Butyl nitrite (3.26 mL, 27.4 mmol) was added to a stirred suspension of amine **170** (2.82 g, 8.2 mmol) in THF (100 mL) at 20 °C and the mixture stirred for 5 min. Diiodomethane (3.26 mL, 40 mmol) and CuI (164 mg, 0.8 mmol) were added and the mixture was stirred at reflux temperature for 95 min. The mixture was cooled and partitioned between EtOAc and water. The organic solution was dried and the solvent evaporated to give a brown oil which was purified by chromatography, eluting with a gradient (0–10%) of EtOAc/pet. ether, to give (i) iodide **171** (2.27 g, 61%) as a yellow solid: mp (EtOAc/pet. ether) 108–109 °C; ^{1}H NMR δ 8.15 (s, 1 H, H-9), 7.70 (s, 1 H, H-5), 3.59–3.67 (m, 2 H, CH_2O), 3.13–3.25 (m, 2 H, CH_2), 2.93–3.05 (m, 2 H, CH_2), 2.73–2.84 (m, 1 H, H-7), 0.86 [s, 9 H, $SiC(CH_3)_3$], 0.04 [s, 6 H, $Si(CH_3)_2$]; ^{13}C NMR δ 155.2, 149.6, 147.6, 133.5, 122.5, 121.7, 114.6, 65.3, 41.9, 36.0, 35.7, 25.8 (3), 18.2, -5.43 (2). Anal. Calcd for $C_{17}H_{24}IN_3O_2Si$: C, 44.6; H, 5.3; N, 9.2. Found: C, 45.1; H, 5.4; N, 9.2%; and (ii) 1-oxide **172** (0.32 g, 12%) as a yellow solid: mp (EtOAc/pet. ether) 120–122 °C; ^{1}H NMR δ 8.91 (s, 1 H, H-3), 8.26 (s, 1 H, H-9), 7.80 (s, 1 H, H-5), 3.61–3.69 (m, 2 H, CH_2O), 3.16–3.27 (m, 2 H, CH_2),

2.96–3.07 (m, 2 H, CH_2), 2.74–2.85 (m, 1 H, H-7), 0.86 [s, 9 H, $SiC(CH_3)_3$], 0.04 [s, 6 H, $Si(CH_3)_2$]; ^{13}C NMR δ 154.2, 153.0, 149.4, 147.3, 134.6, 123.4, 114.6, 65.3, 41.9, 35.9, 35.6, 25.8 (3), 18.2, -5.43 (2). Anal. Calcd for $C_{17}H_{25}N_3O_2Si·¼H_2O$: C, 60.8; H, 7.7; N, 12.5. Found: C, 60.8; H, 7.4; N, 12.5%.

7-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-ethyl-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (173). Method E. Stille coupling of iodide **171** (2.27 g, 5.0 mmol) and Et_4Sn (1.47 mL, 7.5 mmol) with $Pd(PPh_3)_4$ (154 mg, 1.0 mmol) gave 1-oxide **173** (1.57 g, 88%) as a yellow solid: mp (EtOAc/pet. ether) 63–65 °C; ^1H NMR δ 8.23 (s, 1 H, H-9), 7.72 (s, 1 H, H-5), 3.59–3.66 (m, 2 H, CH_2O), 3.14–3.24 (m, 2 H, CH_2), 2.92–3.06 (m, 4 H, H-6, H-8), 2.72–2.83 (m, 1 H, H-7), 1.43 (t, J = 7.5 Hz, 3 H, CH_3), 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.04 [s, 6 H, $Si(CH_3)_2$]. Anal. Calcd for $C_{19}H_{29}N_3O_2Si$: C, 63.5; H, 8.1; N, 11.7. Found: C, 63.3; H, 8.2; N, 11.4%.

(3-Ethyl-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)methanol (35). Method D. Oxidation of 1-oxide **173** (273 mg, 0.76 mmol) with CF_3CO_3H (ca. 30 mmol) gave 1,4-dioxide **35** (35 mg, 18%) as a yellow solid: mp (MeOH/DCM) 157–158 °C; ^1H NMR δ 8.31 (s, 1 H, H-9), 8.26 (s, 1 H, H-5), 3.72 (br d, J = 5.8 Hz, 2 H, CH_2O), 3.25–3.35 (m, 2 H, CH_2), 3.20 (q, J = 7.5 Hz, 2 H, CH_2), 3.00–3.10 (m, 2 H, CH_2), 2.81–2.92 (m, 1 H, H-7), 1.43 (t, J = 7.5 Hz, 3 H, CH_3), OH not observed; HRMS (EI^+) calcd for $C_{13}H_{15}N_3O_3$ (M^+) *m/z* 261.1113, found 261.1115. Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.8; H, 5.8; N,16.1. Found: C, 59.6; H, 5.9; N, 15.9%.

Alternative Preparation of [5-(Acetylamino)-6-nitro-2,3-dihydro-1*H*-inden-2-yl]methyl Acetate (167).



2-Indanecarboxylic Acid (175). A mixture of 2-indanecarbonitrile[17] (**174**) (55.1 g, 385 mmol), cHCl (100 mL) and dioxane (500 mL) was stirred at 60–70 °C for 41 h. The mixture was cooled and dioxane evaporated to give a residue, which was suspended in 1 M HCl (300 mL) and stirred at 20 °C for 15 h. The solid was filtered, washed with water and dried to give acid **175** (54.1 g, 87%) as a white solid: mp (EtOAc/pet. ether) 128 °C (lit.[18] mp 130.2 °C); ^1H NMR δ 10.50 (br s, 1 H, CO_2H), 7.14–7.25 (m, 4 H, H-4, H-5, H-6, H-7), 3.21–3.43 (m, 5 H, H-1, H-2, H-3).

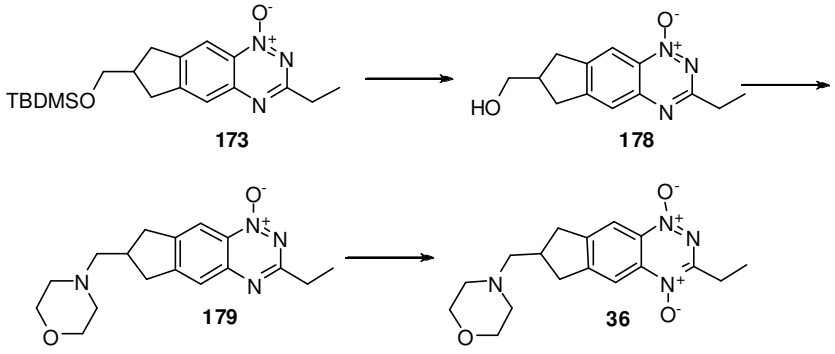
Nitration of 2-Indanecarboxylic Acid (175). 70% HNO_3 (46 mL, 798 mmol) was added dropwise (over 2 h 40 min) to a stirred solution of acid **175** (21.6 g, 133 mmol) in TFA (240 mL) at 0 °C and the solution stirred at 0 °C for 2 h 30 min. The mixture was poured onto ice (1.5 L) and stirred for 30 min. The mixture was extracted with DCM (3 ×

200 mL), the combined organic fraction dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–30%) of EtOAc/pet. ether, to give a mixture (2.2:1 ratio) of 5-nitro-2-indanecarboxylic acid (**164**) and 4-nitro-2-indanecarboxylic acid (**176**) isomers (23.4 g, 85%) as a yellow solid. Chromatography of a small sample gave (i) 5-nitro-2-acid **164** as a yellow solid: spectroscopically identical to that prepared above; and (ii) 4-nitro-2-acid **176** as needles: mp (EtOAc/pet. ether) 151–153 °C; ^{1}H NMR δ 8.04 (dd, *J* = 8.2 Hz, 0.6 Hz, 1 H, H-5), 7.52 (dd, *J* = 7.4 Hz, 0.6 Hz, 1 H, H-7), 7.36 (br t, *J* = 7.8 Hz, 1 H, H-6), 3.72–3.86 (m, 2 H, H-3), 3.31–3.52 (m, 3 H, H-1, H-2), CO_2H not observed. Anal. Calcd for $C_{10}H_9NO_4$: C, 58.0; H, 4.4; N, 6.8. Found: C, 58.1; H, 4.4; N, 6.8%.

Reduction of 5-Nitro and 4-Nitro-2-indanecarboxylic Acids (164) and (176). BH_3·DMS (10 M, 14.7 mL, 147 mmol) was added dropwise (over 20 min) to a stirred solution of acids **164** and **176** (ratio 2.2:1) (23.4 g, 113 mmol) in THF (150 mL) at 20 °C under N_2 and the solution was stirred for 90 min. The reaction was quenched with MeOH (150 mL) and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (10–30%) of EtOAc/pet. ether, to give a mixture (2.0:1 ratio) of (5-nitro-2,3-dihydro-1*H*-inden-2-yl)methanol (**165**) and (4-nitro-2,3-dihydro-1*H*-inden-2-yl)methanol (**177**) (20.9 g, 96%) as an oil which was used without further purification.

[5-(Acetylamino)-6-nitro-2,3-dihydro-1*H*-inden-2-yl]methyl Acetate (167). A solution of nitroindanes **165** and **177** (20.9 g, 109 mmol) in MeOH (200 mL) in two batches were stirred with 5% Pd/C (500 mg) under H_2 (60 psi) for 16 h. The mixtures were combined and filtered through Celite, washed with MeOH and the solvent evaporated to give the corresponding aniline derivative, which was treated with Ac_2O (103 mL, 1.09 mol) and Et_3N (182 mL, 1.31 mol) in DCM (400 mL) at 20 ° C for 25 h. The solvent was evaporated and the residue partitioned between EtOAc and water. The organic fraction was washed with water, dried and the solvent evaporated. The residue was dissolved in TFA (200 mL) and 70% HNO_3 (20 mL, 222 mmol) was added dropwise (over 1 h) at 0 °C and the reaction mixture was stirred at 20 °C for a further 30 min. The mixture was poured into ice/water (800 mL) and extracted with DCM (3 × 200 mL). The combined organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–25%) of EtOAc/pet. ether, to give acetate **167** (16.5 g, 52%) as a tan solid: spectroscopically identical to the sample prepared above.

3-Ethyl-7-(4-morpholinylmethyl)-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1,4-Dioxide (36).

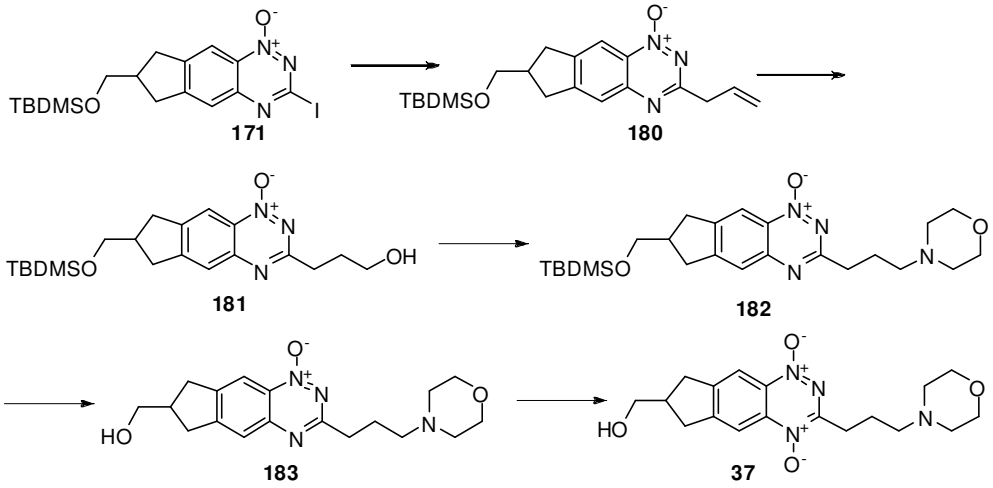


(3-Ethyl-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)methanol (178). A solution of silylether **173** (1.57 g, 4.37 mmol), and 1 N HCl (5 mL) in MeOH (40 mL) was stirred at 20 °C for 1 h. The solution was partitioned between EtOAc and water. The organic layer was dried, the solvent evaporated and the residue was purified by chromatography, eluting with a gradient (0–2%) of MeOH/DCM, to give alcohol **178** (0.84 g, 79%) as a yellow solid: mp (MeOH/EtOAc) 122–123 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.13 (s, 1 H, H-9), 7.77 (s, 1 H, H-5), 4.71 (t, *J* = 5.2 Hz, 1 H, OH), 3.42 (dd, *J* = 6.4 Hz, 5.2 Hz, 2 H, CH_2O), 3.11–3.20 (m, 2 H, CH_2), 2.86–2.96 (m, 4 H, CH_2), 2.59–2.71 (m, 1 H, H-7), 1.32 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 165.9, 153.9, 148.1, 146.8, 131.6, 122.5, 113.8, 63.5, 41.6, 35.3, 35.0, 29.6, 11.8. Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.7; H, 6.2; N, 17.1. Found: C, 63.9; H, 6.2; N, 17.4%.

