5-Benzamidoisoquinolin-1-ones and 5-(ω-carboxyalkyl)isoquinolin-1-ones as isoform-selective inhibitors of PARP-2

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Supplementary Information

Experimental Section

5-Benzamidoisoquinolin-1-one (15a). Compound **1** (50 mg, 0.25 mmol) was stirred with PhCOCl (39 mg, 0.28 mmol) in pyridine (2.0 mL) at 90°C for 16 h. Evaporation and recrystallisation (EtOAc) gave **15a** (57 mg, 86%) as an off-white solid: mp >310°C (decomp.); ^{1}H NMR ($(CD_3)_2SO$) δ 6.52 (1 H, d, *J* = 7.4 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.4, 5.5 Hz, 3-H), 7.50-7.61 (4 H, m, 3',4',5',7-H_4), 7.75 (1 H, d, *J* = 7.6 Hz, 6-H), 8.04 (2 H, d, *J* = 7.0 Hz, 2',6'-H_2), 8.13 (1 H, d, *J* = 7.8 Hz, 8-H), 10.33 (1 H, s, PhCONH), 11.32 (1 H, d, *J* = 4.7 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 100.6, 124.8, 125.9, 127.0, 127.8 (C_2), 128.5 (C_2), 128.9, 130.5, 131.8, 133.2, 134.1, 134.2, 161.6, 166.0; MS (ES^+) *m/z* 287.0801 (M + Na) ($C_{16}H_{12}N_2NaO_2$ requires 287.0796); 265.0952 (M + H) ($C_{16}H_{13}N_2O_2$ requires 265.0977); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(4-Methylbenzamido)isoquinolin-1-one (15b). Compound **1** was treated with 4-methylbenzoyl chloride, as for the synthesis of **15a**, to give **15b** (82%) as an off-white solid: mp 297-300°C; ^{1}H NMR ($(CD_3)_2SO$) δ 2.40 (3 H, s, Me), 6.50 (1 H, d, *J* = 7.0 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.2, 6.7 Hz, 3-H), 7.35 (2 H, d, *J* = 7.6 Hz, 3',5'-H_2), 7.48 (1 H, t, *J* = 7.8 Hz, 7-H), 7.51 (1 H, d, *J* = 8.2 Hz, 6-H), 7.72 (2 H, d, *J* = 7.6 Hz, 2',6'-H_2), 8.11 (1 H, d, *J* = 8.2 Hz, 8-H), 10.25 (1 H, s, ArCONH), 11.31 (1 H, br s, NH); ^{13}C NMR ($(CD_3)_2SO$) δ 21.0, 100.6, 124.7, 127.0, 127.8, 128.8, 129.0, 130.5, 131.3, 133.2, 134.2, 141.8, 161.6, 165.9; MS (ES^+) *m/z* 301.0941 (M + Na) ($C_{17}H_{14}N_2NaO_2$ requires 301.0953); 279.1119 (M + H) ($C_{17}H_{15}N_2O_2$ requires 279.1134); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(4-Nitrobenzamido)isoquinolin-1-one (15c). Compound **1** was treated with 4-nitrobenzoyl chloride, as for the synthesis of **15a**, to give **15c** (71%) as an orange solid: mp >190°C (decomp.); ^{1}H NMR ($(CD_3)_2SO$) δ 6.55 (1 H, d, *J* = 7.5 Hz, 4-H), 7.20 (1 H, dd, *J* = 7.2, 5.8 Hz, 3-H), 7.53 (1 H, t, *J* = 7.9 Hz, 7-H), 7.79 (1 H, d, *J* = 7.2 Hz, 6-H), 8.16 (1 H, d, *J* = 7.9 Hz, 8-H), 8.26 (2 H, d, *J* = 8.5 Hz, 3',5'-H), 8.40 (2 H, d, *J* = 8.5 Hz, 2',6'-H), 10.66 (1 H, s, ArCONH), 11.36 (1 H, d, *J* = 5.2 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 100.46, 123.6, 125.2, 126.0, 129.1, 129.3, 130.4, 132.6, 134.1, 139.9, 134.2, 149.3, 161.6, 164.6; MS (ES^+) *m/z* 332.0639 (M + Na) ($C_{16}H_{11}N_3NaO_4$ requires 332.0647), 310.0827 (M + H) ($C_{16}H_{12}N_3O_4$ requires 310.0828); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(4-Trifluoromethylbenzamido)isoquinolin-1-one (15d). Compound **1** was treated with 4-trifluoromethylbenzoyl chloride, as for the synthesis of **15a**, to give **15d** (72%) as a pale orange solid: mp 319-321°C; ^{1}H NMR ($(CD_3)_2SO$) δ 6.54 (1 H, d, *J* = 7.3 Hz, 4-H), 7.19 (1 H, dd, *J* = 7.3, 4.9 Hz, 3-H), 7.53 (1 H, t, *J* = 7.7 Hz, 7-H), 7.77 (1 H, d, *J* = 7.7 Hz, 6-H), 7.94 (1 H, d, *J* = 7.7 Hz, 8-H), 8.15 (2 H, d, *J* = 8.2 Hz, 3',5-H_2), 8.23 (2 H, d, *J* = 8.2 Hz, 2',6'-H_2), 10.56 (1 H, s, ArCONH) 11.35 (1 H, d, *J* = 4.9 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) (HMBC / HMQC) δ 100.5 (4-C), 125.1 (8-C), 125.9 (q, *J* = 31.5 Hz, 3',5'-C_2), 126.8 (7-C), 126.9 (8a-C), 128.9 (2',6'-C_2), 130.3 (6-H), 130.9 (q, *J* = 31.5 Hz, 4'-C), 132.6 (5-C), 134.0 (4a-C), 137.9 (m, CF_3), 149.5 (1'-C), 161.5 (1-C); MS (ES^+) *m/z* 355.0666 (M + Na) ($C_{17}H_{11}F_3N_2NaO_2$ requires 355.0670), 333.0844 (M + H) ($C_{17}H_{12}F_3N_2O_2$ requires 333.0851); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(4-Fluorobenzamido)isoquinolin-1-one (15e). Compound **1** was treated with 4-fluorobenzoyl chloride, as for the synthesis of **15a**, to give **15e** (68%) as a pale orange solid: mp 302-305°C; ^{1}H NMR ($(CD_3)_2SO$) δ 6.54 (1 H, d, *J* = 7.4 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.4, 6.2 Hz, 3-H), 7.33 (2 H, d, *J* = 8.6 Hz, 2',6'-H_2), 7.54 (1 H, d, *J* = 8.2 Hz, 7-H), 7.69 (1 H, d, *J* = 8.2 Hz, 6-H), 8.03 (2 H, dd, *J* = 9.0, 5.0 Hz, 3',5'-H_2), 8.14 (1 H, d, *J* = 8.2 Hz, 8-H), 10.44 (1

