SUPPLEMENTARY DATA

SUPPLEMENTARY FIGURES

Figure S1. 16 small molecules from the 'lead' group of thirty-three cause an increase in the percentage of cells in G2/M phases of the cell cycle. SKNSH cells with either active (SKNSH-pCMV) or inactive p53 (SKNSH-DNp53) were cultured in the absence or presence of compounds at 10 μM for 48 hours and analysed by two dimensional FACS. The proportion of cells with DNA contents corresponding to cells in G1, S and G2/M are shown. The percentage of cells with a less than 2N DNA content, with a DNA content between 2N and 4N but unable to incorporate BrdU (>2N<4N) and cells with a DNA content that do undergo DNA synthesis (S+) are also shown.

Chemistry experimental for supplementary material

4-(2',5'-Difluorobenzoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (JJ78:2) A solution of **JJ78:1** (1.5 mmol, 0.46 g) and potassium hydroxide (200 mg , 3.6 mmol) in a mixture of ethanol (5 mL) and water (5 mL) was distilled until 5 mL of distillate had collected. The reaction mixture was cooled to ambient temperature and washed with dichloromethane. The aqueous portion was acidified by addition of 10% HCl and the resulting precipitate was collected by filtration. Re-precipitation from hot ethanol provided the desired compound **JJ78:**2 as a white solid (290 mg, 70%): ^{1}H NMR (300 MHz, DMSO-d^{6}) δ ppm 2.07 (3 H, s), 2.20 (3 H, s), 7.25 - 7.48 (3 H, m), 12.00 (1 H, br. s), 12.63 (1 H, br. s).

4-(2',5'-Difluorobenzoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid ethylamide (JJ78:3) To a suspension of **JJ78:2** (91 mg, 0.33 mmol) in dichloromethane (10 mL) was added thionyl chloride (0.3 mL) and DMF (1 drop). The mixture was stirred under an argon atmosphere for 20 hours. A solution of 2 M ethylamine in THF (1 mL) and dichloromethane (10 mL) was then added. After 18 hours the mixture was concentrated *in vacuo* and the residue purified by flash silica chromatography eluting with EtOAc/petroleum ether (1:1) to give the desired product **JJ78:3** as an off-white solid (59 mg, 59%): m.p. 179-181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.23 (3 H, t, *J*=7.2 Hz), 2.18 (3 H, s), 2.39 (3 H, s), 3.40 - 3.56 (2 H, m), 5.86 (1 H, t, *J*=5.0 Hz), 7.02 - 7.21 (3 H, m), 11.13 (1 H, br. s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.10, 13.34, 15.04, 34.60, (dd, *J*=3.6, 24.8 Hz), 117.46 (dd, *J*=8.1, 24.9 Hz), 118.64 (dd, *J*=8.4, 24.2 Hz), 121.90, 122.19, 122.67, 131.40 (dd, *J*=6.3, 18.0 Hz), 138.56, 153.75, 156.97 (dd, *J*=2.3, 9.6 Hz), 160.14, 161.87, 187.64; MS (ES+) m/z 329 $[M+Na]^{+}$; MS (ES-) m/z 305; HRMS calc'd for $C_{16}H_{16}F_2N_2O_2Na$ 329.1078, found 329.1078.

Benzyl 4-(2',5'-Difluorobenzoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (JJ78:4) To a suspension of **JJ78:2** (56 mg, 0.20 mmol) in dichloromethane (5 mL) was added thionyl chloride (0.15 mL). The mixture was stirred under an argon atmosphere for 20 hours. The mixture was concentrated *in vacuo* to give a red solid which was dissolved in toluene (10 mL) under an argon atmosphere. Benzyl alcohol (44 mg, 0.40 mmol) was added followed by triethylamine (27 μL, 0.20 mmol). The mixture was stirred for 18 hours and concentrated *in vacuo* and the residue purified by flash silica chromatography eluting with EtOAc/petroleum ether (0.5:9.5 to 1:4) to give the desired product **JJ78:4** as a pink solid (52 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.28 (3 H, s), 2.29 (3 H, s), 5.32 (2 H, s), 7.12 (3 H, m), 7.39 (5 H, m), 9.22 (1 H, br. s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 11.80, 13.87, 66.24, 116.10 (dd, *J*=3.5, 24.8 Hz), 117.51 (dd, *J*=8.1, 24.9 Hz), 118.31, 119.02 (dd, 8.6, 24.1 Hz), 123.12, 128.26, 128.40, 128.68, 130.30, 135.83, 139.15, 153.93, 156.98, 157.19, 160.24, 161.20; MS (EI+) m/z 369; HRMS calc'd for $C_{21}H_{17}F_2NO_3$ 369.1177, found 369.1176.