3-Ethyl-7-(4-morpholinylmethyl)-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (179). Methanesulfonyl chloride (0.14 mL, 1.7 mmol) was added dropwise to a stirred solution of alcohol **178** (347 mg, 1.4 mmol) and iPr_2NEt (0.49 mL, 2.8 mmol) in DCM (25 mL) at 0 °C, and the solution was stirred at 0 °C for 1 h. Water (25 mL) was added and the mixture extracted with EtOAc (3 × 30 mL). The organic fraction was washed with dilute Na_2CO_3 solution (25 mL) and water (25 mL). The organic solution was dried and the solvent evaporated to give a yellow solid, which was treated with morpholine (0.37 mL, 4.3 mmol) in DMF (10 mL) at 100–110 °C for 10 h. The solution was diluted with EtOAc (200 mL) and washed with Na_2CO_3 solution (50 mL) and water (30 mL). The organic solution was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (50–70%) of EtOAc/pet. ether, to give 1-oxide **179** (398 mg, 89%) as a pale yellow solid: mp (EtOAc) 111–112 °C; ^{1}H NMR δ 8.24 (s, 1 H, H-9), 7.73 (s, 1 H, H-5), 3.73 (t, *J* = 4.6 Hz, 4 H, 2 × CH_2O), 3.19–3.29 (m, 2 H, CH_2), 3.02 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.88–2.99 (m, 2 H, CH_2), 2.77–2.88 (m, 1 H, H-7), 2.47 (t, *J* = 4.6 Hz, 4 H, 2 × CH_2N), 2.38 (d, *J* = 7.6 Hz, 2 H, CH_2), 1.43 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 167.1, 153.6, 147.7, 147.6, 132.3, 123.1, 114.7, 67.0 (2), 63.3, 53.9 (2), 37.6, 37.3, 36.7, 30.6, 12.3. Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 65.0; H, 7.1; N, 17.8. Found: C, 64.9; H, 7.1; N, 17.9%.

3-Ethyl-7-(4-morpholinylmethyl)-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1,4-Dioxide (36). Method D. Oxidation of 1-oxide **179** (503 mg, 1.6 mmol) with CF_3CO_3H (ca 16 mmol) gave 1,4-dioxide **36** (87 mg, 21%) as a yellow solid: mp (MeOH/DCM) 164–165 °C; ^{1}H NMR δ 8.31 (s, 1 H, H-9), 8.25 (s, 1 H, H-5), 3.72 (t, *J* = 4.6 Hz, 4 H, 2 × CH_2O), 3.17–3.34 (m, 4 H, CH_2), 2.80–2.95 (m, 3 H, CH_2, H-7), 2.45 (t, *J* = 4.6 Hz, 4 H, 2 × CH_2N), 2.38 (d, *J* = 7.7 Hz, 2 H, CH_2), 1.43 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR δ 155.7, 154.1, 149.5, 139.2, 134.0, 116.3, 114.3, 67.0 (2), 63.1, 53.9 (2), 37.7, 37.2, 36.6, 23.8, 9.2. Anal. Calcd for $C_{17}H_{22}N_4O_3$: C, 61.8; H, 6.7; N, 17.0. Found: C, 62.1; H, 6.7; N, 16.8%.

{3-[3-(4-Morpholinyl)propyl]-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl}methanol (37).



3-Allyl-7-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (180). Method E. Stille coupling of iodide **171** (5.88 g, 12.9 mmol) and allyltributyltin (4.35 mL, 14.1 mmol) with $Pd(PPh_3)_4$ (0.72 g, 0.64 mmol) gave alkene **180** (4.75 g, 99%) as a yellow solid: mp (EtOAc/pet. ether) 49–52 °C; ^{1}H NMR δ 8.23 (s, 1 H, H-9), 7.74 (s, 1 H, H-5), 6.17–6.24 (m, 1 H, CH), 5.20–5.34 (m, 2 H, CH_2), 3.75–3.80 (m, 2 H, CH_2), 3.59–3.67 (m, 2 H, CH_2O), 3.13–3.25 (m, 2 H, CH_2), 2.92–3.04 (m, 2 H, CH_2), 2.72–2.84 (m, 1 H, H-7), 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.04 [s, 6 H, $Si(CH_3)_2$]; ^{13}C NMR δ 164.1, 154.1, 148.3, 147.6, 133.0, 132.4, 123.0, 118.2, 114.5, 65.4, 42.0, 41.7, 35.8, 35.5, 25.8 (3), 18.3, -5.41 (2); HRMS calcd for $C_{20}H_{30}N_3O_2Si$ (MH^+) *m/z* 372.2107, found 372.2110. Anal. Calcd for $C_{20}H_{29}N_3O_2Si{\cdot}¼H_2O$: C, 63.9; H, 7.9; N, 11.2. Found: C, 63.9; H, 7.7; N, 10.8%.

3-[7-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-3-yl]-1-propanol (181). A solution of 9-BBN (0.5 M, 32.5 mL, 16.3 mmol) in THF was added to a stirred solution of alkene **180** (4.02 g, 10.8 mmol) in THF (50 mL) at 20 °C under N_2 and the mixture was stirred at 20 °C for 30 min. The mixture was cooled to 0 °C, a solution of sodium acetate (3 M, 25 mL, 75 mmol) and then H_2O_2 (70%, 25 mL, 468 mmol) were added carefully and stirred for 10 min. MeOH (100 mL) was added and the mixture stirred at 20 °C for 20 min. The mixture was partitioned between aqueous Na_2CO_3 solution and EtOAc. The combined organic fraction was dried and the solvent evaporated. The residue was purified by chromatography, using a gradient (50–70%) of EtOAc/pet. ether, to give alcohol **181** (2.08 g, 49%) as a pale yellow solid: mp (EtOAc/pet. ether) 93–94 °C; ^{1}H NMR δ 8.22 (s, 1 H, H-9), 7.72 (s, 1 H, H-5), 3.79 (br q, J = 5.1 Hz, 2 H, CH_2O), 3.59–3.67 (m, 2 H, CH_2OSi), 3.12–3.24 (m, 4 H, CH_2), 2.93–3.03 (m, 2 H, CH_2), 2.73–2.84 (m, 1 H, H-7), 2.30 (br s, 1 H, OH), 2.11–2.21 (m, 2 H, CH_2), 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.04 [s, 6 H, $Si(CH_3)_2$]; ^{13}C NMR δ 165.7, 154.2, 148.3, 147.3, 132.3, 122.8, 114.5, 65.4, 62.2, 42.0, 35.8, 35.5, 34.0, 30.6, 25.8 (3), 18.3, -5.41 (2). Anal. Calcd for $C_{20}H_{31}N_3O_3Si{\cdot}¼H_2O$: C, 61.7; H, 8.0; N, 10.8. Found: C, 61.5; H, 7.8; N, 10.9%.

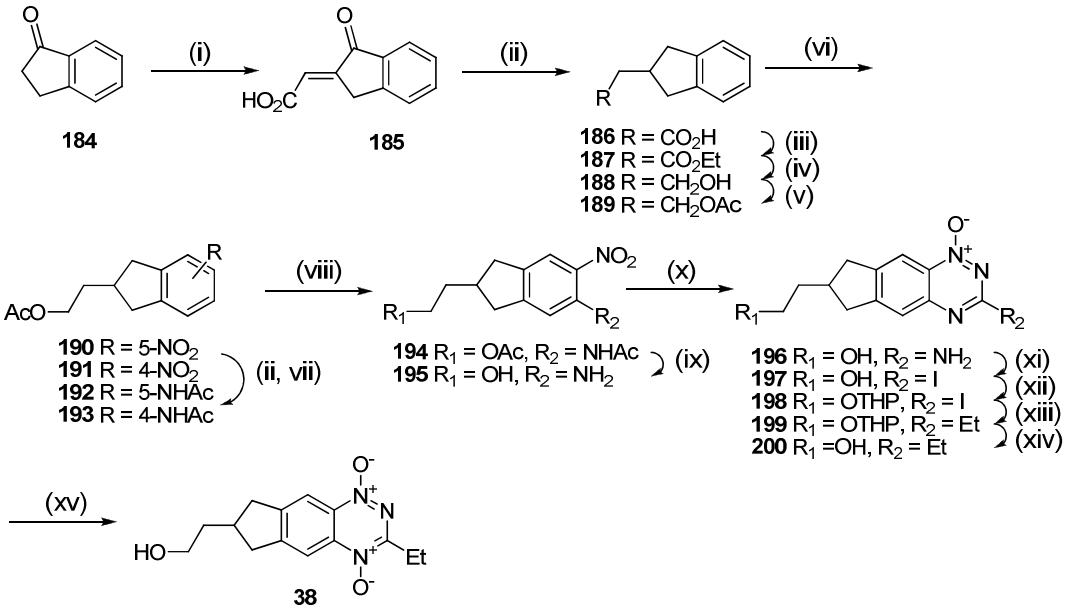
7-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-[3-(4-morpholinyl)propyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (182). Methanesulfonyl chloride (54 μL, 1.3 mmol) was added dropwise to a stirred solution of alcohol **181** (467 mg, 1.2 mmol), and

iPr_2NEt (0.42 mL, 2.4 mmol) in DCM (15 mL) at 0 °C, and the solution was stirred at 0 °C for 20 min. Water (15 mL) was added and the mixture extracted with EtOAc (3 × 30 mL). The organic fraction was washed with dilute Na_2CO_3 solution (30 mL) and water (30 mL). The organic solution was dried and the solvent evaporated to give a brown oil to which morpholine (1.05 mL, 12.0 mmol) in DMF (10 mL) was added and the solution stirred at 20 °C for 70 h. The solution was diluted with EtOAc (200 mL) and washed with Na_2CO_3 solution (30 mL) and water (30 mL). The organic solution was dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (0–30%) of EtOAc/DCM, to give 1-oxide **182** (492 mg, 67%) as an oil: ^{1}H NMR δ 8.23 (s, 1 H, H-9), 7.70 (s, 1 H, H-5), 3.55–3.67 (m, 6 H, CH_2OSi, 2 × CH_2O), 3.14–3.24 (m, 2 H, H-8), 2.93–3.07 (m, 4 H, CH_2, H-6), 2.72–2.84 (m, 1 H, H-7), 2.38–2.51 (m, 6 H, 2 × CH_2N), 2.03–2.14 (m, 2 H, CH_2), 0.87 [s, 9 H, $SiC(CH_3)_3$], 0.04 [s, 6 H, $Si(CH_3)_2$]; HRMS calcd for $C_{24}H_{39}N_4O_3Si$ (MH^+) *m/z* 459.2791, found 459.2784.

{3-[3-(4-Morpholinyl)propyl]-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl}methanol (183). A solution of silyl ether **182** (488 mg, 1.1 mmol), and 1 M HCl (1.18 mL) in MeOH (30 mL) was stirred at 20 °C for 3 h. The solvent was evaporated and the residue was crystallized from MeOH/EtOAc to give alcohol **183** (357 mg, 88%) as the hydrochloride salt: mp (MeOH/EtOAc) 210–212 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.19 (s, 1 H, HCl), 8.16 (s, 1 H, H-9), 7.80 (s, 1 H, H-5), 4.70 (br s, 1 H, OH), 3.75–3.99 (m, 4 H, 2 × CH_2O), 3.41 (d, *J* = 6.6 Hz, 2 H, CH_2O), 3.33–3.51 (m, 2 H, CH_2N), 3.11–3.27 (m, 4 H, CH_2N, H-8), 2.87–3.11 (m, 6 H, 2 × CH_2N, CH_2), 2.59–2.71 (m, 1 H, H-7), 2.22–2.32 (m, 2 H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 163.6, 154.2, 148.4, 146.7, 131.8, 122.5, 113.8, 63.5, 63.0 (2), 55.0, 50.9 (2), 41.6, 35.4, 35.1, 33.1, 20.8. Anal. Calcd for $C_{18}H_{24}N_4O_3 \cdot HCl \cdot ¼CH_3OH$: C, 56.4; H, 6.7; N, 14.4. Found: C, 56.3; H, 6.4; N, 14.6%.