H, br s, ArCONH), 11.33 (1 H, br, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 102.1, 116.3 (d, *J* = 21.5 Hz), 116.5, 126.1, 127.3, 129.5, 131.2 (d, *J* = 9.2 Hz),131.3, 131.8, 133.6, 135.2, 163.0, 164.4 (d, *J* = 283.6 Hz); MS (ES^+) *m/z* $C_{16}H_{11}FN_2NaO_2$ requires 305.0702), 283.0889 (M + H) ($C_{16}H_{12}FN_2O_2$ requires 283.0883); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(4-Chlorobenzamido)isoquinolin-1-one (15f). Compound **1** was treated with 4-chlorobenzoyl chloride, as for the synthesis of **15a**, to give **15f** (77%) as a pale orange solid: mp 347-349°C; ^{1}H NMR ($(CD_3)_2SO$) δ 6.51 (1 H, *J* = 7.5 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.5, 5.2 Hz, 3-H), 7.51 (1 H, *J* = 7.8 Hz, 7-H), 7.63 (2 H, d, *J* = 8.2 Hz, 3',5'-H_2), 7.74 (1 H, d, *J* = 7.8 Hz, 6-H), 8.04 (2 H, d, *J* = 8.2 Hz, 2',6'-H_2), 8.13 (1 H, d, *J* = 7.8 Hz, 8-H), 10.41 (1 H, s, ArCONH), 11.34 (1 H, d, *J* = 4.6 Hz, 2-NH); ^{13}C NMR δ 100.6, 125.0, 125.9, 127.0, 128.5, 127.0, 128.5 (C_2), 128.9, 129.7 (C_2), 130.4, 132.9, 132.9, 134.2, 136.6, 161.6, 165.0; MS (ES^+) *m/z* 321.0399 (M + Na) ($C_{16}H_{11}ClN_2NaO_2$ requires 321.0407), 299.0584 (M + H) ($C_{16}H_{12}ClN_2O_2$ requires 299.0587); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(4-Bromobenzamido)isoquinolin-1-one (15g). Compound **1** was treated with 4-bromobenzoyl chloride, as for the synthesis of **15a**, to give **15g** (81%) as a yellow solid: mp 258-260°C; ^{1}H NMR ($(CD_3)_2SO$) δ 6.51 (1 H, d, *J* = 7.4 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.4, 5.7 Hz, 3-H), 7.52 (1 H, t, *J* = 7.8 Hz, 7-H), 7.71 (2 H, d, *J* = 8.2 Hz, 3',5'-H_2), 7.74 (1 H, d, *J* = 7.4 Hz, 6-H), 7.99 (2 H, d, *J* = 8.2 Hz, 2',6'-H_2), 8.13 (1 H, d, *J* = 7.8 Hz, 8-H), 10.40 (1 H, s, ArCONH) 11.34 (1 H, d, *J* = 5.1 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 99.9, 125.0, 125.9, 127.0, 128.7, 128.5, 128.9, 129.7, 130.4, 132.9, 132.9, 135.2, 136.6, 161.5, 165.2; MS (ES^+) *m/z* 343.1414 (M + H) ($C_{16}H_{12}{}^{79}BrN_2O_2$ requires 343.0082); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(4-Iodobenzamido)isoquinolin-1-one (15h). Compound **1** was treated with 4-iodobenzoyl chloride, as for the synthesis of **15a**, to give **15h** (76%) as a pale grey solid: mp >290 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 6.51 (1 H, d, *J* = 7.4 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.5, 5.4 Hz, 3-H), 7.51 (1 H, t, *J* = 7.6 Hz, 7-H), 7.74 (1 H, d, *J* = 7.4 Hz, 6-H), 7.82 (2 H, d, *J* = 8.2 Hz, 3',5'-H), 7.95 (2 H, d, *J* = 8.2 Hz, 2',6'-H), 8.14 (1 H, d, *J* = 7.8 Hz, 8-H), 10.39 (1 H, s, ArCONH) 11.33 (1 H, d, *J* = 5.1 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 99.5, 100.6, 124.9, 125.9, 127.0, 128.9,129.7, 130.42, 132.9, 133.6, 134.2, 137.4, 161.6, 165.4; MS (ES^+) *m/z* 390.9950 (M + H) ($C_{16}H_{12}IN_2O_2$ requires 390.9944); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(2-Methylbenzamido)isoquinolin-1-one (15i). Compound **1** was treated with 2-methylbenzoyl chloride, as for the synthesis of **15a**, to give **15i** (63%) as an off-white solid: mp 310-313°C; ^{1}H NMR ($(CD_3)_2SO$) δ 2.54 (3 H, s, Me), 6.62 (1 H, d, *J* = 7.5 Hz, 4-H), 7.21 (1 H, t, *J* = 7.0 Hz, 7-H), 7.32 (2 H, d, *J* = 7.0 Hz, 6,8-H_2), 7.41 (1 H, t, *J* = 7.4 Hz, 5'-H), 7.51 (1 H, t, *J* = 7.4 Hz, 4'-H), 7.58 (1 H, d, *J* = 7.4 Hz, 3'-H), 8.10 (1 H, d, *J* = 7.4 Hz, 6'-H), 10.24 (1 H, s, ArCONH), 11.32 (1 H, d, *J* = 5.1 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 19.5, 100.4, 124.5, 125.6, 125.9, 127.0, 127.4, 128.9, 129.7, 130.6, 131.0, 132.9, 133.6, 135.4, 136.8, 161.6, 168.6; MS (ES^+) *m/z* 301.0956 (M + Na) ($C_{17}H_{13}N_2NaO_2$ requires 301.0953), 279.1130 (M + H) ($C_{17}H_{14}N_2O_2$ requires 279.1133); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(2-Iodobenzamido)isoquinolin-1-one (15j). Compound **1** was treated with 2-iodobenzoyl chloride, as for the synthesis of **15a**, to give **15j** (61%) as a pale buff solid: mp 317-320°C; ^{1}H NMR ($(CD_3)_2SO$) δ 6.77 (1 H, d, *J* = 7.9 Hz, 4-H), 7.20 (1 H, t, *J* = 7.9, 5.6 Hz, 3-H), 7.25 (1 H, dt, *J* = 7.6, 1.8 Hz, 4'-H), 7.54-7.63 (3 H, m, 3',5',7-H_3), 7.90 (1 H, d, *J* = 7.9 Hz, 6-H), 7.96 (1 H, d, *J* = 7.9 Hz, 8-H), 8.12 (1 H, d, *J* = 7.6 Hz, 6'-H), 10.41 (1 H, s, ArCONH), 11.34 (1 H, d, *J* = 5.6 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 93.6, 100.5, 124.6, 125.9, 127.1, 128.1,

