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


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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.); 1H NMR ((CD3)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-H4), 7.75 (1 H, d, J = 7.6 Hz, 6-H), 8.04 (2 H, d, J = 7.0 Hz, 2',6'-H2), 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). 13C NMR ((CD3)2SO) δ 100.6, 124.8, 125.9, 127.0, 127.8 (C2), 128.5 (C2), 128.9, 130.5, 131.8, 133.2, 134.1, 134.2, 161.6, 166.0; MS (ES+) m/z 287.0801 (M + Na) (C16H12N2NaO2 requires 287.0796); 265.0952 (M + H) (C16H13N2O2 requires 265.0977); Anal. (C16H12N2O2) 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; 1H NMR ((CD3)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'-H2), 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'-H2), 8.11 (1 H, d, J = 8.2 Hz, 8-H), 10.25 (1 H, s, ArCONH), 11.31 (1 H, br s, NH); 13C NMR ((CD3)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) (C17H14N2NaO2 requires 301.0953); 279.1119 (M + H) (C17H13N2O2 requires 279.1134); Anal. (C16H12N2O2) 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.); 1H NMR ((CD3)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); 13C NMR ((CD3)2SO) δ 100.46, 123.6, 125.2, 126.0, 129.1, 129.3, 130.4, 132.6, 134.1, 139.9, 149.3, 161.6, 164.6; MS (ES+) m/z 332.0639 (M + Na) (C17H14N2NaO4 requires 332.0647), 310.0827 (M + H) (C16H12N2O4 requires 310.0828); Anal. (C16H12N2O2) 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; 1H NMR ((CD3)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'-H2), 8.23 (2 H, d, J = 8.2 Hz, 2',6'-H2), 10.56 (1 H, s, ArCONH) 11.35 (1 H, d, J = 4.9 Hz, 2-NH); 13C NMR ((CD3)2SO) (HMBC / HMQC) δ 100.5 (4-C), 125.1 (8-C), 125.9 (q, J = 31.5 Hz, 3',5'-C2), 126.8 (7-C), 126.9 (8a-C), 128.9 (2',6'-C2), 130.3 (6-H), 130.9 (q, J = 31.5 Hz, 4'-C), 132.6 (5-C), 134.0 (4a-C), 137.9 (m, CF3), 149.5 (1'-C), 161.5 (1-C); MS (ES+) m/z 355.0666 (M + Na) (C17H11F3N2NaO2 requires 355.0670), 333.0844 (M + H) (C17H12F3N2O2 requires 333.0851); Anal. (C16H12N2O2) 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; 1H NMR ((CD3)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'-H2), 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'-H2), 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$_3$)$_2$SO) 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$_{12}$F$_2$NaO$_2$ requires 305.0702, 283.0889 (M + H) (C$_{16}$H$_{12}$F$_2$O$_2$ requires 283.0883); Anal. (C$_{16}$H$_{12}$N$_2$O$_2$) 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$_3$)$_2$SO) 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, 128.7 (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$_2$NaO$_2$ requires 321.0407), 299.0584 (M + H) (C$_{16}$H$_{12}$ClN$_2$O$_2$ requires 299.0587); Anal. (C$_{16}$H$_{12}$N$_2$O$_2$) 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$_3$)$_2$SO) 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$_3$)$_2$SO) 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$_{12}$BrN$_2$O$_2$ requires 343.0082); Anal. (C$_{16}$H$_{12}$N$_2$O$_2$) 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$_3$)$_2$SO) 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$_2$), 7.95 (2 H, d, J = 8.2 Hz, 2',6'-H$_2$), 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$_3$)$_2$SO) δ 99.5, 100.6, 124.9, 125.9, 127.0, 128.9, 129.7, 130.4, 132.9, 133.6, 134.2, 137.4, 161.6, 165.4; MS (ES$^+$) m/z 390.9950 (M + H) (C$_{16}$H$_{12}$I$_2$N$_2$O$_2$ requires 390.9944); Anal. (C$_{16}$H$_{12}$I$_2$N$_2$O$_2$) 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$_3$)$_2$SO) 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$_3$)$_2$SO) δ 19.5, 100.4, 124.5, 125.6, 125.9, 127.0, 127.4, 128.9, 129.7, 130.4, 131.0, 132.9, 133.6, 135.4, 136.8, 168.6; MS (ES$^+$) m/z 301.0956 (M + Na) (C$_{17}$H$_{13}$N$_2$NaO$_2$ requires 301.0953), 279.1130 (M + H) (C$_{17}$H$_{14}$N$_2$O$_2$ requires 279.1133); Anal. (C$_{17}$H$_{14}$N$_2$O$_2$) 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$_3$)$_2$SO) 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$_3$)$_2$SO) δ 93.6, 100.5, 124.6, 125.9, 127.1, 128.1,
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; 1H NMR ((CD3)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 = 7.5 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); 13C NMR ((CD3)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) (C16H11N2NaO2 requires 293.0361), 271.0529 (M + H) (C16H11N2O2 requires 271.0541); Anal. (C16H12N2O2) 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; 1H NMR ((CD3)2SO) δ 1.18-1.86 (11 H, m, cHex-H11), 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); 13C NMR ((CD3)2SO) δ 25.3, 27.4, 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) (C32H16N4NaO4 requires 563.2634), 541.2798 (2 M + H) (C32H17N4O4 requires 541.2815) 293.1248 (M + Na) (C16H14N2NaO2 requires 293.1266), 271.1140 (M + H) (C16H12N2O2 requires 271.1147); Anal. (C16H12N2O2) 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; 1H NMR ((CD3)2SO) δ 1.28 (9 H, s, Bu3), 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, Bu3CONH), 11.29 (1 H, br, 2-NH); 13C NMR ((CD3)2SO) δ 27.4 (C3), 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) (C16H16N2NaO2 requires 267.1109), 245.1291 (M + H) (C16H14N2O2 requires 245.1290); Anal. (C16H12N2O2) C,H,N.