{3-[3-(4-Morpholinyl)propyl]-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl}methanol (37). Method D. Oxidation of 1-oxide **183** (292 mg, 0.8 mmol) with CF_3CO_3H (ca. 8 mmol) gave 1,4-dioxide **37** (169 mg, 61%) as a dull orange solid: mp (MeOH/DCM) 112–114 °C; ^{1}H NMR δ 8.30 (s, 1 H, H-9), 8.26 (s, 1 H, H-5), 3.73 (d, *J* = 6.4 Hz, 2 H, CH_2O), 3.45 (br s, 4 H, 2 × CH_2O), 3.21–3.37 (m, 4 H, H-8, CH_2), 3.00–3.09 (m, 2 H, CH_2,), 2.83–2.92 (m, 1 H, H-7), 2.50 (t, *J* = 6.4 Hz, 2 H, CH_2N), 2.39 (br s, 4 H, 2 × CH_2N), 2.07–2.15 (m, 2 H, CH_2), OH not observed; ^{13}C NMR [$(CD_3)_2SO$] δ 154.1, 153.7, 149.3, 138.7, 133.5, 115.3, 113.3, 66.0 (2), 63.4, 57.2, 53.0 (2), 41.5, 35.6, 35.1, 28.0, 21.0. HRMS calcd for $C_{18}H_{25}N_4O_4$ (MH^+) *m/z* 361.1876, found 361.1878.

2-(3-Ethyl-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)ethanol (38).



(*E*)-2-(1-Oxo-1*H*-inden-2(3*H*)-ylidene)acetic Acid (185). A mixture of 1-indanone (**184**) (25 g, 190 mmol), glyoxylic acid (50% aqueous solution, 70 g, 470 mmol), and cH_2SO_4 (6.25 mL) in dioxane (25 mL) were stirred at reflux temperature for 4 h. The mixture was cooled, the product filtered off, washed with water and dried to give acid **185** (32.8 g, 92%) as a white solid: mp 201–203 °C (lit.[19] mp 205–206 °C); ^{1}H NMR [$(CD_3)_2SO$] δ 12.00 (br s, 1 H, OH), 7.73–7.80 (m, 2 H, H-5, H-7), 7.68 (br d, *J* = 7.7 Hz, 1 H, H-4), 7.49 (t, *J* = 7.9 Hz, 1 H, H-6), 6.55 (t, *J* = 2.4 Hz, 1 H, $CHCO_2$), 4.08 (d, *J* = 1.8 Hz, 2 H, H-3).

2-(2,3-Dihydro-1*H*-inden-2-yl)acetic Acid (186). A solution of acid **185** (10.0 g, 53 mmol) in MeOH (45 mL) and dioxane (150 mL) with Pd/C (10%, 1.0 g) was stirred under H_2 (40 psi) for 16 h. The mixture was filtered through Celite and the solvent evaporated to give acid **186** as an off-white solid: mp 85–88 °C (lit.[19] mp 89–91 °C); ^{1}H NMR δ 8.47 (br s, 1 H, OH), 7.08–7.18 (m, 4 H, H-4, H-5, H-6, H-7), 2.99–3.06 (m, 2 H, H-1, H-3), 2.69–2.74 (m, 1 H, H-2), 2.53–2.60 (m, 2 H, H-1, H-3), 2.48 (d, *J* = 7.4 Hz, 2 H, CH_2CO_2).

Ethyl 2-(2,3-Dihydro-1*H*-inden-2-yl)acetate (187). A solution of acid **186** (32.0 g, 180 mmol) in dry EtOH (250 mL) and cH_2SO_4 (2.0 mL) was stirred at reflux temperature under N_2 for 16 h. The solvent was evaporated, the residue partitioned between ice/water (200 mL) and DCM (50 mL) and the aqueous layer extracted with DCM (2 × 40 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and water, dried and the solvent evaporated to yield ester[20] **187** (33.3 g, 90%) as a brown oil: ^{1}H NMR δ 7.10–7.21 (m, 4 H, H-4, H-5, H-6, H-7), 4.15 (q, *J* = 7.1 Hz, 2 H, CH_2),3.10–3.45 (m, 2 H, H-1, H-3), 2.82–2.94 (m, 1 H, H-2), 2.62–2.68 (m, 2 H, H-1, H-3), 4.48 (d, *J* = 7.4 Hz, 2 H, CH_2CO_2), 1.27 (t, *J* = 7.1 Hz, 2 H, CH_3).

2-(2,3-Dihydro-1*H*-inden-2-yl)ethanol (188). A solution of ester **187** (68.8 g, 337 mmol) in dry THF (250 mL) was added to dropwise to a suspension of $LiAlH_4$ (20.0 g,

501 mmol) in dry THF (500 mL) at 0 °C and the resulting mixture was stirred for 1.5 h. EtOAc was added to quench excess $LiAlH_4$ and then aqueous H_2SO_4 solution (10%, 1 L) was added and the organic fraction separated. The aqueous solution was extracted with EtOAc (3 × 250 mL), and the combined organic fraction dried and the solvent evaporated to give alcohol[20] **188** (54.5 g, 100%) as a yellow oil: ^{1}H NMR δ 7.16–7.25 (m, 2 H, H_{arom}), 7.09–7.14 (m, 2 H, H_{arom}), 3.74 (t, *J* = 6.8 Hz, 2 H, CH_2O), 3.03–3.10 (m, 2 H, CH_2), 2.53–2.66 (m, 3 H, CH_2, CH), 1.82 (q, *J* = 6.8 Hz, 2 H, CH_2), OH not observed.

2-(2,3-Dihydro-1*H*-inden-2-yl)ethyl Acetate (189). Ac_2O (47 mL, 505 mmol) in DCM (50 mL) was added over 1 h to a stirred solution of alcohol **188** (54.5 g, 337 mmol), pyridine (52 mL, 981 mmol) and DMAP (1.65 g, 13 mmol) in DCM (400 mL) and the resulting solution was stirred at 20 °C for 16 h. H_2O (200 mL) was added, and the mixture stirred for 1 h. The organic fraction was washed with aqueous HCl solution (1 M, 100 mL) and H_2O (150 mL), dried and the solvent evaporated to give acetate **189** (68.4 g, 99%) as a pale brown oil: ^{1}H NMR δ 7.16–7.19 (m, 2 H, H_{arom}), 7.09–7.14 (m, 2 H, H_{arom}), 4.16 (t, *J* = 6.8 Hz, 2 H, CH_2O), 3.04–3.10 (m, 2 H, CH_2), 2.48–2.66 (m, 3 H, CH_2, CH), 2.05 (s, 3 H, $COCH_3$), 1.85 (q, *J* = 6.8 Hz, 2 H, CH_2); ^{13}C NMR δ 171.1, 143.0 (2), 126.2 (2), 124.4 (2), 63.5, 39.1 (2), 37.0, 34.3, 21.0. Anal Calcd for $C_{13}H_{16}O_2$: C, 76.4; H, 7.9. Found: C, 76.6; H, 7.9%.

Nitration of 2-(2,3-Dihydro-1*H*-inden-2-yl)ethyl Acetate (189). $Cu(NO_3)_2{\cdot}3H_2O$ (71 g, 294 mmol) was added in portions to a stirred solution of the acetate **189** (30 g, 147 mmol) in DCM (500 mL) and Ac_2O (500 mL) at 0 °C, the resulting mixture allowed to warm to 20 °C and stirred for 16 h. The reaction mixture was poured into ice-water/cNH_3 (2.5:1, 3.5 L) and the layers separated. The aqueous layer was extracted with EtOAc (2 × 500 mL), the combined organic layer dried, the solvent evaporated and the residue was purified by chromatography, eluting with 20% EtOAc/pet. ether, to give an inseparable mixture of 2-(5-nitro-2,3-dihydro-1*H*-inden-2-yl)ethyl acetate (**190**) and 2-(4-nitro-2,3-dihydro-1*H*-inden-2-yl)ethyl acetate (**191**) (ratio **190**:**191** = 3:1) (26.5 g, 72%) as a yellow oil which was used without further purification: Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.6; H, 6.1; N, 5.6. Found: C, 62.9; H, 6.1; N, 5.4%.

Reduction and Acetylation of 2-(5-Nitro-2,3-dihydro-1*H*-inden-2-yl)ethyl Acetate (190) and 2-(4-Nitro-2,3-dihydro-1*H*-inden-2-yl)ethyl Acetate (191). A solution of the nitro-compounds (**190** and **191**) (13.0 g, 52 mmol) in EtOH (50 mL) and MeOH (50 mL) with Pd/C (10%, 250 mg) was stirred under H_2 (45 psi) for 5 h. The solution was filtered through Celite and the solvent evaporated. The residue was dissolved in dioxane (130 mL), Ac_2O (12.3 mL, 130 mmol) added, and the mixture stirred at 20 °C for 16 h. H_2O (60 mL) and then aqueous NH_3 solution (ca 7 M, ca. 50 mL) was added until the solution was basic. The mixture was extracted with EtOAc (3 × 120 mL), the combined organic layer dried and the solvent evaporated to give an inseparable mixture of 2-(5-acetamido-2,3-dihydro-1*H*-inden-2-yl)ethyl acetate (**192**) and 2-(4-acetamido-2,3-dihydro-1*H*-inden-2-yl)ethyl acetate (**193**) (ratio **192**:**193** = 3:1) (13.5 g, 99%) as an orange oil which was used without further purification: HRMS calcd for $C_{15}H_{20}NO_3$ (MH^+) *m/z* 262.1443, found 262.1443.

2-(5-Acetamido-6-nitro-2,3-dihydro-1*H*-inden-2-yl)ethyl Acetate (194). $cHNO_3$ (70%, 13.6 mL, 214 mmol) was added dropwise to a solution of the acetates (**192** and **193**) (27 g, 103 mmol) in TFA (120 mL) at 0 °C and the solution allowed to warm to 20 °C over 1.5 h. The mixture was poured into ice/water (500 mL) and made basic with cNH_3 (ca. 150 mL). The mixture was extracted with DCM (3 × 250 mL), the combined organic layer dried and the solvent evaporated. The residue was filtered through a plug of silica, eluting with 50% EtOAc/pet. ether, the solvent evaporated and the residue recrystallized from EtOAc/pet. ether to give acetamide **194** (18.2 g, 55%) as a pale yellow solid: mp 89–91 °C; ^{1}H NMR δ 10.36 (br s, 1 H, NH), 8.55 (s, 1 H, H-4), 8.01 (s, 1 H, H-7), 4.16 (t, *J* = 6.6 Hz, 2 H, CH_2O), 3.06–3.18 (m, 2 H, H-1, H-3), 2.57–2.73 (m, 3 H, H-1, H-2, H-3), 2.27 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, $COCH_3$), 1.85 (q, *J* = 6.6 Hz, 2 H, CH_2); ^{13}C NMR δ 171.0, 167.0, 153.0, 138.6, 135.4, 133.9, 121.1, 117.6, 63.1, 39.7, 38.2, 37.4, 34.1, 25.6, 21.0. Anal Calcd for $C_{15}H_{18}N_2O_5$: C, 58.8; H, 5.9; N, 9.1. Found: C, 59.2; H, 6.0; N, 8.9%.

2-(5-Amino-6-nitro-2,3-dihydro-1*H*-inden-2-yl)ethanol (195). Acetamide **194** (24.0 g, 78 mmol) was suspended in MeOH (350 mL), H_2O (180 mL) and cHCl (150 mL), and stirred at reflux temperature for 1 h. The resulting orange solution was cooled to 20 °C and the solvent evaporated to give nitroaniline **195** (17.4 g, 100%) as an orange solid: mp 89–91 °C; ^{1}H NMR δ 7.90 (s, 1 H, H-4), 6.62 (s, 1 H, H-7), 6.02 (br s, 2 H, NH_2), 3.74 (t, *J* = 6.6 Hz, 2 H, CH_2O), 2.96–3.04 (m, 2 H, H-1, H-3), 2.49–2.60 (m, 3 H, H-1, H-2, H-3), 1.77 (q, *J* = 6.6 Hz, 2 H, CH_2), 1.40 (br s, 1 H, OH); ^{13}C NMR δ 153.4, 144.3, 133.0, 131.2, 120.9, 113.5, 61.7, 39.3, 38.2, 37.7, 37.2. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.4; N, 12.6. Found: C, 59.7; H, 6.3; N, 12.2%.