128.2, 128.7, 129.2, 131.0, 132.5, 133.2, 139.0, 161.5, 166.4; MS (ES^+) *m/z* 390.9952 (M + H) ($C_{16}H_{12}IN_2O_2$ requires 390.9944); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(Thiophene-2-carboxamido)isoquinolin-1-one (15k). Compound **1**was treated with thiophene-2-carbonyl chloride, as for the synthesis of **15a**, to give **15k** (51%) as an off-white solid: mp 288-291°C; ^{1}H NMR ($(CD_3)_2SO$) δ 6.51 (1 H, d, *J* = 7.4 Hz, 4-H), 7.19 (1 H, dd, *J* = 7.4, 5.4 Hz, 3-H), 7.23 (1 H, dd, *J* = 4.9, 3.6 Hz, 4'-H), 7.52 (1 H, t, *J* = 7.8 Hz, 7-H), 7.70 (1 H, d, *J* = 7.8 Hz, 6-H), 7.83 (1 H, d, *J* = 4.9 Hz, 5'-H), 8.03 (1 H, d, *J* = 3.6 Hz, 3'-H), 8.13 (1 H, d, *J* = 7.8 Hz, 8-H), 10.41 (1 H, s, ArCONH), 11.33 (1 H, d, *J* = 5.4 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 100.2, 125.5, 126.6, 127.2, 128.7, 129.3, 129.9, 131.2, 132.3, 132.9, 134.7, 139.4, 161.2, 162.2; MS (ES^+) *m/z* 293.0347 (M + Na) ($C_{14}H_{10}N_2NaO_2S$ requires 293.0361), 271.0529 (M + H) ($C_{14}H_{11}N_2O_2S$ requires 271.0541); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(Cyclohexanecarboxamido)isoquinolin-1-one (15l). Compound **1** was treated with cyclohexanecarbonyl chloride, as for the synthesis of **15a**, to give **15l** (68%) as an off-white solid: mp 302-305°C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.18-1.86 (11 H, m, cHex-H_{11}), 6.57 (1 H, d, *J* = 7.5 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.3, 6.2 Hz, 3-H). 7.42 (1 H, t, *J* = 7.8 Hz, 7-H), 7.76 (1 H, d, *J* = 7.8 Hz, 6-H), 8.02 (1 H, d, *J* = 7.8 Hz, 8-H), 9.66 (1 H, s, cHexCONH), 11.30 (1 H, d, *J* = 5.1 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 25.3□□, 25.4, 29.3, 44.2, 100.0, 123.6, 125.8, 126.9, 128.5, 128.6, 132.6, 133.1, 161.6, 174.8; MS (ES^+) *m/z* 563.2616 (2 M + Na) ($C_{32}H_{36}N_4NaO_4$ requires 563.2634), 541.2798 (2 M + H) ($C_{32}H_{37}N_4O_4$ requires 541.2815) 293.1248 (M + Na) ($C_{16}H_{18}N_2NaO_2$ requires 293.1266), 271.1140 (M + H) ($C_{16}H_{19}N_2O_2$ requires 271.1147); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(2,2-Dimethylpropanamido)isoquinolin-1-one (15m). Compound **1** was treated with 2,2-dimethylpropanoyl chloride, as for the synthesis of **15a**, to give **15m** (68%) as an off-white solid: mp 305-307°C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.28 (9 H, s, Bu^t), 6.38 (1 H, d, *J* = 7.4 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.4, 4.3 Hz, 3-H), 7.45 (1 H, t, *J* = 7.6 Hz, 7-H), 7.53 (1 H, d, *J* = 7.6 Hz, 6-H), 8.08 (1 H, d, *J* = 7.6 Hz, 8-H), 9.36 (1 H, s, Bu^{t}CONH), 11.29 (1 H, br, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 27.4 (C_3), 40.1, 100.5, 124.6, 125.8, 126.9, 128.7, 130.7, 133.4, 134.5, 161.7, 177.1; MS (ES^+) *m/z* 267.1109 (M + Na) ($C_{14}H_{16}N_2NaO_2$ requires 267.1109), 245.1291 (M + H) ($C_{14}H_{17}N_2O_2$ requires 245.1290); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-(Adamantan-1-ylcarboxamido)isoquinolin-1-one (15n). Compound **1** was treated with adamantane-1-carbonyl chloride, as for the synthesis of **15a** to give **15n** (59%) as an off-white solid: mp 303-306°C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.73-2.04 (15 H, adamantane-H_{15}), 6.36 (1 H, d, *J* = 7.4 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.4, 6.2 Hz, 3-H), 7.42 (1 H, t, *J* = 7.7 Hz, 7-H), 7.52 (1 H, d, *J* = 7.7 Hz, 6-H), 8.07 (1 H, d, *J* = 7.7 Hz, 8-H), 9.29 (1 H, s, adamantaneCONH), 11.29 (1 H, d, *J* = 4.9 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 27.7, 36.1, 38.5, 38.6, 100.5, 124.5, 125.8, 126.9, 128.7, 130.7, 133.4, 134.4, 161.7, 176.6; MS (ES^+) *m/z* 345.1574 (M + Na) ($C_{20}H_{22}N_2NaO_2$ requires 345.1579), 323.1769 (M + H) ($C_{20}H_{23}N_2O_2$ requires 323.1768); Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

5-Benzamido-3-methylisoquinolin-1-one (22). Compound **21** was treated with benzoyl chloride, as for the synthesis of **15a**, to give **22** (72%) as an off-white solid: mp >310°C (decomp.); ^{1}H NMR ($(CD_3)_2SO$) δ □2.12 (3 H, s, Me), 6.33 (1 H, s, 4-H), 7.42 (1 H, t, *J* = 7.8 Hz, 7-H), 7.55 (2 H, t, *J* = 7.9 Hz, 3',5'-H_2), 7.62 (1 H, t, *J* = 7.9 Hz, 4'-H), 7.69 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 8.04-8.09 (3 H, m, 2',6',8-H_3), 10.28 (1 H, s, PhCONH), 11.35 (1 H, s, 2-NH); ^{13}C NMR δ 19.0, 98.7, 124.7, 124.9, 125.1, 127.8, 128.4, 130.6, 131.7, 132.5, 134.2, 134.6, 138.5, 162.3, 166.0; MS (ES^+) *m/z* 301.0948 (M + Na) ($C_{17}H_{14}NaN_2O_2$ requires

301.0953), *m/z* 279.1142 (M + H) ($C_{17}H_{15}N_2O_2$ requires 279.1134); Anal. ($C_{17}H_{14}N_2O_2$) C, H, N.

1-Oxoisoquinoline-5-carboxylic acid (24). Compound **23**[51] (427 mg, 2.5 mmol) was boiled under reflux with KOH in EtOH (20% w/v, 12 mL), under nitrogen, until the production of NH_3 ceased (3 d). The mixture was acidified with aq. HCl (9 M) and the solvent was evaporated. The residue was taken up into MeOH and filtered. Evaporation of the solvent from the filtrate gave **24** (394 mg, 83%) as a white solid: mp >300°C (lit.[51] mp >300°C); ^{1}H NMR (CD_3OD) δ 7.28 (1 H, d, *J* = 7.7 Hz, 4-H), 7.56 (1 H, t, *J* = 7.7 Hz, 7-H), 7.76 (1 H, d, *J* = 7.7 Hz, 3-H), 8.42 (1 H, d, *J* = 7.7 Hz, 8-H), 8.58 (1 H, d, *J* = 7.7 Hz, 6-H).

***E*-3-(1-Oxoisoquinolin-5-yl)propenoic acid (26).** Compound **25**[52] (200 mg, 0.74 mmol), propenoic acid (0.06 mL, 70 mg, 0.49 mmol), $Pd(OAc)_2$ (16 mg, 74 μmol) and Et_3N (186 mg, 1.8 mmol) in EtCN (0.6 mL) were boiled under reflux for 1 h. Aq. HCl (2 M, 20 mL) was added and the precipitate was collected and dried to give **26** (152 mg, 97%) as an off-white solid: mp 314–318°C (lit.[51] 315–318°C); ^{1}H NMR ($(CD_3)_2SO$) δ 6.58 (1 H, d, *J* = 15.8 Hz, =$CHCO_2$), 6.74 (1 H, d, *J* = 7.3 Hz, 4-H), 7.30 (1 H, d, *J* = 7.3, Hz, 3-H), 7.52 (1 H, t, *J* = 7.7 Hz, 7-H), 8.10 (1 H, d, *J* = 15.8 Hz, ArCH=), 8.12 (1 H, d, *J* = 7.7 Hz), 8.27 (2 H, d, *J* = 7.7 Hz, 6,8-H_2), 11.47 (1 H, br s, NH), 12.60 (1 H, br s, CO_2H).