4-(2',5'-Difluorobenzoyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid benzylamide (JJ78:5) JJ78:2 (223 mg, 0.80 mmol) and *N*-hydroxysuccinimide (92 mg, 0.80 mmol) were suspended in dichloromethane (7 mL) under an argon atmosphere and cooled at 0 ºC. A solution of dicyclohexylcarbodiimide (169 mg, 0.82 mmol) in dichloromethane (2 mL) was added with stirring. The mixture was stirred at

0 ºC for 3 hours and allowed to warm to room temperature over 36 hours. The mixture was filtered and the white solid obtained was washed with dichloromethane. The combined dichloromethane fractions were concentrated *in vacuo* and the residue purified by flash silica chromatography eluting with EtOAc/petroleum ether (3:7) to give 4-(2',5'-difluoro-benzoyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid 2,5-dioxo-pyrrolidin-1-yl ester as a white solid (98 mg, 33%). This ester (38 mg, 0.10 mmol) was stirred with benzylamine (12 mg, 0.11 mmol) in dichloromethane (2 mL) under an argon atmosphere for 2 days. The mixture was diluted with dichloromethane (20 mL) and washed with 1 M aqueous hydrochloric acid (2 x 20 mL), water (1 x 10 mL) and saturated brine (1 x 10 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* and the residue purified by flash silica chromatography eluting with EtOAc/petroleum ether (2:3) to give **JJ78:5** as a white solid (25 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.13 (3 H, s), 2.35 (3 H, s), 4.65 (2 H, d, *J*=5.5 Hz), 6.13 (1 H, br. s), 7.11 (3 H, m), 7.33 (5 H, m), 10.40 (1 H, br. s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.17, 13.49, 43.67, 116.16 (dd, *J*=3.5, 24.8 Hz), 117.52 (dd, 8.1, 25.0 Hz), 118.89 (dd, *J*=8.5, 24.2 Hz), 122.29 (d, *J*=15.1 Hz), 122.51, 127.50, 127.70, 128.87, 138.15 (d, *J*=24.2 Hz), 153.86, 157.06 (d, *J*=12.3 Hz), 160.23, 161.78, 187.62; MS (CI+) m/z 369 $[M+1]^+$; HRMS calc'd for $C_{21}H_{19}F_2N_2O_2$ 369.1415, found 369.1418.

Ethyl 4-(2',5'-difluorobenzoyl)-1,3,5-trimethyl-1*H*-pyrrole-2-carboxylate (JJ78:6) JJ78:1 (46 mg, 0.15 mmol), potassium carbonate (22 mg, 0.16 mmol) and methyl iodide (22.7 mg, 0.16 mmol) were stirred in acetonitrile (2 mL) in a sealed tube. The reaction mixture was heated at 60 ºC for 18 h. Further portions of potassium carbonate (10 mg) and methyl iodide (10 μL) were added and the mixture stirred for 8 hours. The reaction mixture was concentrated *in vacuo* and the remaining residue suspended in dichloromethane and filtered. The filtrate was concentrated *in vacuo* and the residue purified by flash silica chromatography eluting with dichloromethane to give **JJ78:6** as a colourless oil (46 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.35 (3 H, t, *J*=7.1 Hz), 2.17 (3 H, s), 2.29 (3 H, s), 3.80 (3 H, s), 4.30 (2 H, q, *J*=7.1 Hz), 7.13 (3 H, m); MS (CI+) m/z 322 $[M+1]^+$; HRMS calc'd for $C_{17}H_{18}F_2NO_3$ 322.1255, found 322.1249.