2-(3-Amino-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)ethanol (196). Method A. Reaction of nitroaniline **195** (17.6 g, 79 mmol) and cyanamide (19.8 g, 471 mmol) gave 1-oxide **196** (18.4 g, 94%) as a yellow-green solid: mp 230–235°C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.92 (s, 1 H, H-9), 7.33 (s, 1 H, H-5), 7.11 (br s, 2 H, NH_2), 4.45 (br s, 1 H, OH), 3.49 (t, *J* = 6.6 Hz, 2 H, CH_2O), 3.06–3.15 (m, 2 H, H-6, H-8), 2.59–2.69 (m, 2 H, H-6, H-8), 2.49–2.54 (m, 1 H, H-7), 1.63 (q, *J* = 6.6 Hz, 2 H, CH_2); HRMS (EI^+) calcd for $C_{12}H_{14}N_4O_2$ (M^+) *m/z* 246.1117, found 246.1115.

2-(3-Iodo-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)ethanol (197). *tert*-$BuNO_2$ (4.0 mL, 30.6 mmol) was added to a suspension of 1-oxide **196** (2.5 g, 10.2 mmol), CuI (2.04 g, 10.7 mmol) and I_2 (1.42 g, 5.6 mmol) in THF (50 mL) and the mixture stirred at reflux temperature for 4 h. The mixture was cooled to 20 °C, filtered and the solvent evaporated. The residue was dissolved in EtOAc (50 mL), washed with aqueous $Na_2S_2O_4$ (5%, 2 × 25 mL), dried, and the solvent evaporated. The residue was purified by chromatography, eluting with 5% MeOH/DCM, to give iodide **197** (1.49 g, 41%) as a pale yellow solid: mp 96–99 °C; ^{1}H NMR δ 8.15 (s, 1 H, H-9), 7.70 (s, 1 H, H-5), 3.79 (t, *J* = 6.5 Hz, 2 H, CH_2O), 3.25–3.33 (m, 2 H, H-6, H-8), 2.68–2.86 (m, 3 H, H-6, H-7, H-8), 1.84 (q, *J* = 6.5 Hz, 2 H, CH_2), 1.42 (br s, 1 H, OH); ^{13}C NMR δ 155.1, 149.4, 147.6, 133.5, 122.4, 121.8, 114.5, 61.4, 39.5, 39.2, 37.8, 37.5; HRMS calcd for $C_{12}H_{13}IN_3O_2$ (MH^+) *m/z* 358.0053, found 358.0053.

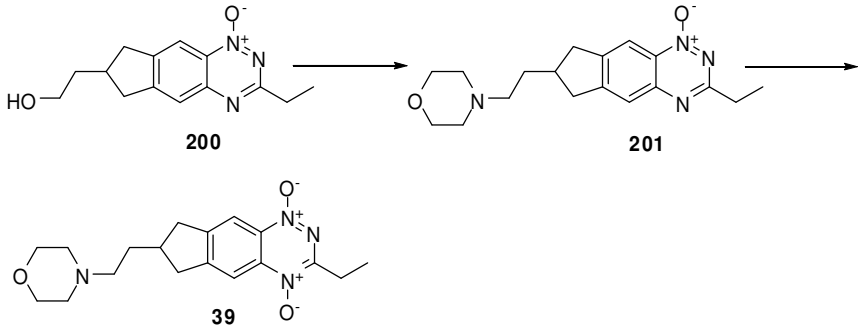
3-Iodo-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl)-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (198). Dihydropyran (2.6 mL, 28.6 mmol) was added dropwise to a solution of alcohol **197** (3.4 g, 9.5 mmol) and PPTS (0.60 g, 2.4 mmol) in DCM (150 mL) and the resulting solution stirred at 20 °C for 1 h. The solvent was evaporated and the residue purified by chromatography, eluting with 50% EtOAc/pet. ether, to give a mixture of diasteroisomers of iodide **198** (4.1 g, 98%) as a pale yellow solid: mp 80–82 °C; ^{1}H NMR δ 8.15 (s, 1 H, H-9), 7.70 (s, 1 H, H-5), 4.58–4.60 (m, 1 H, CHO), 3.84–3.86 (m, 2 H, CH_2O), 3.48–3.54 (m, 2 H, CH_2O), 3.24–3.29 (m, 2 H, H-6, H-8), 2.72–2.86 (m, 3 H, H-6, H-7, H-8), 1.72–1.88 (m, 4 H, CH_2), 1.52-1.61 (m, 4 H, CH_2); ^{13}C NMR δ 155.2, 149.6, 147.6, 133.5, 122.41 and 122.40, 121.8, 114.52 and 114.50, 99.1, 66.0, 62.6, 39.7 and 39.5, 39.4 and 39.2, 38.0, 35.1, 30.8, 25.4, 19.7; HRMS calcd for $C_{17}H_{21}IN_3O_3$ (MH^+) *m/z* 442.0628, found 442.0630.

3-Ethyl-7-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl)-7,8-dihydro-6*H*-indeno[5,6-e][1,2,4]triazine 1-Oxide (199). Method E. Stille coupling of iodide **198** (2.5 g, 5.7 mmol) and $SnEt_4$ (1.7 mL, 8.5 mmol) with $Pd(PPh_3)_4$ (0.65 g, 0.57 mmol) gave a mixture of diastereoisomers of 1-oxide **199** (1.56 g, 80%) as a pale green oil: ^{1}H NMR δ 8.22 (s, 1 H, H-9), 7.71 (s, 1 H, H-5), 4.59–4.61 (m, 1 H, OCH), 3.85–3.89 (m, 2 H, OCH_2), 3.49–3.53 (m, 2 H, CH_2), 3.24–3.31 (m, 2 H, H-6, H-8), 3.02 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.64–2.87 (m, 3 H, H-6, H-7, H-8), 1.53–1.87 (m, 8 H, 4 × CH_2), 1.43 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 166.5, 153.4, 147.5, 147.1, 131.7, 122.16 and 122.15, 113.8, 98.5, 65.6, 62.0, 39.0 and 38.9, 38.6 and 38.5, 37.4, 34.6, 30.2, 30.1, 24.9, 19.2, 11.8.

2-(3-Ethyl-1-oxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)ethanol (200). Methanesulfonic acid (3 drops) was added to a stirred solution of tetrahydropyranyl ether **199** (1.10 g, 3.2 mmol) in MeOH (30 mL) and the mixture was stirred at 20 °C for 1 h. The solvent was evaporated and the residue purified by chromatography, eluting with 5% MeOH/DCM, to give 1-oxide **200** (783 mg, 94%) as a yellow solid: mp 96–99 °C; ^{1}H NMR δ 8.23 (s, 1 H, H-9), 7.72 (s, 1 H, H-5), 3.80 (t, *J* = 6.5 Hz, 2 H, CH_2O), 3.25–3.33 (m, 2 H, H-6, H-8), 3.02 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.68–2.86 (m, 3 H, H-6, H-7, H-8), 1.84 (q, *J* = 6.5 Hz, 2 H, CH_2), 1.43 (t, *J* = 7.6 Hz, 3 H, CH_3), 1.40–1.45 (m, 1 H, OH); ^{13}C NMR δ 167.1, 153.8, 147.9, 147.6, 132.3, 122.7, 114.3, 61.5, 39.4, 39.1, 37.9, 37.5, 30.6, 12.3; HRMS calcd for $C_{14}H_{18}N_3O_2$ (MH^+) *m/z* 260.1399, found 260.1397.

2-(3-Ethyl-1,4-dioxido-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazin-7-yl)ethanol (38). Method D. Oxidation of 1-oxide **200** (144 mg, 0.56 mmol) with CF_3CO_3H (ca. 5.6 mmol) gave (i) starting material **200** (35 mg, 24%) and (ii) 1,4-dioxide **38** (92 mg, 60%) as a yellow solid: mp 152–155 °C; ^{1}H NMR δ 8.29 (s, 1 H, H-9), 8.24 (s, 1 H, H-5), 3.77–3.82 (m, 2 H, CH_2O), 3.29–3.38 (m, 2 H, H-6, H-8), 3.20 (q, *J* = 7.5 Hz, 2 H, CH_2), 2.73–2.90 (m, 3 H, H-6, H-7, H-8), 1.84 (q, *J* = 6.6 Hz, 2 H, CH_2), 1.43 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.34 (t, *J* = 4.9 Hz, 1 H, OH); ^{13}C NMR δ 155.8, 154.3, 149.8, 139.2, 133.8, 115.9, 113.9, 61.3, 39.6, 39.1, 37.8, 37.5, 23.9, 9.3. Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.1; H, 6.2; N, 15.3. Found: C, 60.8; H, 6.3; N, 14.9%.

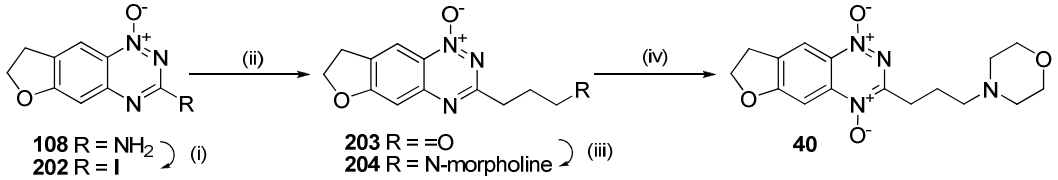
3-Ethyl-7-[2-(4-morpholinyl)ethyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1,4-Dioxide (39).



3-Ethyl-7-[2-(4-morpholinyl)ethyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1-Oxide (201). Methanesulfonyl chloride (0.18 mL, 2.3 mmol) was added to a solution of alcohol **200** (457 mg, 1.76 mmol) and Et_3N (0.37 mL, 2.6 mmol) in DCM (30 mL) at 0 °C, and the mixture was stirred for 1 h. Saturated aqueous $KHCO_3$ solution (20 mL) was added and the aqueous layer extracted with DCM (20 mL). The combined organic layer was dried and the solvent evaporated to give a pale yellow solid (560 mg, 94%) that was used without further purification. The mesylate (560 mg, 1.7 mmol) was dissolved in dry DMF (15 mL), and morpholine (0.22 mL, 2.5 mmol) and Et_3N (0.35 mL, 2.5 mmol) added. The solution was stirred at 100 °C for 3.5 h, cooled and the solvent evaporated. The residue was purified by chromatography, eluting with 5% MeOH/DCM, to give 1-oxide **201** (265 mg, 50%) as a brown oil: ^{1}H NMR δ 8.22 (s, 1 H, H-9), 7.71 (s, 1 H, H-5), 3.73 (t, *J* = 4.7 Hz, 4 H, 2 × CH_2O), 3.23–3.30 (m, 2 H, H-6, H-8), 3.01 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.75–2.84 (m, 2 H, H-6, H-8), 2.58–2.62 (m, 1 H, H-7), 2.43–2.48 (m, 6 H, 3 × CH_2N), 1.73–1.79 (m, 2 H, CH_2), 1.43 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 167.1, 153.8, 147.9, 147.6, 132.3, 122.7, 114.4, 66.9 (2), 57.5, 53.8 (2), 39.4, 39.1, 38.8, 32.0, 30.6, 12.3; HRMS (EI$^+$) calcd for $C_{18}H_{24}N_4O_2$ (M^+) *m/z* 328.1899, found 328.1899.

3-Ethyl-7-[2-(4-morpholinyl)ethyl]-7,8-dihydro-6*H*-indeno[5,6-*e*][1,2,4]triazine 1,4-Dioxide (39). Method D. Oxidation of 1-oxide **201** (265 mg, 0.8 mmol) with CF_3CO_3H (ca. 8 mmol) gave (i) starting material **201** (62 mg, 23%) and (ii) 1,4-dioxide **39** (83 mg, 30%) as a yellow solid which was converted to the hydrochloride salt: mp 131–133 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 13.40 (br s, 1 H, HCl), 8.30 (s, 1 H, H-9), 8.25 (s, 1 H, H-5), 4.32 (t, *J* = 12.0 Hz, 2 H, CH_2), 4.00 (dd, *J* = 12.0, 3.0 Hz, 2 H, H-6, H-8), 3.48 (d, *J* = 12.0 Hz, 2 H, H-6, H-8), 3.32–3.39 (m, 2 H, CH_2), 3.20 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.06–3.09 (m, 2 H, CH_2), 2.88–2.94 (m, 4 H, 2 × CH_2), 2.67–2.73 (m, 1 H, H-7), 2.25–2.28 (m, 2 H, CH_2), 1.43 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 156.0, 152.6, 148.2, 139.3, 133.9, 116.3, 114.3, 63.6 (2), 56.5, 52.0 (2), 39.1, 38.6, 37.8, 28.5, 23.9, 9.3; HRMS calcd for $C_{18}H_{25}N_4O_3$ (MH^+) *m/z* 344.1848, found 344.1846.