Methyl 3-(5-amino-1-oxoisoquinolin-2-yl)propanoate (31). NaH (80 mg, 3.5 mmol) was added to **1** (400 mg, 1.8 mmol) in dry THF (40 mL), followed by methyl propenoate (170 mg, 1.9 mmol) and the mixture was stirred for 2 h. Evaporation and recrystallisation (MeOH) gave **47** (300 mg, 67%) as pale buff crystals: mp 188–190°C; IR ν_{max} 3465, 1715, 1674 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$) δ 2.67 (2 H, t, *J* = 7.0 Hz, CH_2CO_2), 4.09 (2 H, t, *J* = 7.0 Hz, CH_2N), 4.36 (3 H, s, Me), 5.62-5.91 (3 H, br, OH, 2 × NH), 6.72 (1 H, d, *J* = 7.5 Hz, 4-H), 6.84 (1 H, d, *J* = 7.5 Hz, 3-H), 7.16 (1 H, t, *J* = 7.8 Hz, 7-H), 7.31 (1 H, d, *J* = 7.4 Hz 6-H), 7.41 (1 H, d, *J* = 7.8 Hz 8-H); ^{13}C NMR ($(CD_3)_2SO$) δ 33.1, 44.9, 53.9, 100.3, 114.1, 114.8, 123.8, 126.4, 127.2, 130.6, 144.3, 161.2, 172.6; MS (ES^+) *m/z* 269.0922 (M + Na) ($C_{13}H_{14}N_2NaO_3$ requires 269.0902), 247.1068 (M + H) ($C_{13}H_{15}N_2O_3$ requires 247.1083).

5-Amino-2-(2-carboxyethyl)isoquinolin-1-one hydrochloride (32). Ester **31** (302 mg, 1.23 mmol) was boiled under reflux in aq. HCl (6.0 M, 4.0 mL) for 24 h. Evaporation gave **32** (281 mg, 85%) as a pale amber solid: mp 199–201°C ; IR ν_{max} 3240, 2580, 1721, 1638 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$) δ 2.71 (2 H, t, *J* = 6.6 Hz, CH_2CO_2), 3.22-4.58 (4 H, m, OH, NH_2, NH), 4.14 (2 H, t, *J* = 6.6 Hz, CH_2N), 6.71 (1 H, d, *J* = 7.8 Hz, 4-H), 7.46 (1 H, t, *J* = 7.8 Hz, 7-H), 7.56 (2 H, m, 3-H and 7-H), 8.00 (1 H, d, *J* = 7.8 Hz, 8-H); ^{13}C NMR ($(CD_3)_2SO$) δ 33.1 (*C*H_2CO_2), 44.9 (NCH_2), 53.9 (Me), 100.3 (4-C), 114.1 (6-C), 114.8 (8-C), 123.8 (4a-C), 126.4 (8a-C), 127.2 (7-C), 130.6 (3-C), 144.3 (5-C), 161.2 (1-C), 172.6 (*C*O_2Me); MS (ES^+) *m/z* 233.0927 (M + H) ($C_{12}H_{13}N_2O_3$ requires 233.0936).

Spectroscopic data for compounds described in Experimental Section of paper.

5-Aminoisoquinolin-1-one hydrochloride (1). ^{1}H NMR (D_2O) δ 6.76 (1 H, d, *J* = 7.5 Hz), 7.39 (1 H, d, *J* = 7.5 Hz), 7.59 (1.59 (1-H, t, *J* = 8.0 Hz), 7.79 (1 H, d, *J* = 8.0 Hz), 8.27 (1 H, d, *J* = 8.0 Hz).

1-Chloro-5-nitroisoquinoline (13). ^{1}H NMR ($CDCl_3$) δ 7.81 (1 H, t, *J* = 8.2 Hz, 7-H), 8.41 (1 H, dd, *J* = 6.3, 1.2 Hz, 4-H), 8.49 (1 H, d, *J* = 6.3 Hz, 3-H), 8.56 (1 H, dt, *J* = 8.2, 1.2 Hz, 8-H), 8.75 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H).

5-Nitroisoquinolin-1-one (14). ^{1}H NMR ($(CD_3)_2SO$) δ 6.97 (1 H, dd, *J* = 7.7, 0.7 Hz), 7.45 (1 H, dd, *J* = 7.7, 1.8 Hz), 7.66 (1 H, t, *J* = 7.7 Hz), 8.46 (1 H, dd, *J* = 7.7, 1.5 Hz), 8.58 (1 H, ddd, *J* = 7.7, 1.5, 0.7 Hz,), 11.80 (1 H, br s, NH).

5-Benzamidoisoquinolin-1-one (15a). ^{1}H NMR ($(CD_3)_2SO$) δ 6.52 (1 H, d, *J* = 7.4 Hz, 4-H), 7.18 (1 H, dd, *J* = 7.4, 5.5 Hz, 3-H), 7.50-7.61 (4 H, m, 3',4',5',7-H_4), 7.75 (1 H, d, *J* = 7.6 Hz, 6-H), 8.04 (2 H, d, *J* = 7.0 Hz, 2',6'-H_2), 8.13 (1 H, d, *J* = 7.8 Hz, 8-H), 10.33 (1 H, s, PhCONH), 11.32 (1 H, d, *J* = 4.7 Hz, 2-NH); ^{13}C NMR ($(CD_3)_2SO$) δ 100.6, 124.8, 125.9, 127.0, 127.8 (C_2), 128.5 (C_2), 128.9, 130.5, 131.8, 133.2, 134.1, 134.2, 161.6, 166.0; MS (ES^+) *m/z* 287.0801 (M + Na) ($C_{16}H_{12}N_2NaO_2$ requires 287.0796); 265.0952 (M + H) ($C_{16}H_{13}N_2O_2$ requires 265.0977); Anal. ($C_{16}H_{12}N_2O_2$) C, H, N.

3-Methyl-5-nitroisocoumarin (19). IR (KBr) ν_{max} 1746, 1648 1520, 1331 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (3 H, s, Me), 7.13 (1 H, d, *J* = 0.8 Hz, 4-H), 7.55 (1 H, t, *J* = 8.2 Hz, 7-H), 8.41 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.56 (1 H, ddd, *J* = 8.2, 1.2, 0.8 Hz, 8-H); ^{13}C NMR ($CDCl_3$) δ 20.5, 98.4, 121.9, 126.9, 131.4, 131.8, 135.7, 143.8, 158.6, 160.8; MS (EI^+) *m/z* 205.0384 (M) ($C_{10}H_7NO_4$ requires 205.0375), 159 (M – NO_2); Anal. ($C_{10}H_7NO_4$) C, H, N.

3-Methyl-5-nitroisoquinolin-1(2*H*)-one (20). IR (KBr) ν_{max} 3435, 1668, 1523, 1346 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$) δ 2.29 (3 H, s, Me), 6.78 (1 H, s, 4-H), 7.55 (1 H, t, *J* = 7.8 Hz, 7-H), 8.38 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 8.49 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 11.79 (1 H, br s, NH); MS (FAB^+) *m/z* 205.0617 (M + H) ($C_{10}H_9N_2O_3$ requires 205.0613), 189 (M – Me); Anal. ($C_{10}H_8N_2O_3$) C, H, N.