5-(Adamantan-1-y1carboxamido)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; 1H NMR ((CD3)2SO) δ 1.73-2.04 (15 H, adamantane-H3), 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); 13C NMR ((CD3)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) (C20H19N2NaO2 requires 345.1579), 323.1769 (M + H) (C20H21N2O2 requires 323.1768); Anal. (C19H16N2O2) 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.); 1H NMR ((CD3)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), 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-H3), 10.28 (1 H, s, PhCONH), 11.35 (1 H, s, 2-NH); 13C 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) (C17H14NaN2O2 requires
1-Oxoisooquinoline-5-carboxylic acid (24). Compound 23 (427 mg, 2.5 mmol) was boiled under reflux with KOH in EtOH (20% w/v, 12 mL), under nitrogen, until the production of NH₃ 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. mp >300°C); 1H NMR (CD₃OD) 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-Oxoisooquinolin-5-yl)propenoic acid (26). Compound 25 (200 mg, 0.74 mmol), propenoic acid (0.06 mL, 70 mg, 0.49 mmol), Pd(OAc)₂ (16 mg, 74 μmol) and Et₃N (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. 315–318°C); 1H NMR ((CD₃)₂SO) δ 6.58 (1 H, d, J = 15.8 Hz, =CHCO₂), 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-H₂), 11.47 (1 H, br s, NH), 12.60 (1 H, br s, CO₂H).

Methyl 3-(5-amino-1-oxoisooquinolin-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 νmax 3465, 1715, 1674 cm⁻¹; 1H NMR ((CD₃)₂SO) δ 2.67 (2 H, t, J = 6.6 Hz, CH₂CO₂), 4.09 (2 H, t, J = 7.0 Hz, CH₂N), 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); 13C NMR ((CD₃)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) (C₁₃H₁₄N₂NaO₃ requires 269.0902), 247.1068 (M + H) (C₁₃H₁₅N₂O₃ 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 νmax 3240, 2580, 1721, 1638 cm⁻¹; 1H NMR ((CD₃)₂SO) δ 2.71 (2 H, t, J = 6.6 Hz, CH₂CO₂), 3.22-4.58 (4 H, m, OH, NH₂, NH), 4.14 (2 H, t, J = 6.6 Hz, CH₂N), 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); 13C NMR ((CD₃)₂SO) δ 33.1 (CH₂CO₂), 44.9 (NCH₂), 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 (CO₂Me); MS (ES⁺) m/z 233.0927 (M + H) (C₁₂H₁₃N₂O₃ requires 233.0936).
Spectroscopic data for compounds described in Experimental Section of paper.