3-[3-(4-Morpholinyl)propyl]-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazine 1,4-Dioxide (40).



3-Iodo-7,8-dihydrobenzofuro[6,5-*e*][1,2,4]triazine 1-Oxide (202). *tert*-$BuNO_2$ (90%, 3.8 mL, 28.8 mmol) was added to a stirred solution of 1-oxide **108** (2.0 g, 9.8 mmol), CH_2I_2 (3.8 mL, 46.7 mmol) and CuI (1.87 g, 9.8 mmol) in THF (40 mL), and the mixture was stirred at reflux temperature for 7 h. The mixture was cooled to 20 °C, the solvent was evaporated and the residue purified by chromatography, eluting with a gradient (2–10%) of MeOH/DCM, to give iodide **202** (1.50 g, 49%) as a pale yellow solid: mp 192–194 °C; ^{1}H NMR δ 8.19 (t, *J* = 1.6 Hz, 1 H, H-9), 7.10 (s, 1 H, H-5), 4.83 (t, *J* = 8.4 Hz, 2 H, H-7), 3.44 (dt, *J* = 8.4, 1.6 Hz, 2 H, H-8); ^{13}C NMR δ 167.0, 150.4, 136.2, 123.3, 116.4, 105.8, 103.7, 73.4, 29.0; HRMS (EI^+) calcd for $C_9H_6IN_3O_2$ (M^+) *m/z* 314.9505, found 314.9501.

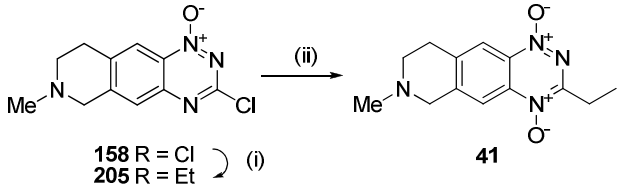
3-(1-Oxido-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazin-3-yl)propanal (203). $Pd(OAc)_2$ (53 mg, 0.24 mmol) was added to a N_2-purged solution of iodide **202** (1.50 g, 4.8 mmol), allyl alcohol (0.91 mL, 13.3 mmol), nBu_4NBr (1.38 g, 4.3 mmol) and $NaHCO_3$ (880 mg, 10.5 mmol) in dry DMF (40 mL) and the solution was stirred at 60 °C for 24 h under N_2. The mixture was quenched with saturated aqueous NH_4Cl solution (150 mL) and filtered. The filtrate was extracted with EtOAc (5 × 50 mL), dried and the solvent evaporated. The residue was purified by chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give aldehyde **203** as a dark oil, which was crystallised from MeOH (532 mg, 45%) as a pale purple solid: mp 140–142 °C; ^{1}H NMR δ 9.92 (s, 1 H, CHO), 8.26 (t, *J* = 1.5 Hz, 1 H, H-9), 7.10 (s, 1 H, H-5), 4.80 (t, *J* = 8.4 Hz, 2 H, H-7), 3.43 (dt, *J* = 8.4, 1.5 Hz, 2 H, H-8), 3.29–3.33 (m, 2 H, CH_2), 3.06–3.10 (m, 2 H, CH_2); ^{13}C NMR δ 200.4, 166.5, 165.0, 150.3, 135.2, 129.0, 116.2, 104.0, 73.1, 40.5, 29.4, 29.0; HRMS calcd for $C_{12}H_{12}N_3O_3$ (MH^+) *m/z* 246.0879, found 246.0881.

3-[3-(4-Morpholinyl)propyl]-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazine 1-Oxide (204). Morpholine (0.22 mL, 2.52 mmol) was added to a solution of aldehyde **203** (220 mg, 0.90 mmol) in MeOH (10 mL) and DMF (10 ml), and the solution stirred for 30 min. $NaCNBH_3$ (176 mg, 2.80 mmol) was added, followed by HOAc (0.12 mL) and the mixture stirred at 20 °C for 30 min. The solvent was evaporated and the residue partitioned between DCM (40 mL) and water (40 mL). The aqueous phase was extracted with DCM (2 × 40 mL), the combined organic phase was dried and the solvent evaporated. The residue was purified by chromatography, eluting with 10% MeOH/EtOAc, to give 1-oxide **204** (210 mg, 74%) as a pale brown solid: mp 96–99 °C; ^{1}H NMR δ 8.27 (t, *J* = 1.6 Hz, 1 H, H-9), 7.11 (s, 1 H, H-5), 4.80 (t, *J* = 8.4 Hz, 2 H, H-8), 3.59 (t, *J* = 4.6 Hz, 4 H, 2 × CH_2O), 3.43 (dt, *J* = 8.4, 1.6 Hz, 2 H, H-7), 2.97–3.01 (m, 2 H, CH_2), 2.44–2.48 (m, 2 H, CH_2), 2.41 (t, *J* = 4.5 Hz, 4 H, 2 × CH_2N), 2.03–2.11 (m, 2 H, CH_2); ^{13}C NMR δ 167.1, 166.4, 150.5, 134.8, 128.9, 116.2, 103.9, 73.0, 67.0 (2), 58.3, 53.5 (2), 53.4, 27.0, 24.9. Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.8; H, 6.4; N, 17.7. Found: C, 60.7; H, 6.5; N, 17.7%.

3-[3-(4-Morpholinyl)propyl]-7,8-dihydrofuro[2,3-*g*][1,2,4]benzotriazine 1,4-Dioxide (40). Method D. Oxidation of 1-oxide **204** (200 mg, 0.63 mmol) with CF_3CO_3H (ca. 6 mmol) gave 1,4-dioxide **40** (88 mg, 43%) as a dark yellow solid: mp 150–154 °C; ^{1}H NMR δ 8.28 (t, *J* = 1.6 Hz, 1 H, H-9), 7.68 (s, 1 H, H-5), 4.87 (t, *J* = 8.5 Hz, 2 H, H-7), 3.48 (dt, *J* = 8.5, 1.5 Hz, 2 H, H-8), 3.44 (t, *J* = 4.4 Hz, 4 H, 2 × CH_2O), 3.22 (t, *J* = 7.2

Hz, 2 H, CH_2), 2.49 (t, *J* = 6.5 Hz, 2 H, CH_2), 2.38 (t, *J* = 4.4 Hz, 4 H, 2 × CH_2N), 2.06–2.13 (m, 2 H, CH_2); ^{13}C NMR δ 166.7, 156.1, 141.7, 136.3, 130.2, 117.8, 96.1, 73.5, 67.0 (2), 58.0, 53.5 (2), 29.0, 28.8, 21.8. Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.8; H, 6.1; N, 16.9. Found: C, 57.8; H, 6.1; N, 16.6%.

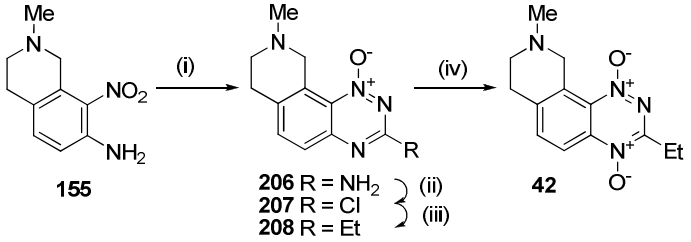
3-Ethyl-7-methyl-6,7,8,9-tetrahydro[1,2,4]triazino[6,5-*g*]isoquinoline 1,4-Dioxide (41).



3-Ethyl-7-methyl-6,7,8,9-tetrahydro[1,2,4]triazino[6,5-*g*]isoquinoline 1-Oxide (205). Method E. Stille coupling of chloride **158** (750 mg, 3.0 mmol) and Et_4Sn (1.2 mL, 6.0 mmol) with $Pd(PPh_3)_4$ (350 mg, 0.3 mmol) gaive 1-oxide **205** (590 mg, 81%) as a brown solid: mp 129–131 °C; ^1H NMR δ 8.21 (s, 1 H, H-10), 7.63 (s, 1 H, H-5), 3.79 (s, 2 H, H-6), 3.16 (t, *J* = 6.0 Hz, 2 H, H-8), 3.02 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.77 (t, *J* = 6.0 Hz, 2 H, H-9), 2.51 (s, 3 H, NCH_3), 1.43 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 167.3, 145.8, 144.6, 138.2, 131.7, 125.0, 118.8, 58.1, 52.3, 45.9, 30.7, 29.6, 12.2; MS (APCI) *m/z* 245 (MH^+, 100%). Anal. Calcd for $C_{13}H_{16}N_4O·¼H_2O$: C, 62.5; H, 6.7; N, 22.4. Found: C, 62.6; H, 6.6; N, 22.4%.

3-Ethyl-7-methyl-6,7,8,9-tetrahydro[1,2,4]triazino[6,5-*g*]isoquinoline 1,4-Dioxide (41). Method D. Oxidation of 1-oxide **205** (590 mg, 2.4 mmol) with CF_3CO_3H (ca. 25 mmol) gave 1,4-dioxide **41** (107 mg, 17%) as a yellow solid: mp 124–128 °C; ^1H NMR δ 8.23 (s, 1 H, H-10), 8.18 (s, 1 H, H-5), 3.83 (s, 2 H, H-6), 3.15–3.24 (m, 4 H, CH_2, H-8), 2.78 (t, *J* = 6.0 Hz, 2 H, H-9), 2.51 (s, 3 H, NCH_3), 1.43 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR δ 149.3, 145.5, 136.5, 135.3, 129.3, 120.5, 116.3, 58.1, 51.9, 45.8, 29.6, 23.9, 9.3; MS (APCI) *m/z* 261 (MH^+, 100%). Anal. Calcd for $C_{13}H_{16}N_4O_2·¼CH_2Cl_2$: C, 56.5; H, 5.9; N, 19.9. Found: C, 56.6; H, 5.9; N, 19.7%.

3-Ethyl-9-methyl-7,8,9,10-tetrahydro[1,2,4]triazino[5,6-*h*]isoquinoline 1,4-Dioxide (42).



9-Methyl-7,8,9,10-tetrahydro[1,2,4]triazino[5,6-*h*]isoquinolin-3-amine 1-Oxide (206). Method A. Reaction of 8-nitroaniline **155** (510 mg, 2.5 mmol) and cyanamide (460 mg, 10.9 mmol) gave 1-oxide **206** (360 mg, 63%) as a brown solid: mp 226–229 °C; ^1H NMR [$(CD_3)_2SO$] δ 7.50 (d, *J* = 8.6 Hz, 1 H, H-5), 7.32 (d, *J* = 8.6 Hz, 1 H, H-6), 7.09 (br s, 2 H, NH_2), 4.09 (s, 2 H, H-10), 2.88 (t, *J* = 5.7 Hz, 2 H, H-7), 2.58 (t, *J* = 5.7 Hz, 2

H, H-8), 2.40 (s, 3 H, NCH_3); MS (APCI) *m/z* 232 (MH^+, 100%). Anal. Calcd for $C_{11}H_{13}N_5O \cdot ¼CH_3OH$: C, 56.5; H, 5.9; N, 29.3. Found: C, 56.6; H, 5.6; N, 29.1%.

3-Chloro-9-methyl-7,8,9,10-tetrahydro[1,2,4]triazino[5,6-*h*]isoquinoline 1-Oxide (207). Method B. Reaction of 1-oxide **206** (295 mg, 1.3 mmol) $NaNO_2$ (105 mg, 1.5 mmol), with subsequent chlorination with DMF/$POCl_3$, gave chloride **207** (240 mg, 75%) as a yellow solid: mp 200–205 °C; ^{1}H NMR δ 7.75 (d, *J* = 8.6 Hz, 1 H, H-5), 7.69 (d, *J* = 8.6 Hz, 1 H, H-6), 4.32 (s, 2 H, H-10), 3.07–3.13 (m, 2 H, H-7), 2.74 (t, *J* = 5.9 Hz, 2 H, H-8), 2.57 (s, 3 H, NCH_3); ^{13}C NMR δ 155.9, 148.1, 138.7, 138.1, 132.5, 130.4, 125.7, 57.2, 50.3, 45.8, 30.9; MS (APCI) *m/z* 251 (MH^+, 100%), 253 (MH^+, 35%). Anal. Calcd for $C_{11}H_{11}ClN_4O$: C, 52.7; H, 4.4; N, 22.4; Cl, 14.1. Found: C, 52.7; H, 4.4; N, 22.2; Cl, 14.4%.