5-Amino-3-methylisoquinolin-1(2*H*)-one (21). IR (KBr) ν_{max} 3476, 3375, 3298, 1655 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$) δ 2.18 (3 H, s, Me), 5.47 (2 H, br, NH_2), 6.44 (1 H, s, 4-H), 6.80 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.05 (1 H, t, *J* = 7.8 Hz, 7-H), 7.32 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 11.06 (1 H, br s, NH); MS (FAB^+) *m/z* 175.0874 (M + H) ($^{12}C_{10}H_{11}N_2O$ requires 175.0871), 159 (M – Me). A sample was converted to the HCl salt: ^{1}H NMR ($(CD_3)_2SO$) δ 2.24 (3 H, s, Me), 4.8 (3 H, br, N^+H_3), 6.43 (1 H, s, 4-H), 7.34 (1 H, dd, *J* = 7,9, 7.6 Hz, 7-H), 7.46 (1 H, d, *J* = 7.6 Hz, 6-H), 7.89 (1 H, d, *J* = 7.9 Hz, 8-H), 11.06 (1 H, br s, NH); ^{13}C NMR ($(CD_3)_2SO$) (HMQC / HMBC) δ 19.2 (Me), 97.2 (4-C), 122.8 (8a-C), 123.8 (4a-C), 125.2 (8-C), 125.5 (6-C), 130.6 (7-C), 133.0 (5-C), 138.6 (3-C), 162.0 (1-C); Anal. ($C_{10}H_{11}ClN_2O$) C, H, N.

3-(1-Oxoisoquinolin-5-yl)propanoic acid (27). ^{1}H NMR ($(CD_3)_2SO$) δ 2.54 (2 H, t, *J* = 7.8 Hz, ArCH_2), 3.09 (2 H, t, *J* = 7.8 Hz, CH_2COOH), 3.17-3.42 (1 H, br, CO_2H), 6.62 (1 H, d, *J* = 7.4 Hz, 4-H), 7.21 (1 H, br d, *J* = 7.8 Hz, 3-H), 7.38 (1 H, t, *J* = 7.4 Hz, 7-H), 7.55 (1 H, d, *J* = 7.4 Hz, 6-H), 8.07 (1 H, d, *J* = 7.4 Hz, 8-H), 11.29 (1 H, br s, NH); ^{13}C NMR ($(CD_3)_2SO$) δ

27.4, 34.8, 100.7, 125.1, 125.9, 126.5, 128.9, 132.2, 136.1, 136.3, 162.0, 173.7; MS (ES^+) *m/z* 240.0682 (M + Na) ($C_{12}H_{11}NaNO_3$ requires 240.0637); 218.0819 (M + H) ($C_{16}H_{15}N_2O$ requires 218.0817).

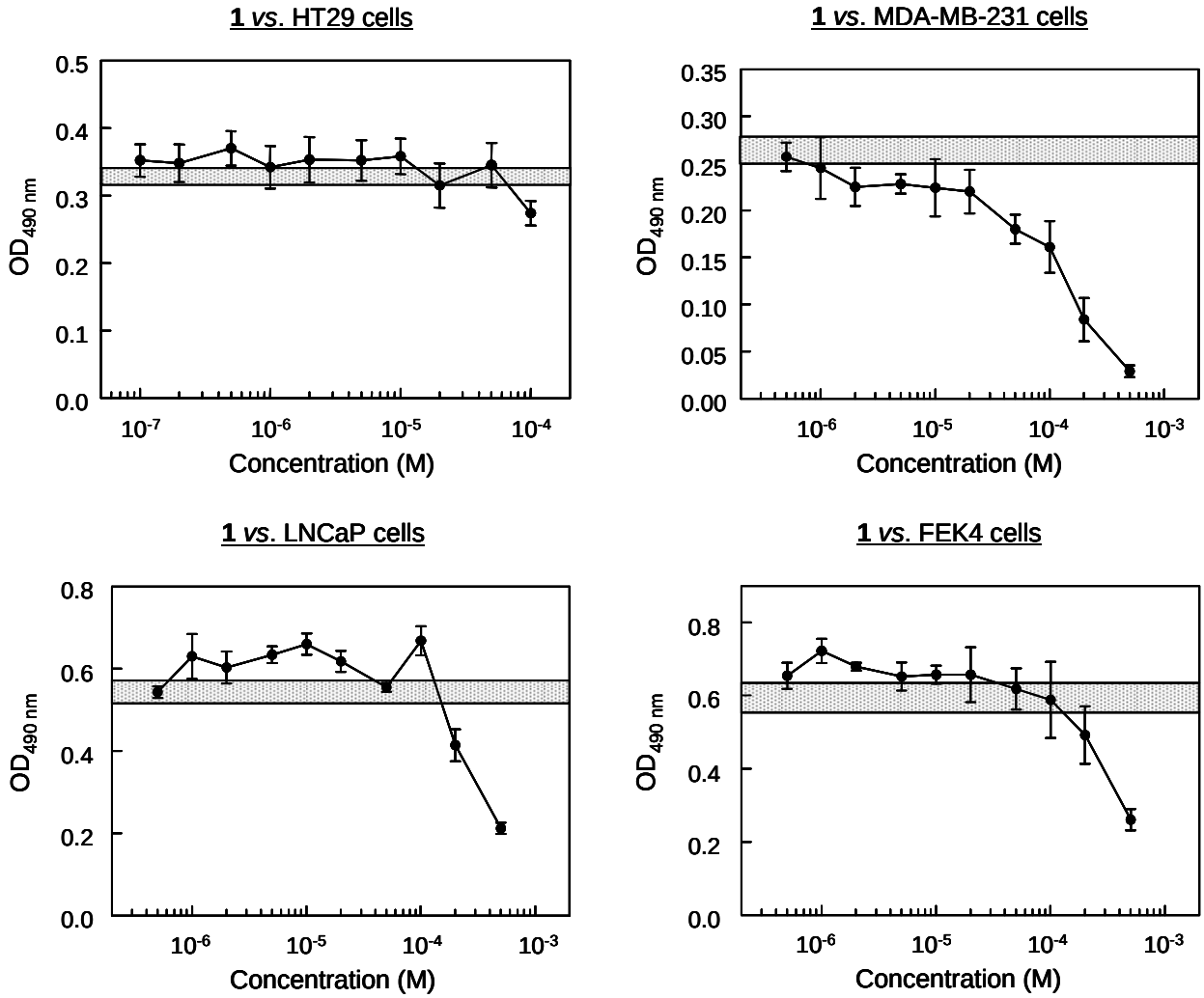
Ethyl 2-(1-oxoisoquinolin-5-ylamino)acetate (28). IR ν_{max} 3437, 1728, 1654 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 1.19 (3 H, t, *J* = 7.2 Hz, Me), 4.01 (2 H, d, *J* = 4.9 Hz, CH_2N), 4.12 (2 H, q, *J* = 7.2 Hz, OCH_2), 6.44 (1 H, t, *J* = 4.9 Hz, CH_2NH), 6.56 (1 H, d, *J* = 7.8 Hz, 4-H), 6.72 (1 H, d, *J* = 7.8 Hz, 3-H), 7.11 (1 H, m, 6-H), 7.22 (1 H, t, *J* = 7.8 Hz, 7-H), 7.46 (1 H, d, *J* = 7.8 Hz, 8-H), 11.2 (1 H, br, NH); ^{13}C NMR ($(CD_3)_2SO$) δ 14.1, 44.8, 60.4, 99.2, 110.5, 114.4, 125.5, 126.8, 126.9, 127.0, 143.1, 162.0, 171.1; MS (ES^+) *m/z* 269.0911 (M + Na) ($C_{13}H_{14}N_2NaO_3$ requires 269.0902), 247.1136 (M + H) ($C_{13}H_{15}N_2O_3$ requires 247.1083).