Ethyl 4-(2',5'-difluorobenzoyl)-1*H*-pyrrole-2-carboxylate (JJ78:17) Synthesized according to general procedure from ethyl pyrrole-2-carboxylate and 2,5-difluorobenzoyl chloride. White solid, 102 mg (73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.38 (3 H, t, *J*=7.2 Hz), 4.36 (2 H, q, *J*=7.0 Hz), 7.08 - 7.22 (2 H, m), 7.21 - 7.33 (2 H, m), 7.46 - 7.58 (1 H, m), 10.06 (1 H, br. s). MS (ES-) m/z 278 $[M-H]^+$; HRMS calc'd for $C_{14}H_{10}F_2NO_3$ 278.0629, found 278.0619.

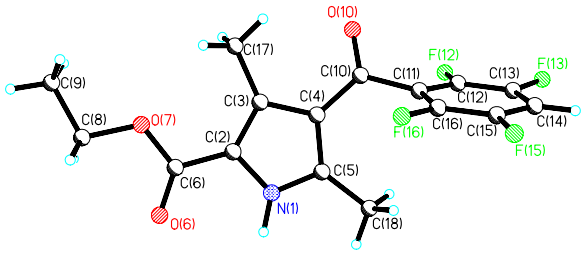
Ethyl 4-(3'-chlorobenzoyl)-1*H*-pyrrole-2-carboxylate (JJ78:18) Synthesized according to general procedure from ethyl pyrrole-2-carboxylate and *m*-chlorobenzoyl chloride. Colourless oil, 49 mg (35%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.39 (3 H, t, *J*=7.0 Hz), 4.38 (2 H, q, *J*=7.1 Hz), 7.32 - 7.35 (1 H, m), 7.40 - 7.48 (1 H, m), 7.50 - 7.60 (2 H, m), 7.72 (1 H, d, *J*=7.7 Hz), 7.78 - 7.85 (1 H, m), 9.65 (1 H, br. s). MS (ES+) m/z 300 $[M+Na]^+$; HRMS calc'd for $C_{14}H_{12}NO_3ClNa$ 300.0403, found 300.0404.

Ethyl 4-[(3'-chlorophenyl)-hydroxyiminomethyl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (JJ78:19) A solution of **JJ78:12** (100 mg, 0.35 mmol) and hydroxylamine hydrochloride (144 mg, 2.1 mmol) in pyridine (3 mL) was heated at reflux under nitrogen atmosphere for 3 hours. After cooling to rt the solution was concentrated *in vacuo*. The resulting residue was resuspended in ethyl acetate (50 mL) and washed with H_2O (3 x 20 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the resulting oil purified by flash silica chromatography eluting with EtOAc/petroleum ether (1:9 to 2:5) to give the desired product **JJ78:19** as a colourless oil (50 mg, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.36 (3 H, t, *J*=7.1 Hz), 2.07 (3 H, s), 2.10 (3H, s), 4.33 (2H, q, *J*=7.1 Hz), 7.29 (1 H, s), 7.32 – 7.41 (2 H, m), 7.50 (1 H, t, *J*= 1.7 Hz), 9.34 (1 H, br. s); MS (ES+) m/z 343 $[M+Na]^+$; HRMS calc'd for $C_{13}H_{20}N_3O_2NaCl_2$ 343.0830, found 343.0829.

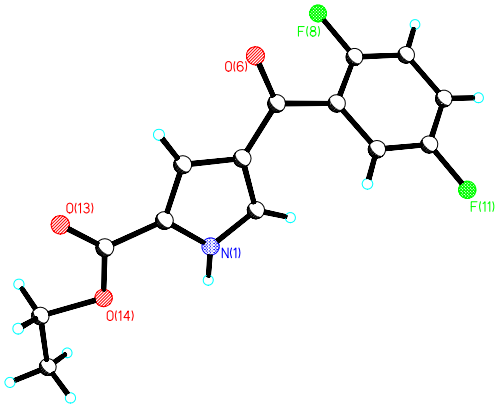
X-ray crystal structure data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 697553 - 697555. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: <mailto:deposit@ccdc.cam.ac.Uk>deposit@ccdc.cam.ac.Uk).

JJ78:1



JJ78:17



JJ78:18