3-Ethyl-9-methyl-7,8,9,10-tetrahydro[1,2,4]triazino[5,6-*h*]isoquinoline 1-Oxide (208). Method E. Stille coupling of chloride **207** (225 mg, 0.9 mmol) and Et_4Sn (0.36 mL, 1.8 mmol) with $Pd(PPh_3)_4$ (108 mg, 0.09 mmol) gave 1-oxide **208** (130 mg, 60%) as a brown solid: mp (MeOH) 99–102 °C; ^{1}H NMR δ 7.75 (d, *J* = 8.6 Hz, 1 H, H-5), 7.62 (d, *J* = 8.6 Hz, 1 H, H-6), 4.38 (s, 2 H, H-10), 3.05–3.11 (m, 2 H, H-7), 2.98 (q, *J* = 7.6 Hz, 2 H, CH_2), 2.73 (t, *J* = 5.9 Hz, 2 H, H-8), 2.57 (s, 3 H, NCH_3), 1.42 (t, *J* = 7.6 Hz, 3 H, CH_3); ^{13}C NMR δ 167.1, 148.4, 137.1, 136.9, 136.3, 129.7, 126.1, 57.4, 50.5, 45.9, 30.7, 30.2, 12.2; MS (APCI) *m/z* (MH^+, 100%). HRMS calcd for $C_{13}H_{17}N_4O$ (MH^+) *m/z* 245.1402, found 245.1403.

3-Ethyl-9-methyl-7,8,9,10-tetrahydro[1,2,4]triazino[5,6-*h*]isoquinoline 1,4-Dioxide (42). Method D. Oxidation of 1-oxide **208** (120 mg, 0.5 mmol) with CF_3CO_3H (ca. 5 mmol) gave 1,4-dioxide **42** (24 mg, 19%) as a red solid: mp 117–121 °C; ^{1}H NMR δ 8.35 (d, *J* = 8.8 Hz, 1 H, H-5), 7.70 (d, *J* = 8.8 Hz, 1 H, H-6), 4.41 (s, 2 H, H-10), 3.18 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.12 (br t, *J* = 5.8 Hz, 2 H, H-7), 2.74 (t, *J* = 5.8 Hz, 2 H, H-8), 2.58 (s, 3 H, NCH_3), 1.42 (t, *J* = 7.5 Hz, 3 H, CH_3); MS (APCI) *m/z* 261 (MH^+, 100%); HRMS calcd for $C_{13}H_{17}N_4O_2$ (MH^+) *m/z* 261.1352, found: 261.1354.

General Method F. Partition coefficients. Octanol-water partition coefficients ($P_{7.4}$) were measured using the shake flask method, using GPR-grade octanol (BDH Laboratory Supplies).[21] Briefly, lipophilic drugs were dissolved directly in octanol-saturated PBS (137 mM NaCl, 2.68 mM KCl, 1.47 mM KH_2PO_4, 8.10 mM Na_2HPO_4, pH 7.4), and hydrophilic drugs in PBS-saturated octanol, to 25–100 μM. Equal volumes of PBS and octanol were mixed on a Bellco roller drum (Bellco Glass, Inc., New Jersey) at 20 rpm for 3 h at ambient temperature. The two solvent layers were separated after a brief spin and analyzed by HPLC directly (aqueous layer), or after addition of 4 volumes of methanol (organic layer).

General Method G. MCL cultures. MCLs were grown from human HT29 colon carcinoma cells as described elsewhere.[22] In brief, 1×10^6 cells were seeded on collagen-coated Teflon microporous support membranes (Biopore™; average thickness 30 μm) in Millicell-CM™ cell culture inserts (Millipore Corporation, Bedford, MA) and grown for 3 days submerged in stirred culture medium (αMEM; GIBCO BRL, Grand Island, NY)

supplemented with 10% heat-inactivated fetal calf serum (GIBCO BRL, Auckland), penicillin (100 U/mL), streptomycin (100 μg/mL) and 2 mM L-glutamine.

General Method H. Determination of diffusion coefficient, *D*, in MCLs. Flux through MCLs was measured in a diffusion chamber as described,[23] using MCLs equilibrated for 60 min with 95% O_2/5% CO_2 at 37 °C in the same medium as above. BTOs were added to the "donor" compartment to 50 μM, along with [^{14}C]urea (Amersham Pharmacia Biotech; 40 MBq/mmol, 7.5 kBq/mL), D-[2-^{3}H]mannitol (ICN Pharmaceuticals Inc., Irvine, CA; 40 MBq/mmol, 20 kBq/mL) and 9(10*H*)-acridone (Sigma-Aldrich, Castle Hill, NSW; 10 μM). Samples were taken from both the donor and receiver compartment for up to 5 h. An aliquot was assayed for radioactivity by dual-label liquid scintillation counting in a Packard Tri-Carb 1500 Liquid Scintillation Analyzer (Packard Instrument Company, Meriden, CT) using Emulsifier-Safe water-accepting scintillant (Packard), and the balance frozen for subsequent HPLC analysis. The concentration-time profiles of [^{14}C]urea in the donor and receiver compartments were numerically fitted to Fick's second law to estimate the average thickness of each MCL (*ca* 175 μm), using the measured value of *D* for [^{14}C]urea in HT29 MCLs.[22] The effective diffusion coefficient of each compound was also determined in the collagen-coated Teflon porous support membrane (D_s) without an MCL present. This latter parameter also takes into account the effect of the unstirred boundary layers on each side of the membrane or MCL. *D* was then determined by fitting the concentration-time profile in both the donor and receiver simultaneously to a Fickian diffusion model with the support membrane and MCL in series as described previously,[23] with addition of reaction terms in the MCL when necessary.

General Method I. HPLC. Samples (200 μL) were deproteinized by addition of 4 μL of 70% (v/v) perchloric acid and chilling on ice followed by centrifugation (12,000 × *g* for 5 min at 4 °C) and subsequent neutralization of the supernatant with 50% (v/v) ammonia (31.5 μL/mL supernatant). Concentrations of the BTOs were determined by reversed-phase HPLC (Alltima C_8 5 μ column, 150 × 2.1 mm; Alltech Associated Inc, Deerfield, IL) using an Agilent HP1100 equipped with a diode-array detector. Mobile phases were gradients of 80% acetonitrile/20% H_2O (v/v) in 450 mM ammonium formate, pH 4.5, at 0.3 mL/min. Quantitation was based on calibration curves in mobile phase (0.1–100 μM), corrected for recovery from medium with serum determined by assaying known concentrations (0.1–100 μM) for each compound under the same conditions.

General Method J. IC_{50} Assays. IC_{50} assays were determined for BTOs under aerobic and hypoxic conditions as previously described.[24] For each experiment, compounds were simultaneously tested under both oxic and hypoxic conditions against the HT29 and SiHa cell lines using a 4 hr drug exposure, and included TPZ as an independent internal control. In all cases, 8-methyl-5-nitroquinoline was used as a second internal control to confirm that strict hypoxia was present during the experiment.[25] Plates were stained as described previously[26] and IC_{50} values determined. Final data was pooled from a series of seven independent experiments and is calculated using inter-experimental means.

General Method K. Metabolism experiments. The potency of BTOs towards anoxic HT29 cells was also assessed using loss of colony forming potential (clonogenicity) as the endpoint, and metabolic consumption of the compounds was assessed in the same experiments as described previously for TPZ.[22] Suspensions of HT29 cells (10 mL at 1 or 2 $\times 10^6$cells/mL) were incubated in αMEM without serum in magnetically stirred 20 mL bottles under flowing 5% CO_2/95% N_2 for 90 min. Drugs were then introduced using deoxygenated DMSO stock solutions to give initial concentrations in the medium (C_0) providing approximately 10% cell survival after one hour. DMSO-only controls were included in each experiment. Samples (0.5 mL) were removed at intervals (typically 5 min, 30 min, 1, 2, 3 h), centrifuged to remove cells, and supernatant stored at –80 °C for subsequent HPLC analysis. The cell pellet was resuspended in fresh αMEM with 5% FBS and serial dilutions made into 5 mL of this medium in 60 mm diameter cell culture dishes. These were incubated at 37 °C for 14 days, stained with methylene blue and colonies (> 50 cells) counted to determine the plating efficiency (*PE*). Surviving fraction was calculated for each time as *PE*(treated)/*PE*(controls). Cell viability was checked with a hemocytometer at the end of drug exposure by their ability to exclude 0.4% trypan blue, and was >85% in all experiments. Oxygen in solution was checked using an OxyLite 2000 O_2 luminescent fiber optic probe (Oxford Optronix Ltd, UK) by methods previously described[22] and oxygen concentrations were < 0.1 μM O_2 in all cases. A reference vial with TPZ (30 μM) was also included in all experiments for quality control.

References

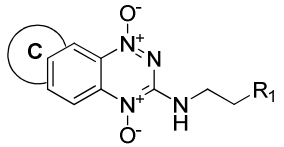
1. Mason, J. C.; Tennant, G. Heterocyclic N-oxides. Part VI. Synthesis and nuclear magnetic resonance spectra of 3-aminobenzo-1,2,4-triazines and their mono- and di-N-oxides. *J. Chem. Soc. (B)* **1970**, 911–916.
2. Hay, M. P.; Hicks, K. O.; Pruijn, F. B.; Pchalek, K.; Siim, B. G.; Wilson, W. R.; Denny, W. A. Pharmacokinetic/pharmacodynamic model-guided identification of hypoxia-selective 1,2,4-benzotriazine 1,4-dioxides with antitumor activity: The role of extravascular transport. *J. Med. Chem.* **2007**, 50, 6392–6404.
3. Schroeder, E.; Lehmann, M.; Rufer, C.; Boettcher, I. Non-steroidal antiinflammatory agents. 6. Antiinflammatory methanesulfonamides. I. *European J. Med. Chem.* **1982**, *17*, 35–42.
4. Murray, R. J.; Cromwell, N. H. Mobile keto allyl systems. 18. Synthesis and charge-transfer interactions of 2-(α-aminobenzyl)-1-indenones. *J. Org. Chem.* **1976**, *41*, 3540–3545.
5. Daly, C. M.; Iddon, B.; Suschitzky, H.; Jordis, U.; Sauter, F. Synthesis of novel 2,3-dihydro-8H-thieno[2,3-d]azepines and 1,2,3,4-tetrahydro-1H-3-benzazepines via photolysis of 6-azido-2,3-dihydrobenzo[b]thiophene and 6-azido-1,2,3,4-tetrahydronaphthalene. *J. Chem. So. Perkin Trans 1* **1988**, 1933–1338.
6. Ward, E. R.; Coulson, T. M. 2,3-Derivatives of naphthalene. II. Preparation of 2,3-dinitronaphthalene and 3-nitro-2-naphthylamine. *J. Chem. Soc.* **1954**, 4545–4547.
7. Ward, E. R.; Pearson, B. D. Isomer ratios in the nitration of 6-acylamino-1,2,3,4-tetrahydronaphthalenes. *J. Chem. Soc.* **1959**, 3635–3638.