5-(Carboxymethylamino)isoquinolin-1-one hydrochloride (29). IR ν_{max} 3134, 2523, 1737, 1608 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.91 (2 H, s, CH_2), 5.23-6.22 (3 H, m, OH, NH_2), 6.58 (1 H, dd, *J* = 7.9, 0.8 Hz, 4-H), 6.72 (1 H, d, *J* = 7.6 Hz, 3-H), 7.10 (1 H, brd, *J* = 7.0 Hz, 6-H), 7.22 (1 H, t, *J* = 8.2 Hz, 7-H), 7.45 (1 H, d, *J* = 7.9 Hz, 8-H), 11.21 (1-H, brs, NH); ^{13}C NMR δ □($(CD_3)_2SO$) 44.8, 99.2, 110.4, 110.5, 114.2, 135.5, 126.9, 127.0, 143.2, 162.0, 172.5; MS (ES^+) *m/z* 219.0757 (M + H) ($C_{11}H_{11}N_2O_3$ requires 219.0770).

Cytotoxicity assay.

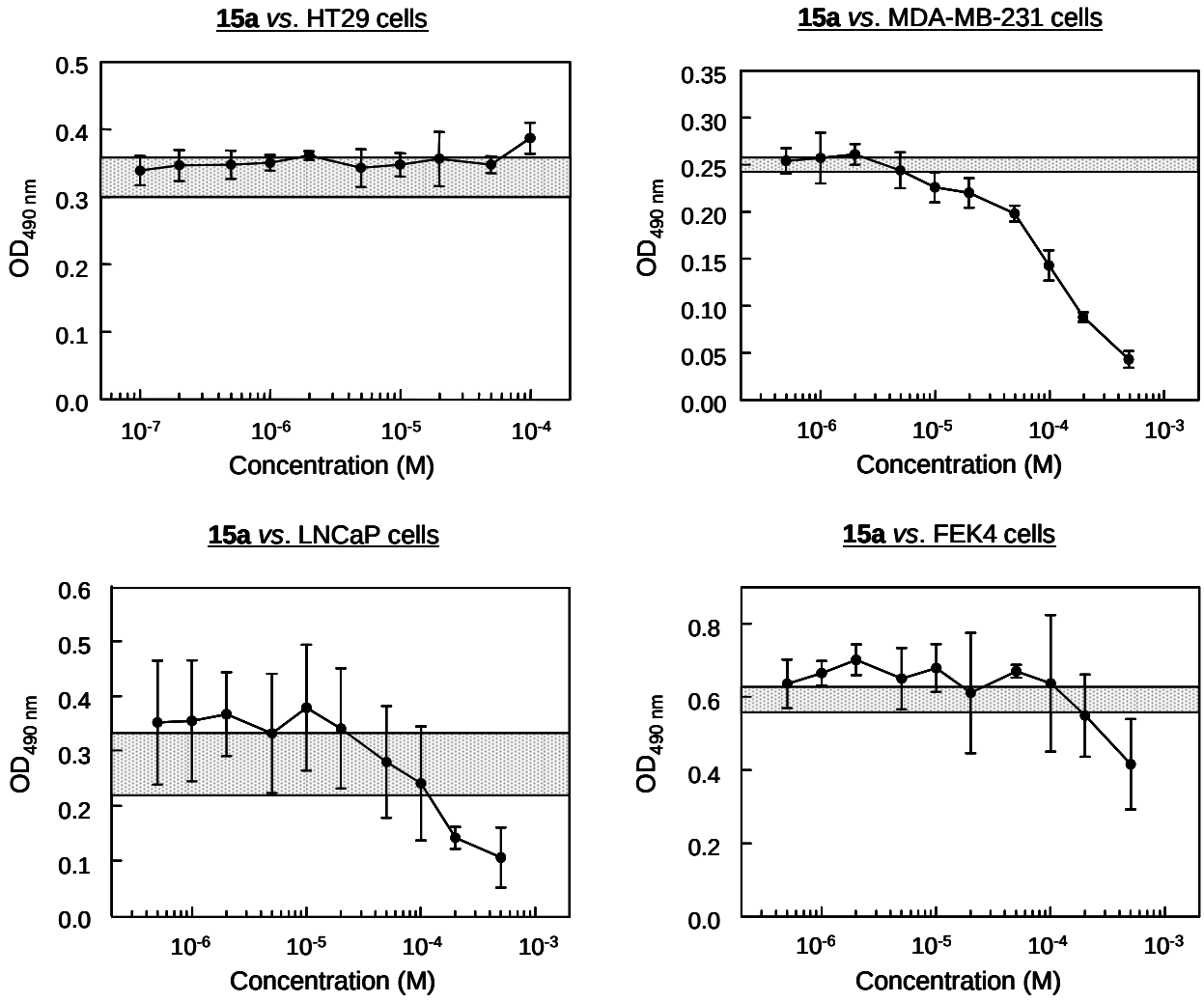
Cell proliferation was determined using the MTS assay (Promega Cell Titer 96® One Solution Cell Proliferation Assay). Cells (500 HT29 cells (Cancer Research UK), 1000 MDA-MB-231 cells (Cancer Research UK), 2000 LNCaP cells (Cancer Research UK) or 1500 FEK4 cells (a kind gift from Professor R. M. Tyrrell, University of Bath)) were seeded into culture medium (50 μL; DMEM with high glucose (4.5 g L^{-1}) and L-Gln, supplemented with penicillin (100 U mL^{-1}), streptomycin 100 μg mL^{-1} and 10% foetal bovine serum (all reagents supplied by Invitrogen)) in 96-well tissue culture plates (Nunc) with four replicants. Plates with cells were then incubated at 37°C, in humidified 5% CO_2 in air for 3-5 hours. Solutions of test compounds in DMSO were diluted 1-in-50 in culture medium; 50 μL of these solutions were added per well to cells, giving a final volume of 100 μL per well containing 1% (v/v) DMSO. Control samples with medium only and 1% (v/v) DMSO only were also included. Plates were incubated for to 7 d. MTS reagent was added at the required time at 20 μL per well, mixed gently and incubated for 1-4 h. The A_{490nm} was measured using a plate reader (VERSAmax tunable plate reader, Molecular Devices) and sample absorbances were corrected for background absorbance. Data were fitted using a logarithmic concentration scale to a dose-response curve using SigmaPlot 11.

Cytotoxicity of 5-AIQ 1 *vs*. HT29 human colon carcinoma cells, MDA-MB-231 human breast carcinoma cells, LNCaP human prostate carcinoma cells and FEK4 human fibroblasts.