5-Aminoisoquinolin-1-one hydrochloride (1). $^1$H NMR (D$_2$O) $\delta$ 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$_3$) $\delta$ 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$_3$)$_2$SO) $\delta$ 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$_3$)$_2$SO) $\delta$ 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, 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); 13C NMR ((CD$_3$)$_2$SO) $\delta$ 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$_2$O$_2$ requires 287.0796); 265.0952 (M + H) (C$_{16}$H$_{13}$N$_2$O$_2$ requires 265.0977); Anal. (C$_{16}$H$_{12}$N$_2$O$_2$) C, H, N.

3-Methyl-5-nitroisocoumarin (19). IR (KBr) $\nu_{\text{max}}$ 1746, 1648, 1520, 1331 cm$^{-1}$; 1H NMR (CDCl$_3$) $\delta$ 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); 13C NMR (CDCl$_3$) $\delta$ 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$_7$NO$_4$ requires 205.0375), 159 (M – NO$_2$); Anal. (C$_{10}$H$_7$NO$_4$) C, H, N.

3-Methyl-5-nitroisoquinolin-1(2$H$)-one (20). IR (KBr) $\nu_{\text{max}}$ 1746, 1648, 1520, 1331 cm$^{-1}$; $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 2.29 (3 H, s, Me), 6.78 (1 H, d, $J = 0.8$ Hz, 4-H), 7.13 (1 H, d, $J = 8.2$ 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$_9$N$_2$O$_3$ requires 205.0613), 189 (M – Me); Anal. (C$_{10}$H$_8$N$_2$O$_3$) C, H, N.

5-Amino-3-methylisoquinolin-1(2$H$)-one (21). IR (KBr) $\nu_{\text{max}}$ 1746, 1648, 1520, 1331 cm$^{-1}$; $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 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) (12C$_{10}$H$_{11}$N$_2$O$_2$ requires 175.0871), 159 (M – Me). A sample was converted to the HCl salt: $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 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); 13C NMR ((CD$_3$)$_2$SO) (HMQC / HMBC) $\delta$ 19.2 (Me), 97.2 (C$_{16}$H$_{13}$N$_2$O$_2$ requires 175.0871), 159 (M – Me).

3-(1-Oxoisoquinolin-5-yl)propanoic acid (27). $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 2.54 (2 H, t, $J = 7.8$ Hz, ArCH$_2$), 3.09 (2 H, t, $J = 7.8$ Hz, CH$_2$COOH), 3.17-3.42 (1 H, s, 4-H), 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); 13C NMR ((CD$_3$)$_2$SO) $\delta$
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$_2$O requires 218.0817).

**Ethyl 2-(1-oxoisquinolin-5-ylamino)acetate (28).** IR $\nu_{\max}$ 3437, 1728, 1654 cm$^{-1}$; $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 1.19 (3 H, t, $J = 7.2$ Hz, Me), 4.01 (2 H, d, $J = 4.9$ Hz, CH$_2$N), 4.12 (2 H, q, $J = 7.2$ Hz, OCH$_2$), 6.44 (1 H, t, $J = 4.9$ Hz, CH$_2$NH$_2$), 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$_3$)$_2$SO) $\delta$ 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$_2$NaO$_3$ requires 269.0902), 247.1136 (M + H) (C$_{15}$H$_{15}$N$_2$O$_3$ requires 247.1083).

**5-(Carboxymethylamino)isoquinolin-1-one hydrochloride (29).** IR $\nu_{\max}$ 3134, 2523, 1737, 1608 cm$^{-1}$; $^1$H NMR ((CD$_3$)$_2$SO) $\delta$ 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 $\delta$ ((CD$_3$)$_2$SO) 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$_2$O$_3$ 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% CO₂ 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 7 d. MTS reagent was added at the required time at 20 μL per well, mixed gently and incubated for 1-4 h. The A₄₉₀nm 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.

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References for Supplementary Information