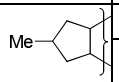
8. Dunn, J. P.; Ackerman, N. A.; Tomolonis, A. J. Analgetic and antiinflammatory 7-aroylbenzofuran-5-ylacetic acids and 7-aroylbenzothiophene-5-ylacetic acids. *J. Med. Chem*. **1986**, *29*, 2326–2329.
9. Blade-Font, A.; de Mas Rocabayera, T. Synthesis of dihydrobenzofurans from phenolic Mannich bases and their quaternized derivatives. *J. Chem. Soc. P1* **1982**, 814–848.
10. Schroeder, E.; Lehman, M.; Clemens, R. Benzofuran derivatives and their use. *US Patent 4,411,910*, **1983**.
11. Krasso, A.; Ramuz, H. Tricyclic imidazole derivatives and their therapeutic use. *US Patent 4599347*, **1986**.
12. Hach, V. Local anesthetics. XI. Simple chroman derivatives. *Coll. Czech. Chem. Commun.* **1959**, *24*, 3136–3140.
13. Brancaccio, G.; Lotteiri, G.; Viterbo, R. Nitration of substituted chromans. *J. Het. Chem.* **1973**, *10*, 623–629.
14. Kleinschmidt, E. G.; Braeuniger, Harald. Bromination with N-bromosuccinimide. II. Reactions with 3,4-dimethylnitrobenzene. *Pharmazie* **1969**, *24*, 29–32.
15. (a) Tercel, M.; Wilson W. R.; Anderson, R. F.; Denny, W. A. Hypoxia-selective antitumor agents. 12. Nitrobenzyl quaternary salts as bioreductive prodrugs of the alkylating agent mechlorethamine. *J. Med. Chem.* **1996**, *39*, 1084–1094; (b) Zhu, Z.; Furr J.; Buolamwini J. K. Synthesis and flow cytometric evaluation of novel 1,2,3,4-tetrahydroisoquinoline conformationally constrained analogues of nitrobenzylmercaptopurine riboside (NBMPR) designed for probing its conformation when bound to the es nucleoside transporter. *J. Med. Chem.* **2003**, *46*, 831–837.
16. Lusinchi, X.; Durand, S.; Delaby, R. Synthesis of some derivatives of N-methyl-1,2,3,4-isoquinoline. Compt. rend. **1959**, *248*, 426–428.
17. Ksander, G. M.; deJesus, R.; Yuan, A.; Fink, C.; Moskal, M.; Carlson, E.; Kukkola, P.; Bilci, N.; Wallace, E.; Neubert, A.; Feldman, D.; Mogelesky, T.; Poirier, K.; Jeune, M.; Steele, R.; Wasvery, J.; Stephan, Z.; Cahill, E.; Webb, R.; Navarrete, A.; Lee, W.; Gibson, J.; Alexander, N.; Sharif, H.; Hospattankar, A. Diaminoindanes as microsomal triglyceride transfer protein inhibitors. *J. Med. Chem.* **2001**, *44*, 4677–4687.
18. Baeyer, A.; Perkin W.H. Jr. On some derivatives of hydrindonaphthene. *Chem. Ber.* **1884**, *17*, 122.
19. Nagasawa M.; Nishioka, H.; Okubo, A.; Arai, H. Preparation of substituted benzocycloalkanoyl-2-acetic acids. *Japanese Patent 04338358*, **1992**.
20. Tanaka, Y.; Niwa, S.; Nishioka, H.; Yamanaka, T.; Torizuka, M.; Yoshinaga, K.; Kobayashi, N.; Ikeda, Y.; Arai, H. New Potent Prolyl Endopeptidase Inhibitors: Synthesis and Structure-Activity Relationships of Indan and Tetralin Derivatives and Their Analogs. *J. Med. Chem.* **1994**, *37*, 2071–2078.
21. Siim, B. G.; Hicks, K. O.; Pullen, S. M.; van Zijl, P. L.; Denny, W. A.; Wilson, W. R. Comparison of aromatic and tertiary amine N-oxides of acridine DNA intercalators as bioreductive drugs – cytotoxicity, DNA binding, cellular uptake, and metabolism. *Biochem. Pharmacol.* **2000**, *60*, 969–978.
22. Hicks, K. O.; Pruijn, F. B.; Sturman, J. R.; Denny, W. A.; Wilson, W. R. Multicellular resistance to tirapazamine is due to restricted extravascular

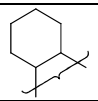
transport: a pharmacokinetic/ pharmacodynamic study in multicellular layers. *Cancer Res*. **2003**, *63*, 5970–5977.

23. Hicks, K. O.; Pruijn, F. B.; Baguley, B. C.; Wilson, W. R. Extravascular transport of the DNA intercalator and topoisomerase poison *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA): diffusion and metabolism in multicellular layers of tumor cells. *J. Pharmacol. Exp. Ther*. **2001**, *297*, 1088–1098.
24. Hay, M. P.; Gamage, S. A.; Kovacs, M. S.; Pruijn, F. B.; Anderson, R. F.; Patterson, A. V.; Wilson, W. R.; Brown, J. M.; Denny, W. A. Structure-activity relationships of 1,2,4-benzotriazine 1,4-dioxides as hypoxia-selective analogues of tirapazamine. *J. Med. Chem.* **2003**, *46*, 169–182.
25. Siim, B. G.; Atwell, G. J.; Wilson, W. R. Oxygen dependence of the cytotoxicity and metabolic activation of 4-alkylamino-5-nitroquinoline bioreductive drugs. *Br. J. Cancer* **1994**, *70*, 596–603.
26. Wilson, W. R.; Thompson, L. H.; Anderson, R.F., Denny, W.A. Hypoxia-selective antitumor agents. 2. Electronic effects of 4-substituents on the mechanisms of cytotoxicity and metabolic stability of nitracrine analogues. *J. Med. Chem*. **1989**, *32*, 31–38.
27. Wilson, W. R.; Pullen, S. M.; Hogg, A.; Hobbs, S. M.; Pruijn, F. B.; Hicks, K.O. *In vitro* and *in vivo* models for evaluation of GDEPT: quantifying bystander killing in cell cultures and tumors. *In:* C. J. Springer (ed.), Suicide Gene Therapy: Methods and Protocols for Cancer. Totowa, NJ: Humana Press, 2003.

Table 1a. Physicochemical, in vitro and modelling parameters for TPZ, BTOs 2 and TTOs 3–19.

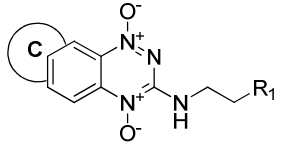


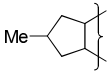
No	Ring C	R_1	pKa[a] amine	$logP_{7.4}$ calc.[b]	Sol.[c] mM	E(1) mV		HT29 IC_{50} hypox μM		HT29 HCR		SiHa IC_{50} hypox μM		SiHa HCR		*D* calc.[d]	
						Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	na[l]	na[l]	na[e]	-0.33	9	-456	8	5.1	0.2	71	3	2.5	0.3	107	9	4.2	1.2
2	na[l]	NMe_2	8.5	-0.85	46	-500	8	7.7	2.2	89	29	2.9	0.29	232	32	2.9	0.8
3		na[l]	0.0	0.79	3			15.2	6	27	1.5	8.3	0.39	31	5	9.8	2.7
4		NMe_2	8.5	-0.07	>51	-486	8	2.3	0.6	152	35	0.7	0.3	111	5	6.5	1.8
5		NEt_2	9.5	0.10	48			4.1		61		1.1		133		7.4	2.1
6		NPr_2	8.7	1.60	20			2.5		77		0.7		91		19.3	5.4
7		N-piperidine	8.7	0.62	1.9			5.8	2.9	49	35	1.3	0.4	143		11.7	3.3
8		CH_2N-morpholine	7.4	0.80	48			21.4	7.9	20	5	8.8	1.7	44	12	9.6	2.7
9		NMe_2	8.5	0.18	>54	-480	9	3.0		67		1.6	1.1	99		8.3	2.3
10		NEt_2	9.5	0.35	>49			4.2	1.5	17	5	0.9	0.2	64	4	9.4	2.6
11		NPr_2	8.7	1.60	40			12.4		7		3.3	0.3	23	10	19.3	5.4
12		N-piperidine	8.7	0.65	36			4.9	0.6	53	11	1.0	0.1	51	1	11.9	3.3
13		CH_2N-morpholine	7.4	0.88	46	-510	8	38		24		13.9		33		10.3	2.9
14		NMe_2	8.5	0.42	>49			3.5	0.4	54	14	1.4	0.3	97	33	10.2	2.9
15		CH_2N-morpholine	7.4	1.29	>49			19	5.6	25	2	8.4	3.2	50	3	13.8	3.9
16		NMe_2	8.5	0.69												12.8	3.6
17		CH_2N-morpholine	7.4	1.45	49			6.3	0.8	25	3	2.6	0.5	54	16	15.2	4.2

18		NMe_2	8.5	0.69	47			3.4		18		1.0		64		12.8	3.6
19		NMe_2	8.5	1.25	>53	-488	8	5.2	0.9	54	32	1.2	0.1	88	32	17.7	4.9

Footnotes: [a]Calculated using ACD pKa. [b]Calculated using ACD logD. [c]Solubility of HCl salts in culture medium. [d]Diffusion coefficient in HT29 MCLs $\times 10^{-7}$ cm^2s^{-1}. [e]Not applicable.

Table 1b. In vitro parameters for TPZ, BTOs 2 and TTOs 3–19.

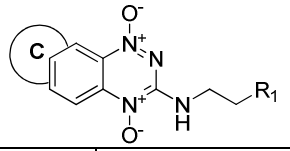


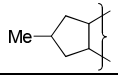
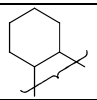
no	Ring C	R_1	Measured D[a]			k_{met}[b] min^{-1}				D for $X_{½}$[c]	$X_{½}$ µm[d]		
			Mean	CV (%)	SEM	Mean	SEM	CV (%)	N(n)[e]		Mean	Error (%)	SEM
1	na[1]	na[1]	4.04	3.2	0.13	0.58	0.04	7.1	64(278)		45	7.8	3.5
2	na[1]	NMe_2	2.3	3.6	0.08	0.54					35		
3		na[1]				0.47					77		
4		NMe_2	5.9	5.6	0.33	0.44					62		
5		NEt_2				1.08					45		
6		NPr_2	19.2	7.0	1.4	1.07					72		
7		N-piperidine	11.9	4.1	0.50	1.25					52		
8		CH_2N-morpholine				0.19					119		
9		NMe_2	8.4	5.5	0.46	0.74					57		
10		NEt_2				0.97					53		
11		NPr_2				0.73					87		
12		N-piperidine				1.60					46		
13		CH_2N-morpholine				0.20					122		
14		NMe_2				1.49					44		
15		CH_2N-morpholine				0.13					173		
16		NMe_2											
17		CH_2N-morpholine				0.69					80		
18		NMe_2				1.78					46		

19		NMe_2				1.52					58		

Footnotes: [a]Diffusion coefficient measured in aerobic HT29 MCLs × 10^{-7} cm^2s^{-1}. [b]First order rate constant for metabolism in anoxic HT29 cell suspensions, scaled to the cell density in MCLs. [c]C, calculated; M, measured. [d]Penetration half distance in anoxic HT29 tumor tissue (see text). [e]Number of separate determinations (total number of data points) for k_{met}.

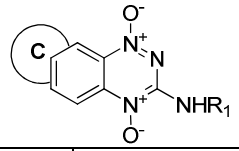
Table 1c. In vitro parameters for TPZ, BTOs 2 and TTOs 3–19.

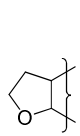
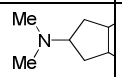


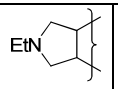
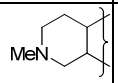
no	Ring C	R_1	PK/PD Model	CT_{10}[a] µM.h		M_{10}[b] µM			AUC_{pred}[c] µM.min	HCD[d]
				Mean	SEM	Mean	SEM	N(n)[e]		
1	na[1]	na[1]	C×M	24.3	1.9	1698	62	49(261)	10200	4.1
2	na[1]	NMe_2	C×M	26.1		1635			13800	2.7
3		na[1]	C×M	106.0		7735			22100	6.3
4		NMe_2		16.0		815			6730	6.4
5		NEt_2		36.3		4521			15300	3.9
6		NPr_2		31.8		3941			7810	6.6
7		N-piperidine	C×M	15.6		2444			3700	4.6
8		CH_2N-morpholine		76.2		1715			9860	9.9
9		NMe_2	C×M	26.3		2219			7630	5.1
10		NEt_2		35.1		3806			10000	5.6
11		NPr_2		66.3		5626			13000	7.9
12		N-piperidine		27.2		5022			13900	3.8
13		CH_2N-morpholine	C×M	176.4		4108			23000	10.0
14		NMe_2	C×M	23.0		3057			11000	2.9
15		CH_2N-morpholine		122.9		1903			13700	11.1
16		NMe_2								
17		CH_2N-morpholine	C×M	41.6		3294			8700	8.2
18		NMe_2	C×M	19.5		4223			11200	3.5
19		NMe_2		30.6		5404			11900	5.1

Footnotes: [a]Area under the concentration-time curve providing 10% surviving fraction in the clonogenic assay. [b]Amount of drug metabolised (per litre of cells) for one log of cell kill when cells are exposed to the CT_{10} for 1 h. [c]Predicted area under the plasma concentration-time curve required to give 1 log of cell kill in addition to that produced by a single 20 Gy dose of gamma radiation. [d]In vivo hypoxic cytotoxicity differential = $LCK_{hypoxic}/LCK_{oxic}$. [e]Number of separate determinations (total number of data points) for CT_{10} and M_{10}.