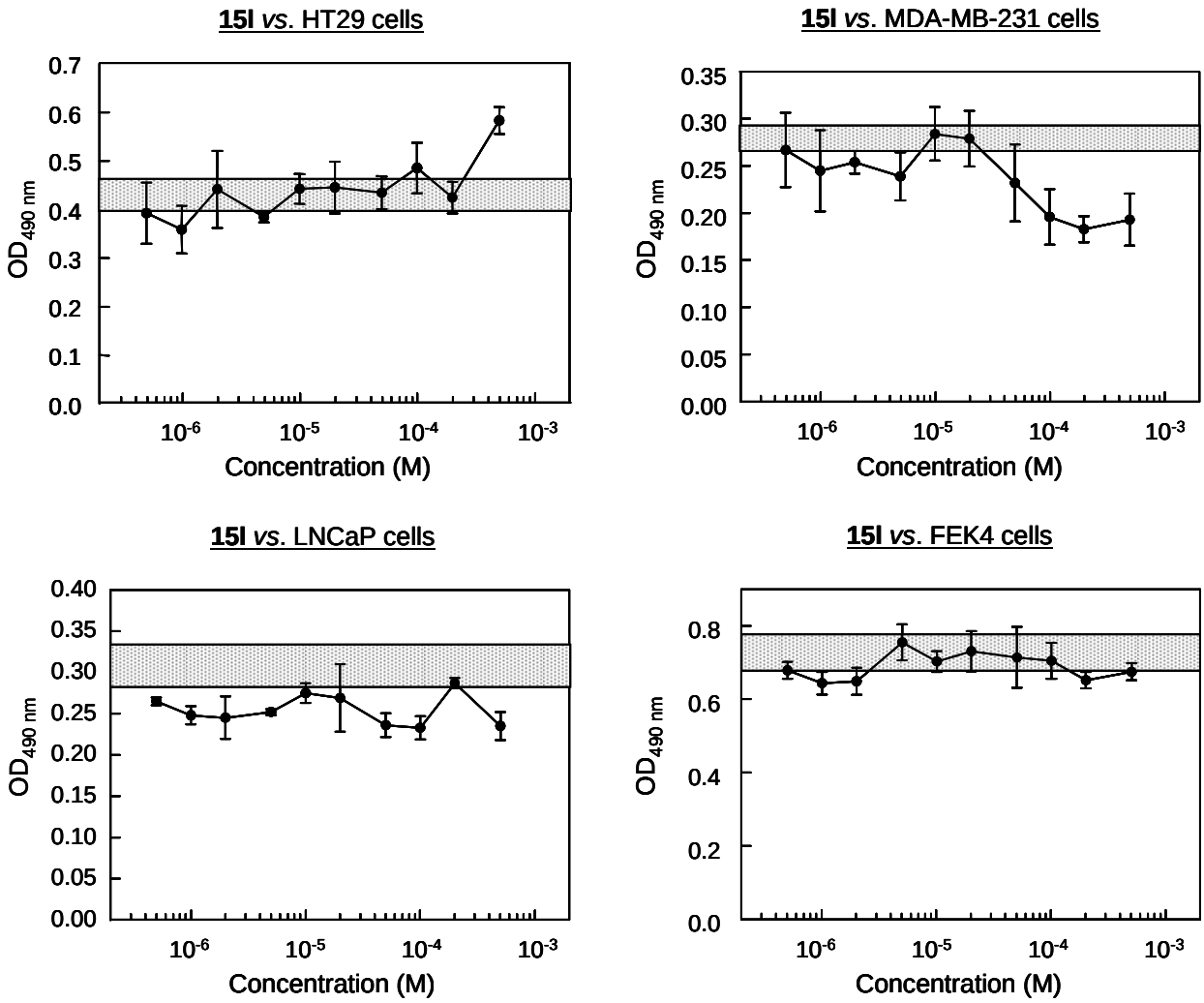
The shaded bars represent the variation in the no-drug control values. Error bars are ± 1 S.D.

Cytotoxicity of 15a *vs*. HT29 human colon carcinoma cells, MDA-MB-231 human breast carcinoma cells, LNCaP human prostate carcinoma cells and FEK4 human fibroblasts.



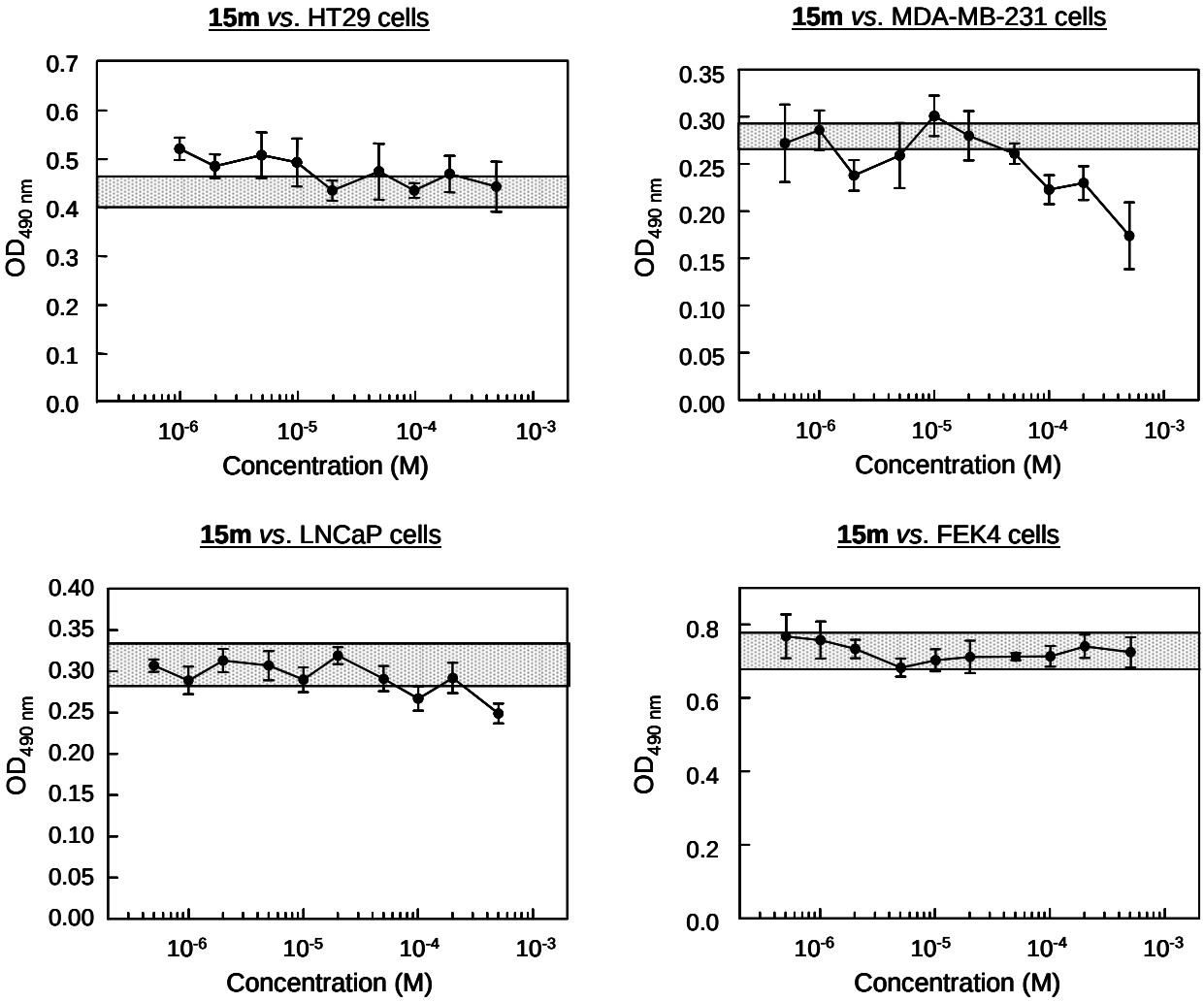
The shaded bars represent the variation in the no-drug control values. Error bars are ± 1 S.D.

Cytotoxicity of 15l *vs.* HT29 human colon carcinoma cells, MDA-MB-231 human breast carcinoma cells, LNCaP human prostate carcinoma cells and FEK4 human fibroblasts.



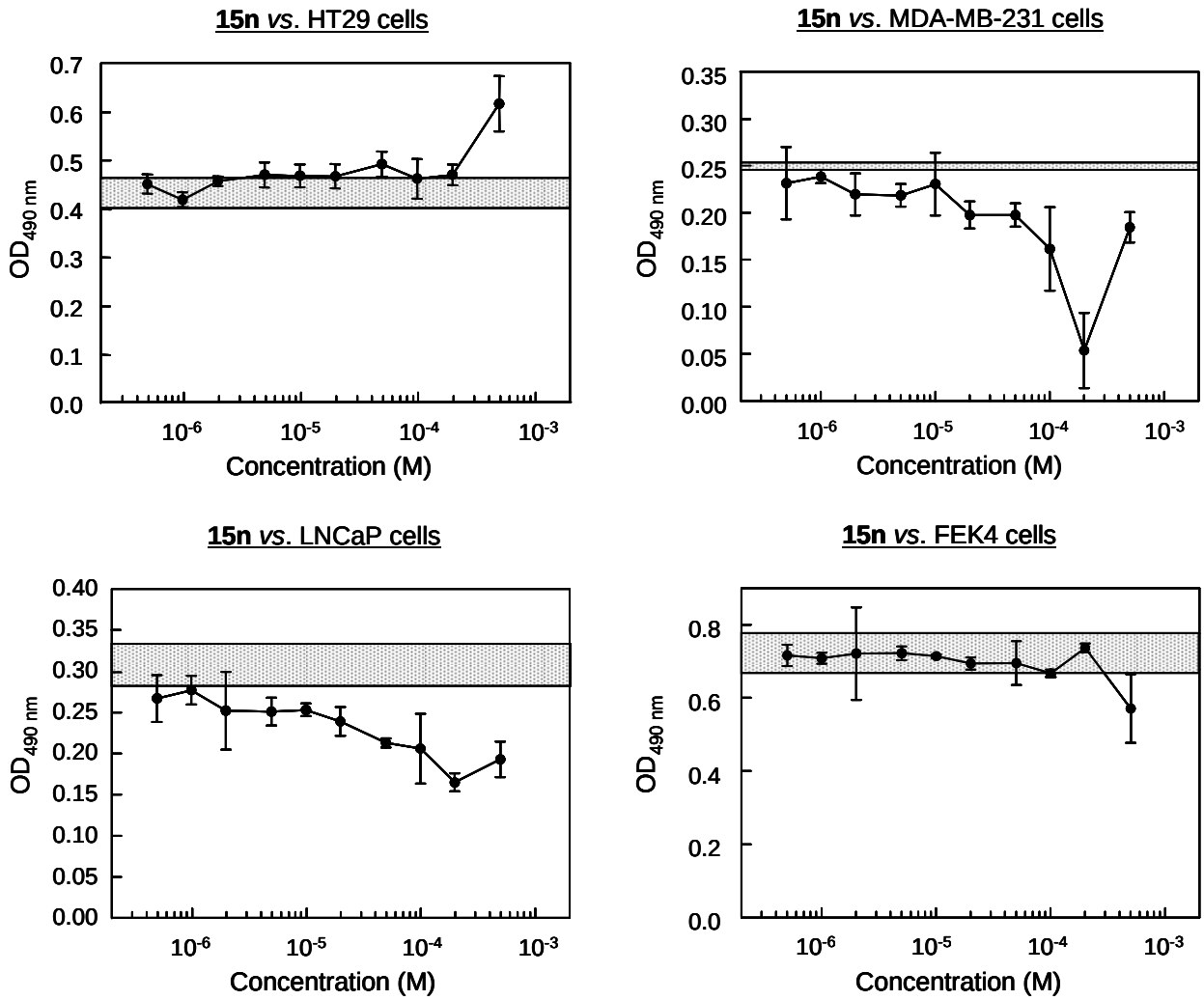
The shaded bars represent the variation in the no-drug control values. Error bars are ± 1 S.D.

Cytotoxicity of 15m *vs*. HT29 human colon carcinoma cells, MDA-MB-231 human breast carcinoma cells, LNCaP human prostate carcinoma cells and FEK4 human fibroblasts.



The shaded bars represent the variation in the no-drug control values. Error bars are ± 1 S.D.

Cytotoxicity of 15n *vs*. HT29 human colon carcinoma cells, MDA-MB-231 human breast carcinoma cells, LNCaP human prostate carcinoma cells and FEK4 human fibroblasts.



The shaded bars represent the variation in the no-drug control values. Error bars are ± 1 S.D.

Elemental microanalysis data.

		Found			Calculated		
Cpd.	**Formula**	**C**	**H**	**N**	**C**	**H**	**N**
15a	$C_{16}H_{12}N_2O_2$	72.67	4.48	10.42	72.72	4.58	10.60
15b	$C_{17}H_{14}N_2O_2$	73.23	4.98	10.22	73.37	5.07	10.07
15c	$C_{16}H_{11}N_3O_4$	61.96	3.38	13.22	62.14	3.58	13.59
15d	$C_{17}H_{11}F_3N_2O_2$	61.23	3.68	8.66	61.45	3.34	8.43
15e	$C_{17}H_{11}F_3N_2O_2$	67.98	3.68	9.62	68.05	3.92	9.92
15f	$C_{16}H_{11}ClN_2O_2$	64.23	3.68	9.32	64.33	3.71	9.38
15g	$C_{16}H_{11}BrN_2O_2$	55.85	3.14	8.02	56.00	3.23	8.16
15h	$C_{16}H_{11}IN_2O_2$	49.16	2.78	7.32	49.25	2.84	7.18
15i	$C_{17}H_{14}N_2O_2$	73.33	5.02	10.11	73.37	5.07	10.07
15j	$C_{16}H_{11}IN_2O_2$	49.12	2.66	7.26	49.25	2.84	7.18
15k	$C_{14}H_{10}N_2O_2S$	62.11	3.55	10.62	62.21	3.73	10.36
15l	$C_{16}H_{18}N_2O_2$	71.31	6.52	10.17	71.09	6.71	10.36
15m	$C_{14}H_{16}N_2O_2$	68.68	6.46	11.31	68.83	6.60	11.47
15n	$C_{20}H_{22}N_2O_2$	69.46	6.46	8.06	69.55	6.42	8.11
19	$C_{10}H_7NO_4$	58.3	3.47	6.78	58.54	3.44	6.83
20	$C_{10}H_8N_2O_3$	58.4	3.99	13.5	58.82	3.95	13.72
21	$C_{10}H_{11}ClN_2O$	56.82	5.01	13.45	57.02	5.26	13.30
22	$C_{17}H_{14}N_2O_2$	73.42	5.06	10.13	73.37	5.07	10.07

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