Table 2a. Physicochemical and in vitro parameters for TPZ and TTOs 20–32.

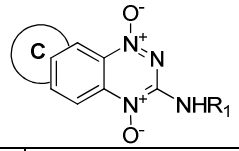


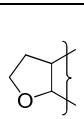
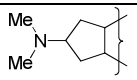
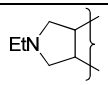
No	Ring C	R_1	pKa[a] amine	$logP_{7.4}$ calc.[b]	Sol.[c] mM	E(1) mV		HT29 IC_{50} hypox μM		HT29 HCR		SiHa IC_{50} hypox μM		SiHa HCR		*D* calc.[d]	
						Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	na[l]	H	na[e]	-0.33	9	-456	8	5.1	0.2	71	3	2.5	0.3	107	9	4.2	1.2
20		$(CH_2)_2NMe_2$	8.5	-1.05	>48	-487	10	2.4	0.1	23	0.2	0.30	0.02	87	9	2.6	0.73
21		$(CH_2)_3$N-morpholine	7.4	-0.27	>49			22	4	8	3	3.4	0.8	28	6	2.8	0.79
22		H	na	-0.04	0.1			117		4		23				3.6	1.0
23		$(CH_2)_2NMe_2$	8.5	-1.01	49	-541	8	5.2	0.3	46	36	1.9	0.2	128	3	2.6	0.74
24		$(CH_2)_2NEt_2$	9.4	-0.68	47			10	4	113	53	3.4	0.7	122	25	2.9	0.81
25		$(CH_2)_3$N-morpholine	7.4	-0.27	46			49	12	6	4	29	4	14	10	2.8	0.79
26		$(CH_2)_2NMe_2$	8.5	-1.09	>50	-541	15	13	7	26	21	5	3	53	17	2.3	0.65
27		$(CH_2)_2NMe_2$	8.5	-0.54	>45	-453	8	1.5		19		0.3		60		3.2	0.90
28		$(CH_2)_3$N-morpholine	7.4	0.48	40			11	3	19	5	3.6	0.5	41	10	4.8	1.3
29		$(CH_2)_2NMe_2$	8.5	-0.26	47			4.1		14		0.7		66		3.9	1.1
30		Et	7.6	0.08	46											7.6	2.1

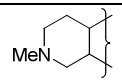
31		H	4.1	-0.57	6	-390	8	1.5				0.8		80		2.7	0.76
32		Et	5.8	-0.29	>47	-462	7	2.6	0.03	59	7	1.1	0.5	100	2	5.4	1.5

Footnotes: [a]Calculated using ACD pKa. [b]Calculated using ACD logD. [c]Solubility of HCl salts in culture medium. [d]Diffusion coefficient in HT29 MCLs × 10^{-7} cm^2s^{-1}. [e]Not applicable.

Table 2b. In vitro parameters for TPZ and TTOs 20–32.

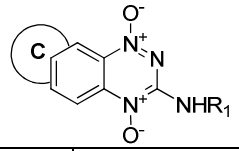


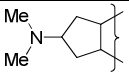
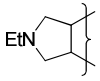
no	Ring C	R_1	Measured D[a]			k_{met}[b] min^{-1}				D for $X_{½}$[c]	$X_{½}$ µm[d]		
			Mean	CV (%)	SEM	Mean	SEM	CV (%)	N(n)[e]		Mean	Error (%)	SEM
1	na[l]	H	4.04	3.2	0.13	0.58	0.04	7.1	64(278)		45	7.8	3.5
20		$(CH_2)_2NMe_2$	4.3	1.5	0.06	3.15					20		
21		$(CH_2)_3$N-morpholine				0.20					64		
22		H											
23		$(CH_2)_2NMe_2$				0.60					36		
24		$(CH_2)_2NEt_2$				0.26					57		
25		$(CH_2)_3$N-morpholine				0.23					60		
26		$(CH_2)_2NMe_2$				0.87					28		
27		$(CH_2)_2NMe_2$	4.5	13.3	0.61	2.43					23		
28		$(CH_2)_3$N-morpholine				0.97					38		
29		$(CH_2)_2NMe_2$				0.59					44		
30		Et											
31		H				2.20					19		

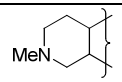
32		Et											

Footnotes: [a]Diffusion coefficient measured in aerobic HT29 MCLs × 10^{-7} cm^2s^{-1}. [b]First order rate constant for metabolism in anoxic HT29 cell suspensions, scaled to the cell density in MCLs. [c]C, calculated; M, measured. [d]Penetration half distance in anoxic HT29 tumor tissue (see text). [e]Number of separate determinations (total number of data points) for k_{met}.

Table 2c. In vitro parameters for TPZ and TTOs 20–32.

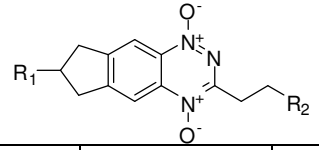


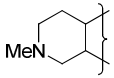
no	R_1	R_2	PK/PD Model	CT_{10}[a] μM.h		M_{10}[b] μM			AUC_{pred}[c] μM.min	HCD[d]
				Mean	SEM	Mean	SEM	N(n)[e]		
1	na[1]	H	C×M	24.3	1.9	1698	62	49(261)	10200	4.1
20		$(CH_2)_2NMe_2$		18.6		6732			23300	1.8
21		$(CH_2)_3$N-morpholine	C×M	116.0		2660			20300	7.4
22		H								
23		$(CH_2)_2NMe_2$	C×M	43.3		3000			22700	2.8
24		$(CH_2)_2NEt_2$	C×M	58.0		1718			12800	6.2
25		$(CH_2)_3$N-morpholine	C×M	82.1		2155			16700	6.6
26		$(CH_2)_2NMe_2$	C×M	42.5		4310			41100	1.6
27		$(CH_2)_2NMe_2$		6.2		1409			14200	0.6
28		$(CH_2)_3$N-morpholine	M[2]	84.6		9422			29900	33.0
29		$(CH_2)_2NMe_2$	C×M	46.1		3124			16600	4.2
30		Et								
31		H	C×M	8.1		2022			41000	0.4

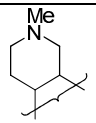
32		Et								

Footnotes: [a]Area under the concentration-time curve providing 10% surviving fraction in the clonogenic assay. [b]Amount of drug metabolised (per litre of cells) for one log of cell kill when cells are exposed to the CT_{10} for 1 h. [c]Predicted area under the plasma concentration-time curve required to give 1 log of cell kill in addition to that produced by a single 20 Gy dose of gamma radiation. [d]In vivo hypoxic cytotoxicity differential = $LCK_{hypoxic}/LCK_{oxic}$. [e]Number of separate determinations (total number of data points) for CT_{10} and M_{10}.

Table 3a. Physicochemical, in vitro and modelling parameters for TPZ and TTOs 33–42.

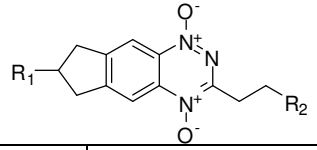


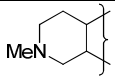
No	R_1	R_2	pKa[a] amine	$logP_{7.4}$ calc.[b]	Sol.[c] mM	E(1) mV		HT29 IC_{50} hypox µM		HT29 HCR		SiHa IC_{50} hypox µM		SiHa HCR		*D* calc.[d]	
						Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	H	na[e]	na[e]	-0.33	9	-456	8	5.1	0.2	71	3	2.5	0.3	107	9	4.2	1.2
33	CH_3	CH_2OH	0.0	1.14	10			13.0	1.3	80	2.2	8.0	0.4	104	4	21.0	5.9
34	CH_3	CH_2N-morpholine	7.1	0.99	36			2.9	0.01	72	13.2	1.7	0.2	134	4	21.0	5.9
35	CH_2OH	H	0.0	0.69	5	-452	7	17		45		6.5	0.2	48	8	17.7	4.9
36	CH_2N-morpholine	H	7.0	0.29	43			4.8	1.3	31	2.1	2.4	0.1	62	19	17.3	4.8
37	CH_2OH	CH_2N-morpholine	7.1	-0.18	48	-408	8	2.4	0.04	121	14	1.8	0.2	206		3.8	1.1
38	$(CH_2)_2OH$	H	na	0.50	2			7.7	1.2	102	57	2.9	0.4	86		15.4	4.3
39	$(CH_2)_2N$-morpholine	H	7.5	0.50	>51	-431	8	3.6	1.1	36	5.2	1.3		84		18.5	5.2
40		CH_2N-morpholine	7.1	-1.30	51	-468	7	8.9	0.4	25	6.1	5.1	0.01	43		3.5	0.98
41		H	5.8	0.09	>47	-344	8	13.1	1.1	2	0.15	3.1	0.1	6		20.9	5.8

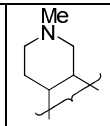
42		H	5.2	0.19												21.6	6.0

Footnotes: [a]Calculated using ACD pKa. [b]Calculated using ACD logD. [c]Solubility of HCl salts in culture medium. [d]Diffusion coefficient in HT29 MCLs × 10^{-7} cm^2s^{-1}. [e]Not applicable.

Table 3b. In vitro parameters for TPZ and TTOs 33–42.

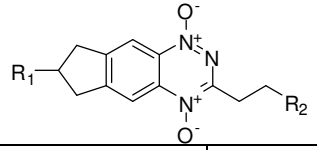


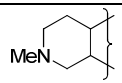
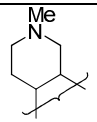
no	R_1	R_2	Measured D[a]			k_{met}[b] min^{-1}				D for $X_{½}$[c]	$X_{½}$ µm[d]		
			Mean	CV (%)	SEM	Mean	SEM	CV (%)	N(n)[e]		Mean	Error (%)	SEM
1	H	na[e]	4.04	3.2	0.13	0.58	0.04	7.1	64(278)		45	7.8	3.5
33	CH_3	CH_2OH				0.24					158		
34	CH_3	CH_2N-morpholine				0.96					80		
35	CH_2OH	H				0.47					104		
36	CH_2N-morpholine	H				0.54					96		
37	CH_2OH	CH_2N-morpholine				0.90					35		
38	$(CH_2)_2OH$	H				0.54					91		
39	$(CH_2)_2N$-morpholine	H				0.54					100		
40		CH_2N-morpholine				0.31					57		
41		H											

42		H											

Footnotes: [a]Diffusion coefficient measured in aerobic HT29 MCLs × 10^{-7} cm^2s^{-1}. [b]First order rate constant for metabolism in anoxic HT29 cell suspensions, scaled to the cell density in MCLs. [c]C, calculated; M, measured. [d]Penetration half distance in anoxic HT29 tumor tissue (see text). [e]Number of separate determinations (total number of data points) for k_{met}.

Table 3c. In vitro parameters for TPZ and TTOs 33–42.



no	R_1	R_2	PK/PD Model	CT_{10}[a] μM.h		M_{10}[b] μM			AUC_{pred}[c] μM.min	HCD[d]
				Mean	SEM	Mean	SEM	N(n)[e]		
1	H	na[e]	C×M	24.3	1.9	1698	62	49(261)	10300	4.1
33	CH_3	CH_2OH		85.3		2394			10300	10.9
34	CH_3	CH_2N-morpholine		18.6		2059			4960	5.8
35	CH_2OH	H	C×M	49.7		2096			4150	9.2
36	CH_2N-morpholine	H	C×M	24.1		1544			3390	8.8
37	CH_2OH	CH_2N-morpholine		24.4		2533			14100	2.7
38	$(CH_2)_2OH$	H	C×M	41.3		2641			6130	8.6
39	$(CH_2)_2$N-morpholine	H	C×M	15.8		984			2560	8.7
40		CH_2N-morpholine		27.6		986			6680	5.7
41		H								
42		H								

Footnotes: [a]Area under the concentration-time curve providing 10% surviving fraction in the clonogenic assay. [b]Amount of drug metabolised (per litre of cells) for one log of cell kill when cells are exposed to the CT_{10} for 1 h. [c]Predicted area under the plasma concentration-time curve required to give 1 log of cell kill in addition to that produced by a single 20 Gy dose of gamma radiation. [d]In vivo hypoxic cytotoxicity differential = $LCK_{hypoxic}/LCK_{oxic}$. [e]Number of separate determinations (total number of data points) for CT_{10} and M_{10}.